



THE LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
in conjunction with EALA

June 11-13, 2026 | Conrad Seoul, Korea



DAY 1 [Thursday, June 11, 2026]

ROOM 1ABC

PG Course 1 | Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Viral Hepatitis (HBV, HCV, HDV, HEV), Primary Biliary Cholangitis, and Autoimmune Hepatitis

• Practical Use of GLP-1 Receptor Agonists in MASLD: Dosing, Patient Counseling, and Safety Considerations
Han Ah Lee (Chung-Ang University)

• Autoimmune Liver Diseases: Autoimmune Hepatitis and Primary Biliary Cholangitis in Clinical Practice
Kyung-Ah Kim (Inje University)

• Optimizing HCV Management in Real-World Practice
Yang-Hyun Baek (Dong-A University)

• HBV-HDV Coinfection: Diagnosis, Natural Course, and Clinical Pitfalls
Jeong Won Jang (The Catholic University of Korea)

3

9

13

21

PG Course 2 | Hepatocellular Carcinoma (HCC), Portal Hypertension, and Alcohol-Related Liver Disease

• Diagnosis and Non-Invasive Assessment of Portal Hypertension
Seung Up Kim (Yonsei University)

• TIPS: Selecting the Right Patient with Portal Hypertension
Yeon Seok Seo (Korea University)

• Alcohol-Related Liver Disease: From Assessment to Management
Young Kul Jung (Korea University)

• Systemic Therapy for HCC: First-Line, Second-Line, and Beyond
Ju Hyun Shim (University of Ulsan)

25

29

31

35

2026 KASL Clinical Practice Guidelines | Liver Cirrhosis

• 2026 KASL Clinical Practice Guidelines: Liver Cirrhosis
Moon Young Kim (Yonsei University Wonju)

39

PG Course 3 | Chronic Hepatitis B

• Updated KASL Guidelines on Chronic Hepatitis B
Won-Mook Choi (University of Ulsan)

• Treatment Strategy for Chronic Hepatitis B: Who, When, and What Goals to Achieve?
Nae-Yun Heo (Inje University)

• Assessing Disease Activity and Fibrosis in Chronic Hepatitis B: Non-Invasive Techniques and Beyond
Beom Kyung Kim (Yonsei University)

• Interactions between HBV and Coexisting Liver Diseases: Clinical Implications in HCV and MASLD
Ki Tae Yoon (Pusan National University)

43

47

51

55

PG Course 4 | Chronic Hepatitis B

• Revisiting the Natural Course of Chronic Hepatitis B: Implications of the Indeterminate Phase
Tetsuo Takehara (The University of Osaka, Japan)

• Risk Stratification and Surveillance Strategies for HCC in Chronic Hepatitis B
Ju Dong Yang (Cedars-Sinai Medical Center, USA)

61

65

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June 11-13, 2026 | Conrad Seoul, Korea

iii

CONTENTS

• Clinical Course and Management Considerations after Antiviral Therapy Discontinuation in Chronic Hepatitis B Tung-Hung Su (National Taiwan University, Taiwan)	67
• Innovative Therapeutic Strategies for Functional Cure in HBV Edward Gane (University of Auckland, New Zealand)	69

ROOM 2AB

Basic Research Workshop 1 | Viral Load-Based Immune Landscapes in Chronic Hepatitis B: From Tolerance to Cure

• Immune Dysfunction in Chronic Hepatitis B: Innate and Adaptive Perspectives Su-Hyung Park (KAIST)	75
• Untreated Chronic HBV: Viremia-Dependent Immune States Sung-Gyoo Park (Seoul National University)	77
• Immune Modulation Mechanisms during Antiviral Therapy Pil Soo Sung (The Catholic University of Korea)	79
• Functional Cure: Mechanisms of Sustained Immune Control Eui-Cheol Shin (KAIST)	83

Basic Research Workshop 2 | Basic and Translational Research Methodologies in HBV Studies

• Molecular Techniques for Analyzing HBV Replication and cccDNA Transcriptional Activity Kyun-Hwan Kim (Sungkyunkwan University)	87
• Cell Culture, in vitro, and Animal Models Heeju Ryu (Sungkyunkwan University)	91
• Sub-Cellular in Situ Profiling of Chronic Hepatitis B Liver Tissue Identifies Spatial Niches of Immune Tolerance in 'Grey Zone' Patients Seunghee Hong (Yonsei University)	93
• High-Dimensional and Multi-Omics Approaches in HBV Research Su Bin Lim (Ajou University)	97

Career Development for Young Investigator | Beyond the White Coat: Diverse Journeys in Modern Medicine

• The Journey of a Physician-Scientist: Bridging the Bench and the Bedside Hyung Jin Choi (Seoul National University)	101
• From Idea to Impact: The Doctor as an Entrepreneur Jeong Seok Lee (KAIST)	105
• The Nature of Medicine as a Servant Chang Wook Kim (The Catholic University of Korea)	107
• On the Frontline of Digital Health: Redefining the Future of Care Min Kyu Han (Kakao Healthcare)	111

ROOM 2C [Park Ballroom]

Ultrasound Trainee Session

• Getting Started with Upper Abdominal Ultrasonography Seul Ki Han (Yonsei University Wonju)	115
• Ultrasound Scanning Techniques: Liver Hyun Yang (The Catholic University of Korea)	119
• Ultrasound Scanning Techniques: Pancreato-Biliary, Spleen, and Vascular Young Youn Cho (Chung-Ang University)	123

CONTENTS

• Ultrasound Approaches to Common Diseases: A Practical Guide for Beginners Hyunwoo Oh (Sungkyunkwan University)	127

ROOM 3

Ultrasound Trainer Session 1

• Current Status and Future Directions for Maintaining Abdominal Ultrasound Certification Systems Tae-Suk Kim (Kangwon National University)	131
• Why Advanced Ultrasound Matters: Expanding the Role Beyond Screening Yeowool Kang (Dong-A University)	135
• Mastering Advanced Ultrasound: From Stepwise Implementation to Clinical Pearls Woo Sun Rou (Chungnam National University)	137
• Enhancing Diagnostic Clarity: Global Standard Lexicons for Professional Ultrasound Reporting Young Chang (Soonchunhyang University)	141

Ultrasound Trainer Session 2

• Advanced Shear Wave Elastography (SWE): Multi-Vendor Comparison Jae Seung Lee (Yonsei University)	145
• Current Role of Ultrasound and CEUS in the LI-RADS Framework Soung Won Jeong (Soonchunhyang University)	151
• Mastering Doppler for Portal Hypertension: From Waveform Analysis to Clinical Decision Making Hyun Jung Chung (Yonsei University Wonju)	155
• Deep Learning-Based Quality Control in Abdominal Ultrasound Soo Young Park (Kyungpook National University)	159

DAY 2 [Friday, June 12, 2026]

ROOM 1AB

KASL-KAHBPS-KLCA-KLTS Joint Symposium | Expanding Horizons in Surgical Management of Hepatic Malignancies

• Expanding Indications for Surgery and Transplantation in Hepatic Malignancies: Ethics, Donor Considerations, and Future Perspectives Dong Hyun Sinn (Sungkyunkwan University)	165
• Downstaging and Conversion to Resection or Transplantation for Advanced HCC Using Systemic and Locoregional Therapies Yun Bin Lee (Seoul National University)	169
• Surgical Management of Uncommon Hepatic Malignancies Sang Jin Kim (Korea University)	173
• Liver Transplantation for Uncommon Hepatic Malignancies: Beyond Current Criteria Sang-Hoon Kim (University of Ulsan)	177

KASL Symposium 1 | Redefining the Natural History of Chronic Hepatitis B: Expanding Treatment Paradigms

• Immunological Features of Chronic Hepatitis B: Stage-Independent Patterns of HBV-Specific T Cell Responses Nina Le Bert (Duke-NUS Medical School, Singapore)	183

- Clarifying the Indeterminate Phase in Chronic Hepatitis B: Defining Its Natural Course and Virological Characteristics
[Gi-Ae Kim](#) (*Kyung Hee University*)
- Impact of Antiviral Therapy in the Indeterminate Phase of Chronic Hepatitis B: Who Should Be Treated
[Yao-Chun Hsu](#) (*I-Shou University, Taiwan*)
- Latest Updates on Novel Biomarkers for Chronic Hepatitis B
[Yasuhito Tanaka](#) (*Kumamoto University, Japan*)

185

189

191

KASL Leading Research Achievement Award

- Inspired to Question, Learning to Answer: A Physician-Scientist's Journey Through Hepatology
[Jeong-Hoon Lee](#) (*Seoul National University*)

195

President's Choice Lecture

- From Clinical Research to Policy: An Epidemiologist's Journey toward Viral Hepatitis Elimination
[Chien-Jen Chen](#) (*Academia Sinica, Taiwan*)

199

KASL-AASLD Joint Symposium | Beyond Steatosis: Metabolic, Muscular, and Oncologic Implications of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

- Public Health and Policy Implications in the Metabolic Era
[Won Sohn](#) (*Sungkyunkwan University*)
- Contemporary MASLD Management: Integrating Available Therapies, Metabolic Care, and Prevention of Sarcopenia
[Hye Won Lee](#) (*Yonsei University*)
- Near-Future MASLD Therapies: Resmetirom, GLP-1 Receptor Agonists and Emerging Agents
[Kathleen E. Corey](#) (*Harvard Medical School, USA*)
- Rethinking HCC Surveillance in the MASLD Era: From Non-Cirrhotic Risk to Global Strategies
[Ju Dong Yang](#) (*Cedars-Sinai Medical Center, USA*)

203

207

211

213

KASL Symposium 3 | From Cure to Care: Remaining Challenges in HBV Management

- Expanding Indications for Nucleos(t)ide Analogue Therapy in Chronic Hepatitis B: Clinical Benefits and Long-Term Outcomes
[Dong Hyun Sinn](#) (*Sungkyunkwan University*)
- Personalizing Antiviral Therapy in Hepatitis B: Balancing Safety, Efficacy, and HCC Prevention
[Tung-Hung Su](#) (*National Taiwan University, Taiwan*)
- Discontinuation of Antiviral Therapy in Chronic Hepatitis B
[Yao-Chun Hsu](#) (*I-Shou University, Taiwan*)
- Immune Mechanisms Driving HBsAg Decrease with Various Anti-HBV Therapeutics
[Seng-Gee Lim](#) (*National University of Singapore, Singapore*)

217

221

223

225

KASL Symposium 4 | Management Strategies for Chronic Viral Hepatitis

- Beyond Cure: Practical Care for Hepatitis C Patients with MASLD
[Takumi Kawaguchi](#) (*Kurume University, Japan*)
- The Need for Greater Awareness and an Evolving Treatment Landscape in Hepatitis D Infection
[Young Kul Jung](#) (*Korea University*)
- Low Level Viremia in Chronic Hepatitis B Patients Receiving Nucleos(t)ide Analogues: Clinical Impact and Management
[Chun-Jen Liu](#) (*National Taiwan University, Taiwan*)
- AI-Driven Strategies for Chronic Hepatitis B: From Prediction to Post-Cure Risk Stratification
[Moon Haeng Hur](#) (*Seoul National University*)

229

233

235

237

ROOM 1C

Mini Special Interest Group 1 | The KASL Viral Hepatitis Study Group

- Unmet Needs in the Clinical Practice of Chronic Viral Hepatitis: From Functional Cure to Personalized HCC Surveillance
[Janghan Jung](#) (*Hallym University*)

241

KASL Symposium 2 | Autoimmune Liver Diseases and Beyond

- Immunopathogenesis and Overlap Syndromes in Autoimmune Liver Diseases
[Ja Kyung Kim](#) (*Yonsei University*)
- Hard-to-Treat Autoimmune Liver Diseases: Lessons from Clinical Cases
[Soon Kyu Lee](#) (*The Catholic University of Korea*)
- Treatment Optimization in Autoimmune Hepatitis: When First-Line Therapy Fails
[Atsumasa Komori](#) (*Nagasaki University, Japan*)
- Beyond Ursodeoxycholic Acid: The Next Chapter in Primary Biliary Cholangitis Treatment
[Yu Jun Wong](#) (*Duke-NUS Medical School, Singapore*)

245

249

253

257

Special Interest Group 1. KCSG & CHESS Joint Symposium | Leading the Frontiers of Cirrhotic Portal Hypertension in East Asia

- Emerging Evidence: Ongoing Prospective Trials in Cirrhosis from Korea
[Seong Hee Kang](#) (*Korea University*)
- LiverRCT: CHESS Ongoing Randomized Controlled Trials of Cirrhotic Portal Hypertension
[Xiaolong Qi](#) (*Liver Health Consortium in China (CHESS), China*)
- Clinical Insights from the Korean Multicenter HVPG Cohort
[Tom Ryu](#) (*Soonchunhyang University*)
- Vasomics: CHESS Emerging Technologies of Cirrhotic Portal Hypertension
[Ling Yang](#) (*Southeast University, China*)

261

263

267

271

Hepatology Associates

- Evaluation and Management of Abnormal Liver Function Tests in Clinical Practice
[Byeong Geun Song](#) (*Sungkyunkwan University*)
- Assessing Tumor Response in HCC: RECIST and mRECIST
[Hyo Jung Park](#) (*University of Ulsan*)
- Practical Approaches to Metabolic Dysfunction-Associated Steatohepatitis (MASH) Therapy and Complication Management
[Ha Il Kim](#) (*Hanyang University*)
- How to Report Complications: CTCAE and SUSAR
[Taekeun Park](#) (*Seoul National University*)

275

279

283

287

ROOM 2AB [Park Ballroom]

KLCA Symposium 1 | From Detection to Prevention: Evolving Strategies in Hepatocellular Carcinoma (HCC) Diagnosis and Chemoprevention

- Controversies in Imaging-Based Diagnosis of HCC: Revisiting Major Features and Regional Differences
[Hyo Jung Park](#) (*University of Ulsan*)
- AI-Driven Prediction and Risk Stratification for HCC Surveillance
[Hyunjae Shin](#) (*Seoul National University*)

293

297

• Biomarkers for HCC Diagnosis and Surveillance: Beyond AFP Hye Won Lee (Yonsei University)	303
• Chemoprevention in MASLD: Can We Reduce the Risk of HCC? Jeong Eun Song (Daegu Catholic University)	307

2026 KLCA-NCC Practice Guidelines for Hepatocellular Carcinoma

• 2026 KLCA-NCC Practice Guidelines: Hepatocellular Carcinoma Bo Hyun Kim (National Cancer Center) Do Young Kim (Yonsei University)	312

KLCA-ILCA Joint Symposium | Who Is the Best Partner for Anti-PD-1/PD-L1 in Advanced HCC: VEGF Inhibition vs. CTLA-4 Blockade

• Evolving Landscape of Immunotherapy in HCC: Finding the Optimal Partner Eui-Cheol Shin (KAIST)	315
• Anti-VEGF as a Partner to PD-L1 Blockade Antonio D'Alessio (King's College Hospital, UK)	317
• Dual Immune Blockade in HCC Bo Hyun Kim (National Cancer Center)	319

KLCA Symposium 2 | Managing MASLD-HCC: A Comprehensive Overview of Treatment Modalities and Strategies

• MASLD-HCC Carcinogenesis: Genetics and Metabolic Drivers Su Jong Yu (Seoul National University)	323
• Immunity and Resistance in MASLD-HCC: Strategies for Immune Checkpoint Inhibitor Therapy Arndt Vogel (University of Toronto, Canada)	327
• Prognostic Imaging: Assessing Risk and Predicting Outcomes in MASLD-HCC Sunyoung Lee (Yonsei University)	329
• Tailoring Immunotherapy for MASLD-HCC: Challenges and Emerging Strategies Takahiro Kodama (The University of Osaka, Japan)	331

ROOM 2C

KASL Branch Early Morning Workshop 1 | [Gyeonggi-Incheon]

• Clinical and Epidemiological Analysis of HEV Infection Based on the Nation-Wide Surveillance of Hepatitis E in Japan Jong-Hon Kang (Teine Keijinkai Hospital, Japan)	335

Translational Research 1 | Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Pathogenesis and Metabolic-Immune Cross-Talk

• MASLD Phenotypic Diversity: From Genetic Discovery to Precision Medicine Stratification Stefano Romeo (Karolinska Institutet, Sweden)	339
• When Blood Ages Badly: Pathological Impact of Clonal Hematopoiesis on Advanced Aging–Driven MASH Yong-Hyun Han (Kangwon National University)	341
• The Metabolic Triad in MASLD-MASH: Glucose, Lipid, and Amino Acid Dysregulation Tatsuya Kanto (Japan Institute for Health Security, Japan)	343

Translational Research 2 | Cutting-Edge Technologies in Liver Research: From Spatial Omics to Precision Therapeutics

• Hepatic Stellate Cell Activation and Fibrosis Reversal Mechanisms David A. Brenner (Sanford Burnham Prebys, USA)	347
• Multi-Omics and Single-Cell Spatial Insights for HCC Target Discovery Jeong Seok Lee (KAIST)	349
• Transcriptional Regulation of Hepatic Stellate Cell Phenotypes during Liver Fibrosis Resolution Wonseok Lee (Gachon University)	351
• Multi-Modal Analysis of Human Stellate Cells Identifies Novel Therapeutic Targets for MASLD Hyun Young Kim (Dankook University)	355

KLTS Coordinator Session | The Liver Transplant Patient Journey: Narratives and Experiences

• Analysis of Symptoms in Liver Transplant Recipients and Living Donors JiYeon Choi (Yonsei University)	359
• Physical and Psychosocial Experiences of Living Liver Donors in Korea: A Qualitative Systematic Review Sunyoung Son (Gangnam Severance Hospital)	363
• Depressive Symptoms and Self-Care in Liver Transplant Recipients Seo Ha Jung (Yonsei University)	365

Data Science Camp 1

• Principles of Cohort Study Design: From Question to Data W. Ray Kim (Mayo Clinic, USA)	371
• How to Conduct Successful Multinational Cohort Studies Jeong-Hoon Lee (Seoul National University)	373
• From Statistical Associations to Causal Inference: The Role of Regression and Propensity Score Methods Sehee Kim (University of Ulsan)	379
• Applying Survival and Multivariable Analysis in Clinical Research: Interpreting the Results Dong Keon Yon (Kyung Hee University)	383

Data Science Camp 2

• Target Trial Emulation in Hepatology Research: A Practical Guide from Real-World Evidence to Causal Inference Kyunga Kim (Sungkyunkwan University)	387
• Application of Directed Acyclic Graphs (DAGs) in Liver Research Sun Jae Jung (Yonsei University)	391
• Application of Vibe Coding in Liver Disease Research Ji Won Han (The Catholic University of Korea)	395
• Sensitivity Analysis Methodologies in Epidemiologic Research Hyesung Lee (Kangwon National University)	399

Translational Hepatology | Integrative Approaches to Liver Diseases: Biomarkers, Microbiome, and Mendelian Randomization

• Promotion of Precision Health Using Molecular and Genomic Biomarkers in Liver Diseases Chien-Jen Chen (Academia Sinica, Taiwan)	403
• Microbiome-Metabolite Cross-Talk in Liver Diseases Ki-Tae Suk (Hallym University)	407
• Genetic Causal Inference in Liver Diseases Using Mendelian Randomization Sung Won Chung (University of Ulsan)	409

ROOM 3

KLTS Symposium 1 | Liver Transplantation for HCC with Portal Vein Tumor Thrombosis: Redefining the Impossible

• Who, When, and Why: Selection Criteria and Timing for Liver Transplantation in HCC with Portal Vein Tumor Thrombosis Jae Geun Lee (Yonsei University)	413
• Downstaging to Transplant: Converting the Unresectable to the Transplantable Prashant Bhangui (Medanta Institute, India)	419
• Operative Strategy and Technical Pitfalls in Liver Transplantation for HCC with Portal Vein Tumor Thrombosis Deok-Bog Moon (University of Ulsan)	421
• Post-Transplant Care and Recurrence Management: Adjuvant and Salvage Strategies Kwang-Woong Lee (Seoul National University)	425

KLTS Symposium 2 | Body Composition and Fluid Dynamics in Liver Transplantation

• Beyond Body Mass Index (BMI): Clinical Utility of InBody and Bioimpedance in Liver Transplant Evaluation Suk-Won Suh (Chung-Ang University)	429
• Prognostic Significance of Sarcopenia and Visceral Fat in Liver Transplant Recipients Toshimi Kaido (St. Luke's International Hospital, Japan)	433
• Extracellular Water Imbalance and Fluid Overload: Impact on Early Graft Function and Complications Minseob Kim (Seoul National University)	437
• Body Composition after Liver Transplantation: Clinical Prediction, Risk Stratification, and Therapeutic Intervention Seung-Young Oh (Seoul National University)	441

KLTS Symposium 3 | Liver Transplantation in the Era of MASLD

• The MASLD Era and Its Impact on the Liver Donor Pool Bo-Hyun Jung (Inje University)	445
• From Selection Criteria to Classification System: A Novel Framework of Liver Transplantation for Hepatocellular Carcinoma Fengqiang Gao (Zhejiang University, China)	447
• Recurrent Steatosis in Living Donors after Pre-Donation Weight Reduction and Subsequent Weight Regain Young-In Yoon (University of Ulsan)	451
• Recurrent and de novo MASLD after Liver Transplantation Tae-Seok Kim (Keimyung University)	453

ROOM 4A

KASL Branch Early Morning Workshop 2 | [Daejeon-Sejong-Chungcheong]

• Management of Hepatic Hydrothorax in Patients with Hepatorenal Syndrome: A Hemodynamic-Centered Approach Hyuk Soo Eun (Chungnam National University)	457

Health Insurance & Policy Forum

• National Viral Hepatitis Elimination Strategy Hyungmin Lee (Korea Disease Control and Prevention Agency)	463
• Reimbursement Principles and History of Viral Hepatitis Treatment Ae Ran Kwak (Health Insurance Review and Assessment Service)	465

• Unmet Need of Clinical Practice in Chronic Viral Hepatitis Soon Sun Kim (Ajou University)	467

ROOM 4B

KASL Branch Early Morning Workshop 3 | [Daegu-Gyeongbuk]

• Clinical Application of Non-Invasive Modalities for Fibrosis Assessment in MASLD Byoung Kuk Jang (Keimyung University)	471

ROOM 4D

KASL Branch Early Morning Workshop 4 | [Gwangju - Jeonnam]

• Regionally Led Project for HCV Micro-Elimination: Jindo-gun Min-Ho Shin (Chonnam National University)	475

DAY 3 [Saturday, June 13, 2026]

ROOM 1AB

KASL Symposium 5 | Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Alcohol-Related Liver Disease (MetALD)

• Outcomes and Prognosis in MASLD: Genetic Determinants from Single-Nucleotide Polymorphisms to Beyond Stefano Romeo (Karolinska Institutet, Sweden)	481
• MASLD vs. MetALD: Interactions between Alcohol Intake and Metabolic Risk Factors Sang Gyune Kim (Soonchunhyang University)	483
• Standardizing Histological Grading and Staging in Metabolic Dysfunction-Associated Steatohepatitis (MASH) Clinical Trials: Consensus Position Statements from the International Pathology Group Young Nyun Park (Yonsei University)	491
• Future of MASH Treatment: GLP-1/GIP Agonists, Resmetirom, and Beyond Dae Won Jun (Hanyang University)	493

State-of-the-Art Lecture

• Developing Drugs for Liver Fibrosis David A. Brenner (Sanford Burnham Prebys, USA)	499

2026 KASL Clinical Practice Guidelines: Chronic Hepatitis B

• Management of Chronic Hepatitis B: 2026 KASL Update In Hee Kim (Jeonbuk National University)	503

KASL Symposium 7 | Liver Cirrhosis, Portal Hypertension, and Acute-on-Chronic Liver Failure (ACLF): Advancing the Continuum of Care from Organ Failure to Recovery

• ACLF across Definitions: Harmonizing Diagnostic Criteria and Organ Failure Assessment Jung Hee Kim (Hallym University)	507
• Management of Acute Kidney Injury in ACLF: Current Evidence and Unmet Needs Rakhi Maiwall (Institute of Liver and Biliary Sciences, India)	511

CONTENTS

• Achieving Recompensation in Cirrhosis: Evidence and Future Directions Yu Jun Wong (Duke-NUS Medical School, Singapore)	515
• ACLF: Transplant before It's Too Late Dong-Sik Kim (Korea University)	517

ROOM 1C

KASL-AASLD Breakfast Workshop | The Evolving Landscape of Liver Transplantation: From Policy to Practice

• Expanding the Donor Pool: Donation after Circulatory Death, Donation after Brain Death, and Ex-vivo Graft Management Strategies Parissa Tabrizian (Icahn School of Medicine at Mount Sinai, USA)	521
• Optimizing Allocation and Policy Models: Balancing Equity and Efficiency in Opt-in vs. Opt-out Systems Willscott Naugler (Oregon Health & Science University, USA)	523
• Expanding Recipient Criteria for HCC: Lessons from Living Donor Liver Transplantation and Regional Experiences Suk Kyun Hong (Seoul National University)	527

KASL Symposium 6 | Transformative Strategies for Functional Cure of Chronic Hepatitis B: Novel Insights and Future Perspectives

• Antisense Oligonucleotides vs. siRNA: Which Represents the Better Option for HBV Treatment? Man-Fung Yuen (The University of Hong Kong, Hong Kong)	533
• Rationale and Selection of Gene Therapies in Chronic Hepatitis B Edward Gane (University of Auckland, New Zealand)	537
• Do Capsid Inhibitors Have a Role in Achieving HBV Cure? Sang Hoon Ahn (Yonsei University)	541
• Endpoints of Chronic Hepatitis B Therapy: Partial, Functional, and Sterilizing Cure Seng-Gee Lim (National University of Singapore, Singapore)	543

Advances in Experimental Hepatology

• At the Frontline of Metabolic Liver Disease: Stress and Inflammation Michael Karin (Sanford Burnham Prebys, USA)	547
• Unveiling the Impact: Hepatic Glutamate and Its Receptor in Liver Disease Won-Il Jeong (KAIST)	549
• Senescent Hepatocytes as Tumor Seedbeds in MASH: Lessons from Single-Cell Maps Michael Karin (Sanford Burnham Prebys, USA)	553

ROOM 2AB

2026 KLCA Practice Guidances | Stereotactic Body Radiation Therapy

• Stereotactic Body Radiation Therapy: KLCA Expert Consensus-Based Practical Recommendations Sang Min Yoon (University of Ulsan)	557

KLCA Symposium 3 | Therapeutic Update and Emerging Therapy in HCC

• Carbon Ion Therapy: The Next Step in Precision Radiotherapy Kei Shibuya (Gunma University, Japan)	561

CONTENTS

• Advances in Interventional Oncology: From TACE to TARE and Beyond Gyoung Min Kim (Yonsei University)	565
• Novel Molecular and Cellular Therapies in HCC: The Next Wave Stephen Lam Chan (The Chinese University of Hong Kong, Hong Kong)	567
• Multidisciplinary Horizons: From Immune Checkpoint Blockade to Liver Transplantation Ju Dong Yang (Cedars-Sinai Medical Center, USA)	569

ROOM 2C

Mini Special Interest Group 2 | The KASL Abdominal Ultrasound Study Group

• Ultrasound Assessment of Liver Fibrosis: Comparison with 2D Shear Wave Elastography and FibroScan Jeong-Ju Yoo (Soonchunhyang University)	573

Artificial Intelligence (AI) in Hepatology

• Decoding Tumor Microenvironment Heterogeneity and Therapeutic Response via Advanced Transformer Modeling of Spatial Transcriptomics Junil Kim (Soongsil University)	577
• Deep Learning and Digital Pathology in HCC: From Diagnosis to Prognosis Sung Hak Lee (The Catholic University of Korea)	579
• Multimodal AI and Large Language Models for Cancer Research Seng Chan You (Yonsei University)	581

Special Interest Group 2 | The KASL Alcohol-Related Problem Study Group

• Update on Clinical Trial Design and Endpoints in Alcohol-Associated Liver Disease Heechul Nam (The Catholic University of Korea)	585
• Immune Dysfunction in Alcohol-Associated Liver Disease Wonhyo Seo (Ewha Womans University)	589
• Gut–Liver Axis in Alcohol-Associated Liver Disease: Mechanistic Insights and Translational Implications Ki-Tae Suk (Hallym University)	591

Special Interest Group 3 | The KASL Steatotic Liver Disease Study Group: Novel Technologies in Steatotic Liver Disease (SLD) Research

• MASH Pathogenesis through Single-Cell Analysis Murim Choi (Seoul National University)	595
• Human Periportal Liver Assembloids for in vitro Tissue Modeling Yohan Kim (Sungkyunkwan University)	597
• Advances in SLD Diagnosis Using 3D Multiparametric Imaging Chulhong Kim (POSTECH)	601

ROOM 3

KAHBPS Symposium 1 | Expanding Indications for Hepatic Resection in HCC: Challenging the Boundaries

• Resection Beyond BCLC Guidelines: Surgical Outcomes in BCLC B or C Young Chul Yoon (The Catholic University of Korea)	605
• Bridging with Locoregional Therapy: Role of TARE, TACE in Downstaging Dongho Hyun (Ewha Womans University)	609

CONTENTS

• From Unresectable to Resectable: How Immunotherapy Is Changing the Surgical Landscape Jeong-Ju Yoo (<i>Soonchunhyang University</i>)	611
• Surgical Considerations after Neoadjuvant or Conversion Therapy in HCC Kiyoshi Hasegawa (<i>The University of Tokyo, Japan</i>)	613

KAHBPS Symposium 2 | How AI Is Transforming Future Liver Surgery

• Intraoperative Assessment and AI-Assisted Coaching System in Hepatobiliary Surgery Xin Wang (<i>Sichuan Univ., China</i>)	617
• Augmented Reality for Preoperative Planning and Intraoperative Visualization Maki Sugimoto (<i>Teikyo University, Japan</i>)	619
• Real-Time AI Navigation in Minimally Invasive Surgery Daichi Kitaguchi (<i>University of Tsukuba, Japan</i>)	621
• AI-Powered Computational Pathology and Radiology: Reshaping Surgical Decision Making in Primary and Metastatic Liver Cancer Xin Wang (<i>The Chinese University of Hong Kong, Hong Kong</i>)	625

KAHBPS Symposium 3 | How to Approach Benign Liver Tumors

• Advanced Imaging Modalities and Differential Diagnosis: A Radiologist's Perspective Dong Ik Cha (<i>Sungkyunkwan University</i>)	629
• Risk Stratification and Indication for Surgical Resection: A Surgeon's Perspective Euisoo Han (<i>The Catholic University of Korea</i>)	633
• Minimally Invasive Approaches in the Management of Benign Liver Tumors Kyeong Sik Kim (<i>Hanyang University</i>)	635
• Surveillance after Surgery Outcomes and Recurrence: A Surgeon's Perspective Min-Su Park (<i>Kyung Hee University</i>)	639

ROOM 4A

KASL Branch Early Morning Workshop 5 | [Busan-Ulsan-Gyeongnam]
Functional Cure-Paradigm Shift in CHB Treatment

• Unmet Needs in Current Treatment of Chronic Hepatitis B Sang Yi Moon (<i>Dong-A University</i>)	643
• Working Toward Functional Cure of Chronic Hepatitis B Jeong Heo (<i>Pusan National University</i>)	647

ROOM 4B

KASL Branch Early Morning Workshop 6 | [Gangwon]

• Recent Progress in Treatment of Portal Hypertension Minjong Lee (<i>Ewha Womans University</i>)	651

ROOM 4D

KASL Branch Early Morning Workshop 7 | [Jeonbuk]

• Risk Stratification for Hepatocellular Carcinoma in MASLD: Who Should Be Screened? Chang Hun Lee (<i>Jeonbuk National University</i>)	657

CONTENTS

Plenary Presentation 1

PP 1-1	Early Antiviral Therapy Reduces the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B: Causal Evidence from a Multinational Regression Discontinuity Study	660
	Hyunjae Shin , Terry Cheuk-Fung Yip, Byeong Geun Song, Dong Hyun Sinn, Mi Na Kim, Jun Yong Park Min Kyung Park, Lilian Yan, Won-Mook Choi, Young Youn Cho, Han Ah Lee, Soo Young Park, Jeong-Ju Yoo, Heejoon Jang, Bo Hyun Kim, Gi-Ae Kim, Ji-Won Han, Gwanghyeon Choi, Young-Suk Lim, Grace Lai-Hung Wong, Ju Dong Yang, George Papatheodoridis, Sabela Lens, Ramazan Idilman, Pietro Lampertico, Moon Haeng Hur, Yun Bin Lee, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee	
PP 1-2	Sustained Enrichment of Butyrate- and Acetate-Producing Microbes Is Associated with Better Outcomes to Atezolizumab Plus Bevacizumab in Advanced Hepatocellular Carcinoma	661
	Soon Kyu Lee , Hye Won Lee, Juhyeong Ko, Joo Yeon Jhun, Jong Young Choi, Jung Hyun Kwon, Soon Woo Nam, Mi-La Cho, Yunju Jeong	
PP 1-3	Tailored Surgical Approaches for Hepatocellular Carcinoma in Caudate Lobe	661
	Sang-Hoon Kim , Sung-Gyu Lee, Deok-Bog Moon, Ki-Hun Kim	
PP 1-4	Early Post-Transplant Recipient-Derived Cell-Free DNA Predicts One-Year Graft Survival in Liver Transplant Recipients	663
	Eun-Ki Min , Yu Jin Park, Yongseop Lee, Deok-Gie Kim, Dong Jin Joo, Saeam Shin, Su Jin Jeong, Seung Tae Lee, Jae Geun Lee	

Plenary Presentation 2

PP 2-1	Clinically Meaningful Rates of Functional Cure in Patients with Chronic Hepatitis B Infection Treated with Bepirovirsen: B-Well Phase 3 Trials	666
	Jinlin Hou, Seng-Gee Lim , Robert Elston	
PP 2-2	Efficacy and Safety Results from Emerald-3: A Phase 3, Randomized Study of Tremelimumab plus Durvalumab with or without Lenvatinib Combined with Transarterial Chemoembolization (TACE) in Participants (pts) with Unresectable Embolization-Eligible Hepatocellular Carcinoma (eeHCC)	666
	Jeong Heo , Zhenggang Ren, Joseph P. Erinjeri, Ghassan K. Abou-Alfa, Riccardo Lencioni, Yasuaki Arai, Mohamed Bouattour, Maria A. González-Carmona, Yabing Guo, Ai-Bing Xu, Gustavo Vasconcelos Alves, Arunee Dechaphunkul, Gwo Fuang Ho, Yueh Ni Lim, Hong-Tao Hu, Sri Harsha Tekumalla, Vimal Dave, Xavier Monzonís, Masatoshi Kudo, Jia Fan	
PP 2-3	Development and Validation of a Machine-Learning Model for Waitlist Mortality Using the Largest Global Cohort of Over 195,000 Subjects	667
	Gyung Sun Lim , Moon Haeng Hur, Ju Dong Yang, Yun Jung Kim, Suk Kyun Hong, Jonggi Choi, Byeong Geun Song, Jeong-Ju Yoo, Hye Won Lee, Ji Won Han, Xingshun Qi, Su Lin, Jing Wang, Fernando Gomes Romeiro, Changyeon Kim, Minsuk David Kim, Jae Woong Yoon, Hyunjae Shin, Yun Bin Lee, Cho Eun Ju, Su Jong Yu, Youngrok Choi, Kwang-Woong Lee, Won-Mook Choi, Young-In Yoon, Dong Hyun Sinn, Jong Man Kim, Sangbin Han, Jaehong Jeong, Jun Yong Park, Deok-Gie Kim, Jae-Geun Lee, Ho Joong Choi, Eunice Xiang-Xuan Tan, Mark D. Muthiah, Hong-Yi Lin, Oliver Tavabie, Salim I Khakoo, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee	
PP 2-4	Phase 3 Trial of Survodutide in Adults with Obesity and MASLD	668
	Kyung Moon Kim , on behalf of the SYNCHRONIZE™-MASLD Committees , Investigators	

Free Paper Presentation

1. LC, Liver Failure & Autoimmune Diseases 1

FP-1	Multimodal Computed Tomography–Clinical Integration for Noninvasive Grading of Hepatic Venous Pressure Gradient	672
	Seul Ki Han , Jin Gyo Jeong, JangHoon Ru, Jung Hyung Jung, Sejung Yang, Sang Gyune Kim, Jhii-Hyun Ahn, Moon Young Kim	
FP-2	CT-Based Spleen Volume and Laboratory Markers Differentiate Porto-Sinusoidal Vascular Disorder from Cirrhosis across Global Cohorts	672
	Subin Heo , Maxime Ronot, Seung Soo Lee, Won-Mook Choi	
FP-3	Increased CD169 Expression on Peripheral Monocytes is Associated with Liver Damage in Autoimmune Hepatitis	673
	Ga Won Han , Mi Hyun Kwon, Kwon Yong Tak, Hee Sun Cho, Ji Won Han, Jeong Won Jang, Pil Soo Sung	
FP-4	Multimodal Clinical DILI Prediction with Quantum-Derived Molecular Representation	673
	Yujin Kim , Seoeun Park, Soon Sun Kim, Ji Eun Han, Hyo Jung Cho, Jae Youn Cheong, Charmgil Hong	
FP-5	Urgent Liver Transplantation for Acute-on-Chronic Liver Failure in National Data: Impact of Dynamic MELD Change and Donor Type on Survival	674
	Jongman Kim , Sang Jin Kim, Boram Park, Kyunga Kim, YoungRok Choi, Geun Hong, Jun Yong Park, Young Seok Han, Nam-Joon Yi, Soon-Young Kim, Jung-Bun Park, Youngwon Hwang, Dong-Hwan Jung	

FP-6 Clinical and Epidemiologic Characteristics of Autoimmune Hepatitis in Korea: Treatment Patterns and Outcomes 675
Soon Kyu Lee, Gwang Hyeon Choi, Ahlim Lee, Jeong-Ju Yoo, U Im Chang, Ja Kyung Kim, Hye Yeon Chon, Seung Kak Shin, Kyung-Ah Kim, Hae Lim Lee, Heechul Nam, Jung Hyun Kwon, Jung Hee Kim, Bo Hyun Kim, Hyung Joon Yim, Sook-Hyang Jeong, Ji-Won Park, Young-Joo Jin

FP-7 Efficacy and Safety of Seladelpar in the Asian Subpopulation of Patients with Primary Biliary Cholangitis: Results from RESPONSE and ASSURE 675
Sook-Hyang Jeong, Heo Jeong, Won Young Tak, Young Seok Kim, Kang Mo Kim, Jun Sik Yoon, Christopher L. Bowlus, Xin Qi, Robert Kustra, Catherine Frenette, Sushela Carroll, Daria B. Crittenden, Yoon Jun Kim

FP-8 Shear Wave Elastography Combined with ALBI Score Enhances Prediction of Hepatic Decompensation in Advanced Chronic Liver Disease 676
Jaejun Lee, Hyun Yang, Si Hyun Bae, Sun Hong Yoo, Soon Woo Nam, Jiwoon Yoon, Jung Hyun Kwon, Soon Kyu Lee

2. Surgery, Technical Issues

FP-9 Treatment Outcomes of Liver Abscesses: Efficacy of Ultrasound-Guided Percutaneous Drainage and Surgical Interventions in a Consecutive Case Series (2019–2025) 677
Onlasyn Ibekenov, Daulet Kyzhyrov, Bolatbek Baymakhanov, Shokan Kaniev, Maksat Doshanov, Nurzhan Byrzhanbaev, Chingiz Sadykov

FP-11 A Retrospective Comparative Study on Cone Unit–Based Wide-Margin Laparoscopic Anatomical Hepatectomy and Conventional Laparoscopic Anatomical Hepatectomy in the Treatment of Hepatocellular Carcinoma 677
Yu Cheng, Zuobin Cheng², Piyou Ji

FP-12 Surgical Resection Beyond BCLC Recommendations Improves Survival in Intermediate and Advanced HCC: Nationwide Evidence from Korea 678
Minseob Kim, Young Rok Choi

FP-13 Clinical Feasibility of Living Donor Liver Transplantation in Patients with Acute-On-Chronic Liver Failure: An International Multicenter Study 678
Hye-Sung Jo, Su Young Hong, Sadhana Shankar, Takeo Toshima, Tonguc Utku Yilmaz, Seisuke Sakamoto, Dong-Sik Kim, Kwang-Woong Lee

FP-14 Hierarchical Quantification of Surgical Workflow of Laparoscopic Left Lateral Sectionectomy Using Step–Task–Action Triplets: Experimental Analysis of the LLS48 Dataset 679
Han Sang Park, Namkee Oh, Jinsoo Rhu, Jongman Kim, Gyu-Seong Choi

FP-15 Adequate Surgical Margin, Not Resection Type, Determines Long-Term Outcomes after Liver Resection for Hepatocellular Carcinoma 679
Boram Lee, Ho-Seong Han, Yoo-Seok Yoon, Jai Young Cho, Hae Won Lee, Yeshong Park

3. HCC, Clinical 1

FP-16 Longitudinal Elevation of IL-10 Following Atezolizumab plus Bevacizumab Is Associated with Favorable Response and Survival in Advanced Hepatocellular Carcinoma 680
Soon Kyu Lee, Soon Woo Nam, Jung Hyun Kwon

FP-17 Outcomes of Continuing Atezolizumab–Beveracizumab Beyond 2 Years in Patients with Advanced HCC: Preliminary Report of a Multicenter Retrospective Cohort Study using Landmark Analysis 680
Sung Won Chung, Jeayeon Park, Bo Hyun Kim, Jiwon Yang, Byeong Geun Song, Eun Sun Jang, Jihyun An, Su Jong Yu, Ju Hyun Shim

FP-18 Association of Radiotherapy with Atezolizumab plus Bevacizumab with Survival in Advanced Hepatocellular Carcinoma 681
Gyung Sun Lim, Hyunjae Shin, Byeong Geun Song, Sung Won Chung, Hyun-Cheol Kang, Jinhong Jung, Jeong Il Yu, Hee Chul Park, Moon Haeng Hur, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

FP-19 Differential Therapeutic Effectiveness of Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma by Chronic Hepatitis B Viral Activity 682
Yunmi Ko, Hyunjae Shin, Byeong Geun Song, Moon Haeng Hur, Youngsu Park, Jeayeon Park, Yuri Cho, Yun Bin Lee, Eun Ju Cho, Bo Hyun Kim, Su Jong Yu, Dong Hyun Sinn, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

FP-20 Refining Patient Selection for Proton Beam Therapy in Hepatocellular Carcinoma: Utility of mALBI Grade and Quantitative ALBI Score Increments 683
Sooyeon Sim, Jeong Ha Lee Nalee Kim, Jeong Il Yu, Hee Chul Park, Yong-Han Paik, Jung Yong Hong, Gyu-Seong Choi, Woo Kyoung Jeong, Min Woo Lee, Sang Yun Ha

FP-21 Genomic Profiles as Determinants of Therapeutic Efficacy in Hepatocellular Carcinoma: Towards Precision Medicine 683
Kwon Yong Tak, Pil Soo Sung

FP-22 Ambient Particulate Matter Exposure and Liver Cancer Incidence and Post-Diagnosis Mortality: A Nationwide Cohort Study 684
Byeong Geun Song, Dong Hyun Sinn

4. MASLD & ALD, Clinical

FP-23 Alcohol-Use Trajectories and Major Adverse Liver Outcomes in MetALD: A Nationwide Longitudinal Cohort Study 685
Jun Hyuk Lee, Jimin Park, Sung Ho Ahn, So Young Jeon, Hye Sun Lee, Jonghyun Lee, Jonghyun Kim, Hyo Young Lee, Eileen L Yoon, Dae Won Jun

FP-24 Phase 3 ESSENCE Trial: Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis (MASH) 685
Jun Yong Park, Won Kim, Philip N. Newsome, Arun J. Sanyal, Iris Kliers, Laura Harms Østergaard, Michelle T. Long, Mette Skalhøi Kjær, Anna Cali, Elisabetta Bugianesi, Mary Rinella, Michael Roden, Vlad Ratziu

FP-25 Shear Wave Elastography Is Comparable to Vibration-Controlled Transient Elastography for Predicting Liver-Related Events in a FIB-4–Based Two-Step Risk Stratification Strategy 686
Jaejun Lee, Hyun Yang, Si Hyun Bae, Sun Hong Yoo, Soon Woo Nam, Jiwoon Yoon, Jung Hyun Kwon, Soon Kyu Lee

FP-26 Distinct Phenotype of Cryptogenic Steatotic Liver Disease and Its Unfavourable Long-Term Outcomes Including Liver-Related Death 686
Eileen L. Yoon, Hyo Young Lee, Jong Hyun Lee, Joo Hyun Oh, Inseok Hwang, Chan Hee Park, Sejung Kim, Huiyul Park, Ae Jeong Jo, Dae Won Jun

FP-27 Moderate Alcohol Consumption and Liver-Related Events in MASLD: Risk Thresholds and the Impact of Cumulative Intake 687
Han Ah Lee, Na Ryung Choi, Moonki Lee, Yaeji Lim, Young Youn Cho, Hyung Joon Kim, Hwi Young Kim, Jae Yoon Jeong

FP-28 Redefining the “At-Risk” Population in MASLD: A Multicenter Cross-Cohort Analysis of Liver Injury and Long-term Outcomes using Non-Invasive Tests 688
Han Ah Lee, Sang Gyune Kim, Soo Young Park, Young Youn Cho, Hyung Joon Kim, Yeon Seok Seo, Seung Up Kim, Dae Won Jun, On behalf of the VCTE-based Liver Investigation Network (V-LINK) Study group

FP-29 Cost-Effectiveness of Resmetirom Treatment for Suspected ‘At-Risk MASH’ Based on Transient Elastography without Biopsy 688
Jeong-Yeon Cho, Eileen L. Yoon, Mimi Kim, Huiyul Park, Nathorn Chaiyakunapruk, Hye-Lin Kim, Dae Won Jun

FP-30 Serum Osteoprotegerin Predicts Liver and Cardiometabolic Outcomes in Metabolic Dysfunction-Associated Steatotic Liver Disease 689
Hyo Young Lee, Jonghyun Lee, Woochang Hwang, Jae Eun Ryu, Chan Hee Park, Seongjun Lee, Jaehyun Choi, Hyobin Jeong, Sungbin Jung, Eileen L. Yoon, Dae Won Jun

5. HBV 1

FP-31 Long-Term Persistence of the Parabolic Association Between Baseline HBV DNA and Hepatocellular Carcinoma Risk after Antiviral Therapy 689
Hyeyeon Hong, Gi-Ae Kim, Jonggi Choi, Gwang Hyeon Choi, Yun Bin Lee, Dong Hyun Sinn, Young-Suk Lim, Won-Mook Choi

FP-32 Clinical Impact of Antiviral Therapy on Reducing HCC and Cirrhosis Risks in the Indeterminate Phase of Chronic Hepatitis B 690
Jaehong Jeong, Han Ah Lee, Sang Gyune Kim, Soo Young Park, Young Youn Cho, Hyung Joon Kim, Yeon Seok Seo, Dae Won Jun, Seung Up Kim, On behalf of the VCTE-based Liver Investigation Network (V-LINK) Study group

FP-33 Clinical Benefits of Antiviral Therapy in the Indeterminate Phase of Chronic Hepatitis B: A Systematic Review and Meta-Analysis 691
Han Ah Lee, Won-Mook Choi, Gi-Ae Kim, Chang Hun Lee, Tae Hyung Kim, Hee Chul Nam, Byeong Geun Song, Jeong-Ju Yoo, Yun Bin Lee, Hye Won Lee, Hyo Young Lee, Young Eun Chon, Gwang Hyeon Choi, Miyoung Choi, Ji Won Han, Moon Haeng Hur, Bo Hyun Kim, In Hee Kim, Dong Hyun Sinn

FP-34 NGS-Based X/Precore Genetic Heterogeneity Improves Identification of the True Immune Tolerant Phase in HBeAg-Positive Chronic Hepatitis B 691
Jae Mo Han, Hye Seon Kim, Jung Eun Jang, Hee Sun Cho, Kwon Yong Tak, Soon Kyu Lee, Ji Won Han, Pil Soo Sung, Hae Lim Lee, Sung Won Lee, Jung Hyun Kwon, Si Hyun Bae, Hyun Woong Lee, Jeong Won Jang

FP-35	Higher Unglycosylated HBsAg Proportion May Predict Faster Decline Kinetics of HBsAg in Chronic Hepatitis B Chunfeng Li, Andrew Lopez, Nadine Peinovich, Savrina Manhas, Yu Hu, Jiani Li, Christopher Richards, Caleb Marceau, Ross Martin, <u>Jeong Heo</u> , Edward Gane Frida Abramov, Hongmei Mo, Evguenia Maiorova	692
FP-36	Changes to an Active Lifestyle and Risks of Mortality and Liver-Related Events in Adults with Chronic Hepatitis B: A Nationwide Cohort Study Byeong Geun Song, <u>Myeongcheol Lee</u> , Juhee Cho, Geum-Youn Gwak, Danbee Kang, Dong Hyun Sinn	692
FP-37	High Treatment Adherence Reduces HCC in Cirrhosis, with Additional Benefit from TAF <u>Yoon E Shin</u> , Jae Young Kim, Jeong Ju Yoo, Sang Gyune Kim, Young Seok Kim	693
FP-38	Long-Term Clinical Trajectories of Chronic Hepatitis B in the Lamivudine Era: Insights from a 25-Year Real-World Study <u>Jaejun Lee</u> , Hyun Yang, Kwon Yong Tak, Ji Won Han, Pil Soo Sung, Sung Won Lee, Do Seon Song, Myeong Jun Song, Jung Hyun Kwon, U Im Chang, Chang Wook Kim, Soon Woo Nam, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon, Jeong Won Jang	694

6. HCC, Basic

FP-39	Secretory Nidogen 1 Triggers the Endocytic Recycling of $\beta 5$ Integrin in Hypoxia Induced Liver Cancer Metastasis <u>Yaqi Xu</u> , Li Chen, Judy Wai Ping Yam, Xiaowen Mao	694
FP-40	Application of CRISPR/Cas9 Technology to Develop a Hepatocellular Carcinoma Model Using Human Primary Hepatocyte Organoids <u>Michael Girma Mamu</u> , Michael Adisasmita, Hyomin Lee, Soraya Salas-Silva, Kyung Yun Jung, Kyeong Geun Lee, Kungsik Kim, Ji Hyun Shin, Junho Hur, Yohan Kim, Dongho Choi	695
FP-41	The PLD2–APP–OTC Axis Regulates Urea Cycle Activation and Tumor Growth in Hepatocellular Carcinoma <u>Hei Gwon Choi</u> , In Soo Kim, Young Suk Kim, Ha Neul Kim, Hyuk Soo Eun	696
FP-42	Soluble FAP Activates STAT3 and Induces IL-6 to Sustain Cancer-Associated Fibroblast Activation via a Positive Feedback Loop in Hepatocellular Carcinoma <u>Deok Hwa Seo</u> , Jae Yong Ryu, Eui Soo Han, Ho Joong Choi, Young Kyoung You, Kwon Yong Tak, Jeong Won Jang, Pil Soo Sung	696
FP-43	SFRP4 ⁺ Cancer-Associated Fibroblasts Drive EMT and an Immunosuppressive Tumor Microenvironment in Hepatocellular Carcinoma <u>Sujin Kim</u> , Hye Ri Ahn, Jiwon Hong, Dooyeon Kim, Soobeen Moon, Hui Gyeong Kim, Tae Jun Park, Su Bin Lim, Hyo Jung Cho	697
FP-44	Large-Scale Whole-Genome Sequencing Reveals the Mutagenic Processes Underlying Hepatocellular Carcinoma Seongyeol Park, <u>Joonoh Lim</u> , Eun-Woo Choi, Su young Hong, YoungRok Choi, Kwang-Woong Lee, Jeong-Hoon Lee, Young Seok Ju, Suk Kyun Hong	697
FP-45	Longitudinal Single-Cell Profiling Reveals Distinct Immune Trajectories Associated with Response and Resistance to Atezolizumab–Bevacizumab in HCC <u>Myung Ji Goh</u> , Mi-So Park, Hyeonbin Jo, Byeong Geun Song, Wonseok Kang, Dong Hyun Sinn, Geum-Youn Gwak, Moon Seok Choi, Joon Hyeok Lee, Hong-Hee Won, Yong-Han Paik	698
FP-46	Immune Cell Profiling and Real-World Long-Term Efficacy of Adjuvant Cytokine-Induced Killer Cell Therapy for Hepatocellular Carcinoma <u>Hyunjae Shin</u> , Hyejung Lee, Youngsu Park, Byeong Geun Song, Moon Haeng Hur, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Joon Hyeok Lee, Jung-Hwan Yoon, Joo-Young Park, Jeong-Hoon Lee	698

7. MASLD & ALD, Basic

FP-47	A Stage Specific NETs-Related Signature in Alcoholic Steatohepatitis: From Molecular Subtyping to Therapeutic Vulnerabilities <u>Wei Gao</u> , Zhiyong Lin, Yuntao Bao Mingjiang Liu, Guangtao Ma, Xianxiang Chen, Shuiping Yu, Yonglian Zeng	699
FP-48	Single-Cell Transcriptomic Profiling Reveals Stage-Specific Reprogramming of Peripheral NK Cells from Compensatory Hyperactivation to Terminal Exhaustion during Alcohol-Associated Liver Disease Progression <u>Jae Kyeong Lee</u> , Young-Sun Lee, Ha Seok Lee, Yewon Jeong, Min Kyoung Jo, Wonju Jung, Tae Hyung Kim, Eunho Choi, Seong Hee Kang, Sun Young Yim, Yang Jae Yoo, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Kyoung Jae Won, Gi-Hoon Nam, Jong Eun Yeon	701
FP-49	Blocking the Gut–Liver IgA Axis Attenuates Macrophage-Mediated Inflammation and Injury in Alcohol-Associated Liver Disease <u>Min Gu Kim</u> , Kwon Yong Tak, Pil Soo Sung	701

FP-50	Spatial Transcriptomics Reveals Macrophage–Fibroblast Crosstalk as a Driver of MASH Fibrosis and Guides CD47-Engineered Extracellular Vesicle Therapy <u>Young-Sun Lee</u> , Hyobin Kim, Minjeong Kwon, Hyeyoon Nam, Gihhoon Nam, Eunho Choi, Yang Jae Yoo, Seong Hee Kang, Sun Young Yim, Tae Hyung Kim, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon	702
FP-51	Hepatic CSE Deficiency Impairs Systemic Glutathione Homeostasis and Promotes Liver–Kidney Redox Imbalance in Obesity Gibong Jang, You Ri Park, Yong Kwon Han, Isao Ishii, <u>Se Young Jang</u> , Kwon Moo Park	703
FP-52	The Single-Cell Landscape of MASLD-Specific Liver Sinusoidal Endothelial Cell Subclusters Jae Eun Ryu, Seongjun Lee, Jaehyun Choi, Eileen Laurel Yoon, Hayoung Jang, Jung Ho Lee, Hyeewon Seo, Geon Woo Park, Ju young Jin, Hyun Je Kim, Hyo Young Lee, Jai Hoon Yoon, Jin Kim, Hyun Sung Kim, Hyobin Jeong, <u>Dae Won Jun</u>	703
FP-53	Metabolic Stress Transforms DNA Damaged Biliary Epithelial Cells into Hepatocellular Carcinomas <u>Won Hee Lee</u> , Won-Il Choi, Byung-Kwan Jeong, Jun Yong Park, Young Seok Ju, Hail Kim	704
FP-54	Aging-Associated Clonal Hematopoiesis in TET2-Mutant HSCs Drives Myeloid Expansion and Accelerates Liver Inflammation and Fibrosis in MASH <u>Hanna Lee</u> , Yong-Hyun Han	704

8. MASLD, Clinical

FP-55	Proposal of a Body Mass Index-Based Subclassification for Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake <u>Norihiro Imai</u> , Han Ah Lee, Young-Sun Lee, Shang-Chin Huang, Kai-Chi Chang, Shih-Chieh Chien, Seung Up Kim, Sang Gyune Kim, Dae Won Jun, Soo Young Park, W. Ray Kim, Takumi Kawaguchi, Jee-Fu Huang	708
FP-56	Serum Free Triiodothyronine to Free Thyroxine Ratio and Risk of Developing Metabolic Dysfunction-Associated Steatotic Liver Disease: A Large-Scale Cohort Study <u>Hyunwoo Oh</u> , Yoosoo Chang, Won Sohn, Kyoung A Ko, Hyemi Kwon, Soo Jin Park, Yong Kyun Cho, Byung Ik Kim, Sarah H. Wild, Christopher D. Byrne, Seunggho Ryu	708
FP-57	Dynamic Transitions in Steatotic Liver Disease Subtypes and Risk of Liver-related Events: A Nationwide Cohort Study <u>Yewan Park</u> , Jooyi Jung, Seungbong Han, Gi-Ae Kim	709
FP-58	Development and Validation of M-SLD: A Novel Noninvasive Model for Steatotic Liver Disease Referenced Against Histology and MRI-PDFF <u>Hyo Jin Nam</u> , Hae Young Kim, Sung Won Chung, Byungchul Cho, Jiwon Yang, Won-Mook Choi, Jonggi Choi, Danbi Lee, Ju Hyun Shim, Seung Soo Lee, Kang Mo Kim, Young-Suk Lim, Han Chu Lee	710
FP-59	Metabolic–Alcohol Spectrum of Steatotic Liver Disease and Risk of Incident Gout: A Multi-National Cohort Study in Korea, Japan, and the United Kingdom <u>Yeo Wool Kang</u> , Yang Hyun Baek, Sang Yi Moon, Min kook Son	711
FP-60	Liver-Related Outcomes in Diabetes-Associated MASLD with Low Fatty Liver Index: A Nationwide Cohort Study Hyein Han, <u>Moon Haeng Hur</u> , Hyunjae Shin, Sungho Won, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim	711
FP-61	Potential Influence of PNPLA3 Genotype on Semaglutide Response in Metabolic Dysfunction–Associated Steatotic Liver Disease: Real-World Data in Korean Cohort <u>Hee Sun Cho</u> , Jaejun Lee, Jung Hoon Cha, Mi Young Byun, Seok Keun Cho, Kwon Yong Tak, Ji Won Han, Hyun Yang, Jeong Won Jang, Si Hyun Bae, Pil Soo Sung	712
FP-62	Liver Fibrosis Burden and ECG-Detected Incident Atrial Fibrillation in Metabolic Dysfunction–Associated Steatotic Liver Disease <u>Tom Ryu</u> , Jaejun Lee, Young Chang, Jeong-Ju Yoo, Sae Hwan Lee, Soung Won Jeong1, Sang Gyune Kim, Jae Young Jang, Young Seok Kim, Hong Soo Kim, Keungmo Yang	713

9. HCC, Clinical 2

FP-63	A Mechanism-Informed Six-Gene Prognostic Signature of Hepatocellular Carcinoma Derived from the Multi-Target Anti-Tumor Mechanism of Icaritin <u>Mei Yao</u> , Zhi-Yong Lin, Cheng Zhang, Yong-Yuan Jian, Kai-Yong Huang, Ruiling Su, Xue-Lin Tan, Bo Peng, Kun Dong, Chun-Qiang Dong, Jun-Ze Chen	714
FP-64	Comparative Effectiveness of Atezolizumab–Bevacizumab vs. Durvalumab–Tremelimumab in Unresectable HCC: A Systematic Review and Novel Machine Learning-Based Indirect Meta-Analysis Ji Won Han	715

FP-65

Synergistic Efficacy of Radiation Therapy Combined with Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma with Vp4 Portal Vein Tumor Thrombosis: A Multicenter Study

715

Young Joo Park,

Hyun Young Woo, Ki Yeon Yi, Jun Sik Yoon, Yeo Wool Kang, Jung Eun Song, Joon Ho Jeong, Yu Rim Lee, Jae Hyun Yoon, Young Mi Hong, Sang Youn Hwang, Soo Young Park, Yang Hyun Baek, Jeong Heo, Won Young Tak, Sung-Bum Cho

FP-66

Development of an Early Prediction Model for Atezolizumab–Bevacizumab Treatment Response in Patients with Advanced Hepatocellular Carcinoma: An Interim Analysis of a Prospective Cohort Study

716

Minsuk David Kim,

Moon Haeng Hur, Dong Ho Lee, Jae Woong Yoon, Gyungsun Lim, Hyunjae Shin, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

FP-67

PNPLA3, but Not a Five-Variant Polygenic Risk Score, Predicts Hepatocellular Carcinoma in Korean MASLD

717

Jaejun Lee,

Jung Hoon Cha, Hee Sun Cho, Hyun Yang, Mi Young Byun, Seok Keun Cho, Seong Wook Yang, Si Hyun Bae, Seung Up Kim, Su Jong Yu, Pil Soo Sung

FP-68

Overcoming the Limitations of GALAD: SeeLiver Enables Superior Early and AFP-Negative HCC Detection

718

Je-Hyun Baek,

Hyojin Kim, Wonseok Oh, Juri Park, Saeyoung Lee, Won Suk Yang, Soon Sun Kim, Jae Youn Cheong

FP-69

In-Context Learning-Based Prediction of 5-Year Hepatocellular Carcinoma Risk in Chronic Hepatitis B

718

Soyeon Park,

Heeseo Jeong, Soon Sun Kim, Jae Youn Cheong, Charmgil Hong

FP-70

The Obesity Paradox in Hepatocellular Carcinoma: Insights from Continuous and Interaction-Based Analyses of Body Mass Index after Hepatic Resection

719

Boram Lee,

Ho-Seong Han, Yoo-Seok Yoon, Jai Young Cho, Hae Won Lee, Yeshong Park

10. HBV & HCV

FP-71

RE-LIVE Study (Re-Linkage to Pan-Viral Hepatitis): Interim Results from a Multicenter Observational Study on Care Engagement in Chronic Viral Hepatitis

719

Jae Hyun Yoon,

Young-Sun Lee, Yang Jae Yoo, Yu Rim Lee, Seul Ki Han

FP-72

Association between Chronic Hepatitis C and Extrahepatic Malignancies: A Nationwide Cohort Study Short Title: HCV and Extrahepatic Malignancies

720

Han Ah Lee, Dong Hyeon Lee,

Yujin Jeong, Jeayeon Park, Yunmi Ko, Moon Haeng Hur Hyunjae Shin, Yun Bin Lee, Young Youn Cho, Su Jong Yu, Won Kim, Yong Jin Jung, Hyung Joon Kim, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

FP-73

Impact of Hepatitis C Virus Treatment on the Risk of Cardiovascular Disease: A Nationwide Population-Based Cohort Study in South Korea

721

Min Kyung Park,

Hwa Young Choi, Gwang Hyun Choi, Eun Sun Jang, Moran Ki, Kyung-Ah Kim2, Sook-Hyang Jeong

FP-74

Outcomes of Direct-Acting Antiviral Agents in Chronic Hepatitis C Patients with Pre-Existing HCC

721

Hyun Young Woo,

Jeong Heo, Kiyoun Yi, Young Joo Park

FP-75

Moderate HBV DNA Levels Are Associated with the Highest Risk of Hepatocellular Carcinoma in Chronic Hepatitis B: A Systematic Review and Meta-Analysis

722

Jeong-Ju Yoo,

Young Eun Chon, Gi-Ae Kim, Han Ah Lee, Heechul Nam, Won-Mook Choi, In Hee Kim, Young-Suk Lim, Dong Hyun Sinn

FP-76

HBV Core-Related Antigen Levels Correlate with Quantitative HBsAg Levels Regardless of HBeAg Status and Antiviral Therapy

722

Soon Kyu Lee,

Soon Woo Nam, Jung Hyun Kwon

FP-77

Distinct Virological Features and Quasispecies Dynamics in Advanced Fibrosis by HBeAg Status in Chronic Hepatitis B with Normal or Mildly Elevated ALT

723

Hye Seon Kim,

Jung Eun Jang, Jae Mo Han, Hee Sun Cho, Kwon Yong Tak, Soon Kyu Lee, Ji Won Han, Pil Soo Sung, Hae Lim Lee, Sung Won Lee, Jung Hyun Kwon, Si Hyun Bae, Hyun Woong Lee, Jeong Won Jang

FP-78

Incidence and Risk Stratification of Hepatitis B Reactivation in Patients Receiving Anti-CD38 Monoclonal AntibodyTherapy

724

Kwon Yong Tak,

Jaejun Lee, Jeong Won Jang, Soon Kyu Lee, Pil Soo Sung

11. Liver Transplantation 1

FP-79

Graft Weight, Not GRWR, Predicts Recipient Survival in Living Donor Liver Transplantation: Implications for Donor Pool Expansion from a Stratified Analysis of 2,506 Cases

724

Selvakumar Naganathan

FP-80

Single-Cell and Bulk RNA Sequencing Reveal MCL1 as a Key Regulator of Mitochondrial Function in Liver Ischemia-Reperfusion Injury

725

Xianxiang Chen,

Hao Xing, Yuntao Bao, Guandou Yuan, Songqing He, Fang Xiao

FP-81

Integration of a Pre-Transplant 15-Protein Serum Proteomic Signature Predicts Recurrence after Liver Transplantation for HCC: A Multicenter KOTRY Registry Study

728

Suk Kyun Hong, Sung Won Chung,

Junho Park, Yeongshin Kim, Dongyoon Shin, Jeong-Hoon Lee, Kwang-Woong Lee, Youngsoo Kim

FP-82

Donor Complications in Modern LDLT

728

Gayoung Kim,

Suk Kyun Hong, Min Kyoung Kim, Sang Hyuk Park, Minseob Kim, Jae-Yoon Kim, Su Young Hong, Youngrok Choi, Kwang-Woong Lee

FP-83

Optimal Duration of Endoscopic Biliary Stenting after Living Donor Liver Transplantation: A Machine Learning Risk Stratification Analysis

729

Ji Won Han,

In Seok Lee

FP-84

Development and Validation of a LI-RADS-Based Competing Risk Survival Models for Liver Transplant Recipients with HCC

729

Yeongseok Hwang,

Hahn Yi, Jihyun An, Subin Heo, Sang Hyun Choi, YoungRok Choi, Kwang-Woong Lee, Gi-won Song, Dong Ho Lee, Namkug Kim, Ju Hyun Shim

FP-85

Artificial Intelligence–Driven Preoperative Risk Stratification for Early Allograft Failure in Living Donor Liver Transplantation

730

Dae-Hyeon Won,

Yujin Han, Hangsik Shin, Young-In Yoon

12. HBV 2

FP-86

Combination Therapy with Toll-Like Receptor 7 Agonist and Programmed Death Ligand 1 Antibody Restores HBV-Specific CD8+T Cells in Virally Suppressed Chronic Hepatitis B

730

Yuying Chen,

Di Wu, Ting Wu, Weiming Yan, Qin Ning

FP-87

High Viral Suppression in Chronic HBV Infection Subjects With Pevifoscorvir Sodium Monotherapy

731

Man-Fung Yuen,

Kosh Agarwal, Alina Jucov, Alexei Haceatrean, Min Wu, Stanley Wang, Kha Le, Jen Rito, Lawrence M. Blatt, Sushmita Chanda, Tse-I Lin, Edward Gane

FP-88

Reduction of HBV Antigens Observed after 96 Weeks of 300 mg Pevifoscorvir Sodium Monotherapy is Sustained During Long-term Follow-up

731

Lung-Yi Mak,

Andreas Jekle, Mark Anderson, Sushmita Chanda, Lilian Adame, Tiffany Fortney, Heleen Roose, Lawrence Blatt, Rene Geissler, Min Wu, Kha Le, Gavin Cloherty, Tse-I Lin, Man-Fung Yuen

FP-89

Exposure to Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate and the Risk of Hepatocellular Carcinoma

732

W. Ray Kim,

Young-Suk Lim, Harry L.A. Janssen, Sang Hoon Ahn, Ira M. Jacobson, Masashi Mizokami, Grace Lai-Hung Wong, Frida Abramov, Leland J. Yee, Hongyuan Wang, Catherine Frenette, Scott K. Fung, Patrick Marcellin, Wai-Kay Seto, Kosh Agarwal, Jinlin Hou, Seng Gee Lim, Jia-Horng Kao, Maria Buti

FP-90

Early Antiviral Therapy and the Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Patients with Normal Alanine Aminotransferase Levels: A Prospective Phase II Study

733

Dong Hyun Sinn,

Ji Hoon Kim, Hyung Joon Kim, June Sung Lee, Jae Young Jang, Yoon Jun Kim, Joon Hyeok Lee

FP-91

Association between Metabolic Dysfunction-Associated Steatotic Liver Disease and Hepatocellular Carcinoma Risk in Adults with Chronic Hepatitis B: A Nationwide Population-Based Cohort Study

733

Jia-Ling Wu,

Cheng-Hao Tseng, Ying-Nan Tsai, Shang-Chen Tseng, Yao-Chun Hsu

FP-92

Kinetic Breakpoints and Immune Remodeling during Quantitative HBsAg Decline in Chronic Hepatitis B

734

Sung Won Chung,

Hyunjae Shin, Hyejung Lee, Changyeon Kim, Moon Haeng Hur, Jeong Seok Lee, Minsuk David Kim, Gyung Sun Lim, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Joo-Young Park, Jeong-Hoon Lee

FP-93

Comparative Risk of Hepatocellular Carcinoma among Oral Antiviral Agents in Patients with Chronic Hepatitis B: A Systematic Review and Network Meta-Analysis

735

Heechul Nam,

Hyo Young Lee, Sungryul Shim, Jeong-Ju Yoo, Young Eun Chon, Han Ah Lee, Gwang Hyeon Choi

13. LC, Liver Failure & Autoimmune Diseases 2

FP-94

How Hepatitis C Screening Entered South Korea's National Health Screening Program: A Policy Analysis Using Kingdon's Multiple Streams Framework

736

Seunghyun Lewis Kwon,

Seul-Ki Kang, Jiyoung Yu, Gwang Hyeon Choi, Chang Hun Lee, Eun Sun Jang, In Hee Kim, Seung-Hoon Chae, Young Joon Park, Hyungmin Lee

FP-95

Heterogeneous Associations of Clonal Hematopoiesis with Liver Disease Outcomes: A Two-Cohort Study

736

Hyunjae Shin,

Gangpyo Ryu, Suk Kyun Hong, YoungRok Choi, Nam-Joon Yi, Kwang-Woong Lee, Kyung-Suk Suh, Moon Haeng Hur, Yun Bin Lee, Jeong-Hoon Lee, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Youngil Koh, Eun Ju Cho

FP-96	xCT-Dependent Cysteine Metabolism Sustains Pro-Resolving TREM2⁺ MDMs in Liver Fibrosis	737
	<u>Kyurae Kim</u> , Jangsu Jeon, Sung Eun Choi, Kwon Yong Tak, Keungmo Yang, Min Jeong Kim, Katherine Po Sin Chung, Jihyo Byun, Kwangwoo Lee, Hyuk Soo Eun, Jong-Eun Park, Sang Kyum Kim, Won-Il Jeong	
FP-97	Cortisol Metabolic Reprogramming in Liver Cirrhosis with Diagnostic and Prognostic Implications	737
	Soyeon Park, Minjeong Park, Hye Won Yang, Jeayeon Park, Su Jong Yu, Seung Shin Park, Man Ho Choi, <u>Eun Ju Cho</u> , Jung Hee Kim	
FP-98	Targeting DNA Stress Response as a Synthetic Lethal Strategy for Activated Hepatic Stellate Cells	738
	<u>Eui Jin Lee</u> , Ja Hyun Koo	
FP-99	Impact of Cardiometabolic Risk Factors and Alcohol Consumptions in Decompensated Liver Cirrhosis	738
	<u>Keungmo Yang</u> , Jaejun Lee, Ji Won Han, Pil Soo Sung, Chang Wook Kim, Heechul Nam, Ahlim Lee, U Im Chang, Do Seon Song, Hae Lim Lee, Hee Yeon Kim, Sung Won Lee, Jeong Won Jang	
FP-100	Efficacy of Albumin Therapy in Patients with Decompensated Cirrhosis: A Systematic Review and Meta-Analysis	739
	Han Ah Lee, <u>Seul Ki Han</u> , Jae Seung Lee, Jae Hyun Yoon, Moon Young Kim	
FP-101	Comparative Effectiveness of Antibiotic Prophylaxis for Spontaneous Bacterial Peritonitis in Patients with Cirrhosis: A Network Meta-Analysis of Randomized Trials	739
	<u>Moon Haeng Hur</u> , Han Ah Lee, Do Seon Song, Jeong Ju Yoo, Jeong Eun Song, Seul Ki Han, Sung Won Chung, Gi-Ae Kim, Seong Hee Kang, Seung Kak Shin, Yeonjung Ha, Young Chang, Jae Hyun Yoon, Jae Seung Lee, Young Kul Jung, Sang Gyune Kim, Moon Young Kim	

14. Liver Transplantation 2

FP-102	Correlation of Early Post-Operative Outcomes on Graft Weight Variations in Right Lobe Recipient Living-Donor Liver Transplantation: A Single Center Retrospective Study	740
	<u>Meynard Keynes Dela Cruz</u> , Earnest Caizer Dela Cruz, Mukesh Kumar, Sreejith Sreekumar, Selvakumar Naganathan, Peush Sahni, Subhash Gupta	
FP-103	Randomized Trial Comparing Postoperative Outcomes of PTFE vs. Polyethylene Terephthalate Grafts in Neo-Middle Hepatic Vein Reconstruction for Right Lobe Living Donor Liver Transplantation	741
	<u>Mrunal Awalekar</u> , Guhan Venkatakrishnan, Shweta Mallick, Krishnanunni Nair, Madhu Srinivasan, Christi Tv, Binoj St, Dinesh Balakrishnan, Unnikrishnan Gopalakrishnan, Ramachandran Narayanamenon, Sudheer Ov, Sudhindran Surendran	
FP-104	Sequential NRP and Hypothermic versus Normothermic Ex-Situ Perfusion in Extended Criteria DCD Liver Transplantation: A Randomized Prospective Trial	741
	<u>Lorenzo Petagna</u> , Arianna Trizzino, Jessica Bronzoni, Giulia Cirillo, Serena Babboni, Daniele Pezzati1, Emanuele Balzano, Caterina Martinelli, Ranka Vukotic, Stefania Petruccelli, Gabriele Catalano, Paola Carrai, Giovanni Tincani, Giuseppina Basta, Davide Ghinolfi	
FP-105	Translational Application of Acellular Dermal Matrix for Hepatic Vein Reconstruction in LDLT: From Bench Validation to Clinical Efficacy	742
	Seok-Hwan Kim	
FP-106	Initial Extreme High Titer Does Not Worsen Outcomes When Adequate Desensitization Is Performed in ABO-Incompatible Living Donor Liver Transplantation	742
	<u>Sung-Min Kim</u> , Gi-Won Song, Young-In Yoon, Deok-Bog Moon, Chul-Soo Ahn, Shin Hwang, Tae-Yong Ha, Dong-Hwan Jung, Ki-Hun Kim, Gil-Chun Park, Sung-Gyu Lee	
FP-107	Sex Disparities in Liver Transplant Prioritization across Scoring Systems: A Korean Multicenter Cohort Study	743
	<u>Jeayeon Park</u> , Ji Won Han, Pil Soo Sung, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Yoon Jun Kim, Jung-Hwan Yoon, Jeong Won Jang, Do Seon Song, Su Jong Yu	

Oral Poster Presentation

1. HBV & MASLD 1

OP-1	Direct Effects of the Glucagon/GLP-1 Receptor Dual Agonist Survodutide on Liver Endpoints Beyond Weight Loss: Insights from a Phase 2 Trial in People with Metabolic Dysfunction-Associated Steatohepatitis and Fibrosis	746
	Mazen Noureddin, Arun J. Sanyal, Pierre Bedossa, Mandy Fraessdorf, Corinna Schoelch, Elena Startseva, Guy W. Neff, Eric J. Lawitz, Elisabetta Bugianesi, Quentin M. Anstee, Philip N. Newsome, Vlad Ratziu, Azadeh Hosseini-Tabatabaei, Jörn M. Schattenberg, Naim Alkhouri, Ramy Younes, <u>Jinhong Cho</u>	
OP-2	Iron-Driven Hepatokine Dysregulation Promotes Systemic Metabolic Dysfunction in MASLD	746
	<u>Hye Jin Jo</u> , Seo Jeong Jo, Hao Yuxin, Won Kim, Chang Yeob Han	
OP-3	Assessment of Liver Function Test in Vegetarian and Non-Vegetarian	747
	Santosh Kumar Gupta	

OP-4	Statin Prescription and Major Adverse Cardiovascular Events by Antiviral Therapy in Chronic Hepatitis B: A Nationwide Real-World Study	747
	<u>Jisoo Lee</u> , Jae-Young Kim, Seryoung Kim, Sang Gyune Kim, Young Seok Kim, Jeong-Ju Yoo	
OP-5	Tenofovir Alafenamide Improves ALT and HCC Risk Stratification in Chronic Hepatitis B with Normal or Mildly Elevated ALT	748
	<u>Jaehong Jeong</u> , Dong Yun Kim, Jae Seung Lee, Mi Na Kim, Hye Won Lee, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Seung Up Kim	
OP-6	Cas9–gRNA Circular Templates Reduce Hepatitis B Virus Replication via cccDNA Degradation	749
	<u>Deok Hwa Seo</u> , Yeochan Yun, Min Gu Kim, Songmee Bae, Yong Kwang Park, Hyeon-Yeol Cho, Pil Soo Sung	

2. MASLD & ALD, Basic

OP-7	A Study to Evaluate the Impact of Zinc Deficiency on Liver Fibrosis in Lean vs. Obese Metabolic Dysfunction-Associated Steatotic Liver Disease Patients	749
	<u>Archana Chaudhari</u> , Aashal Bhavesh Shah	
OP-8	Differential Activation of Complement System Drives Immune Cell Differentiation to Promote Nonalcoholic Fatty Liver Disease Progression	750
	Mingjiang Liu, <u>Hao Xing</u> , Wei Gao, Guangtao Ma, Yuntao Bao, Zhiyong Lin, Shilian Chen, Yulan Li, Chenyi Zhuo, Huizhao Su, Zhenya Guo, Zaiwa Wei, Rensheng Wang, Guandou Yuan, Yonglian Zeng, Songqing He	
OP-9	Fibroblast- and Macrophage-Derived Thrombospondin-1 Orchestrates the Fibroinflammatory Niche in Metabolic Dysfunction-Associated Steatohepatitis-Induced Fibrosis	751
	<u>Sung Woo Cho</u> , Jung Hoon Cha, Deok Wha Seo, Mi Hyun Kwon, Kwon Yong Tak, Hee Sun Cho, Keungmo Yang, Si Hyun Bae, Pil Soo Sung	
OP-10	Zonation-Dependent Enrichment and Spatial Remodeling of Intrahepatic CD3⁺ T Cells in MASLD Fibrosis	752
	<u>Min Su Cha</u> , Kwon Yong Tak, Pil Soo Sung	
OP-11	Establishment of a CO₂-Independent Platform for iPSC-Derived Hepatocyte Differentiation to Enable 3D Bioprinting in Space	752
	<u>Chae Eun Lee</u> , Dongho Choi, Ji Hyun Shin, Heeju Kim	

3. MASLD & ALD, Clinical

OP-12	Patterns of Alcohol Consumption and Clinical Spectrum of Alcohol-Related Liver Disease in a Rural Setting in Nepal: A Hospital-Based Study	753
	<u>Rekha Poudel</u> , Sushant Bhattarai, Nishma Shrestha	
OP-13	Clonal Hematopoiesis of Indeterminate Potential and Metabolic Dysfunction-Associated Steatotic Liver Disease: Comprehensive Analysis of Biopsy-Proven Cohorts	754
	<u>Yun Kyu Lee</u> , Hyungtai Sim, Sae Kyung Joo, Heejoon Jang, Dong Hyeon Lee, Jeong Hwan Park, Keon Wook Kang, Murim Choi, Won Kim, On Behalf of the Innovative Target Exploration of NAFLD (ITEN) consortium	
OP-14	Trends in the Prevalence of Steatotic Liver Disease and Its Subtypes in Korea: A Nationwide Population-Based Study (2007–2023)	754
	Sang Hun Park, Min Na Kim, <u>Jun Sik Yoon</u> , Sung Jae Park, Youn Jae Lee	
OP-15	Multiparametric Ultrasound for the Evaluation of MASLD: An Individual Patient Data Meta-Analysis and External Validation of Prediction Models for MASH and At-Risk MASH	755
	Dong Ho Lee	
OP-16	Referral Burden and Second-Tier Testing in Two-Step Algorithms for Detecting Significant Hepatic Fibrosis among Asian Community-Based Type 2 Diabetes Mellitus	756
	Ye Ji Kwon,Eileen L. Yoon,Yoshihiro Kamada, Hyo Young Lee Han Ah Lee, Jonghyun Lee, Jonghyun Kim, Sung Hwan Yoo, Lee Youjung, Toshio Watanabe, Hideki Fujii, Seung Up Kim, <u>Dae Won Jun</u>	

4. LC, Liver Failure & Autoimmune Diseases 1

OP-17	Impact of Glycemic Control on Liver-Related Events in Patients with Hepatitis B Virus-Related Cirrhosis and Type 2 Diabetes Mellitus	756
	Hana Park, <u>Dong Yun Kim</u> , Hye Won Lee, Jun Yong Park, Sang Hoon Ahn, Do Young Kim	

OP-18

Hepatic Safety and Clinical Outcomes of Fexuprazan Compared with Proton Pump Inhibitors in Patients with Liver Cirrhosis

757

Jun Sik Yoon,

Jeong-Ju Yoo, Sung Jae Park, Young Seok Kim, Youn Jae Lee, Sang Gyune Kim

OP-19

The Paradigm Shift toward DOACs in Liver Cirrhosis: A Longitudinal Analysis of Prescription Dynamics and Clinical Outcomes

757

Jeong-Ju Yoo,

Minae Park, Sang Gyune Kim, Eun Young Cho

OP-20

Integrative Signed Network and Literature Mining Framework Identifies Novel Molecular Regulators of Liver Fibrosis

758

Minkyung Gu, Yunseo Bong, Ga-young Kim, Myung-gyu Kim, Seol Hee Park, Wonhyo Seo

OP-21

SE-1 Antibody-Mediated Surface Engineering of MSC-Derived Exosomes Enables Selective Targeting of Liver Sinusoidal Endothelial Cells

758

Jin Suk Lee,

Mi Ra Lee, Seul Ki Han, Chung Hyun Jung, Soon Koo Baik, Moon Young Kim

OP-22

An Investigation into the Effects of Microplastic Exposure on Hepatic Function through Hydro-Dynamic Injection

759

Yujin Lee,

Wonjae Lee, Junseo Bae, Eunjeong Kim

5. Liver Transplantation

OP-23

Pink1/Parkin Signaling Regulates Liver Regeneration by Modulating Sigma-1 Ubiquitination and Hepatocyte Succinate Production

759

Jian Xu,

Yuechen wang, Haoming Zhou

OP-24

Aspartate Aminotransferase (AST) Level on Day 4 as a Predictor of Steroid Response in Biopsy Proven Rejection after Liver Transplantation

760

Radhika Venugopal,

Dinesh Jothimani, Mukul Vij, Mohamed Rela

OP-25

Recurrent Autoimmune Hepatitis after Liver Transplantation in a Young Woman: A Case Report with Histological Overlap of Chronic Rejection

761

Gulbanu Pernebayeva,

Marzhan Zhanasbayeva, Kulpash Kaliaskarova, Nurzhanova Arailym, Svetlana Kurash

OP-26

Extra-Anatomical Portal Inflow Reconstruction Using Splanchnic and Collateral Veins in Living Donor Liver Transplantation for Portal Vein Thrombosis

762

Young-In Yoon,

Deok-Bog Moon, Dong-Hwan Jung, Sung-Gyu Lee

OP-27

Safety and Feasibility of Left Lobe Graft in Living Donor Liver Transplantation: A Comparative Study with Right Lobe Graft

762

Eunjin Lee,

Namkee Oh, Youngju Ryu, Hayeon Do, Jiyoung Baik, Suk Min Gwon, Jae Hyun Kwon, Han Sang Park, Inho Lee, Yoonsun Choi, Jinsoo Rhu, Gyu-Seong Choi, Jongman Kim

OP-28

Engineering Immune-Evasive Vascularized Liver Modules Using CRISPR-Edited Hypoimmune Stem Cells

763

Hee Ju Kim,

Soraya Salas Silva, Chae Eun Lee, Ji Hyun Shin, Kyeong Sik Kim, Songwan Jin, Gyeong Woon Kong, Youngju Son, Kangin Lee, Jae Young Lee, Donghwan Kim, Jinah Jang, Dayoon Kang, Daekeun Kim, Dongho Choi

6. HCC, Basic 1

OP-29

A Novel Copper Ionophore A3 Combined with PX-478 Induces Cuproptosis and Enhances Immunogenic Cell Death in Hepatocellular Carcinoma

763

Yuntao Bao,

Guandou Yuan, Songqing He, Yu - Lan Li

OP-30

Nidogen 1 mRNA Vaccine Facilitates T Cell Homing and Induces Anti-Tumor Immunity against Hepatocellular Carcinoma

764

Xia Lu,

Liu Jia, Xia Heng, Xue Tingmao, Zha Gao-Feng, Xiao Zhijie, Mao Xiaowen

OP-31

High Ammonia Promotes EHHADH-Dependent Pyrimidine Degradation to Induce Cell Death in HCC

765

Jinhui Wei,

Baohua Hou, Shanzhou huang

OP-32

Exosomal miR-30a-5p Serves as a Predictive Biomarker and Therapeutic Target for Atezolizumab/Bevacizumab Therapy in Advanced HCC

765

Eunho Choi,

Young-Sun Lee, Hyobin Kim, Minjeong Kwon, Hyeyoon Nam, Gihhoon Nam, Yang Jae Yoo, Seong Hee Kang, Sun Young Yim, Tae Hyung Kim, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon

OP-33

Baseline Peripheral Blood Frequency of CD69+ TRM-Like T Cells Predicts Response to Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma

766

Min Seo Park,

Kwon Yong Tak, Jeong Won Jang, Hee Sun Cho, Jeong Won Jang, Ji Won Han, Pil Soo Sung

OP-34

PLD1 Knockdown Suppresses Hepatocellular Carcinoma Growth and Progression through Upregulation of IGFALS

766

Ha Neul Kim, Hei Gwon Choi, In Soo Kim, Young Suk Kim, Yu Gyeong Lee, Hyuk Soo Eun

7. HCC, Clinical

OP-35

GAAD Score as a Diagnostic and Prognostic Marker from Cirrhosis to Hepatocellular Carcinoma

767

Silvia Cagnin,

Ada Aita, Alessandra Biasiolo, Giovanna Tretti, Santina Quarta, Annalisa Stefani, MariagraziaRuvoletto, Pietro Guerra, Rossella Donghia, Gianluigi Giannelli, Patrizia Pontisso, Martina Montagnana, Andrea Martini

OP-36

Stereotactic Body Radiation Therapy as an Add-on to Targeted Agents in Patients with Locally Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

768

Mohamed Hamouda Elkasaby,

Mohamed Sherif Ali Ahmed ,Atef A. Hassan

OP-37

Identifying the Novel Target and Immunotherapy Strategies for the Precision Treatment of Hepatocellular Carcinoma

768

Hongping Xia

OP-38

An Anchored Matching-Adjusted Indirect Comparison of First-Line Systemic Therapies in Advanced HCC

769

Ji Won Han

OP-39

Thioredoxin as a Novel Sensitive Marker of Early Diagnosis in Hepatocellular Carcinoma

770

Tae Hee Lee,

Hyuk Soo Eun

OP-40

Multicenter Propensity-Weighted Comparison of Hepatic Arterial Infusion Chemotherapy and Tyrosine Kinase Inhibitors in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Atezolizumab–Bevacizumab

771

Jae-Sung Yoo, Kwon Yong Tak,

Hee Sun Cho, Ji Won Han, Jeong Won Jang, Jaejun Lee, Hyun Yang, Si Hyun Bae, Chang Wook Kim, Hae Lim Lee, Hee Yeon Kim, Sung Won Lee, Suho Kim, Jung Suk Oh, Ho Jong Chun, Hee Chul Nam, Pil Soo Sung

8. HCC & LC

OP-41

Low Tumor Burden Predicts Benefit from Transarterial Treatment in Hepatocellular Carcinoma with Extrahepatic Metastasis: A Nationwide Cohort Study

772

Jaejun Lee,

Hyun Yang, Keungmo Yang, Ji Won Han, Pil Soo Sung, Jeong Won Jang, Si Hyun Bae

OP-42

Sequential Transarterial Radioembolization and Atezolizumab plus Bevacizumab Improves Survival in Advanced Hepatocellular Carcinoma: A Propensity Score-Matched Analysis

772

Yunmi Ko,

Hyunjae Shin, Moon Haeng Hur, Jeayeon Park, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

OP-43

Surgical Resection versus Non-Surgical Treatment for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis

773

Seok-Hwan Kim, Sang-Hoon Kim,

Hae-Won Lee, Dong-Sik Kim

OP-44

Evaluating the Clinical Utility of Large Language Models for Hepatocellular Carcinoma Treatment Recommendations: A Nationwide Registry Study

774

Keungmo Yang,

Jaejun Lee, Jeong Won Jang, Pil Soo Sung, Ji Won Han

OP-45

PAK4–YAP Axis Controls Hepatic Stellate Cell Activation and Liver Fibrogenesis

775

Gil Hwan Kim,

Hyunsoo Rho, Chang Hun Lee, You-Jung Hong, Eun Ju Bae, Byung-Hyun Park, Chang Yeob Han

OP-46

Periportal Arginine Deficiency Drives Macrophage Senescence to Blunt Aged Liver Regeneration

776

Haoran Hu,

Yuan Liang, Hao Wang, Feng Cheng, Haoming Zhou

9. Surgery, Technical Issues

OP-47

Comparison of Surgical Outcomes between Robotic and Laparoscopic Liver Resection

776

Ulil Albab Habibah

OP-48

Laparoscopic Surgery for Liver Echinococcus

777

Mylytkbay Rysmakhanov

OP-49

Surgery for Hepatocellular Carcinoma Patients with Portal Vein Main Trunk Thrombosis (Vp4): Initial Experience of a Single Center

777

Giang Nguyen,

Trong Nguyen

OP-50	Overcoming the Lack of Dedicated Vascular Clamps in Laparoscopic Anatomical Liver Resection: The “Double Foley Loop” Technique as a Cost-Effective Alternative	778
	<u>Nguyen Kieu Hung</u> , Nguyen Minh Trong, Nguyen Truong Giang	

10. Others

OP-51	A Retrospective Study of Endogenous Endophthalmitis-Related Pyogenic Liver Abscess: An Increasing Complication in North Vietnam	778
	Nguyen Duc Thang	
OP-52	Mobile Self-Management Coaching Program for Chronic Liver Disease with Metabolic Risk Factors in Middle-Aged Men: A Pilot Randomized Controlled Trial	778
	<u>Seo Jin Lee</u> , Seo Eun Bae, Sang Hoon Ahn, Hye Won Lee, Mi Na Kim, Yeon Soo Jang	
OP-53	Chirality-Dependent Nanoparticle Activation of Dendritic Cells Induces Inflammasome-Associated Inflammatory Responses to Drive Liver Inflammation	779
	<u>Da-Min Han</u> , Joo-Hyun Lim, Yong-Hyun Han	
OP-54	Deacetylated α -Tubulin in Biliary Epithelial Cells Drives Hepatic Ductular Reaction	779
	<u>Ho Jae Ryu</u> , Ja Hyun Koo	
OP-55	Quantum-Informed Molecular Representation Learning for Preclinical Drug-Induced Liver Injury Prediction	780
	<u>Seoeun Park</u> , Yujin Kim, Soon Sun Kim, Ji Eun Han, Hyo Jung Cho, Jae Youn Cheong, Charmgil Hong	
OP-56	Complacency, Knowledge, and Awareness across the Hepatitis Care Cascade: A Population-Based Survey	781
	Seunghyun Lewis Kwon, Seul-Ki Kang, DaeHyun Koh ² , Chang Hun Lee ³ , In Hee Kim ³ , Hyungmin Lee, <u>Hanul Park</u> ⁴	

11. HBV 2

OP-57	HBV Infection Accelerates Hepatocyte Senescence and Induces T Cell Exhaustion via SASP Secretion Pathway	784
	<u>Ran Zhao</u> , Zhize Yuan, Xinyao Du, Weiming Yan, Qin Ning	
OP-58	Age-Standardized Trends in Chronic Viral Hepatitis in Mongolia: Implications for HBV, HCV, and Delta Co-Infection Burden (2022–2024)	785
	<u>Nyam Biziya</u> , Bayarmaa Nyamaa, Oyundelger Munkhtuvshin, Doljinsuren Enkhbayar	
OP-59	Clinical and Biochemical Characteristics of Acute Hepatitis B and Viral Coinfections in Hospitalized Patients in Mongolia	786
	<u>Oyungerel Lkhagva-Ochir</u> , Oyunbold Ganbayar, Dulguun Batdelger	
OP-60	Hepatic Biochemical Abnormalities in Chronic Hepatitis B: Evidence from a Tertiary Care Hospital in Nepal	786
	<u>Arun Bahadur Chand</u> , Bindu Sen, Rajendra Dev Bhatt, Shiba Kumar Rai	
OP-61	A Nationwide Seroepidemiology Study of Hepatitis D Virus Infection in South Korea	787
	<u>Jeong Eun Song</u> , Ju-Yeon Cho, Kwang Il Seo, Young-Kul Jung, Moon Young Kim, In Hee Kim, Jin Dong Kim, Ji Won Han, Heechul Nam, Jung Hyun Kwon, Myeong Jun Song, Seok-Hwan Kim, Hee Yeon Kim, Sung Won Lee, Jeong Won Jang	

12. HBV & HCV

OP-62	Current Status of Acute HCV Infection in Mongolia (2024–2025)	788
	<u>Dulguun Batdelger</u> , Oyunbold Ganbayar, Oyungerel Lkhagva-Ochir	
OP-63	Study of the Association between Liver Fibrosis and Renal Impairment in Chronic Hepatitis C	788
	<u>Gantogtokh Dashjamts</u> , Chuluunbileg Batbold, Yumchinsuren Tsendendorj, Tsogdulam Sumiyabazar, Bolor Ulziitsogt, Ganchimeg Dondov, Tegshjargal Badamjav, Tulgaa Lonjid, Chia-Yen Dai, Batbold Batsaikhan	
OP-64	Exploring Predictors of Hepatitis C Treatment Uptake among People Who Use Drugs (PWUDs): A Prospective, Multicenter Study	789
	<u>Gwang Hyeon Choi</u> , Young-Hoon Cheon, Do Hoon Kwon, Sung Nam Jo, Og-Jin Jang, Min Kyung Park, Eun Sun Jang, Sook-Hyang Jeong	
OP-65	Associated Factors of HCV Transmission between Couples Using National Health Insurance Data	790
	<u>Hwa Young Choi</u> , Moran Ki	
OP-66	Re-Engagement to Rescue Therapy with Sofosbuvir/Velpatasvir/Voxilaprevir in Hepatitis C after Direct-Acting Antiviral Failure	791
	<u>Jae Seung Lee</u> , Wonseok Kang, Ki Tae Yoon, Sang Gyune Kim, Moon Young Kim, Jae Yoon Jeong, Hyung Joon Yim, Byung Kuk Jang, Soo Young Park, Tae Hee Lee, Seung Up Kim	

OP-67	Real-World Effectiveness and Safety of Pangenotypic Direct-Acting Antivirals in Patients with Chronic Hepatitis C: A Large-Scale Multicenter Cohort Study	791
	Seok-Hwan Kim, <u>Myeong Jun Song</u> , Jihye Lim, Keungmo Yang, Heechul Nam, Chang Wook Kim, Hae Lim Lee, Hee Yeon Kim, Sung Won Lee, Ahlim Lee, Do Seon Song, U Im Chang, Soon Kyu Lee, Jung Hyun Kwon, Soon Woo Nam, Jaejun Lee, Hyun Yang, Si Hyun Bae, Ji Won Han, Pil Soo Sung, Jeong Won Jang	

13. MASLD, Clinical

OP-68	Fat-to-Muscle Ratio and Subtype-Specific Protective Effects of Exercise in Steatotic Liver Disease: A Large-Scale Cohort Study	792
	<u>Hana Park</u> , Hye Won Park, Hye-Sook Chang, Jaewon Choe, Sungwon Park, Ji Young Lee	
OP-69	Impact of Hyperuricemia on the Mortality in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease	792
	<u>Aryoung Kim</u> , Danbee Kang, Sung Chul Choi, Dong Hyun Sinn, Geum-Youn Gwak	
OP-70	Safety and Efficacy of Lactobacillus Delbrueckii Subsp. Lactis CKDB001 in Metabolic-Associated Steatotic Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Trial	793
	<u>Jung Hee Kim</u> , Hyunchoe Joung, Jieun Choi, Hyun Ho Song, Young-Kul Jung, Sung Eun Kim, Sunghee Lee, Chang Hun Shin, Do Yup Lee, Ki Tae Suk	
OP-71	Differential Prognostic Roles of Muscle and Adiposity in MASLD: Insights from MRI-Based Body Composition Analysis	794
	<u>Keungmo Yang</u> , Jaejun Lee, Tom Ryu	
OP-72	The MASLD Journey in the General Population: Linkage-to-Care and Patient-Reported Uptake of Fibrosis Risk Assessment	794
	<u>Joo Hyun Oh</u> , Jun-Hyuk Lee, Sang Bong Ahn, Eunjoo Kwon, Eileen L Yoon, Hyo Young Lee, Seon Cho, Dae Won Jun	
OP-73	Development and Validation of an AI-Based Prediction Model for Cardiovascular Disease Events in Patients with MASLD	795
	<u>Yewon Park</u> , Han Ah Lee, Sang Gyune Kim, Soo Young Park, Young Youn Cho, Hyung Joon Kim, Yeon Seok Seo, Seung Up Kim, Dae Won Jun, On behalf of the VCTE-based Liver Investigation Network (V-LINK) Study group	

14. LC, Liver Failure & Autoimmune Diseases 2

OP-74	Current Status and Prognosis of Autoimmune Hepatitis Based on the Japanese AIH Registry	795
	<u>Atsushi Tanaka</u> , Kazumichi Abe, Masanori Abe, Hiromasa Ohira	
OP-75	Noninvasive Risk Stratification of Advanced Fibrosis in Autoimmune Liver Disease Using Machine Learning	796
	<u>E. Ben George</u> , Raja Al-Hinai, Amira Al-Nasseri	
OP-76	Hepatocyte ApoJ Accelerates Injury-Induced Liver Fibrosis by Orchestrating Ranbp2-Mediated SUMOylation and Subsequent STAT3 Activation	796
	<u>Shanyu Zhao</u> , Zhaohong Mo, Kai Ke, Gangping Feng, Mingbei Zhong, Xinghuang Yi, Qiongguang Huang, Guandou Yuan, Songqing He, Shuangdi Duan	
OP-77	Succinate-SUCNR1 Signaling in Endothelial Contributes to Liver Fibrosis Progression	797
	<u>Jian Xu</u> , Yuechen Wang, Haoming Zhou	
OP-78	VCAM Serves as a Potential Biomarker in Paediatric Portal Hypertension	798
	<u>Tengfei Si</u> , Huihong Yu, Bethany Tucker, Fabiola Di Dato, Qing Shao, Xiaohong Huang, Bowen Gao, Xuan Luo, Eirini Kyranas, Yun Ma, Tassos Grammatikopoulos	
OP-79	Anti-STC1 as a Therapeutic Strategy for Liver Fibrosis	799
	Alfred Suen, Kristy Chan, Veronica Cheuk, Clive Chung, <u>Regina Lo</u>	

15. LC, Liver Failure & Autoimmune Diseases 3

OP-80	Clinically Meaningful Improvements in Moderate to Severe Pruritus Patients with Primary Biliary Cholangitis Treated with Seladelpar: 30 Months of ASSURE	799
	Gideon M. Hirschfield, Andreas E. Kremer, Cynthia Levy, Kris V. Kowdley, Hany Elbeshbeshy, <u>Jeong Heo</u> , Kyung Min Kwon, Jie Liu, Caroline Burk, Daria B. Crittenden, Marilyn J. Mayo	
OP-81	Human Albumin Infusion for Large-Volume Paracentesis in Liver Cirrhosis: A Systematic Review and Meta-Analysis	800
	<u>Jae Seung Lee</u> , Jae Hyun Yoon, Seul Ki Han, Han Ah Lee, Do Seon Song	
OP-82	Serum Albumin Response to Intravenous Albumin and Its Association with Short-Term Prognosis in Patients with Acute Decompensated Cirrhosis	800
	Seul Ki Han, Jung Hyun Jung, Soon Koo Baik, Moon Young Kim, <u>Hyeonho Choi</u>	

OP-83

Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) for the Differential Diagnosis and Prognosis of Acute Kidney Injury in Liver Cirrhosis: A Systematic Review and Meta-Analysis

801

Seong Hee Kang, Seoul Ki Han, Seung Kak Shin, Young Jang, Jae Seung Lee, Jung Ju Yoo, Jeong Eun Song, Seong Won Jung, Ki Ae Kim, Mun Haeng Heo, Han Ah Lee, Yeon Jeong Ha, Jae Hyun Yoon, Do Seon Song, Young Kul Jung, Ki Tae Suk, Yeon Seok Seo, Moon Young Kim

OP-84

Ascites Microbiome Alterations Associated with Hepatocellular Carcinoma in Patients with Decompensated Cirrhosis

801

Jun Sik Yoon, Sung Jae Park, Youn Jae Lee

OP-85

Trends in Prevalence, Etiology, and Healthcare Costs of Cirrhosis in Korea (2008–2023): A National Population-Based Study

802

Sungchan Kang, Jeehye Lee, Hana Park, Jeong Han Kim

16. MASLD, Basic & Clinical

OP-86

Fumaric Acid as a Novel Metabolite Biomarker for Diagnosis of Metabolic Dysfunction-Associated Steatohepatitis in Obese Subjects

803

Yoonseok Lee, Oh Sang Kwon, Yun Soo Kim, Ju Hyun Kim, Seung Kak Shin

OP-87

Extending Stemness and Longevity of Human Chemically Derived Hepatic Progenitors Using a Novel Drug

803

Seunghhee Kim, Salas-Silva Soraya, Ji Hyun Shin, Dongho Choi

OP-88

Long-Term Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease after Thyroidectomy and Thyroid Hormone Therapy in Thyroid Cancer Survivors: A Nationwide Study

804

Jiwoo Lee, Yun Mi Choi, Yeonjung Ha

OP-89

Emerging Indices Outperform Traditional Fibrosis Scores in Young MASLD across Divergent Screening Goals

804

Ahlim Lee, Chang In Han, Keungmo Yang, Hyun Yang, Pil Soo Sung, Si Hyun Bae, Jaejun Lee

OP-90

Prospective Evaluation of Steatosis Noninvasive Tests for Two-Year Monitoring in MASLD

804

Yoonseok Lee, Yun Soo Kim, Ju Hyun Kim, Seung Kak Shin, Oh Sang Kwon

OP-91

CXCR4-Expressing Peripheral CD8 T Cells Are Activated and Recruited to the Liver in Alcohol-Associated Liver Disease

805

Gil Won Lee, Min seo Park, Kwon Yong Tak, Hee Sun Cho, Ji Won Han, Pil Soo Sung

17. Liver Transplantation & ALD

OP-92

Early Postoperative C3a Predicts Early Allograft Dysfunction after Liver Transplantation

805

Nazokat B. Rustamova, Diloram A. Musakhodjaeva, Takhir A. Askarov

OP-93

Body Mass Index ≥34 KG/M² Does Not Compromise Safety or Hepatic Regeneration in Living Liver Donors: A Propensity-Matched Cohort Study

806

Selvakumar Naganathan, Hemant Sharma, Subash Gupta

OP-94

Long-Term Outcomes of the First Donor Hemighepatectomy Using 3D Laparoscopy in Kazakhstan: Experience from a Single Center

806

Gani Kuttymuratov, Myltykbay Rysmakhanov, Nadiyar Musin, Aset Elemesov

OP-95

Long-Term Outcomes after Alcohol-Associated Hepatitis among Adults with Type 2 Diabetes Mellitus

807

Pojsakorn Danpanichkul, Yanfang Pang, Patrawadee Wongrujipairoj, Thanida Auttapracha, Donghee Kim, Ahmad Anouti, Matheus D. Souza, Karn Wijarnpreecha, Thomas G. Cotter, Douglas A. Simonetto, Suthat Liangpunsakul, Juan Pablo Arab, Luis Antonio Díaz

OP-96

The Addition of an mTOR Inhibitor Is Associated with Increased Gut Microbial Diversity in Liver Transplant Recipients: A Prospective Pilot Study

808

Soon Kyu Lee, Yunju Jeong, Ho Joong Choi, Young Kyoung You, Jeong Won Jang, Pil Soo Sung, Ji Won Han, Mi-La Cho, Jong Young Choi

OP-97

Left Lobe Liver Transplantation Using a Flipped Technique: Comparable Survival with Improved Portal Vein Alignment

809

Young Jin Yoo, Eun-Ki Min, Deok Gie Kim, Jae Geun Lee, Myoung Soo Kim, Dong Jin Joo

18. HCC, Basic 2

OP-98

Targeting Cell Surface LANCL1 with Monoclonal Antibodies Suppresses Tumorigenesis in Hepatocellular Carcinoma

809

Yu Man Tsui, Diana Chui-Yee O, Irene Oi-Lin Ng

OP-99

Spatially Resolved Transcriptomics Reveals Terminal CD8⁺ T Cell Exhaustion Driven by Chronic Inflammatory Signaling as a Key Determinant of Poor Response to Atezolizumab plus Bevacizumab in Advanced HCC

810

Sungjun Jang, Young-Sun Lee, Hyobin Kim, Minjeong Kwon, Hyeyoon Nam, Gihhoon Nam, Eunho Choi, Yang Jae Yoo, Seong Hee Kang, Sun Young Yim, Tae Hyung Kim, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon

OP-100

Development of in Vitro Tumor Microenvironment Model for Immunotherapy Optimization and Synergistic Effects of uPAR Inhibitor in Hepatocellular Carcinoma Immunotherapy

810

Yoon Gi Chae, Min Kyung Kim, Yoon Seok Lee, Oh Sang Kwon, Yun Soo Kim, Ju Hyun Kim, Seung Kak Shin

OP-101

Multi Cohort Integrative Profiling of Cytochrome P450 Genes Identifies CYP2R1 as a Metabolic and Immunogenomic Biomarker Linking DNA Repair and Myeloid Suppression in Hepatocellular Carcinoma

811

Hyun Sun Jung, Geum Ok Baek, Moon Gyeong Yoon, Nayoung An, Jae Youn Cheong, Soon Sun Kim, Jung Woo Eun

OP-102

Shelterin Component TPP1 Drives Tumor Progression and Predicts Poor Prognosis in Hepatocellular Carcinoma

811

Jung Eun Jang, Hye Seon Kim, Jin Seoub Kim, Jae Mo Han, Hee Sun Cho, Kwon Yong Tak, Ji Won Han, Pil Soo Sung, Si Hyun Bae, Jeong Won Jang

OP-103

Clustering of Intrahepatic Cholangiocarcinoma Subtypes Using Whole-Genome Sequencing

812

Sung Hyun Kim, Kyung Sik Kim

19. HCC, Clinical 3

OP-104

Prognostic Factor and Risk Stratification in Hepatocellular Carcinoma: Insights from Cox Regression and Kaplan-Meier Analysis in a Male-Dominated Cohort

812

Nguyen Cong Long, Luu Thi Minh Diep, Nguyen Thanh Tung, Nguyen Minh Ngoc, Doan Thi Ngoc Ha, Nguyen Van Hieu

OP-105

Real-World Effectiveness of the STRIDE Regimen in Hepatocellular Carcinoma: Initial Experience from a Tertiary Center in Vietnam

813

Manh Duy Pham, Loc Quang Bui, Huy Le Trinh, Anh Dinh Tran

OP-106

Real-World Clinical Outcomes of Nivolumab plus Ipilimumab for Unresectable Hepatocellular Carcinoma: A Multicenter Cohort Study

814

Tomoharu Yamada, Takeshi Okamoto², Mayuko Kondo³, Ryota Masuzaki⁴, Shuntaro Obi⁵, Mitsuhiro Fujishiro, Ryosuke Tateishi

OP-107

MRI-Based Surveillance for Hepatocellular Carcinoma Using Risk-Stratified Screening Intervals in Patients with Cirrhosis: A Prospective Cohort Study

815

Byeong Geun Song, Dong Hyun Sinn

OP-108

Comparative Effectiveness of Subsequent Systemic Therapies after Atezolizumab–Bevacizumab Failure in Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

815

Moon Haeng Hur, Han Ah Lee, Yuri Cho, Byeong Geun Song, Young Chang, Young-Sun Lee, Minjong Lee, Mi Na Kim, Eun Sun Jang, Soon Sun Kim, Do Seon Song, Su Jong Yu, Hyung-Don Kim, Hyung Joon Kim, Haeryoung Kim, Miyoung Choi, Do Young Kim, Joon Hyeok Lee, Bo Hyun Kim, Ju Hyun Shim

OP-109

External Beam Radiotherapy versus Local Ablation Therapy for the Treatment of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

816

Sun Hyun Bae, Seo Hee Choi, Sang Min Yoon, Jeong Il Yu, Hyun-Cheol Kang, Nalee Kim, Tae Hyun Kim, Hee Chul Park

20. Biliary and Pancreatic Disease & Others

OP-110

Self-Supervised Learning Model Integrates Plain and Contrast-Enhanced CT for Preoperatively Identifying Gangrenous Cholecystitis: A Multicenter Study

817

Guandou Yuan, Qingping Guo, Shengjie Xie, Siyang Li, Jinpeng Zheng, Haiqing Yang, Songqing He

OP-111

Staged Minimally Invasive Strategy for the Management of Complicated Gallstone Disease in Pregnancy

818

Onlasyn Ibekenov, Daulet Kyzhyrov, Bolatbek Baymakhanov, Shokan Kaniev, Erlan Abrashev, Mazhit Abdykadyrov

OP-112

Survival Analysis of Peritoneal Metastasis in Pancreatic Cancer Receiving Hyperthermic Intraperitoneal Chemotherapy

819

Yaolin Xu, Yueming Zhang, Wei Wang, Wenquan Wang, Liang Liu, Wenhui Lou

OP-113

Antibiotic Prophylaxis in Emergency Cholecystectomy: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

819

Mohamed Hamouda Elkasaby, Mohamed Sherif Ali Ahmed, Atef A. Hassan

OP-114

A Safe and Oncologic Feasibility of Laparoscopic Pancreaticoduodenectomy for Pancreatic Cancer: Experience from a Developing Country without Robotic Platforms

820

Tuan Hiep Luong, Ham Hoi Nguyen, Thanh Kiem Nguyen, Van Duy Le, Dinh Toi Do, Viet Anh Do

OP-115	Low Prealbumin Predicts Early Recurrence after Pancreatic Cancer Surgery: A Retrospective Cohort Study	820
	Myeong Hun Oh , Hyung Il Seo	

Poster Exhibition

1. Autoimmune Liver Disease

PE-1	Metagenomic Identification of Gut Microbial Signatures as Non-Invasive Diagnostic Markers in Autoimmune Hepatitis and Primary Biliary Cholangitis	824
	Moon Gyeong Yoon , Doo Pyo Hong ³ , Du Yeon Shin ³ , Geum Ok Baek ¹ , Hyun Sun Jung, Nayoung An, Jae Youn Cheong, Jung Woo Eun, Soon Sun Kim	

2. Acute Liver Failure and Drug-Induced Liver Injury

PE-1	Acute Liver Injury following Self-Poisoning with Glory Lily (Gloriosa Superba) and a Detergent Containing Potassium Permanganate (KMnO4) and Oxalic Acid (H2C2O4)	824
	Thilini Madushanka Wijerathna	

3. Alcohol-Related Liver Disease, Basic

PE-1	The Mechanisms of the ASGR1–Clathrin Axis in Hepatocyte Phagocytosis of Erythrocytes Driving Iron Overload in Alcoholic Liver Disease	825
	Chaowen Zheng , Yuanxi Jiang, Chaosi Qian, Sebastian Mueller, Liping Liu	
PE-2	Biophysical Modeling of Alcohol-Dependent ASIC1a Channel Current and Its Role in ER Stress–Mediated Hepatocyte Injury	825
	Chitaranjan Mahapatra , A Pradhan	
PE-3	Integrative Transcriptomic Network Analysis Identifies Ferroptosis-Associated CXCL8 (IL-8) and Enables Therapeutic siRNA Design in Alcohol-Related Liver Disease	826
	Reny Rosalina , Rian Ka Praja	
PE-4	Survival of Patients with Nodular Regenerative Hyperplasia: A Mayo Clinic Platform Use Case	827
	Bridgette B. McNally , W. Ray Kim	

4. Liver Cirrhosis, Portal Hypertension with Cx. Basic

PE-1	Altered T Cell Immune Profile and Its Prognostic Implications in Children with Portal Hypertension: A Pilot Study	827
	Tengfei Si , Huihong Yu, Bethany Tucker, Fabiola Di Dato, Qing Shao, Xiaohong Huang, Bowen Gao, Xuan Luo, Cody Chan, Pauline Kane, Dylan Lewis, Eirini Kyranas, Yun Ma, Tassos Grammatikopoulos	
PE-2	Therapeutic Effects of Empagliflozin in a Murine Model of TAA-Induced Liver Fibrosis	828
	Mi Ra Lee , Seul Ki Han, Jin Suk Lee, Chung Hyun Jung, Soon Koo Baik, Moon Young Kim	

5. Liver Cirrhosis, Portal Hypertension with Cx. Clinical

PE-1	Analysis of Lesions of Liver in Postmortem Cases in Indian Population	829
	Amar Ranjan , Harshita Dubey, Sathya Veera Merla	
PE-2	Rule-out Cut-off of 2D-Shear Wave Elastography for Excluding Significant Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease	829
	Joo Hyun Oh , Jonghyun Lee, Miyoung Choi, Kento Imajo, Masato Yoneda, Hideki Fujii, Hyo Young Lee, Eileen L. Yoon, Mimi Kim, Dae Won Jun	
PE-3	Development and External Validation of an Explainable AI Model for Predicting Hepatic Decompensation in Chronic Liver Disease	829
	Doljinsuren Enkhbayar , Nyam Biziya, Batbaatar Lkhagvasuren, Oyundelger Munkhtuvshin	
PE-4	Correlation of Lactate-Albumin Ratio Multiple by Age with Short- and Long-Term Survival in Patients with Cirrhosis Combined with Sepsis	830
	Xu Yao , Xiaohong Wang, Dan Yang, Jia Xu, Jingyuan Liao, Qiong Yan, Xiaomin Shi, Shiqi Li, Mingming Deng, Xiaowei Tang	

PE-5	Association between Platelet-Albumin-Bilirubin Index and Mortality in Cirrhotic Patients Combined with Sepsis: A Retrospective Cohort Study from the MIMIC-IV Database	831
	Xu Yao , Xiaohong Wang, Dan Yang, Jia Xu, Jingyuan Liao, Qiong Yan, Xiaomin Shi, Mingming Deng, Fangfang Yuan, Xiaowei Tang	
PE-6	Identification of Four Novel Patient Subgroups with Distinct Mortality and Quality of Life Using Machine Learning Tools in Acutely Decompensated Cirrhosis	832
	Binbin Peng, Chao Sun	
PE-7	Hidden Chloride Load from Packaged Broth Activates Macula Densa Signaling and Vasopressin Release Worsening Edema and Hyponatremia in Cirrhosis	833
	Falakh Abdillah , Silvi Oktasari, Darius Laia, Mirza Aulia Rahmawati, Andra Zuhri Marpaung	
PE-8	Seven-Day Clinical Trajectory as a Predictor of 90-Day Mortality in Patients with ACLF: A Multicenter Study from the KACLiF Cohort	833
	Seul Ki Han , Jihye Lim, Sung-Eun Kim, Moon Young Kim, on behalf of The Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group	
PE-9	Prognostic Value of the HOPE-EVL Score for Mortality in Patients with Acute Esophageal Variceal Bleeding Treated with Endoscopic Variceal Ligation	834
	Chu Thi Thanh , Nguyen Cong Long	
PE-10	Diagnostic Performance of Raw versus Age-Education Adjusted QuickStroop for PHES-Defined Minimal Hepatic Encephalopathy in Cirrhosis	834
	Akash Roy , Utkarsh Bhattad, Shruti Keyal, Awanish Tewari, Nikhil Sonthalia, Sarthak Chakrabarti, Sourish Roy, Rajat Khandelwal, Anand Kulkarni, Uday Chand Ghoshal, Jasmohan Bajaj, Rajender Reddy, Mahesh Kumar Goenka	
PE-11	Spleen Stiffness Measurement vs Conventional Non-Invasive Markers as Predictors of Esophageal Varices in Advanced Chronic Liver Disease: A Multivariate Analysis	835
	Resha Dermawansyah Rusman , Muhammad Luthfi Parewangi, Nu'man AS Daud, Fardah Akil, Rini Bachtiar, Susanto Kusuma, Amelia Rifai	
PE-12	Portal Hypertensive Ischemic Enteropathy without Mesenteric Thrombosis: Reversible with TIPS Despite Extreme Hyperlactatemia	836
	I-Ji Jeong , Deok-Bog Moon, Eun-Kyoung Jwa, Sung Min Kim, Dae Hyeon Won	

6. HBV, Basic

PE-1	Identification of Aberrantly Expressed Genes in Hepatocellular Carcinoma Associated with Chronic Hepatitis Virus Infections: A Transcriptomic Analysis	837
	Saumya K. Patel , Daxa Parmar, Rakesh M. Rawal	
PE-2	Six Concurrent Layers of Effector Suppression in the Immune Tolerant Phase of Chronic Hepatitis B: A Tissue-Separated Single-Cell Transcriptomic Analysis	837
	Young Min Park	
PE-3	Deep Learning-Guided Discovery of the YKEFGAS Motif and AI-Assisted Capsid Assembly Modulator Design for Hepatitis B Virus	838
	Young Min Park	

7. HBV, Clinical

PE-1	HBsAg Quantification in CHB Patients Treated with ETV, TDF or TAF and Association with the Risk of HCC	839
	Yunmi Ko , Jung Hwan Yu, Young-Joo Jin, Jin-Woo Lee	
PE-2	Hepatitis D Virus Seroprevalence among HBsAg Positive Patients in a Major Australian Tertiary Referral Centre	840
	Saad Shams Bin Shaheen , Yinzhu Wang, Salim Maher, Anjla Devi, Asma Baig, Cameron Gofton	
PE-3	Sarcopenia Delays Early Virological Response but Does Not Affect Long-Term Prognosis in Patients with Chronic Hepatitis B and Liver Cirrhosis	840
	Chang Hun Lee , Yeonwoo Cha, Byung Chul Jin, Yun Chae Lee, Seung Young Seo, Seong Hun Kim, Sang Wook Kim, Seung Ok Lee, In Hee Kim	
PE-4	Comparison of Quantitative HBsAg Decline between Entecavir and Tenofovir Alafenamide in Patients with Chronic Hepatitis B	841
	Jungnam Lee , Young-Joo Jin	
PE-5	Longitudinal Renal Function Trajectories in Chronic Hepatitis B Patients on Anti-Viral Treatment: A Nationwide Population-Based Study in Korea	841
	Jae Hyun Yoon , Young Eun Seo, Sung Bum Cho, Jungkuk Lee	

8. HCV, Basic

PE-1	Molecular Epidemiology, Genotype Distribution, and Public Health Burden of Hepatitis C Virus in Nepal: A Review Promish Neupane , Asmita Ghimire ²	842
PE-2	Multimodal Artificial Intelligence for Prognostic Prediction in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis Rahmat Fauzan , Syafriyon, Derizal, Rahmat Fauzan	843

9. HCV, Clinical

PE-1	Hepatic Biochemical Abnormalities in Chronic Hepatitis C Patients: Insights from a Tertiary Hospital in Nepal Bindu Sen , Arun Bahadur Chand	843
PE-2	Real-World Effectiveness and Safety of 8-Week Glecaprevir/Pibrentasvir for Persons Who Inject Drugs and with Human Immunodeficiency Virus Infection Patients from Taiwan Nationwide HCV Registry Chung-Feng Huang, Te-Sheng Chang, Ching-Chu Lo, Chao-Hung Hung, Chienwei Huang, Lee-Won Chong, Pin-Nan Cheng, Ming-Lun Yeh, Cheng-Yuan Peng, Chien-Yu Cheng, Jee-Fu Huang, Ming-Jong Bair, Chih-Lang Lin, Chi-Chieh Yang, Hsing-Tao Kuo, Tsai-Yuan Hsieh, TzongHsi Lee, Pei-Lun Lee, Wenchiu Wu, Chih-Lin Lin, Wei-Wen Su, Sheng-Shun Yang, Chia-Chi Wang, Jui-Ting Hu, Lien-Ray Mo, Chun-Ting Chen, Yi-Hsiang Huang, Chun-Chao Chang, Chia-Sheng Huang, Guei-Ying Chen, Chien-Neng Kao, Chi-Ming Tai, Chun-Jen Liu, MeiHsuan Lee, Pei-Chien Tsai, Chia-Yen Dai, Jia-Horng Kao, Han-Chieh Lin, Wan-Long Chuang, Kuo-Chih Tseng, Chi-Yi Chen, Ming-Lung Yu	844
PE-3	Risk of Pancreatic Cancer between Hepatitis C and Non-Hepatitis C Cohorts in Korea, 2002-2024 Byung-Woo Kim , Yoon Park, Moran Ki	845
PE-4	Clinical Manifestations of Acute Hepatitis C Virus Infection with Syphilis Co-Infection B.Nomin, T. Bayarnyam , L. Purevsod, G. Khorolgarav, M. Oyungerel, V. Nyamtsengel	845

10. MASLD, Basic

PE-1	Dynamic Immune Landscape of NAFLD Highlights pDCs as Predictive Biomarkers for Disease Progression Shan Wang , Chaosi Qian, Siyuan Li, Chaowen Zheng	846
PE-2	Defective Mitochondria Trigger Hepatic Stellate Cell Transdifferentiation to Promote Liver Fibrosis Ji Su Han , Ja Hyun Koo	847
PE-3	Bile Acid Homeostasis Restoration by MK53 Peptide Ameliorate Metabolic-Associated Steatohepatitis in Experimental Models Yu-Ting Hsu , Hung-Yu Sun	847
PE-4	Liver Stiffness Impairs Hepatic Lipid Transport via Mechanorepression of LXRA in MASLD Na Young Lee , Ja Hyun Koo	847
PE-5	Zfp469 Deletion Attenuates Liver Fibrosis by Downregulating Extracellular Matrix Production in Hepatic Stellate Cells Nantawat Sattthawiwat , Chaiboot Ariyachet	848
PE-6	Gut Microbiota-Derived Nicotinamide Compounds Regulate Fatty Acid β -Oxidation and Inflammation in Metabolic Dysfunction-Associated Steatotic Liver Disease Su A Kim , Minsu Kim, Hyeonseung Oh, Suyeon Kim, Ki Tae Suk	849
PE-7	Strain-Specific Effects of Lactobacillus acidophilus Improve Hepatic and Microbial Dysregulation in MASLD and Diabetes Hee Jin Park , Su A Kim, Jeong Min Kim, Ho Yeong Yoon, Ki Tae Suk	849
PE-8	Hepatocellular NOX2 Aggravates Metabolic Dysfunction-Associated Steatotic Liver Disease by Disrupting Mitochondrial Homeostasis and Lipid Metabolic Process Ziyi Yang, Chao Sun	850
PE-9	Diagnostic Accuracy of Noninvasive Tests for Hepatic Steatosis in MASLD: An Umbrella Review Victor Juan Vera-Ponce , Jhosmer Ballena-Caicedo, Fiorella E. Zuzunaga Montoya	851
PE-10	SGK1 Inhibition Attenuates Liver Fibrosis by Suppressing Hepatic Stellate Cell Activation Hye-Young Seo , Ji Yeon Park, Jae Seok Hwang, Mi-Kyung Kim, Byoung Kuk Jang	852
PE-11	Maternal Obesity Induced Trained Immunity on the Development of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in Offspring Moonhyung Lee , Hyun Phil Shin	852

PE-12	Reversal of Hepatic Stellate Cell Activation Is Facilitated by Regression-Associated Hepatokine Myeung Gi Choi , Ja Hyun Koo	853

11. MASLD, Clinical

PE-1	Sedentary Behavior, Recreational Activity and Mortality Risk among US Adults with Metabolic Dysfunction Associated Steatotic Liver Disease: A Cohort Study Jiasuer Alifu , Fuad A. Abdu, Wenliang Che	853
PE-2	Association of Endothelial Activation with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Unraveling the Mediating Role of Hepatic Enzymes in a National Cohort Fuad A. Abdu , Jiasuer Alifu, Nuo Ma, Abdul-Quddus Mohammed, Tingting Shi, Lu Liu, Guoqing Yin, Wen Zhang, Wenliang Che	855
PE-3	Plasma Transcriptomic Signatures of Metabolic-Associated Steatotic Liver Disease across Egypt, Palestine and the United Arab Emirates: A Multi-Country Pilot Study Metwally Am , Al Sabbah H, Qasrawi R, Hafez W	856
PE-4	Risk-Associated and Clinically Informative Biomarkers for Cardiovascular Risk Stratification in Metabolic Dysfunction-Associated Steatotic Liver Disease Jiaxin Zhong , Yiwei Zhao, Huifen He, Yi Lan, Zixin Cai	856
PE-5	CT Attenuation-Based Hepatic Steatosis Assessment Using 3D Organ Segmentation: Impact of Tube Voltage and Need for Cutoff Adjustment Jeongin Yoo, Ijin Joo , Sun Kyung Jeon, Junghoan Park, Jeong Min Lee	857
PE-6	Association of PNPLA3/FTO Gene Polymorphisms with Hepatic Steatosis: Mongolian Subjects Yumchinsuren Tsedendorj , Dolgion Daramjav, Gantogtokh Dashjamts, Bolor Ulziitsogt, Chuluunbileg Batsaikhan, Tsogdulam Sumiyabazar, Tegshjargal Badamjav, Batbold Batsaikhan, Tulgaa Lonjid	858
PE-7	Prevalence and Risk Factors of Metabolic Dysfunction-Associated Steatotic Liver Disease among Adults with Hyperuricemia in Vietnam Linh Nguyen Thi Xuan , Le Anh Van, Can Thi Thanh Tam, Le Trung Hieu, Dao Duc Tien	858
PE-8	Evaluating the ZJU Index's Effectiveness in Predicting All-Cause Mortality among US Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease: A Comparative Analysis with Triglyceride-Glucose to Waist-to-Height Ratio Yiling Yang , Mingrong Huang, Xu Yao, Lü Muhan, Xiaowei Tang	859
PE-9	Comparison of Effectiveness between Phentermine/Topiramate and Liraglutide in Obese Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease Sung Jun Park, Yeonjung Ha, Joo Ho Lee, Kwan Sik Lee, Young Eun Chon	860
PE-10	Automated Staging of Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Using Deep Learning and Explainable AI Dalene Ephme Ben George	860
PE-11	From Gums to Liver: Association between Periodontal Health and Fatty Liver Risk among Metal-Exposed Industrial Workers Rahmath Meeral , Hemanth Kumar, Prathyusha Mahanta	861
PE-12	TyG Index as a Marker of Metabolic Liver Injury in Patients with Type 2 Diabetes Mellitus: A Cross Sectional Study Naufal Abdurrahman , Chairun Nisa' Nuraini, Nabila	862
PE-13	CT-Measured Waist Circumference as a Surrogate Marker of Histologic Disease Activity in Hepatic Steatosis Young Hyeon Ahn , Tom Ryu, Hyeyoung Kim, Sae Hwan Lee	862
PE-14	Hidden Burden of Metabolic Dysfunction-Associated Steatotic Liver Disease in Asymptomatic Adults: A Large Community-Based Screening Study from Rural Nepal Saroj Pokhrel , Milan Tiwari, Krishna Timilsina, Shankar Baral, Yam prasad Sharma	863
PE-15	Hepatic Steatosis Linked to Cancer Therapy in the Indian Population Amar Ranjan , Harshita Dubey, Beena Jad, Sathya V Merla, Kuldeep Meena, Soyeb Aftab, Sayak Biswas	864
PE-16	Clinical Trajectory and Predictors of Progression in Compensated Metabolic Dysfunction-Associated Steatohepatitis Lkhagvasuren Batbaatar , Nyam Biziya, Doljinsuren Enkhbayar, Oyundelger Munkhtuvshin	864
PE-17	Segmental Fatty Liver as a Diagnostic Clue for Primary Sclerosing Cholangitis Taehan Kim, Nae-Yun Heo , Seong Je Kim, Jun Seong Hwang	865

PE-18 Causal Forests Reveal Older Adults with MASLD and High Visceral Adiposity Deriving the Strongest Fibrosis Improvement after Structured Weight Loss 865
[Aminatus Saadah](#), Louis Widyatma Wibisana, Farah Miftakhul Ilfa, Deni Adam Sutiadi

PE-20 Night Shift Eating, Sleep Fragmentation, and Sarcopenic Obesity Accelerate Fibrotic MASLD in Older Adults With Multimorbidity 866
[Asniah Asniah Saadah](#), Anekawati, Novita Sari

PE-21 Impact of Metabolic Dysfunction Associated Steatotic Liver Disease on Hepatocellular Carcinoma Risk in Patients with Chronic Viral Hepatitis: A Nationwide Cohort Study 866
[Young Chang](#), Jinhye Cha, Hoyoung Na, Jooyeon Lee, Jimi Choi

PE-22 Association of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) with GERD Prevalence and Endoscopic Severity in Primary Care 867
Min Seong Kim

PE-23 Prevalence, Clinical Characteristics, and Liver Fibrosis Burden of MASLD in a Central European Population – Findings from the Białystok plus Study 868
[Karol Zmudka](#), Marlena Dubatówka, Ma ł gorzata Chlabicz, Pawe ł Sowa, Urszula Roszkowska, Damian Piotrowski, Karol Kamiński, Jerzy Jaroszewicz

PE-25 Small Vulnerable Newborns Have Higher Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Meta-Analysis 868
Noha Hammad

12. Others, Medical

PE-1 Albumin-Bilirubin Score for Predicting the Risk of Progression to End-Stage Liver Disease and All-Cause Mortality in Elderly Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease 869
Xuemei Ming

PE-2 Leveraging Decentralization, Integration, and Task-Shifting to Achieve Micro-Elimination of Hepatitis C among Prisoners in Northern India 870
[Ajeet Singh Bhadoria](#), Mehndiratta A, Gairola R, Somvanshi R, Jamil M, Luhmann N

PE-3 A Multifaceted Approach to Combat Liver Diseases: The Preventive Hepatology Initiative at AIIMS Rishikesh 870
[Ajeet Singh Bhadoria](#), Amrita Mehndiratta, Rohit Gupta, Meenu Singh, Samiran Nundy

PE-4 Impact of a National Transplant Coordination Program on Organ Donation Activity in Kazakhstan 871
[Zulkharnay Gaini](#), Zharikov Serik, Nurgaliyev Arslan

PE-5 The Influence of Limited Time Feeding on the mRNA Expression of the IL-6 Gene and CYP 11A1 Protein within the Cells of the Ileum Epithelium, Alongside the Rhythmic Dynamics of Gut Microbiota in Prediabetic States 872
[Qulsoom Naz](#), Kauser Usman, Baby Anjum

PE-6 Ethics of Interaction with Chinese Liver Transplantation 872
David Matas

PE-7 Humoral Immune Imbalance in Chronic Liver Disease after COVID-19 873
Diloram Musakhodjaeva

PE-8 A Rare Case of Acute Hepatitis E Virus Infection 873
[Munkh-Uyanga Erdenechuluun](#), Enkh-Amar Ayush, Dulguun Batdelger

PE-9 Health-Related Quality of Life and Associated Factors in Outpatients with Chronic Liver Disease: A Cross-Sectional Study at 108 Military Central Hospital 874
[Can Thi Thanh Tam](#), Le Trung Hieu, Le Anh Van

PE-10 Hidden Burden of Liver Diseases amongst Sanitation Staff of a Tertiary Care Institute in Northern India 874
[Pooja Bhadoria](#), Basavaraj Shankar Yankannavar, Aakash Sachdeva, Ramya T, Ram Kumar, Ravi Kant, Ajeet Singh Bhadoria

PE-11 Beta-2 Adrenergic Signaling Drives Early Hepatocyte Proliferation via TNFR2 and Neutrophil Recruitment 875
[Katherine Po Sin Chung](#), Kyurae Kim, Sung Eun Choi, Min Jeong Kim, Eunmi Lee, Kwang Woo Lee, Jihyo Byun, Jaewoo Oh, Jae Min Han, Jun Ho Byun, Won-Il Jeong

PE-12 Frailty and Sarcopenia Modify the Prognostic Impact of Liver Disease in Community-Dwelling Older Adults: A Prospective Cohort Study 876
[Jihye Lim](#), Sunghwan Ji, Tai Joon An, Yun-Hee Lee, Jun-Pyo Myong, Hyeon-Gi Jeon, Ha Il Kim, Hwa Jung Kim, Il-Young Jang

PE-13 Dietary Red Meat Consumption, Viral Hepatitis Status, and Serum Ferritin Levels: A Cross-Sectional Analysis 876
Khatanzul Ganbold

PE-14 Global, Regional, and National Burdens of Acute Viral Hepatitis in Adolescents and Young Adults Aged 15-39 Years from 2000 to 2021: A Trend Analysis 877
[Tao Li](#), Xianxiang Chen

PE-15 Time-Resolved Analysis of Early Hepatic Injury Responses Using Precision-Cut Liver Slices 877
[Da Young Lee](#), Ja Hyun Koo

PE-16 Evaluation of the Enzymatic Profile and Clinical Spectrum of Patients with Suspected Liver Disease Presenting to a Tertiary Care Center in Pokhara, Nepal 878
[Ganga Sagar Bhattarai](#), Dipendra Nath Poudel, Deependra Hamal

13. Liver Cancer, Basic

PE-1 The Mongolian Anomaly and the Southeast Asian Cluster: Mapping the 2022 Liver Cancer Epidemic across Asia 878
Ulil Albab Habibah

PE-2 A Novel Inhibitor Suppresses Hepatocellular Carcinoma Progression by Targeting sEV Secretion via the RBBP7/GLDC Pathway 879
[Claudia Wing Lam Tam](#), Samuel Wan Ki Wong, Sissi Yam Yuet Lam, Clive Yik Sum Chung, Judy Wai Ping Yam

PE-3 Proteomic Characterization of Integrin β4-Enriched Lung-Targeting Small Extracellular Vesicle-Corona Complex along Pulmonary Metastasis of Hepatocellular Carcinoma 879
[Tung Him Ng](#), Aijun Liang, Judy Wai Ping Yam

PE-4 Targeting Dickkopf-1 Unlocks Synergistic Antitumor Immunity with PD-L1 Blockade in Hepatocellular Carcinoma 880
Yuri Cho, Jin Sook Kim, Narae Jung, Sang Hyun Seo, Kyung Joo Cho, Hye Jung Park, Hyemi Kim, Jun Yong Park, Seung Up Kim

PE-5 Identification of a Metastasis-Associated snoRNA with Therapeutic Potential in Hepatocellular Carcinoma 880
[Geum Ok Baek](#), Hyung Seok Kim, Moon Gyeong Yoon, Hyun Sun Jung, Nayoung An, Soon Sun Kim, Jae Youn Cheong, Jung Woo Eun

PE-6 Kuan-Sin-Yin Enhances Anti-PD1 Efficacy in Hepatocellular Carcinoma by Promoting CD8+ T Cell Infiltration and Cytotoxic Function 881
[Shuoshuo Ma](#), Xiaolun Huang

PE-7 Circular RNA SCAP Regulates Genomic Stability and PARP Inhibitor Sensitivity in Hepatocellular Carcinoma via the let-7b-5p/RAD51C Axis 882
[Chaiyaboot Ariyachet](#), Archittapon Nokkeaw

PE-12 Epigenetic Regulation of Laminin-γ2 Monomer Promotes Metastatic Potential in Hepatocellular Carcinoma 882
[Nobuaki Funahashi](#), Ozora Ishikawa, Noa Tajitsu, Naohiko Koshikawa.

PE-13 Brown Adipose Tissue Activation Suppresses Hepatocellular Carcinoma via Metabolic Competition and PI3K/AKT/mTOR Inhibition 883
[Le Cui](#), Judy Wai Ping Yam

PE-14 The Effect of Exomeres on Cancer Stemness in Hepatocellular Carcinoma 883
[Jingyi Wang](#), JWP Yam

PE-15 Identification of Streptococcus Salivarius as a Novel Biomarker for Predicting and Enhancing PD-1 Responses in Hepatocellular Carcinoma 884
[Melody Yu Song Li](#), Xue Qian Wu, Terence Kin Wah Lee

PE-16 High Methionyl-tRNA Synthetase 1 Expression Is an Independent Predictor of Early Recurrence after Curative Resection in Hepatocellular Carcinoma 884
[Sung Hwan Yoo](#), Ji Hae Nahm, Jung Il Lee, Jin Hong Lim Hyun Woong Lee

PE-17 Integrated Proteomic and Transcriptomic Profiling of IL-4/IL-13–Conditioned Macrophage Secretome in Hepatocellular Carcinoma 885
[Sae-Bom Jeon](#), Aki Uesugi, Aejin Lee, Jiwon Hong, Jestlin Ng, Yunjin Go, Su Bin Lim

PE-18 Novel Copper(II) Complexes for Synergistic Tumor Immunotherapy via Cuproptosis, Apoptosis, and Chemodynamic Therapy 885
[Yu-Lan Li](#), Yuntao Bao, Zhiyong Lin, Wei Gao, Yonglian Zeng, Guandou Yuan, Songqing He

PE-19 Multiomics Profiling of Plasma and Buffy Coat Reveals Predictive Biomarkers for Immunotherapy Response in Hepatocellular Carcinoma 887
[Jiwon Hong](#), Su Bin Lim, Hyo Jung Cho

PE-20	Matrix Stiffness-Induced AGRIN in Exomere Promotes Angiogenesis to Drive Hepatocellular Carcinoma Charlotte Jiaqi Lai , Cherie Lot Sum Yeung, Le Cui, Tung Him Ng, Aijun Liang, Kwan Ming Ng, Judy Wai Ping Yam	887
PE-21	PLD1-Mediated PERK Signaling Promotes Hepatocellular Carcinoma Progression under Glucose DeprivationC Young Suk Kim , Hei Gwon Choi, Ha Neul Kim, Yugyeong Lee, Hyuk Soo Eun	888
PE-22	Regional Disparities in Liver Cancer Incidence in Mongolia: A Population-Based Analysis (2022–2024) Bayarmaa Nyamaa , Nyam Biziya, Oyundelger Munkhtuvshin, Doljinsuren Enkhbayar	888
PE-23	p53-Regulated tsRNA-6 Mediating DNA Homologous Recombination Repair Promotes Proliferation in HCC Cells Yan Li , Guanzi Chen, Lijuan Liao, Yusheng Jie, Songqing He, Wenli Xu	889
PE-24	An LTR Retrotransposon-Derived Microprotein PRMH1 Interacts with Rad51 to Promote Homologous Recombination Repair and Hepatocellular Carcinoma Progression Lijuan Liao , Qiuli Xie, Pengzhan Deng, Tingfeng Xu, Jie Zhang, Songqing He, Wenli Xu	889
PE-25	Citrullinated Fibrinogen as a Potential Biomarker in Hepatocellular Carcinoma: Development of Monoclonal Antibodies Byungki Jang , Ji-Won Park, Eun-Kyoung Choi, Sung-Eun Kim	890
PE-26	Integrated Proteomics and Metabolomics Analysis Reveals Molecular Signatures Associated with Liver Cancer in a Preclinical Model of Acute Hypoxia Stress Sanju Yadav , Rupinder Kalra, Narendra Kumar Sharma, Ved Prakash Diwedi, Jaswinder Singh Maras, Nasir Salam	890
PE-27	Does MBOAT7 rs641738 Polymorphism Influence Hepatocellular Carcinoma Susceptibility? A Meta-Analysis Md Abdullah Al Maruf	892
PE-28	Spatial Architecture of POSTN-Expressing Fibroblasts and T Cells Shapes an Aggressive Notch-Active Niche in Combined Hepatocellular Carcinoma and Cholangiocarcinoma Seokhwi Kim , Chan Mo Yang, Seung Yong Yoon, So Mi Heo, Jaehong Lim, Taebum Lee, Chang Ho Ahn	892
PE-29	Circulating MIR-184 and MIR-206 as Predictive Biomarkers for Early Recurrence in HBV-Related Hepatocellular Carcinoma: A Prospective Study Sang-Hoon Kim , Ki-Hun Kim, Eunyounng Tak, Ryunjin Lee	893
PE-30	Expression and Role of PD-L1 and SOX10 in Hepatocellular Carcinoma Jae Do Yang , Mi Rin Lee, Hee Chul Yu	894
PE-31	C1QC-High Macrophages Define an Immune-Interactive Tumor Microenvironment Associated with Immunotherapy Response In Advanced Hepatocellular Carcinoma Dooyeon Kim , Hye Ri Ahn, Sujin Kim, Soobeen Moon, Hui Gyeong Kim, Hyo Jung Cho	894
PE-32	Comparison of a Generative Artificial Intelligence Model and a Hepatobiliary Multidisciplinary Team Recommendations in the Management of Hepatocellular Carcinoma: A Retrospective Study Cristina Ciulli , Emanuele Scarpa, Pasquale Chiacchio, Alessandro Fogliati, Mauro Alessandro Scotti, Antonio Ciaccio, Antonio Rovere, Christian Cotsoglu, Rita Niespolo, Federica Elisei, Michele Pietro Aprigliano, Lorenzo Ripamonti, Mattia Garancini, Fabrizio Romano	894
PE-33	Identification of WDR54 as Novel Therapeutic Targets for Hepatocellular Carcinoma Won Jae Lee , Yujin Lee, Jun Seo Bae, Eunjeong Kim	895
PE-34	A Cancer-Associated Fibroblast Gene Signature Is Associated with Immune Microenvironment Features and Predicts Clinical Outcomes in Hepatocellular Carcinoma Hye Ri Ahn , Sujin Kim, Dooyeon Kim, Soobeen Moon, Hui Gyeong Kim, Hyo Jung Cho	896
PE-35	Atezolizumab and Bevacizumab Therapy Combined with Expanded NK Cells Significantly Prolongs Survival in Vivo Hepatocellular Carcinoma Model Sang Youn Hwang , Wan Jeon, Yu Su Park, Woo Chang Sohn	896
PE-36	Comparative Feasibility of Liquid Biopsy Modalities for Immunotherapy Biomarker Discovery in Hepatocellular Carcinoma: Focus on Exosomal miRNA Yoonseok Lee	897
PE-38	AMBRA1 Inhibits Hepatocellular Carcinoma Progression and Cancer Stemness by Regulating Nucleocytoplasmic Transport Yimiao He , Man Tong	898
PE-39	INPP5B Regulates Lipid Metabolism and Cancer Stemness in Hepatocellular Carcinoma Linglin Liu , Man Tong	898
PE-40	An Investigation of GPATCH4 as a Potential Oncogene in Hepatocellular Carcinoma Jun Seo Bae , Yujin Lee, Wonjae Lee, Eunjeong Kim	899

14. Liver Cancer, Clinical

PE-1	Association of Tumor Location with Therapeutic Outcomes after Radical Resection for Hepatocellular Carcinoma: A Retrospective Study Yongshuang Lv	899
PE-2	Early-Onset Liver Cancer Burden in Southeast Asia: Sex-Specific and Nutrition-Related Patterns from the Global Burden of Disease Study Zavia Putri Salsabila , Zulfania Rahmah	900
PE-3	Prognostic Impact of Acute-on-Chronic Liver Failure in Hepatocellular Carcinoma with Acute Decompensation Hyeon Uk Kwon , Jae Eun Kim, Ji Yoon Kwak, Ji Hee Han, Hankyu Jeon, Jung Woo Choi, Ra Ra Cha, Jae Min Lee, Hyun Jin Kim, Sang Soo Lee	900
PE-4	Impact of Transitional-Phase Parenchymal Signal Intensity on LI-RADS Performance in Hepatocellular Carcinoma Yong Jun Jung , Seong Hyeon Cho ² , Subin Heo, Sang Hyun Choi	901
PE-5	Unveiling Heterogeneous Sex Effects on Hepatocellular Carcinoma Survival: A Machine Learning-Based Individualized Analysis Using a Nationwide Registry Ji Won Han , Do Seon Song	902
PE-6	Sex Disparities in Hepatocellular Carcinoma: Epidemiologic Insights into Stage-Driven Survival and Treatment Inequality from a Nationwide Cohort Ji Won Han , Do Seon Song	903
PE-7	Cytokeratin 19 Expression Stratifies Outcomes with Hepatic Arterial Infusion Chemotherapy but Not Atezolizumab plus Bevacizumab in Advanced Hepatocellular Carcinoma Kwon Yong Tak , Keungmo Yang, Hee Sun Choi, Ji Won Han, Suho Kim, Jung Suk Oh, Jeong Won Jang, Pil Soo Sung	903
PE-8	Gaps in Essential Diagnostics for Early Detection of Hepatocellular Carcinoma in India Sahil Arora , Pooja Gupta	904
PE-9	Malignant Transformation of Infantile Hepatic Hemangioma to Angiosarcoma in a Four-Year Old Male Anmol Anmol , Vikrant Sood, Seema Alam, Rajeev Khanna, Bikrant B Lal	905
PE-10	A New Machine Learning-Based Algorithm to Identify Patients with Hepatocellular Carcinoma Silvia Cagnin , Giulia Lorenzoni, Davide Stefanelli, Pietro Guerra, Alessandra Biasiolo, Dario Gregori, Patrizia Pontisso, Andrea Martini	906
PE-11	Advanced Hepatocellular Carcinoma Achieving Complete Response to Atezolizumab and Bevacizumab: A Report of Two Cases Hoa Nguyen , Thang Tran	906
PE-12	Impact of SGLT2 Inhibitors on Liver-Related Outcomes in Patients with Type 2 Diabetes and Viral Hepatitis: A Korean Nationwide Cohort Study Seong Hee Kang , Ji-Mi Choi, Hyung Joon Yim ¹ , Young Kul Jung, Sun Young Yim, Young-Sun Lee, Yeon Seok Seo, Ji Hoon Kim, Jong Eun Yeon	907
PE-14	Real-World Effectiveness of Atezolizumab plus Bevacizumab in High-Risk Unresectable Hepatocellular Carcinoma: A Multicenter Propensity Score-Matched Cohort Study Young Eun Seo , Chan Joong Bae, Won Jae, Sun Young Chun, Jun Sik Yoon, Yanghyun Baek, Yeo Wool Kang, Woo Sun Rou, Jung Eun Song, Joonho Jeong, Won Young Tak, Yu Rim Lee, Soo Young Park, Young Mi Hong, Sang Youn Hwang, Hyun Chin Cho, Hyun Young Woo, Jeong Heo, Jae Hyun Yoon, Sung-Bum Cho	907
PE-15	Prognostic Stratification in Real-World Patients with Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab Young Eun Seo , Chan Joong Bae, Won Jae, Sun Young Chun, Jun Sik Yoon, Yanghyun Baek, Yeo Wool Kang, Woo Sun Rou, Jung Eun Song, Joonho Jeong, Won Young Tak, Yu Rim Lee, Soo Young Park, Young Mi Hong, Sang Youn Hwang, Hyun Chin Cho, Hyun Young Woo, Jeong Heo, Jae Hyun Yoon, Sung-Bum Cho	908
PE-16	Efficacy and Safety of Hepatic Arterial Infusion Chemotherapy Sequential Therapy versus Atezolizumab and Bevacizumab in the First Line Treatment of Infiltrative Hepatocellular Carcinoma with Portal Vein Thrombosis: A Cohort Study with Propensity Score Matching Young Eun Seo , Chan joong Bae, Sang Hwa Song, Yang Seok Koh, Chan Park, In Woo Choi, Jae-Uk Jeong, Jae Hyun Yoon, Ki-Hyun Kim, Wan-sik Lee, Young-Eun Joo, Eun Myung, Sung Bum Cho	909
PE-17	Targeted Therapy Reversing Malignant Biliary Obstruction in Advanced Hepatocellular Carcinoma: A Mechanistic Clinical Observation Challenging the Bilirubin Contraindication Threshold for Lenvatinib Amr Aly Abdelmoety, Abdelrahman Zakaria , Aly Soliman, Soad Zaki, Hoda Abdelmoety	909

PE-18	SeeLiver+: A Multi-Marker LC-MS/MS Platform for Improved Early HCC Detection and Liver Disease Stratification Hyojin Kim , Wonseok Oh, Juri Park, Saeyoung Lee, Won Suk Yang, Soon Sun Kim, Jae Youn Cheong, Je-Hyun Baek	910
PE-19	Clonorchis sinensis Infection and Preoperative Treatment Status: Influence on Recurrence and Survival after Curative Resection of Hepatocellular Carcinoma Yin Fan , Yongheng Zhou, Yingjian Wei, Zhongshun Liu,Guandou Yuan, Songqing He, Linfeng Mao	911
PE-20	Comparison of Treatment Efficacy and Safety Profile of Atezolizumab plus Bevacizumab in BCLC B and C Patients with Hepatocellular Carcinoma Sun Young Chun, Yeo Wool Kang, Jung Eun Song, Joonho Jeong, Yu Rim Lee, Jun Sik Yoon, Young Mi Hong, Sang Youn Hwang, Hyun Young Woo, Soo Young Park, Yanghyun Baek, Jeong Heo, Won Young Tak, Young Eun Seo,Sung-Bum Cho, Jae Hyun Yoon	911
PE-21	Comparative Efficacy and Safety of Subsequent Systemic Therapies Following Lenvatinib or Sorafenib Failure in HCC: A Meta-Survival Analysis Han Ah Lee , Moon Haeng Hur, Yuri Cho, Byeong Geun Song, Young Chang, Young-Sun Lee, Minjong Lee, Mi Na Kim, Eun Sun Jang, Soon Sun Kim, Do Seon Song, Su Jong Yu, Hyung-Don Kim, Hyung Joon Kim, Haeryoung Kim, Miyoung Choi, Do Young Kim, Joon Hyeok Lee, Bo Hyun Kim, Ju Hyun Shim	912
PE-22	Surgery for Hepatocellular Carcinoma Patients with Portal Vein Main Trunk Thrombosis (VP4): Initial Experience of a Single Center Giang Nguyen , Trong Nguyen, Hung Nguyen	913
PE-23	Surgical Outcomes and Adherence to Quality Performance Indicators of Hepatectomy for Hepatocellular Carcinoma from the Up-Philippine General Hospital CancerSurg Study Ivi Patrice Torres , Dante Ang, Marie Carmela Lapitan	913
PE-24	Risk Factors and Prognosis of Primary Curative Hepatectomy in Hepatocellular Carcinoma Patients Hieu Banh , Song Huy Nguyen-Dinh	913
PE-25	Intrahepatic Cholangiocarcinoma in Cirrhotic versus Non-Cirrhotic Patients: Clinicopathologic, MRI, and Prognostic Features Dong Hwan Kim , Yong Jun Jung, Sang Hyun Choi	914
PE-26	Development and Validation of a Dynamic Prognostic Nomogram for Conditional Survival in Hepatocellular Carcinoma: An Analysis from the Korea Liver Cancer Registry Jae Hyun Kwon , Eun-Kyoung Jwa, Jong Woo Lee, Eunyoungh Tak, Shin Hwang, Korean Liver Cancer Study Group	915
PE-28	Combination of Radiotherapy and Durvalumab/Gemcitabine/Cisplatin Therapy Improve Survival in Biliary Tract Cancer (Especially Extrahepatic Bile Duct Cancer) Patients Sang Youn Hwang , Jung Woo Im, Ki Jung Jeon, Hyung Jun Kim, Beom Jin Shin, Wan Jeon	915
PE-29	Pretreatment Neutrophil-to-Lymphocyte Ratio as a Predictive Marker for Tumor Response to Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma: A Multicenter Retrospective Study Young Mi Hong , Jun Sik Yoon, Yu Rim Lee, Jae Hyun Yoon, Hyun Young Woo, Sang Youn Hwang, Yeo Wool Kang, Joonho Jeong, Sung-Bum Cho, Jung Eun Song	916
PE-30	Transarterial Radioembolization versus Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis Gun Ha Kim , In Joon Lee, Hyo-Cheol Kim, Dongho Hyun	916
PE-31	Improving Early Detection of Hepatocellular Carcinoma in the Modern Era: Evidence from a Population Registry Indri Purnamasari	917
PE-32	Entecavir versus Tenofovir for Tertiary Prophylaxis in HBV-Related Hepatocellular Carcinoma: Evidence from a Nationwide Cohort Chang Wook Park , Gwang Hyeon Choi, Min Kyung Park, Eun Sun Jang, Jin-Wook Kim, Sook-Hyang Jeong	918
PE-34	Serum Proteomic Biomarkers for Predicting Immunotherapy and Targeted Therapy Response in Advanced Hepatocellular Carcinoma Eunho Choi , Maryam Adelipour, Hyojin Hwang, Jeongkwon Kim, Young-Sun Lee, Ji Hoon Kim	918
PE-35	A Novel Prognostic Model Integrating the ASAP Score and Neutrophil-to-Lymphocyte Ratio in Advanced Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab: A Multicenter Cohort Study Jeayeon Park , Ji Won Han, Pil Soo Sung, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Yoon Jun Kim, Jung-Hwan Yoon, Jeong Won Jang, Do Seon Song, Su Jong Yu	919

15. Liver Transplantation

PE-1	Use of Bariatric Surgery in Liver Donors before Surgery Gani Kuttymuratov, Bikhanov Nurzhan , Alatayev Bagdat, Suleimenov Timur, Tzoi Dimitri	919
PE-2	Construction of an Imaging-Omics Machine Learning Prediction Model for Post-Liver Transplantation Recurrence of Liver Cancer Based on ECV Xiaoyong Ye , Lin Zhou, Qiang He	920
PE-3	The Fibrinogen-to-Albumin Ratio (FAR) Predicts Prognosis in Hepatocellular Carcinoma Patients after Liver Transplantation: Development and Validation of a Novel Nomogram Kexin Wang , Xiaoyong Ye, Zhili Ji	921
PE-4	Pediatric Liver Transplantation: Experience of a Single Center Sultan Murat , Dastan Rustemov, Ruslan Utebaliev, Arailym Assainova, Erken Kakenov	922
PE-5	Splenic Artery Embolization Modulates Portal Hemodynamics and Improves Cytopenia after Living Donor Liver Transplantation Arslan Nurgaliyev , Myltykbay Rysmakhanov, Akhmet Seidakhmetov	922
PE-6	Impact of Portal Vein Thrombosis on Waitlist and Post-Transplant Survival in Patients with End-Stage Liver Disease Seidakhmetova Nazerke , Rysmakhanov Myltykbay, Nurgaliyev Arslan	923
PE-7	Impact of Adult Living Donor Liver Transplantation on Waitlist Mortality in Kazakhstan Zulkharnay Aidar , Nurgaliyeva Aigerim, Zharikov Serik	923
PE-8	A Novel Inflammatory and Nutrition-Based Risk Score for Predicting Overall Survival in Hepatocellular Carcinoma Patients after Liver Transplantation Guang Jia , Xiaoyong Ye, Zhili Ji ²	924
PE-9	Liver Graft Rejection after Liver Transplantation in Kazakhstan: A Single-Center Experience Malika Khassenova , Lyazzat Nur, Marzhan Zhanasbayeva	925
PE-10	Turning Perfusate into Prognosis: AI-Enabled Real-Time Prediction of Early Liver Allograft Dysfunction Surendar Arulalan , Gayathri Saravnan	925
PE-11	Intravenous Fetal Renal Stem Cell Therapy Is Associated With Reduction of Urinary Microalbumin in Post–Liver Transplant Nephropathy: A Prospective Pilot Study Nurbek Ilyasov , Akhmet Seidakhmetov,Gaini Zulkharnay, Olga Ulyanova, Ainur Doszhan	926
PE-12	Integrative Machine Learning-Based Prediction of Primary Cilia Biomarkers to Mitigate Biliary Complications in Liver Transplant Patients Anindya Amanda Damayanti	926
PE-13	Management of Hepatic Hydrothorax in Cirrhosis: A Single-Center Experience in Patients Awaiting Liver Transplantation Yerlan Nurgaliyev , Akhmet Seidakhmetov, Nurbek Ilyasov, Myltykbay Rysmakhanov, Aidos Kulmaganbetov, Aibolat Smagulov	927
PE-17	A Comprehensive Clinical Evaluation of Early Graft Function, Survival, and Postoperative Complications in Liver Transplantation Manvendra Singh	927
PE-18	ABO-Incompatible Living Donor Liver Retransplantation in a Pediatric Patient with Graft Failure due to Recurrent Progressive Familial Intrahepatic Cholestasis Jaryung Han , Young Seok Han	928
PE-19	Split Liver Transplantation: Two Adults Recipients Jaryung Han , Young Seok Han	928
PE-20	Exosomes from Chemically Derived Hepatic Progenitor Cells Protect Against Liver Ischemia Reperfusion Injury Kidus Haile Yemaneberhan , Minseok Kang, A-Reum Kim, Soraya Salas-Silva, Shin Ji Hyun, Kyeong Sik Kim, Dongho Choi	929
PE-21	Liver Transplantation beyond Milan Criteria after Successful Downstaging for Hepatocellular Carcinoma: Early Experience from a Developing Transplant Center Cheon-Soo Park	929
PE-22	Short-Course Maribavir as a Rapid Salvage Option in Preemptive CMV Management after Liver Transplantation: A Case Series Study Min Kyoung Kim , Gayoung Kim, Sang Hyuk Park, Minseob Kim, Jae-Yoon Kim, Su Young Hong, Suk Kyun Hong, Youngrok Choi, Kwang-Woong Lee	930

PE-23	Clinical Impact of Early Postoperative Tacrolimus Levels on Rejection and Biliary Complications in ABO-Incompatible Living Donor Liver Transplantation: A Comparative Study	930
	Sehyeon Yu , Hye-Sung Jo, Sumin Jeon, Yoo Jin Choi, Young-Dong Yu, Dong-Sik Kim	
PE-24	Chinese-Style Modified Piggyback Liver Transplantation	931
	Xiaolong Miao , Jinzhen Cai, Yong Zhang, Xin Wang, Bin Wu, Yandong Sun, Yang Xin, Hui Zhang	
PE-25	Prognostic Impact of COVID-19 Infection After Liver Transplantation: A Multicenter Analysis using the KOTRY Database	931
	Youngju Ryu , Eunjin Lee, Hayeon Do, Jiyoung Baik, Suk Min Gwon, Namkee Oh, Jinsoo Rhu, Gyu-Seong Choi, Jongman Kim	
PE-26	Clinical Value of Inflammatory Indexes in Predicting Post-Transplantation Prognosis in Hepatocellular Carcinoma	932
	Han-xuan Wang , Xiao-yong Ye, Ren Lang	
PE-27	External Validation and Clinical Refinement of the SNAPP Score for Predicting Hepatocellular Carcinoma Recurrence after Living Donor Liver Transplantation	932
	Rak-Kyun Oh , Seok-Hwan Kim	
PE-28	Diagnostic Performance of Non-Invasive Steatosis Assessment Tools in Living Liver Donors	933
	Byeong-Gon Na , Shin Hwang, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Woo-Hyoung Kang, Sang Hoon Kim, Sung-Min Kim, Hyo Jung Ko, Minha Choi, Dae Hyeon Won, Sung-Gyu Lee	
PE-29	Poor Outcomes of Living-Donor Liver Transplantation Using Grafts with a Graft-To-Recipient Weight Ratio below 0.7: A Large-Single Center Cohort Study	933
	Sang-Hoon Kim , Deok-Bog Moon, Sung-Gyu Lee, Shin Hwang, Ki-Hun Kim Kim	
PE-30	GRWR 0.7% Is a Safe Threshold in Standard Living Donor Liver Transplantation: Outcome Analysis of 2,506 Cases	934
	Selvakumar Naganathan	

16. Biliary and Pancreatic Surgery

PE-1	Aging Shapes Immunosuppressive Niches in Gallbladder Cancer	934
	Lei Kong , Shengxin Gu, Mingyang Wang, Xiaoling Song, Jun Gu	
PE-2	Spatial Fibroblast–NK Crosstalk Drives Immunosuppressive Niches in Gallbladder Cancer	935
	Lei Kong , Shengxin Gu, Mingyang Wang, Xiaoling Song, Jun Gu	
PE-3	Pylorus Resecting Pancreatoduodenectomy with or without Feeding Jejunostomy- A Randomized Controlled Trial	935
	Vaibhav Varshney , Kaushal Rathore, Raghav Nayar, Ankit Rai	
PE-4	Outcomes of Reinforcement Patch around Pancreaticojejunostomy on Clinically Relevant Pancreatic Fistula after Pancreatoduodenectomy- A Randomized Controlled Trial	936
	Vaibhav Kumar Varshney , Shaikh Muna Afroz	
PE-5	Safety and Outcomes of Laparoscopic Echinococcectomy for Hepatic Hydatid Cysts: A 10-Year Single-Center Experience	937
	Aikorkem Sadykova , Aidos Kulmaganbetov, Aibolat Smagulov, Aidar Zulkharnay	
PE-6	En Bloc Right Hepatic Trisectionectomy with Total Caudate Lobectomy and Portal Vein Resection for Hilar Cholangiocarcinoma: A Non-Touch Technique	937
	Tuan Hiep Luong , Thanh Khiem Nguyen, Ham Hoi Nguyen, Van Duy Le, Dinh Toi Do, Viet Anh Do	
PE-7	Clinical Significance of a Key Tumor Suppressor Gene as a Prognostic and Translational Biomarker in Periapillary Adenocarcinoma	938
	Asgar Ali , Sadhana Sharma, Sundeep Singh Saluja	
PE-8	Total Laparoscopic Radical Antegrade Modular Pancreato-Splenectomy with Left-Posterior Artery First-Approach for Distal Pancreatic Cancer: Step-by-Step Technique	939
	Van Duy Le , Hiep Luong Tuan, Khiem Nguyen Thanh, Hoi Nguyen Ham	
PE-9	Laparoscopic Total Pancreatectomy with En Bloc Total Mesopancreas Dissection Using a Tail-First, Counterclockwise Approach	940
	Khiem Nguyen Thanh , Van Duy Le, Tuan Hiep Luong	
PE-12	Liver Capsule as a Preferable Site for Xenogeneic Islet Cell Implantation in Experimental Diabetes	940
	Nodirjon Ruzimurodov , Tamara Aripova, Tohir Askarov	
PE-13	Intraoperative and Early Postoperative Complications After 2,645 Laparoscopic Cholecystectomies: A 15-Year Single-Center Experience	941
	Aidos Kulmaganbetov , Aibolat Smagulov, Zhalgas Yerzhanov	

PE-14	Hepatic Function Optimization in Malignant Obstructive Jaundice	941
	Pulatbek Mannobjonov , Robiya Keldiyorova	
PE-15	Laparoscopic Left-Sided Hepatectomy Guided by Dilated Bile Ducts as Anatomical Landmarks for Hepatolithiasis: A Single-Center Preliminary Study	942
	LE Trung Hieu , LE Anh Van, VU Van Quang, LE Van Thanh	
PE-17	The Role of the Family in Supporting Gallstone Prevention through Dietary Compliance and Family-Based Education: Literature Review	943
	Rahmat Fauzan , Putri Ayu	
PE-20	Diagnostic Relevance of Neutrophil Gelatinase-Associated Lipocalin in Cholangiocarcinoma and Biliary Tract Cancers among Elderly Patients	943
	Pardeep Kumar , Ankush Kumar, Sagar Verma	
PE-21	Early Prediction of Severe Acute Pancreatitis Using Initial Inflammatory Biomarkers: A Simple and Effective Risk Stratification Model	944
	Thu LTH , Dinh Anh Nguyet, Le Quoc Tuan, Le Thi Hoang Yen	
PE-22	Bile Mycobiome Diversity Classifies Fungal Peptide Signature for Early Prediction of Gallbladder Carcinoma	944
	Sanju Yadav , Nupur Sharma, Manisha Yadav, Neha Sharma, Gaurav Tripathi, Sushmita Pandey, Babu Mathew, Vasundhra Bindal, Vipul Sharma, Vinayendra Pamecha ² , Jaswinder Singh Maras	
PE-23	How We Perform Laparoscopic Total Pancreatectomy: Tail-First Mobilization, Counterclockwise Total Mesopancreas Dissection	945
	Van Duy Le , Khiem Nguyen Thanh, Hoi Nguyen Ham, Hiep Luong Tuan	
PE-24	Estimated Time Frame for Malignant Progression of High-Grade Dysplasia in the Ampulla of Vater: Three Clinical Cases	946
	Myeong Hun Oh , Hyung Il Seo	
PE-25	Modeling Pancreatic Cancer Initiation Using Normal Human Pancreatic Organoids with Crispr-Induced TP53 Loss	946
	Eden Demere Amare , Soraya Salas-Silva, Miji Kim, Hyungsung Kim, Yun Kyung Jung, Ji Hyun Shin, Dongho Choi	
PE-26	Impact of Sarcopenia on Surgical Outcomes in Patients Undergoing Pancreaticoduodenectomy (PD): A Tertiary Care Center Experience in Odisha- India	947
	Swamy Rajesh Hudugur	
PE-27	Afferent Loop Decompression and Outcomes after Pancreaticoduodenectomy: A Prospective Cohort with Propensity Matched Controls	947
	Swamy Rajesh Hudugur	
PE-28	Review of Multivariate Logistic Regression Analysis of Serum CA 19-9 and Hematological Profiles in Distinguishing Pancreatic Malignancy from Chronic Pancreatitis	948
	Devi Yulia Rahmi	
PE-30	Computational Analysis of BMI SDS as a Predictive Marker For Choledocholithiasis : A Literature Review	948
	Muhammad Irzaq	
PE-31	Incidence, Predictive Factors and Post-Operative Outcomes of Patients Undergoing Pancreatoduodenectomy for Non-Pancreatic Periapillary Cancer with Para-Aortic Lymph Node Metastases	949
	Gnaneshvar Manivannan, Raj Kumar Nagarajan , Kalayarasan Raja	
PE-32	From Hands to Ports: A Comparative Outcome Analysis of Minimally Invasive and Open Distal/Central Pancreatectomy	949
	Rishav Kumar , Kush S Parikh	
PE-34	Early Surgery vs. Delayed Surgery in Chronic Pancreatitis: Does Timing Influence the Outcomes?: A Comprehensive Analysis of Clinical Outcomes from a Tertiary Care Center, India	950
	Swamy Rajesh Hudugur	
PE-35	Precision Medicine Approaches to Chronic Pancreatitis: Integrating Machine Learning with Clinical Data for Early Detection of Disease Progression	950
	Rara Yulianda , Rani Marsyanda	
PE-36	Clinico-Pathological Profile, Surgical Outcome and Survival Analysis after Pancreaticoduodenectomy: 7-Year Experience from Tertiary Care Teaching Hospital in Odisha	951
	Swamy Rajesh Hudugur	
PE-37	Hepatobiliary Tuberculosis Presenting with Biliary Tree Alterations: A Case Report and Literature Review	951
	Quoc Dang	

PE-38

A Machine Learning–Driven Model for Predicting Biliary Drainage Success in Malignant Biliary Obstruction Using Endoscopic Ultrasound Data

Roland Helmizar

952

PE-39

Early Detection and Resectability in Pancreatic Head Adenocarcinoma: A Contemporary Overview

Abdelali Guellil

952

PE-40

Improving Outcomes in Bile Duct Injuries: A Contemporary Surgical Perspective

Abdelali Guellil

952

PE-41

Multimodal Strategy in Duodenum-Preserving Pancreatic Head Resection for an Inflammatory Pancreatic Head Tumor

Omira Abdulbasit, Faisal Romancap, Rocelyn Santos, Ameerah Mantawil, Brent Andrew Viray

953

PE-42

Hepatobiliary Outcomes in the Era of GLP-1 Therapy: Insights from a Large Randomized Evidence Base

Hendrianus Hendrianus, Steven Herbert, Stevan Cuy, Irwan Deputra Hamdani

953

PE-43

Laparoscopic En-Bloc Lymphadenectomy for Biliary Malignancies

Shiming Yi, Yong Wei, Haitao Wang, Zuobin Cheng, Yu Cheng

954

PE-44

Near-Infrared Fluorescence Cholangiography Using Indocyanine Green in Laparoscopic Choecystectomy: A Meta-Analysis of Visualization Rates and Complications

Mohamed Hamouda Elkasaby, Mohamed Sherif Ali Ahmed, Atef A. Hassan

955

PE-45

Long-Term Outcomes of Endobiliary Radiofrequency Ablation plus Stenting in Malignant Biliary Obstruction: A Patient-Level Meta-Analysis of Randomized Trials

Mohamed Hamouda Elkasaby, Mohamed Sherif Ali Ahmed, Atef A. Hassan

955

PE-46

Assessment of G10 Intraoperative Scoring System for Conversion in Patients Undergoing Laparoscopic Cholecystectomy: A Cross-Sectional Study from Nepal

Suman Baral, Anand Bhattarai

956

17. Liver Surgery

PE-1

Analysis of the Correlation between Surgical Team Coordination Quality and Perioperative Complications in Laparoscopic Anatomical Hepatectomy and Development of a Risk Prediction Model

Shihao Yang

956

PE-2

The Impact of Bariatric Surgery on the Development of Liver Fibrosis: A Single-Center Experience

Murat Sultan, Bikhanov Nurzhan, Alatayev Bagdat, Suleimenov Timur

957

PE-3

Impact of Bariatric Surgery on the Development of Liver Fibrosis

Bikhanov Nurzhan, Kuttymuratov Gani, Alatayev Bagdat, Suleimenov Timur, Tzoi Dimitri

957

PE-5

In Vivo Monitoring of Hepatic Ischemia Using a Dual-Enzyme Activated Near-Infrared Fluorescence Probe

Hoseo Lee, Ja Hyun Koo

958

PE-6

Laparoscopic Anatomical Left Hepatectomy Guided by the Dilated Bile Duct and Middle Hepatic Vein for Hepaticolithiasis in a Patient with Situs Inversus Totalis: How I Do It

LE Trung Hieu, LE Anh Van, VU Van Quang, LE Van Thanh

958

PE-7

Deep Learning–Based Prognostic Prediction in Hepatocellular Carcinoma: Implications for Minimally Invasive Liver Surgery

Zavia Putri Salsabila, Zulfania Rahmah, Violetta Meitrie Sugianto

959

PE-9

Digital and Intelligent Liver Surgery: A Systematic Review of Precision, Visualization, and Decision-Support Technologies

Hilmi Ardian Sudiarto, Nadira Putriana

960

PE-10

Early Diagnosis of Liver Impairment Based on Biochemical Markers: A Random Forest Predictive Modeling Approach

Rani Marsyanda

961

PE-11

Introducing Robot-Assisted Liver Resection in a Single-Surgeon Program: A Team-Based Approach and Early Outcomes

Ikumi Hamano

961

PE-13

Diaphragmatic Hernia after Living Donor Hepatectomy: Clinical Burden, Risk Factors, and Exploratory Biomarker Associations

Byeong-Gon Na, Shin Hwang, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Woo-Hyoung Kang, Sang Hoon Kim, Sung-Min Kim, Hyo Jung Ko, Minha Choi, Dae Hyeon Won, Sung-Gyu Lee

962

18. Others, Surgical

PE-5

Management Patterns and Outcomes of Liver Abscess in a Tertiary Care Center: Experience from 108 Patients

Maanasa Bhaskar Raj Kumar, Raj Kumar Nagarajan, Theakarajan Rajendiran, Gnaneshvar Manivannan

962

PE-6

Mapping Cellular Proportion Shifts Using Imaging Biomarkers to Develop a Cell Composition-Based Staging System That Informs Actionable Surgical and Device Guidelines for the Prevention of POPF

Siddharthan Rajagopal

963

PE-7

A Case Report: Intraoperative Discovery of a Left-Sided Gallbladder: The Role of Preoperative Imaging

Elizabeth Catameo, Crisostomo Arcilla

963

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PG COURSE 1

**Metabolic Dysfunction-Associated
Steatotic Liver Disease (MASLD),
Viral Hepatitis (HBV, HCV, HDV, HEV),
Primary Biliary Cholangitis, and
Autoimmune Hepatitis**

Chairs

Moon Seok Choi (Sungkyunkwan Univ.)

Yoon Jun Kim (Seoul National Univ.)



**Han Ah Lee***Chung-Ang University*

Self Introduction

2018	Ph.D. in Korea University
2016-2017	Clinical Fellow in Hepatology (Korea University Anam Hospital)
2018-2020	Clinical Assistant Professor in Hepatology (Korea University Anam Hospital)
2022-2023	Clinical Assistant Professor in Hepatology (Ewha Womans University Mokdong Hospital)
2024-	Assistant Professor in Hepatology (Chung-Ang University Hospital)

Research Interests

Metabolic Dysfunction-Associated Steatotic Liver Disease, Hepatitis B Virus

Representative Publications

1. Metabolic Dysfunction-Associated Steatotic Liver Disease and Risk of Cardiovascular Disease: A Nationwide Cohort Study (Gut. 2024)
2. Effects of Intermittent Calorie Restriction in Nondiabetic Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease. (Clin Gastroenterol Hepatol. 2025)
3. Cardiovascular Risk from Metabolic Dysfunction-Associated Steatotic Liver Disease, Cardiometabolic Risk Factor Count, and Their Longitudinal Changes: A Nationwide Cohort Study. (Am J Gastroenterol. 2024)
4. A Machine Learning Model to Predict Liver-Related Outcomes after the Functional Cure of Chronic Hepatitis B. (J Hepatol. 2025)
5. Identification of Patients with Favorable Prognosis after Resection in Intermediate-Stage Hepatocellular Carcinoma. (Int J Surg. 2024)

Practical Use of GLP-1 Receptor Agonists in MASLD: Dosing, Patient Counseling, and Safety Considerations

Han Ah Lee*Chung-Ang University*

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), are now the most prevalent chronic liver disorders worldwide, driven by the rising global burden of obesity and type 2 diabetes mellitus (T2DM). Beyond hepatic outcomes, patients with MASLD carry a substantially increased risk of cardiovascular mortality, T2DM, and chronic kidney disease, underscoring the need for therapies that address the entire cardiometabolic continuum. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a central pharmacologic strategy in this context. The recent accelerated approval of semaglutide for biopsy-confirmed MASH with stage F2–F3 fibrosis, based on the ESSENCE trial, has formally established a GLP-1 RA as a disease-modifying therapy for MASLD, complementing the thyroid hormone receptor- β agonist resmetirom.

1. Mechanism and Clinical Evidence in MASLD

GLP-1 RAs exert pleiotropic metabolic effects relevant to MASLD, including glucose-dependent insulinotropic action, delayed gastric emptying, central appetite suppression, and substantial weight reduction. Their hepatic benefits are predominantly indirect, mediated through improvement in insulin resistance, reduction in visceral and hepatic adiposity, and attenuation of lipotoxicity. In the phase 3 ESSENCE trial, once-weekly semaglutide 2.4 mg administered for 72 weeks achieved both co-primary endpoints — MASH resolution without worsening of fibrosis, and fibrosis improvement of ≥ 1 stage without worsening of MASH — in patients with biopsy-confirmed MASH and F2–F3 fibrosis. Liraglutide and dulaglutide have also demonstrated favorable effects on hepatic steatosis and aminotransferases in earlier phase 2 studies, although without histologic endpoints sufficient for regulatory approval. Importantly, GLP-1 RAs also confer well-established cardiovascular and renal benefits in patients with T2DM and obesity, making them particularly attractive in the MASLD population, where cardiovascular disease is the leading cause of death.

Beyond pure GLP-1 RAs, the dual GIP/GLP-1 receptor agonist tirzepatide has also shown compelling activity in MASH. In the phase 2 SYNERGY-NASH trial, 52 weeks of once-weekly tirzepatide (5, 10, or 15 mg) achieved MASH resolution without worsening of fibrosis in 44–62% of patients versus 10% with

placebo, with a dose-dependent benefit on fibrosis improvement. Although tirzepatide is not currently approved for MASH and a phase 3 confirmatory trial is ongoing, these findings position incretin-based combination receptor agonism as a particularly promising therapeutic axis in MASLD.

2. Patient Selection and Dosing Considerations

In current practice, GLP-1 RAs are most appropriately considered for patients with MASLD who have coexisting T2DM, obesity (BMI ≥ 30 kg/m², or ≥ 27 kg/m² with metabolic comorbidities), or biopsy- or non-invasively confirmed MASH with significant fibrosis (F2–F3). Patients with compensated cirrhosis (F4) were not included in the pivotal MASH trials, and therefore use in this population should be individualized.

Semaglutide is initiated subcutaneously at 0.25 mg once weekly, with a stepwise dose escalation every 4 weeks (0.5 mg → 1.0 mg → 1.7 mg → 2.4 mg) to mitigate gastrointestinal adverse effects. For patients in whom MASH is the principal indication, the target maintenance dose is 2.4 mg weekly, as used in ESSENCE. When tolerability is limiting, a slower titration schedule (e.g., maintaining each step for 6–8 weeks) is reasonable. For patients with concomitant T2DM, semaglutide may be initiated as part of glucose-lowering therapy at the standard 0.5–1.0 mg weekly range and uptitrated to 2.4 mg if MASH-directed therapy is desired.

Tirzepatide, currently approved for T2DM and obesity but not for MASH, may also be considered off-label for MASLD patients with these comorbidities, initiated at 2.5 mg weekly with stepwise escalation every 4 weeks toward a target of 10–15 mg weekly based on tolerability and therapeutic goal.

3. Patient Counseling: Setting Expectations and Supporting Adherence

Effective patient counseling is essential to maximize the benefit of GLP-1 RA therapy. Three key domains should be addressed before initiation. First, expected benefits should be clearly communicated: progressive weight loss of approximately 10–15% of baseline body weight over 12 months, improvement in glycemic control, and a meaningful probability of MASH resolution and fibrosis regression with sustained treatment. Patients should understand that hepatic improvement typically requires at least 12 months of therapy and is dependent on adequate dose and adherence. Second, gastrointestinal symptoms — nausea, early satiety, dyspepsia, constipation, and occasional vomiting — are common during dose escalation but generally transient. Patients should be advised to eat smaller meals, avoid high-fat or excessively large portions, and remain well hydrated. Third, lifestyle modification remains foundational; GLP-1 RA therapy should be framed as complementary to, not a substitute for, dietary modification, physical activity, and reduction in alcohol consumption. Patients should also be counseled on injection technique, storage requirements, and the importance of consistent weekly dosing.

4. Safety Considerations and Monitoring

GLP-1 RAs are generally well tolerated, but several safety considerations warrant attention. Gastrointes-

tinal adverse effects are the most common cause of discontinuation; structured titration and proactive counseling substantially reduce this risk. Acute pancreatitis remains a labeled warning, although population-based data have not demonstrated a clear causal association; the agent should nonetheless be discontinued if pancreatitis is suspected and should not be re-initiated in patients with a history of pancreatitis. Cholelithiasis and cholecystitis occur at a modestly increased rate, particularly in the context of rapid weight loss. GLP-1 RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. The risk of hypoglycemia is low in monotherapy but increases when used in combination with sulfonylureas or insulin, necessitating dose reduction of these agents at initiation. Recent reports have also highlighted concerns regarding delayed gastric emptying in the perioperative setting; current guidance suggests withholding weekly GLP-1 RAs for at least one week before elective procedures requiring general anesthesia.

Recommended monitoring during therapy includes assessment of body weight, glycemic parameters, and tolerability at each visit; periodic measurement of liver enzymes, lipid profile, and renal function; and reassessment of liver fibrosis using non-invasive tests (e.g., FIB-4, VCTE, or MRE) approximately every 6–12 months to evaluate hepatic treatment response. Discontinuation should be considered in cases of intolerable adverse effects, suspected pancreatitis, planned pregnancy, or absence of meaningful clinical response after an adequate treatment duration.

5. Conclusion

The approval of semaglutide for MASH marks a paradigm shift in MASLD management, positioning GLP-1 RAs at the intersection of hepatology, endocrinology, and cardiovascular medicine, while emerging evidence with dual GIP/GLP-1 receptor agonists such as tirzepatide signals a rapidly expanding incretin-based therapeutic landscape. Successful implementation in routine practice requires individualized patient selection, careful dose titration, anticipatory counseling regarding gastrointestinal symptoms and realistic outcome expectations, and structured longitudinal monitoring of both metabolic and hepatic endpoints. When applied within this framework, GLP-1 RAs offer not only meaningful hepatic benefit but also broader cardiometabolic protection in a patient population at substantial systemic risk.

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Self Introduction

Education

1995	M.D., College of Medicine, Seoul National University, Seoul, Korea
2000	MS.c., in Internal Medicine, Graduate School, Seoul National University, Seoul, Korea
2002	Ph.D., in Internal Medicine, Graduate School, Seoul National University, Seoul, Korea

Professional Experience

1995.03-1996.02	Internship, Seoul National University Hospital
1996.03-2000.02	Residency, Internal Medicine in Seoul National University Hospital
2000.03-2002.02	Fellowship, Hepatology in Seoul National University Hospital
2006.04-2007.05	Visiting Scholar, MGH, Harvard Medical School
2002.03-Present	Professor, Internal Medicine in Ilsan Paik Hospital Inje University

Academic Activities

Chairperson of Clinical Practice Guidelines Committee of KASL for the Management of Autoimmune Hepatitis 2022

Research Interests

Autoimmune Liver Disease, Viral Hepatitis

Representative Publications

1. Kim. KA. Transient elastography for assessing liver fibrosis in autoimmune liver diseases: Excellent performance but limited details: Editorial on “Diagnostic accuracy of vibration-controlled transient elastography for staging liver fibrosis in autoimmune liver diseases: A systematic review and meta-analysis”. Clin Mol Hepatol 2025;31-275-276.
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Autoimmune Liver Diseases: Autoimmune Hepatitis and Primary Biliary Cholangitis in Clinical Practice

Kyung-Ah Kim Inje University

Autoimmune Hepatitis (AIH) is a chronic immune-mediated liver disease presenting across a broad spectrum of clinical presentations, ranging from asymptomatic elevation of liver enzymes to acute hepatitis, acute liver failure, chronic hepatitis, and established cirrhosis. It can affect individuals of any age, sex, and ethnicity.

Diagnosis is based on a composite assessment of clinical, biochemical, serological, and histological features. Key diagnostic features include characteristic autoantibodies, elevated serum immunoglobulin G levels, and liver histology demonstrating interface hepatitis with lymphoplasmacytic infiltration. Validated scoring systems provide additional support in diagnostically challenging cases.

First-line treatment consists of glucocorticoids combined with azathioprine, which effectively induces and maintains remission in the majority of patients. In those intolerant of or refractory to standard therapy, mycophenolate mofetil represents the preferred alternative. Long-term management requires careful monitoring for both disease activity and treatment-related complications, including osteoporosis, diabetes mellitus, and neutropenia. Early diagnosis and timely initiation of therapy are essential to prevent disease progression and improve long-term outcomes.

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease characterized by the progressive destruction of small intrahepatic bile ducts. While it predominantly affects middle-aged women, it can occur across a wide age range and in both sexes. The clinical presentation varies from asymptomatic cholestatic liver enzyme abnormalities to fatigue, pruritus, and, in advanced stages, cirrhosis and its complications.

Diagnosis is established based on a combination of biochemical, serological, and histological findings. Hallmark features include persistent elevation of alkaline phosphatase, the presence of antimitochondrial antibodies, and characteristic histology demonstrating chronic nonsuppurative cholangitis and bile duct loss. Liver biopsy is generally unnecessary but may be warranted in atypical presentations or when overlap with other autoimmune liver diseases is suspected.

Ursodeoxycholic acid remains the cornerstone of therapy, with demonstrated benefits in biochemical response and transplant-free survival. Patients with an inadequate response should be considered for

second-line agents, including elafibranor, seladelpar, or off-label fibrates. Long-term management focuses on monitoring disease progression and addressing complications such as osteoporosis, fat-soluble vitamin deficiency, and portal hypertension. Symptom-directed treatment, particularly for pruritus and fatigue, is also essential for improving quality of life. Early diagnosis and risk stratification are critical for optimizing outcomes and guiding individualized management strategies.

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Self Introduction

Education

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Postgraduate Career

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전)대한간학회 전산위원회

전)2022 APASL 조직위원회

Research Interests

Viral Hepatitis, MASLD, HCC

Representative Publications

1. Liver Stiffness Measurements After Oral Antivirals Effectively Predict the Risk of HCC in Patients With Chronic Hepatitis C. *J Gastroenterol Hepatol.* 2025 Oct;40(10):2568-2579. Yu Rim Lee¹, Hyun Young Woo², Young Oh Kweon³, Won Young Tak³, Se Young Jang³, Jung Gil Park⁴, Min Kyu Kang⁴, Jeong Eun Song⁵, Byoung Kuk Jang⁶, Changhyeong Lee⁵, Byung Seok Kim⁵, Jae Seok Hwang⁶, Woo Jin Chung⁶, Jeong Heo², Nae-Yun Heo⁷, Seung Ha Park⁷, Jun Sik Yoon⁸, Joonho Jeong⁹, Sang Gyu Kwak¹⁰, Yeowool Kang¹¹, Yang Hyun Baek¹¹, Soo Young Park³.
2. Long-Term Hepatic and Extrahepatic Outcomes of Chronic Hepatitis C Patients After Sofosbuvir-Based Treatment (LONGHEAD Study). *Infect Dis Ther* 2025 May;14(5):1089-1101. Chung-Feng Huang^{#1}, Jeong Heo^{#2}, Rong-Nan Chien³, Yang-Hyun Baek⁴, Jia-Horng Kao⁵, Ju-Hyun Kim⁶, Ting-Tsung Chang⁷, Kwan-Soo Byun⁸, Jyh-Jou Chen⁹, Sook-Hyang Jeong¹⁰, Tsung-Hui Hu¹¹, Young-Seok Kim¹², Cheng-Yuan Peng¹³, Won-Young Tak¹⁴, Horng-Yuan Wang¹⁵, Seung-Kew Yoon¹⁶, I-Shyan Sheen³, Youn-Jae Lee¹⁷, Yu-Chun Hsu¹⁸, Hyung-Joon Yim¹⁹, Pei-Chien Tsai¹, Ming-Lun Yeh¹, Sang-Hoon Ahn²⁰, Chia-Yen Dai¹, Seung-Woon Paik²¹, Jee-Fu Huang¹, Yoon-Jun Kim²², Wan-Long Chuang¹, Young-Suk Lim²³, Ming-Lung Yu²⁴.
3. Associations between non-insulin-based insulin resistance surrogate markers and liver-related outcomes in metabolic dysfunction-associated steatotic liver disease: a nationwide cohort study in South Korea. *BMC Gastroenterol* 2025 Apr 18;25(1):274. Sang Yi Moon^{#1,2}, Minkook Son^{#3,4}, Yeo Wool Kang⁵, Myeongseok Koh⁵, Jong Yoon Lee⁵, Yang Hyun Baek⁶.
4. Metabolic Dysfunction-Associated Steatotic Liver Disease, Alcohol Consumption, and the Risk of Atrial Fibrillation: A Nationwide Population-Based Study. *J Am Heart Assoc* 2025 Jul 15;14(14):e042003. Minkwan Kim¹, Minkook Son^{2,3}, Sang Yi Moon^{3,4}, Yang Hyun Baek⁴.
5. Impact of gastrectomy on the risk of alcohol-associated liver disease in patients with gastric cancer. *Sci Rep* 2026 Feb 17;16(1):9453. Sang Yi Moon^{#1,2}, Yang Hyun Baek^{#1,3,4}, Dongwoo Kang⁵, Jungkuk Lee⁵, Yeo Wool Kang¹, Minkook Son^{2,6}, Hongqun Liu³, Samuel S Lee^{7,8}, Junho Park^{9,10,11}

Optimizing HCV Management in Real-World Practice

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Introduction

The introduction of direct-acting antiviral (DAA) therapy has significantly improved the management of chronic hepatitis C virus (HCV) infection, enabling sustained virologic response (SVR) rates of over 95% in the majority of patient groups. However, in real-world practice, treatment outcomes are influenced by a broader spectrum of clinical scenarios than those typically represented in clinical trials. These include advanced liver disease, comorbidities, renal impairment, hepatocellular carcinoma (HCC), viral coinfections and prior treatment failure. Optimizing HCV care therefore requires individualized strategies informed by real-world evidence and evolving clinical experience.

Pretreatment Assessment in Real-World Practice

Pretreatment evaluation is essential to optimize treatment outcomes and ensure safety in real-world HCV management. Beyond confirming active HCV infection, clinicians should assess disease severity, comorbid conditions, and factors influencing reinfection risk or treatment response.

General Clinical Evaluation and Treatment Considerations

A detailed review of the patient's current medications is required to identify potential drug–drug interactions (DDIs) with DAAs. Concomitant use of agents such as statins, antiarrhythmics, anticonvulsants, immunosuppressants, and antiretroviral drugs may necessitate dose adjustment or selection of alternative antiviral regimens.¹ Use of validated drug–interaction tools is recommended to minimize clinically significant DDIs.

Special clinical conditions, including the presence of HCC and pregnancy, should be assessed prior to treatment initiation. These conditions may influence both the timing and selection of therapy, as well as overall treatment goals.

Liver Disease Severity and Fibrosis Assessment

The severity of liver disease is a key determinant of prognosis, treatment strategy, and need for post-treatment surveillance. Evaluation of hepatic fibrosis stage is essential to identify patients at risk for complications such as HCC and to guide long-term follow-up strategies.

Liver fibrosis can be assessed using noninvasive methods, including serum biomarker panels and tran-

sient elastography, which are now widely preferred due to their safety and accessibility.² Although liver biopsy remains the reference standard, its use has declined significantly given the high efficacy of DAAs and the limitations associated with invasive procedures.

Importantly, distinguishing compensated from decompensated cirrhosis is critical. Decompensated cirrhosis, defined by complications such as ascites, variceal bleeding, hepatic encephalopathy, or jaundice, requires specialized management and often referral to a liver transplant center. In these patients, treatment decisions should be individualized based on residual liver function and transplant eligibility.^{3,4}

Screening for Viral Coinfections and Hepatitis B Status

All patients initiating DAA therapy should undergo comprehensive hepatitis B virus (HBV) serologic screening, including HBsAg, anti-HBc, and anti-HBs, to determine current or prior HBV infection. This is essential due to the well-documented risk of HBV reactivation during or after DAA treatment.⁵⁻⁷ Appropriate monitoring or prophylactic antiviral therapy should be considered based on serologic status.

Screening for HIV coinfection is also necessary, as coinfecting patients require careful evaluation of potential drug–drug interactions with antiretroviral therapy.^{8,9}

Risk of Reinfection

Assessment of reinfection risk is an important component of pretreatment evaluation and post-cure counseling. High-risk populations include individuals with ongoing intravenous drug use, patients undergoing hemodialysis, those with a history of unsafe medical or invasive procedures, and persons with HIV coinfection.^{10,11} These groups require targeted harm-reduction strategies and long-term surveillance to prevent reinfection and maintain treatment success.

Comorbid Conditions Affecting Liver Disease

Comorbid liver conditions should be carefully assessed, as they may influence both disease progression and treatment outcomes. These include MASLD, alcohol-related liver disease, other chronic hepatopathies and chronic kidney disease (CKD).¹²⁻¹⁴

Assessment of MASLD is recommended, as it may persist after viral eradication and remains an independent risk factor for HCC.

Alcohol consumption in particular remains a significant modifiable risk factor that accelerates fibrosis progression and increases the risk of hepatic complications.

Although routine screening for autoimmune hepatitis is not universally recommended, clinicians should consider evaluation in patients with suggestive biochemical or clinical features. HCV infection may coexist with autoimmune phenomena, and distinguishing between chronic viral hepatitis and AIH overlap is important in atypical or treatment-refractory cases.

Estimated glomerular filtration rate should be assessed to guide regimen selection, although most

modern DAAs are safe even in severe renal impairment.¹⁵⁻¹⁷

Pregnancy and Special Populations

The presence of pregnancy must be identified prior to initiating antiviral therapy, as treatment decisions should be individualized due to evolving evidence regarding the safety of DAAs during gestation. In general, HCV management in pregnancy requires careful risk–benefit assessment and consideration of vertical transmission risk.¹⁸

Patients with a history of HCC or awaiting liver transplantation require individualized timing of antiviral therapy.^{19,20}

History of Prior DAA Exposure

Identification of previous treatment failure is essential for selecting appropriate retreatment regimens.^{21,22}

Treatment Strategy

Antiviral therapy should be offered to all patients with acute or chronic hepatitis C who do not have contraindications to treatment.¹ The evolution of pangenotypic DAAs has enabled a simplified treatment approach in most HCV-infected patients. Current real-world practice increasingly favors short-duration, once daily oral regimens with minimal monitoring requirements.

In treatment-naïve patients without cirrhosis or with compensated cirrhosis, a simplified treatment strategy using either sofosbuvir/velpatasvir for 12 weeks or glecaprevir/pibrentasvir for 8 weeks is recommended, regardless of genotype.^{1,23}

The simplified treatment strategy is not recommended for patients with prior HCV treatment experience, HBV co-infection, compensated cirrhosis with end stage renal disease (ESRD), decompensated cirrhosis (Child–Pugh score ≥7), pregnancy, suspected or confirmed HCC, or a history of liver transplantation.

Table 1. Simplified HCV treatment strategies¹

Subjects for simplified HCV treatment		Exclusion*
Indication	Adults with HCV infection (any genotype) who meet both of the following: 1) No prior HCV treatment 2) No cirrhosis or compensated cirrhosis (Child–Pugh class A)	1) Prior HCV treatment 2) Hepatitis B virus coinfection 3) Compensated cirrhosis with end-stage renal disease (eGFR<30 mL/min/1.73 m ²) 4) Current or prior decompensated cirrhosis (Child–Pugh score ≥7) 5) Pregnancy 6) Hepatocellular carcinoma 7) Liver transplantation recipient
Drugs	Sofosbuvir/velpatasvir 1 tablet once daily for 12 weeks or glecaprevir/pibrentasvir 3 tablets once daily for 8 weeks	

Retreatment of DAA Failures

Although first line DAA regimens are highly effective, treatment failure still occurs in a minority of patients, particularly in those with prior exposure to NS5A inhibitors or protease inhibitors. Retreatment strategies have been well explored in real-world cohorts. The fixed combination of sofosbuvir/velpatasvir/voxilaprevir has demonstrated high efficacy in patients previously failing sofosbuvir- or protease inhibitor-based therapies, including glecaprevir/pibrentasvir regimens.²¹ Salvage regimens have shown SVR rates comparable to treatment-naïve populations, highlighting the importance of selecting potent, multiclass antiviral combinations in the retreatment setting.²²

In more complex cases, individualized approaches including prolonged therapy duration or addition of ribavirin have been explored. Case-based evidence suggests that even multidrug resistant infections can be successfully managed with extended or sequential DAA strategies.^{24,25} These findings underscore the need for resistance aware retreatment planning in patients with prior DAA exposure.

Retreatment following Sofosbuvir-Based Treatment Failure¹

- Patients with HCV GT 1,2,4,5 or 6 without cirrhosis or with compensated cirrhosis
 - 1) Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (A1)
 - 2) Glecaprevir/pibrentasvir for 16 weeks in patients without prior exposure to NS5A inhibitors or NS3/4A protease inhibitors (A1)
- Patients with HCV GT 3 with or without compensated cirrhosis
 - 1) Patients without cirrhosis : sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (A1)
 - 2) Patients with cirrhosis : sofosbuvir/velpatasvir/voxilaprevir + weight-based ribavirin for 12 weeks (C2) (if, contraindications or experience poor tolerance to use of ribavirin : may be trated with sofosbuvir/velpatasvir/voxilaprevir for 24 weeks)
- Decompensated patients with HCV GT 1-6 infection
 - : sofosbuvir/velpatasvir + weight-based ribavirin for 24 weeks (C2)

Retreatment following Glecaprevir/Pibrentasvir Treatment Failure

- Patients with HCV GT 1-6, with or without compensated cirrhosis
 - 1) Patients without cirrhosis : sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (B1)
 - 2) HCV GT 3 or cirrhosis
 - : sofosbuvir/velpatasvir/voxilaprevir + weight-based ribavirin for 12 weeks
 - : sofosbuvir/velpatasvir/voxilaprevir alone for 24 weeks if ribavirin is contraindicated or poorly tolerated (C2)
 - 3) SOF + GLE/PIB + weight-based RBV for 16 weeks (B1)

Retreatment following Failure of Multiple DAA Regimens

- Patients with HCV GT 1-6 with or without compensated cirrhosis

- 1) Sofosbuvir/velpatasvir/voxilaprevir + weight-based ribavirin for 24 weeks (B1)
 - 2) Glecaprevir/pibrentasvir + sofosbuvir & weight-based ribavirin for 16 weeks (B1)
- Patients with cirrhosis and GT 3 or prior failure with glecaprevir/pibrentasvir + sofosbuvir
 - : extending treatment to 24 weeks (B1)

Treatment in Special Populations

Decompensated Cirrhosis

Patients with decompensated cirrhosis represent a particularly vulnerable population. Real world studies have confirmed that DAA therapy is generally safe and can lead to meaningful improvements in hepatic function, although outcomes depend strongly on baseline disease severity.^{3,26} Regimens such as sofosbuvir/velpatasvir with or without ribavirin have demonstrated efficacy in improving virologic and clinical outcomes in patients with Child-Pugh B or C cirrhosis.^{4,27} However, some individuals in advanced disease continue to progress despite achieving SVR, indicating that antiviral therapy should be initiated before irreversible hepatic decompensation occurs. Large cohort studies have consistently shown that earlier treatment initiation is associated with better survival and liver-related outcomes.^{3,28}

Renal Impairment

CKD and ESRD are common comorbidities in HCV infected patients. Historically, treatment options were limited due to concerns regarding drug accumulation and toxicity. However, modern DAA regimens, particularly glecaprevir/pibrentasvir, have demonstrated excellent safety and efficacy in patients with severe renal impairments, including those on dialysis.¹⁷ Sofosbuvir-based regimens, once avoided in advanced CKD, are now supported by accumulating evidence showing no clinically significant deterioration in renal function in most patients.^{15,16}

HCC

The relationship between DAA therapy and HCC remains an important clinical consideration. Early observational studies raised concerns regarding potential increased recurrence of HCC after viral eradication.²⁹ However, subsequent large multicenter studies and meta-analysse have not confirmed a consistent increase in recurrence risk and instead suggest improved overall survival following successful antiviral therapy.^{30,31}

HBV Coinfection

A critical issue in HBV/HCV coinfection is hepatitis B reactivation during or after DAA therapy. Meta-analyses have demonstrated a measurable risk of HBV reactivation, particularly in HBsAg-positive patients not receiving prophylactic antiviral therapy.⁵⁻⁷ Accordingly, screening for HBV infection and appropriate prophylaxis or monitoring are essential components of HCV treatment protocols.

Conclusion

Optimizing HCV management in real world practice requires integration of simplified antiviral strategies with individualized patient assessment. While pangenotypic DAAs have significantly reduced treatment complexity, clinical consideration remains substantial, particularly in patients with advanced liver disease, renal impairment, coinfections, or prior treatment failure.

A structured approach encompassing epidemiologic awareness, systematic pretreatment evaluation, simplified but stratified treatment selection and appropriate use of modern antiviral agents allows clinicians to achieve high cure rates across diverse patient populations. Continued accumulation of real-world evidence will further refine treatment algorithms and support the global goal of HCV elimination.

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Self Introduction

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Research Interests

- HBV Direct Oncogenic Potential and Integration into the Host Genome
- Genomic Alterations and Biomarker Discovery in Liver Diseases and Hepatocarcinogenesis
- Optimized Patient Management and Risk Stratification in Chronic Liver Diseases

Representative Publications

1. Nam H, Kim DY, Jang JW. Development and validation of a risk prediction model for patients with hepatocellular carcinoma receiving atezolizumab-bevacizumab. *Hepatology* 2026;83:1098-1110. (Corresponding Author)
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HBV-HDV Coinfection: Diagnosis, Natural Course, and Clinical Pitfalls

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Hepatitis D virus (HDV), also known as hepatitis delta virus, is a defective single-stranded circular RNA virus that requires hepatitis B surface antigen (HBsAg) provided by hepatitis B virus (HBV) for viral entry, assembly, and secretion. Because of this unique dependence on HBV, HDV infection occurs only as HBV-HDV coinfection or as superinfection in individuals with pre-existing chronic HBV infection. HDV belongs to the Deltavirus genus within the Kolmioviridae family, and 8 genotypes have been identified. Its distinctive virologic features and similarities to plant viroids have led HDV to be considered an “enigmatic” or “neglected” virus.

Globally, HDV infection is estimated to affect approximately 12–72 million people, although the true prevalence remains uncertain because of marked geographic heterogeneity and inconsistent screening practices. Higher prevalence rates have been reported in Central Asia, Eastern Europe, and parts of Africa. Current discrepancies in prevalence estimates likely reflect differences in anti-HDV testing coverage, reflex HDV RNA confirmation, and regional epidemiologic variation. Despite its clinical significance, only 20–50% of infected individuals are believed to have been diagnosed, largely due to limited awareness and insufficient implementation of routine HDV testing in HBsAg-positive patients.

HDV is transmitted through exposure to infected blood and body fluids, similarly to HBV. In low- and middle-income countries, major routes of transmission include contaminated needles, unsterilized medical equipment, and sharing of contaminated household items such as toothbrushes. In developed countries, approximately 70% of newly acquired HDV infections are associated with injection drug use and high-risk sexual behavior.

Clinically, chronic hepatitis D is considered the most severe form of chronic viral hepatitis. Acute HBV-HDV coinfection results in spontaneous clearance of both viruses in approximately 95% of cases, whereas HDV superinfection in patients with chronic HBV infection progresses to chronic HDV infection in more than 90% of patients. Compared with HBV monoinfection, HDV infection is associated with significantly more rapid progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related mortality. At diagnosis, 30–70% of patients already have cirrhosis, and up to 70% may progress to cirrhosis within 5–10 years. More than half of affected patients may die from liver-related complications within 10 years of diagnosis. Detectable HDV RNA is associated

with particularly high risks of compensated cirrhosis, decompensation, HCC, and LT. Nevertheless, recent studies suggest that disease progression may be heterogeneous, and some patients may experience a relatively indolent clinical course.

Prevention of HDV infection primarily relies on prevention of HBV infection. HBV vaccination effectively prevents HDV infection by eliminating susceptibility to HBV; however, no vaccine is currently available to protect individuals who are already HBsAg-positive from HDV superinfection.

Therapeutic options for chronic hepatitis D remain limited. Conventional HBV nucleos(t)ide analogues such as entecavir and tenofovir are ineffective against HDV replication. Pegylated interferon alfa (Peg-IFN α) remains the standard therapy in most countries and can suppress HDV replication while reducing liver-related events, including hepatic decompensation, HCC, LT, and mortality. Reported annual rates of liver-related events decrease from approximately 8.5% to 3.3% during interferon-based therapy. However, treatment efficacy is modest, relapse is common, and adverse effects—including fatigue, depression, and bone marrow suppression—frequently limit treatment tolerability. Peg-IFN α is also contraindicated in patients with hepatic decompensation.

Novel HDV-specific therapies are now emerging. Bulevirtide (BLV), an entry inhibitor that blocks the sodium taurocholate cotransporting polypeptide (NTCP) receptor on hepatocytes, prevents HDV entry into hepatocytes and has recently been approved in Europe for treatment of chronic hepatitis D. Phase 3 studies demonstrated virologic and biochemical response rates of up to 56% after 96 weeks of BLV monotherapy. Combination therapy with BLV and Peg-IFN has been associated with a greater HDV RNA decline and higher sustained virologic response when compared to either monotherapy alone. However, the optimal duration for BLV treatment, alone or in combination with PEG-IFN, remains undetermined. In addition, the patient populations most likely to benefit from combination therapy with BLV and Peg-IFN (de novo, add-on, or sequential approaches) have yet to be clearly defined.

In summary, HDV infection represents the most aggressive form of chronic viral hepatitis, characterized by accelerated progression to cirrhosis, liver failure, and HCC compared with HBV monoinfection. Despite its substantial clinical burden, HDV remains underdiagnosed and undertreated worldwide. Standardized anti-HDV screening and reflex HDV RNA testing in HBsAg-positive individuals are essential for early diagnosis and linkage to care, while development of more effective and tolerable therapies remains a major unmet need.

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PG COURSE 2

Hepatocellular Carcinoma (HCC), Portal Hypertension, and Alcohol-Related Liver Disease

Chairs
Young Seok Kim (Soonchunhyang Univ.)
Jin-Woo Lee (Inha Univ.)





Seung Up Kim
Yonsei University

Self Introduction

Prof. Seung Up Kim is a member of Korean Association of the Study of the Liver and Korean Liver Cancer Study Group. He has more than 300 SCI(E) original, peer reviewed publications as primary or corresponding author. He acted as an Editor-in-Chief of Clinical and Molecular Hepatology from 2019 to 2013 and impact factor increased from 4 to 14. He also acts as an Associate Editor of Journal of Gastroenterology and Hepatology, an Editorial Board of Clinical Gastroenterology and Hepatology, and an Academic Editor of PLoS One, Clinical and Translational Hepatology, and International Journal of Molecular Science. He is an invited referee for more than 20 SCI(E) journals including Lancet Gastroenterology and Hepatology, Gastroenterology, Hepatology, Journal of Hepatology, Gut, etc.

Research Interests

His Major Research Interests Include Metabolic Associated Steatotic Liver Disease, Sarcopenia, Viral Hepatitis, Liver Fibrosis, Liver Cirrhosis, and Liver Cancer.

Representative Publications

1. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. Lin H, Lee HW, Yip TC, Tsochatzis E, Petta S, Bugianesi E, Yoneda M, Zheng MH, Hagström H, Boursier J, Calleja JL, Goh GB, Chan WK, Gallego-Durán R, Sanyal AJ, de Lédinghen V, Newsome PN, Fan JG, Castéra L, Lai M, Harrison SA, Fournier-Poizat C, Wong GL, Pennisi G, Armandi A, Nakajima A, Liu WY, Shang Y, de Saint-Loup M, Llop E, Teh KK, Lara-Romero C, Asgharpour A, Mahgoub S, Chan MS, Canivet CM, Romero-Gomez M, Kim SU, Wong VW; VCTE-Prognosis Study Group. JAMA. 2024 Apr 16;331(15):1287-1297. doi: 10.1001/jama.2024.1447.

2. Prognostic performance of the two-step clinical care pathway in metabolic dysfunction-associated steatotic liver disease. Yip TC, Lee HW, Lin H, Tsochatzis E, Petta S, Bugianesi E, Yoneda M, Zheng MH, Hagström H, Boursier J, Calleja JL, Goh GB, Chan WK, Gallego-Durán R, Sanyal AJ, de Lédinghen V, Newsome PN, Fan JG, Castéra L, Lai M, Fournier-Poizat C, Wong GL, Pennisi G, Armandi A, Nakajima A, Liu WY, Shang Y, de Saint-Loup M, Llop E, Teh KK, Lara-Romero C, Asgharpour A, Mahgoub S, Chan MS, Canivet CM, Romero-Gomez M, Kim SU, Wong VW. J Hepatol. 2025 Jan 23:S0168-8278(25)00021-2. doi: 10.1016/j.jhep.2025.01.014.

3. AI-Safe-C score: Assessing liver-related event risks in patients without cirrhosis after successful direct-acting antiviral treatment. Lin H, Cheuk-Fung Yip T, Lee HW, Meng X, Che-To Lai J, Ahn SH, Pang W, Lai-Hung Wong G, Zeng L, Wai-Sun Wong V, de Lédinghen V, Kim SU. J Hepatol. 2025 Mar;82(3):456-463. doi: 10.1016/j.jhep.2024.09.020.

4. PAGE-B incorporating moderate HBV DNA levels predicts risk of HCC among patients entering into HBeAg-positive chronic hepatitis B. Chun HS, Papatheodoridis GV, Lee M, Lee HA, Kim YH, Kim SH, Oh YS, Park SJ, Kim J, Lee HA, Kim HY, Kim TH, Yoon EL, Jun DW, Ahn SH, Sydsa V, Yurdaydin C, Lampertico P, Calleja JL, Janssen H, Dalekos GN, Goulis J, Berg T, Buti M, Kim SU, Kim YJJ. Hepatol. 2024 Jan;80(1):20-30. doi: 10.1016/j.jhep.2023.09.011

5. Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. Lee HH, Lee HA, Kim EJ, Kim HY, Kim HC, Ahn SH, Lee H, Kim SU. Gut. 2024 Feb 23;73(3):533-540. doi: 10.1136/gutjnl-2023-331003.

Diagnosis and Non-Invasive Assessment of Portal Hypertension

Seung Up Kim Yonsei University

Portal hypertension is one of the most important pathophysiologic consequences of chronic liver disease and represents a key determinant of clinical outcomes. It plays a central role in the development of major complications of cirrhosis, including gastroesophageal varices, ascites, hepatic encephalopathy, and hepatic decompensation. The presence and severity of portal hypertension therefore provide critical prognostic information and influence decisions regarding surveillance, prevention, and therapeutic interventions. Early identification of clinically significant portal hypertension (CSPH) is particularly important because it marks the transition from compensated to decompensated disease risk and guides the initiation of preventive strategies such as non-selective beta-blocker therapy or endoscopic surveillance for varices.

The hepatic venous pressure gradient (HVPG) measurement has long been considered the reference standard for the diagnosis and quantification of portal hypertension. HVPG provides direct hemodynamic information and has been extensively validated as a predictor of clinical outcomes. Threshold values such as HVPG ≥10 mmHg for CSPH and ≥12 mmHg for variceal bleeding risk have been widely accepted in clinical research and practice. However, despite its clinical utility, HVPG measurement remains an invasive procedure that requires specialized expertise and facilities, which limits its widespread implementation in routine clinical practice. In many regions and clinical settings, access to HVPG measurement is restricted, and repeated measurements for longitudinal monitoring are often impractical.

Because of these limitations, considerable efforts have been made over the past decade to develop reliable non-invasive methods for assessing portal hypertension. Advances in imaging technologies and biomarker research have led to the emergence of several promising tools that allow clinicians to estimate portal pressure and stratify risk without invasive procedures. Among these, elastography-based techniques have gained particular attention. Liver stiffness measurement (LSM) using vibration-controlled transient elastography has been extensively studied and shown to correlate with portal pressure and fibrosis severity. LSM has become widely used in clinical practice not only for staging liver fibrosis but also for identifying patients at risk of CSPH.

More recently, the role of spleen stiffness measurement (SSM) has been increasingly recognized. Because splenic congestion reflects the hemodynamic consequences of portal hypertension, spleen stiffness may provide complementary information to liver stiffness. Several studies have demonstrated that SSM improves diagnostic accuracy for CSPH and high-risk varices when used in combination with LSM and other clinical parameters. In addition, simple laboratory parameters such as platelet count have proven useful as indirect markers of portal hypertension because thrombocytopenia often reflects hypersplenism and splenic sequestration associated with portal pressure elevation.

The integration of these parameters into composite diagnostic algorithms has significantly improved the performance of non-invasive assessment strategies. International consensus recommendations, particularly those from the Baveno VI and Baveno VII workshops, have incorporated non-invasive criteria to guide clinical decision-making. For example, patients with compensated advanced chronic liver disease who have low liver stiffness values and adequate platelet counts can safely avoid screening endoscopy for varices, thereby reducing unnecessary procedures and healthcare burden. Conversely, higher liver stiffness thresholds have been proposed to identify patients with a high probability of CSPH who may benefit from early therapeutic interventions.

In addition to elastography-based approaches, other imaging modalities such as magnetic resonance elastography and advanced cross-sectional imaging techniques are being explored for the evaluation of portal hypertension. Serum-based biomarkers and fibrosis panels have also been investigated as adjunctive tools, although their performance is generally inferior to elastography-based methods. Nevertheless, combining multiple non-invasive markers may further enhance diagnostic accuracy and improve risk stratification across diverse etiologies of chronic liver disease, including viral hepatitis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease.

Despite these advances, non-invasive assessment of portal hypertension still has several limitations. The performance of individual markers may vary depending on disease etiology, stage of fibrosis, and the presence of confounding conditions such as inflammation or cholestasis. Furthermore, while non-invasive tests are increasingly used to estimate the probability of CSPH, they cannot yet fully replace HVPG measurement in all clinical contexts, particularly in research settings or when precise hemodynamic assessment is required.

This lecture will review the current concepts and recent advances in the diagnosis and non-invasive assessment of portal hypertension. The session will focus on the clinical relevance of portal hypertension, the principles and limitations of HVPG measurement, and the growing role of non-invasive tools such as liver and spleen elastography. Particular emphasis will be placed on practical algorithms that integrate elastography findings, laboratory markers, and guideline-recommended thresholds to guide

clinical decision-making. By summarizing the latest evidence and consensus recommendations, this lecture aims to provide clinicians with a practical framework for the evaluation of portal hypertension in patients with chronic liver disease and to highlight future directions for improving non-invasive risk stratification.



Yeon Seok Seo
Korea University

Self Introduction

Medical Licenses and Board Certifications

1996.03	Korean License of Medical Doctor (License Number, 58571)
2001.02	Korean Board Certification of Internal Medicine (License Number, 7516)
2006	Korean Board Certification of Gastroenterology (License Number, 1-06-910)

Educational Backgrounds and Degree

1990.03-1996.02	M.D. & Bachelor in Medical Science: Korea University College of Medicine, Seoul, Korea
1997.09-1999.08	Master in Internal Medicine a) Graduate School of Korea University, Seoul, Korea b) Title of Master Thesis: Effect of 12 Month Lamivudine Therapy in Patients with HBeAg Positive Chronic Hepatitis B c) Director: Prof. Chang Hong Lee, M.D., PhD.
1999.09-2006.02	Doctor of Philosophy in Internal Medicine a) Graduate School of Korea University, Seoul, Korea b) Title: Comparison of Antiviral Efficacy between Adefovir Dipivoxil in Lamivudine (LMV) Resistant Status and LMV in Nucleoside Naïve Status in Chronic Hepatitis B Patients c) Director: Prof. Jong Eun Yeon, M.D., PhD.

Lists of Training, Employments and Military Service

1996.03-1997.02	Full Rotating Internship Training
1997.03-2001.02	Residency Training of Internal Medicine
2001.04-2004.04	Military Service for 36 Months (Medical officer, Captain)
2004.05-2005.02	Gastroenterology Fellowship, Korea University Guro Hospital, Seoul, Korea
2005.03-2006.02	Clinical Assistant Professor, Korea University Guro Hospital, Seoul, Korea
2006.03-2007.02	Clinical Assistant Professor, Korea University Anam Hospital, Seoul, Korea
2007.03-2010.02	Assistant Professor, Korea University College of Medicine, Seoul, Korea
2010.03-2011.02	Associate Professor, Korea University College of Medicine, Seoul, Korea
2011.03-2012.11	Research Fellowship, Mayo Clinic, Rochester, MN, USA
2012.12-2016.02	Associate Professor, Korea University College of Medicine, Seoul, Korea
2012.12-Present	Professor, Korea University College of Medicine, Seoul, Korea

Professional Affiliations

1996.03-Present	Member, Korean Medical Association
2001.03-Present	Member, Korean Association of Internal Medicine
2005.08-Present	Member, Korean Society of Gastrointestinal Endoscopy
2006.10-Present	Member, Korean Association for the Study of the Liver
2006.10-Present	Member, Korean Liver Cancer Study Group
2006.10-Present	Member, Korean Society of Gastroenterology

TIPS: Selecting the Right Patient with Portal Hypertension

Yeon Seok Seo Korea University

Liver cirrhosis represents the end stage of chronic liver disease. In liver cirrhosis, due to the architectural distortion and increased intrahepatic resistance, portal hypertension is commonly accompanied, which is associated with the development of major complications of liver cirrhosis, including gastroesophageal varices, ascites, and hepatic encephalopathy.

The transjugular intrahepatic portosystemic shunt (TIPS) has emerged as a pivotal interventional modality for the management of complications caused by portal hypertension. By creating a channel between the portal and hepatic veins, TIPS effectively decompresses the portal pressure.

The primary clinical indication for TIPS is the management of variceal bleeding, particularly in cases refractory to pharmacologic and endoscopic therapy. In addition, some studies suggested that early TIPS placement in high-risk patients, such as patients with Child-Pugh class C or class B with active bleeding, significantly reduced rebleeding rates and improve survival rates.

Another major indication for TIPS is refractory ascites. In patients with refractory ascites, TIPS improves natriuresis and reduces the formation of ascites by decreasing portal pressure and improving effective arterial blood volume. This leads to suppression of the renin–angiotensin system (RAS) and sympathetic nervous system activation, both of which are central to sodium and water retention in cirrhosis.

On the other hand, TIPS is associated with significant complications, such as development of hepatic encephalopathy (HE) and deterioration of liver function. The diversion of portal blood flow away from the liver reduces hepatic clearance of neurotoxins such as ammonia, thereby increasing the risk of HE. The incidence of post-TIPS HE ranges from 25% to 50%. And, while TIPS improves portal hypertension, it may reduce hepatic perfusion, particularly in patients with limited hepatic reserve. This can lead to hepatic decompensation in some cases. Therefore, appropriate patient selection is critical, with contraindications including severe liver failure, uncontrolled infection, severe pulmonary hypertension, and significant right heart dysfunction.

In conclusion, TIPS is an effective intervention for the management of complications related to portal hypertension in liver cirrhosis. Its clinical significance lies in its ability to directly target the hemodynamic basis of these complications. While it offers substantial benefits in selected patients, its use requires careful consideration of indications, contraindications, and potential complications. Ongoing research and refinement in patient selection and procedural techniques are expected to further enhance the role of TIPS in the management of cirrhosis.



Young Kul Jung
Korea University

Self Introduction

Prof. Young Kul Jung is a Professor in the Department of Internal Medicine at Korea University College of Medicine, Republic of Korea. He is a hepatologist specializing in hepatitis B virus, cirrhosis, alcohol-related liver disease, and hepatocellular carcinoma, with a strong focus on clinical outcomes and translational research.

He received his MD (1999), Master's degree (2004), and PhD (2012) from Korea University College of Medicine. He completed his internship and residency at Korea University Medical Center, followed by fellowship training in gastroenterology and hepatology.

Prof. Jung has held academic positions at Gachon University Gil Medical Center and Korea University Ansan Hospital, where he has been a Professor since 2019. He was a Visiting Professor at the Kyoto University Center for iPS Cell Research and Application (CiRA) from 2018 to 2019, where he expanded his research into regenerative medicine and cell-based therapies.

He recently served as Director of the Clinical Practice Guideline Committee of the Korean Association for the Study of the Liver (KASL) and is actively involved in multiple national academic societies. His research integrates multicenter clinical cohorts (KACLiF) with mechanistic studies, particularly focusing on hepatitis immune responses and prognostic modeling in alcohol-related liver disease and acute-on-chronic liver failure.

Research Interests

- Viral Hepatitis (HBV) and Antiviral Outcomes
- Alcohol-Related Liver Disease (ALD) and Acute-on-Chronic Liver Failure (ACLF)
- Liver Cirrhosis and Decompensation
- Hepatocellular Carcinoma (HCC)
- Immune Mechanisms and NK Cell Biology in Liver Disease
- Regenerative Medicine and iPS Cell-Based Therapy

Representative Publications

1. Lee JS, Lee SW, Lee HL, Yoo JJ, Seo YS, Yu SJ, Yim HJ, Jung YK, et al. Besifovir dipivoxil maleate versus other antivirals in reducing hepatocellular carcinoma in chronic hepatitis B. *Scientific Reports*. 2025 Aug 29;15(1):31879.
2. Yoon E, Kim JH, Jung YK, et al. Rifaximin treatment in patients with severe alcohol-associated hepatitis: randomized, double-blind, placebo-controlled trial. *Annals of Hepatology*. 2025 Jan;30(1):101749.
3. Kim JH, Kim S-E, Song DS, Kim HY, Yoon EL, Park JW, Tae H Kim, Jung YK, et al. Aetiology of chronic liver disease as a factor for risk stratification in acute decompensation: prospective observational study. *Annals of Medicine*. 2025 Jan 24;57(1):2428431.
4. Sohn W, Lee Y-S, Kim SS, Kim JH, Jin YJ, Kim GA, Sung PS, Yoo J-J, Chang Y, Lee EJ, Lee HW, Choi M, Yu SJ, Jung YK, Jang BK; Korean Association for the Study of the Liver. KASL clinical practice guidelines for the management of metabolic dysfunction-associated steatotic liver disease 2025. *Clinical and Molecular Hepatology*. 2025 Feb 19;31(Suppl):S1-S31.
5. Lim J, Kim S-E, Jo AJ, Kim JH, Han SK, Kim TH, Yim HJ, Jung YK, et al.; KACLiF Study Group. Effect of diabetes on mortality and liver transplantation in alcoholic cirrhosis with acute decompensation. *Hepatology International*. 2024 Jul 17;18(5):1579-1588.

Alcohol-Related Liver Disease: From Assessment to Management

Young Kul Jung Korea University

Alcohol-related liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide and encompasses a dynamic spectrum ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Alcohol-associated hepatitis (AH), the most severe inflammatory manifestation of ALD, is characterized by acute hepatic decompensation, systemic inflammation, and high short-term mortality, reaching 20–50% at 3 months in severe cases. Early identification and accurate assessment are critical for improving outcomes and rely on a combination of clinical history, biochemical parameters, and exclusion of alternative causes of liver injury. Diagnostic frameworks have been refined to allow classification of probable and definite AH without mandatory liver biopsy in most cases, facilitating timely therapeutic intervention.

Risk stratification plays a central role in clinical decision-making. Prognostic scoring systems such as the Model for End-Stage Liver Disease (MELD), Maddrey's discriminant function (MDF), and the Lille score are widely used to define disease severity, guide treatment selection, and assess response to therapy. Severe AH, typically defined by MELD ≥ 20 or MDF ≥ 32 , is associated with poor prognosis and warrants consideration of disease-specific therapy. Corticosteroids remain the cornerstone of treatment in selected patients with severe AH and have been shown to improve short-term survival, particularly at 28 days. However, their benefit does not extend to long-term survival, and their use is limited by adverse events, most notably infections, which occur in a substantial proportion of patients and are independently associated with increased mortality.

Recent studies have focused on optimizing therapeutic strategies to improve outcomes and minimize complications. Modifications in corticosteroid regimens, including early response-guided discontinuation using the Lille score and dose tapering strategies, have been proposed to reduce infection risk without compromising efficacy. In addition, combination therapies targeting key pathogenic mechanisms such as inflammation, oxidative stress, and immune dysregulation—including agents such as N-acetylcysteine, S-adenosylmethionine, and metadoxine—have shown potential benefits in selected studies, although results remain heterogeneous and further validation is required. Emerging therapeutic approaches targeting the gut–liver axis, microbiome modulation, and liver regeneration pathways are currently under active investigation and may provide novel avenues for treatment.

Beyond pharmacological therapy, comprehensive management of ALD requires a multidisciplinary approach. Sustained alcohol abstinence remains the most important determinant of long-term survival and disease modification. Nutritional support is also essential, as malnutrition is highly prevalent in patients with AH and is associated with worse outcomes. Management of complications, including infections, hepatic encephalopathy, ascites, and renal dysfunction, is critical to improving both short- and long-term prognosis. In carefully selected patients with severe AH who do not respond to medical therapy, early liver transplantation has emerged as a life-saving intervention, with growing evidence supporting its survival benefit in appropriately selected candidates.

In conclusion, the management of ALD requires an integrated, stage-based approach that combines early diagnosis, dynamic risk stratification, and individualized therapeutic strategies. While corticosteroids remain the mainstay of treatment for severe AH, ongoing advances in the understanding of disease pathophysiology are driving the development of novel therapies. Future research should focus on precision medicine approaches, including biomarker-driven treatment selection and optimization of multidisciplinary care pathways, to further improve clinical outcomes in this high-risk population.

Keywords

Alcohol-related liver disease; Alcohol-associated hepatitis; Corticosteroids; Risk stratification; Liver transplantation



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Ju Hyun Shim
University of Ulsan

Self Introduction

Post Graduate Training

- 2000.3-2001.2 Internship, Seoul National University Hospital, Seoul, Korea
- 2001.3-2005.2 Residency, Seoul National University Hospital, Seoul, Korea
- 2007.3-2008.2 Public Health Doctor, National Cancer Center, Goyang, Korea
- 2008.3-2010.2 Fellowship, Dept of Gastroenterology, Asan Medical Center
- 2010.3-2015.2 Assistant Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center
- 2015.3-2020.2 Associate Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center
- 2020.3-Present Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center

Educational Background

- 1994.3-2000.2 Bachelor's Degree, College of Medicine, Seoul National University, Seoul, Korea
- 2003.3-2005.2 Master's Degree, College of Medicine, Seoul National University, Seoul, Korea
- 2009.3-2011.2 Doctor's Degree, University of Ulsan College of Medicine, Seoul, Korea

Research Interests

Hepatocellular Carcinoma Clinical Trials and Translational Researches

Representative Publications

1. Hwang Y, Heo S, An J, Na SK, Kim SO, Song IH, Nault JC, Song GW, Choi SH, Shim JH. Imaging-based Liver Transplant Eligibility in HCC: Analysis of 1,094 Patients Using LI-RADS and Asia-Pacific Guideline-based Criteria. Liver Cancer. 2026. in press. (Corresponding author)
2. Kim YR, Kim E, Kim HI, Han S, An J, Shim JH. Updated Network Meta-Analysis of First-Line Systemic Treatments for Advanced HCC: Consistent Role of TACE. Liver Cancer. 2025 Jun 12;15(1):117-134. (Corresponding author)
3. Yu D, Hwang Y, Ju JS, Heo S, Kim SO, Choi SH, Song GW, An J, Shim JH Network meta-analysis and validation study of expanded liver transplantation criteria for HCC: Significant role of AFP. Clin Mol Hepatol. 2026, in press (Corresponding author)
4. Yang J, Hwang Y, Ju JS, Han S, An J, Shim JH. Impact of newer antihyperglycemic agents on hepatic complications: A systematic review and meta-analysis of data from 5.3 million patients with type 2 diabetes mellitus. Hepatology. 2026, in press (Corresponding author)
5. An J, Park R, Kim E, Na SK, Kim HI, Song IH, Cho YS, Kang JH, Lee HC, Han S, Nault JC, Choi SH, Shim JH. LI-RADS for Diagnosing Hepatocellular Carcinoma in Patients with Noncirrhotic Chronic Hepatitis C. Radiology. 2025 Mar;314(3):e241856. (Corresponding author)

Systemic Therapy for HCC: First-Line, Second-Line, and Beyond

Ju Hyun Shim University of Ulsan

Background

Systemic therapy has become a cornerstone in the management of advanced hepatocellular carcinoma (HCC), particularly in patients who are not eligible for curative or locoregional treatments. Over the past decade, treatment paradigms have rapidly evolved from single-agent tyrosine kinase inhibitors (TKIs) to immune checkpoint inhibitor (ICI)-based combination therapies, significantly improving survival outcomes and reshaping clinical decision-making.

First-Line Systemic Therapy

In the first-line setting, ICI-based combination regimens are now considered the standard of care. The combination of atezolizumab and bevacizumab demonstrated superior overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) compared to sorafenib in the landmark IMbrave150 trial. Similarly, dual ICI therapy with durvalumab plus tremelimumab (STRIDE regimen) showed a significant OS benefit over sorafenib in the HIMALAYA trial, with durable long-term survival. More recently, nivolumab plus ipilimumab has also demonstrated improved OS and higher response rates in the CheckMate 9DW trial. In addition, lenvatinib remains a valid alternative, demonstrating non-inferior OS and superior PFS compared to sorafenib in the REFLECT trial. These approaches are broadly consistent across international guidelines.

Treatment selection must be individualized based on patient-specific factors, including liver function, bleeding risk, autoimmune conditions, and prior liver transplantation. Atezolizumab plus bevacizumab requires careful screening and management of gastroesophageal varices due to bleeding risk, whereas dual ICI regimens may be preferred in patients with contraindications to anti-angiogenic therapy. In patients with impaired liver function (e.g., ALBI grade 2/3 or Child-Pugh B), outcomes remain inferior and evidence is limited.

Second-Line Therapy

Following failure of first-line ICI-based therapy, second-line treatment strategies remain less well defined due to the lack of randomized controlled trials. Current evidence, largely derived from phase II

studies and real-world data, supports the use of TKIs such as lenvatinib, regorafenib, and cabozantinib. Ramucirumab represents a biomarker-driven option for patients with elevated alpha-fetoprotein (AFP ≥ 400 ng/mL). In selected cases, ICI rechallenge or combination strategies may be considered, although evidence remains limited. Practice guidelines recommend switching to agents with different mechanisms of action, while highlighting the lack of high-level evidence in this setting.

Later-Line Therapy and Treatment Sequencing

For patients previously treated with TKIs, regorafenib, cabozantinib, and ramucirumab have demonstrated survival benefits in randomized trials following sorafenib failure. Immunotherapy may also be considered in selected cases, although its role beyond the first-line setting remains less clearly defined. Treatment sequencing becomes increasingly complex in later lines, and only a subset of patients proceed due to progressive liver dysfunction.

The high response rates associated with ICI-based therapies have enabled new treatment paradigms, including conversion therapy. Some patients initially considered unresectable may become eligible for curative interventions such as resection, transplantation, or locoregional therapies following systemic treatment.

Conclusion

Systemic therapy for HCC has undergone a paradigm shift toward immunotherapy-based combinations, resulting in improved survival outcomes. While international guidelines are largely aligned in overall treatment direction, differences remain in patient selection and treatment sequencing. Future research should focus on optimizing sequencing strategies, identifying predictive biomarkers, and refining treatment approaches to further improve outcomes in HCC.

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1. Korean Liver Cancer Association-National Cancer Center, Korea. Korean Liver Cancer Association–National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. *Clinical and Molecular Hepatology*. 2022;28(4):583–705.
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3. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922–1965.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatocellular carcinoma. *Journal of Hepatology*. 2025;82(2):315–374.
5. Vogel A, Chan SL, Dawson LA, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2025;36(5):491–506.
6. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *Journal of Clinical Oncology*. 2024;42(15):1830–1850.

THE LIVER WEEK 2026

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2026 KASL CLINICAL PRACTICE GUIDELINES

Liver Cirrhosis

Chair
Jae Young Jang (Soonchunhyang Univ.)





Moon Young Kim
Yonsei University Wonju

Self Introduction

Professor Moon Young Kim is currently a Professor of the Department of Internal Medicine, Yonsei University Wonju College of Medicine. He has been provided medical treatments and researched mainly on gastroenterology and hepatology for over 15 years. His specialized areas are liver sinusoidal endothelial cell pathophysiology and related hepatic fibrosis and he has worked on preclinical studies on the mechanism of endothelial dysfunction/portal hypertension. Recently he has focused on cell therapy by using stem cells for hepatic fibrosis and angiogenesis. He is also interested in non-invasive diagnosis of hepatic fibrosis or portal hypertension using contrast-enhanced ultrasonography. From the clinical research point, the impact of gut microbiota on cirrhosis/portal hypertension and the application of treatment is one of his main research projects.

Research Interests

Assessment and Treatment of Portal Hypertension and Cirrhosis
Stem Cell Therapy for Hepatic Regeneration and Anti-Fibrosis
The Cross Talk between Sinusoidal Remodeling, Angiogenesis and Hepatic Fibrosis
Noninvasive Evaluation of Hepatic Fibrosis and Portal Hypertension Using Contrast Enhanced Ultrasonography

Representative Publications

1. KASL clinical practice guidelines for liver cirrhosis: Ascites and related complications 2026. Song DS, Yoo JJ, Song JE, Kang SH, Shin SK, Han SK, Chung SW, Kim GA, Hur MH, Lee HA, Ha Y, Chang Y, Yoon JH, Lee JS, Kim SG, Jung YK, Kim MY. Clin Mol Hepatol. 2026 Apr 28. doi: 10.3350/cmh.2026.0281. Online ahead of print. PMID: 42050795 Free article. No abstract available.

2. Multicenter Prospective Cohort Study on Clinical Outcomes and Fibrosis Patterns in Biopsy-Proven Steatotic Liver Disease Subtypes. Kim GA, Jang H, Kim MY, Park JH, Park JG, Cho EY, Jeong JY, Jeong S, Han SK, Kwon H, Jung Y, Hwang GS, Lee YR, Park SY, Kim SG, Kim W. Gastroenterology. 2026 Jun;170(7):1571-1583. doi: 10.1053/j.gastro.2026.01.007. Epub 2026 Jan 29. PMID: 41620039

3. Preclinical Analysis of Bone Marrow-Derived Stem Cell Therapy Response and Transcriptomic Overlap Analysis in a Severe Alcoholic Hepatitis Mouse Model. Hong S, Han SK, Lee MR, Lee T, Baik SK, Lee JS, Kim MY. Gut Liver. 2026 Jan 16. doi: 10.5009/gnl250425. Online ahead of print. PMID: 41540830 Free article.

4. Protein and Macronutrient Metabolism in Liver Cirrhosis: About Sarcopenia. Han SK, Baik SK, Kim MY. Nutrients. 2025 Oct 24;17(21):3346. doi: 10.3390/nu17213346. PMID: 41228421

5. Transplantation of Autologous Bone Marrow-Derived Mesenchymal Stem Cells for the Treatment of Decompensated Liver Cirrhosis: A Real-World Evidence Study in a Population-Based Cohort. Han SK, Kim SH, Koh SB, Kim MY. Gut Liver. 2025 Sep 8. doi: 10.5009/gnl250016. Online ahead of print. PMID: 40916722

2026 KASL Clinical Practice Guidelines:
Liver Cirrhosis

Moon Young Kim Yonsei University Wonju

The 2026 KASL Clinical Practice Guidelines for Ascites-Related Complications in Liver Cirrhosis were revised to reflect advances in the diagnosis, treatment, and prognostic assessment of ascites and its associated complications since the previous 2017 guideline. Ascites remains one of the most common complications of decompensated cirrhosis and is associated with poor survival outcomes, underscoring the importance of timely diagnosis and appropriate management.

The most significant feature of this clinical guideline revision is that the committee independently conducted a systematic review and meta-analysis on important topics, actively incorporated the results into the text, and used them as the basis for the guideline recommendations. The guideline development process included comprehensive evaluation of domestic and international literature published through September 2025, with recommendations formulated according to the quality of evidence and strength of recommendation.

The main directions of the revision are as follows:

● Strengthening the Evidence Regarding the Role and Utility of Albumin

Recent randomized controlled trials and meta-analyses have demonstrated that albumin contributes to the reduction of complications of liver cirrhosis—particularly ascites-related complications—and the improvement of prognosis, going beyond simple improvement of colloid osmotic pressure through antioxidant and anti-inflammatory effects, improvement of vascular endothelial function, and stabilization of circulatory dynamics. Accordingly, this guideline summarizes the latest evidence regarding the physiological role and therapeutic utility of albumin through a systematic review and presents evidence for its use in various clinical situations, such as ascites control, infection, and renal failure.

● Incorporating the Latest Evidence for TIPS and Strengthening Recommendations

While TIPS was previously recognized primarily as a rescue treatment for refractory ascites or variceal bleeding, recent studies report that TIPS administered at an earlier stage contributes to improved survival rates. Therefore, this revision re-evaluates the utility of TIPS in ascites control and the treatment of hepatorenal syndrome through a systematic review.

- **Revision of the Guidelines for the Diagnosis and Management of Cirrhosis-Associated Acute Kidney Injury Reflecting Updated International Diagnostic Criteria**

Recently, the Acute Dialysis Quality Initiative International Club of Ascites (ADQI-ICA) reported recommendations regarding the diagnosis and treatment of acute kidney injury based on expert consensus. However, these recommendations are still subject to global debate, with many arguing that further verification through additional research is necessary. Accordingly, this clinical guideline presents its own proprietary diagnostic criteria and treatment strategies by incorporating and reconciling recently reported research results with existing guidelines. This approach enhances flexibility in clinical judgment and application in practice while leaving room for future changes through additional research. Furthermore, it incorporates detailed assessments of the necessity for renal replacement therapy following early diagnosis, hemodynamic optimization strategies, and the evidence supporting concomitant albumin use.

- **In Addition, the Recommendations Were Revised through the Evaluation of the Safety and Clinical Utility of Ultrasound-Guided Paracentesis, the Re-Evaluation of the Evidence for Prophylactic Antibiotic Therapy in Spontaneous Bacterial Peritonitis, and the Confirmation of the Clinical Utility of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Acute Renal Injury Associated with Liver Cirrhosis.**

The guidelines are intended for healthcare professionals involved in the care of patients with cirrhosis caused by chronic hepatitis B, chronic hepatitis C, metabolic dysfunction-associated steatotic liver disease, alcohol-related liver disease, and other chronic liver diseases. Development was led by a multidisciplinary committee of experts under the Korean Association for the Study of the Liver (KASL), with input from related specialty societies and external reviewers.

The final guideline addresses nine major clinical domains, including the diagnosis and management of ascites, refractory ascites, hyponatremia, spontaneous bacterial peritonitis, AKI and HRS, hepatic hydrothorax, hernia, and medication use in patients with cirrhosis. The guidelines were officially announced at Liver Week 2026 and will be updated as new evidence emerges.

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PG COURSE 3

Chronic Hepatitis B

Chairs

Byung-Cheol Song (Jeju National Univ.)

Young Oh Kwon (Kyungpook National Univ.)





Won-Mook Choi
University of Ulsan

Self Introduction

Prof. Won-Mook Choi is an Assistant Professor of the Department of Gastroenterology, Asan Medical Center.

Prof. Choi graduated from Seoul National University College of Medicine with his medical degree in 2010 and graduated from KAIST with his PhD degree in 2019. He completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital in 2015 and completed his fellowship at the Department of Gastroenterology at Asan Medical Center in 2021.

Since 2022, Prof. Choi has held several roles in academic societies, and currently serves as Treasurer of the Korean Association for the Study of the Liver, Secretary of the Hepatitis B Clinical Practice Guidelines Revision Committee, Member of the Publication Committee of the Korean Liver Cancer Association, and Member of the Planning Committee of the Korean Association of Internal Medicine.

Research Interests

Chronic Hepatitis B, Hepatocellular Carcinoma, Portal Hypertension

Representative Publications

1. Heo S, Yang J, Park J, Hui RW, Song BG, Song IH, Yoon YI, Cheung TT, Chung SW, Choi J, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Seto WK, Lee JH, Choi WM (corresponding). Association Between Viral Replication Activity and Postoperative Recurrence of HBV-Related Hepatocellular Carcinoma. *Aliment Pharmacol Ther*. 2025 May;61(10):1680-1691.
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Updated KASL Guidelines on Chronic Hepatitis B

Won-Mook Choi University of Ulsan

The prevalence of hepatitis B virus (HBV) in Korea has decreased to less than 3% since 2018 due to the results of national immunization and perinatal infection prevention projects, but it still shows a prevalence of 3–4% in the 40–60s age group, with a total of about 1.2 million infected people. Chronic hepatitis B (CHB) is a major risk factor for the occurrence of liver cirrhosis and hepatocellular carcinoma (HCC) in Korea, and the mortality rate related to liver disease caused by hepatitis B is 18.9 per 100,000 population. It is far exceeding the World Health Organization (WHO)'s target of 4 or less, so active management is urgently needed. Even though safe and effective oral antiviral drugs are now available for CHB and proven to prevent HCC and reduce mortality rates during long-term treatment, the treatment rate among all hepatitis B patients in Korea remains at a mere 22.2%.

The existing hepatitis B guidelines limit the treatment target to the immunoinactive phase with elevated ALT based on the immunological natural history classification. However, with the accumulation of recent studies on the natural history of CHB, it has been suggested that the existing immunological disease stage classification has limitations in fully reflecting the clinical course of all patients. With increasing reports on disease progression and HCC risks and efficacy of antiviral treatment for patients in the 'grey zone' or 'indeterminate phase' who are not clearly defined by conventional classifications, the necessity for guideline revisions has been raised. These updates should reflect the latest evidence across the entire spectrum of CHB management, including clinical judgment on treatment initiation and the continuation or termination of antiviral therapy.

Recently, major international guidelines—including those from the WHO, the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD)—have been updated to reflect this paradigm shift. Although the AASLD has maintained a relatively conservative stance, both the WHO and EASL have substantially broadened their treatment indications. This expansion is supported by the accumulated long-term evidence demonstrating that currently available nucleos(t)ide analogues exhibit minimal resistance, excellent tolerability, and proven efficacy in reducing hard clinical outcomes such as HBV-related HCC and mortality. As a result, the conceptual framework of treatment is gradually shifting away from ALT-based criteria toward a virus-centered approach, in which suppression of viral replication itself is regarded as a key strategy to more efficiently prevent

HCC development. Nevertheless, the criteria used to define the natural history of CHB still differ across guidelines, and the persistent reliance on ALT continues to generate ambiguity—exemplified by the so-called ‘indeterminate phase’—that complicates clinical decision-making.

The Korean Association for the Study of the Liver (KASL) has continuously developed and revised clinical practice guidelines to improve the level of care for liver diseases in Korea and to establish standardized medical guidelines. In response to the recent expansion of treatment indications in international guidelines related to hepatitis B and the growing need to respond to the WHO strategy for hepatitis B elimination, the existing guidelines announced in 2022 have been completely revised. In particular, this revision redefines the classification of the natural history of CHB based on viral load rather than ALT, in line with recently accumulated evidence on the risk of disease progression and HCC. By anchoring the natural history on serum HBV DNA levels, the updated KASL guideline resolves the ambiguity of the indeterminate phase and allows the disease stage and treatment indication to be linked in a more intuitive and seamless manner. Building on this redefined framework, the treatment indication has been correspondingly expanded and simplified, providing a more straightforward and clinically applicable strategy for both initiation and long-term management of antiviral therapy.

This guideline aims to provide practical guidance to medical staff in charge of the diagnosis and treatment of CHB patients in Korea, thereby supporting rational medical decision-making for each patient. Ultimately, it aims to reduce the liver-related mortality and occurrence of HCC caused by CHB, improve the quality of life of patients, and contribute to reducing the burden of socioeconomic diseases.

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Nae-Yun Heo
Inje University

Self Introduction

Prof. Heo graduated from Pusan National University College of Medicine with his medical degree in 2001, and had a resident training in Internal Medicine and fellowship in the Department of Gastroenterology in Asan Medical Center, Seoul, Korea.

Prof. Heo has been affiliated to Inje University Haeundae Paik Hospital since 2011, and a professor of Division of Gastroenterology since 2022.

Prof. Heo is currently the Director of Informatics Committee of the Korean Association of the Study of the Liver (2026-)

Research Interests

He is interested in the hepatology including chronic viral hepatitis, liver cirrhosis, and metabolic dysfunction-associated liver disease, and hepatocellular carcinoma.

Representative Publications

1. 2025 KASL clinical practical guidelines for management of hepatitis C. Clin Mol Hepatol 2026;32:1-52.
2. Diagnostic performance of procalcitonin for bacterial infection in severe alcoholic hepatitis compared with C-reactive protein. BMC Gastroenterology 2024;24:428.
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4. Epidemiology of autoimmune liver disease. Korean j Gastroenterol 2023;81:59-65.
5. Efficacy and Safety of Biphenyl Dimethyl Dicarboxylate and Ursodeoxycholic Acid Combination in Chronic Hepatitis Related to Metabolic Syndrome Components. Korean J Gastroenterol 2021;77:179-189.

Treatment Strategy for Chronic Hepatitis B: Who, When, and What Goals to Achieve?

Nae-Yun Heo

Inje University

Chronic hepatitis B (CHB) remains a major cause of liver-related morbidity and mortality in Korea, leading to cirrhosis and hepatocellular carcinoma (HCC), particularly in middle-aged and older individuals. Since the introduction of nucleos(t)ide analogues (NUCs) in the early 2000s, the risk of cirrhosis-related complications has markedly decreased. However, despite effective viral suppression, patients remain at a substantial risk of developing HCC. Early antiviral therapies were limited by suboptimal antiviral potency and the emergence of drug resistance during long-term treatment. Therefore, treatment decisions were traditionally based not only on serum hepatitis B virus (HBV) DNA levels but also on alanine aminotransferase (ALT), a surrogate marker of hepatic necroinflammation. Patients with active viral replication and elevated ALT levels, corresponding to the immune-active phase, were considered candidates for treatment, whereas those in the immune-tolerant or inactive phases were generally monitored without therapy.

However, this phase-based treatment strategy has important limitations. Approximately 30% of patients fall into an indeterminate or “grey zone,” characterized by high HBV DNA levels but normal or minimally elevated ALT levels. Accumulating evidence suggests that a substantial proportion of these patients have significant liver fibrosis and are at increased risk of HCC, highlighting the inadequacy of relying solely on ALT to guide treatment decisions. With the development of more potent NUCs with a high genetic barrier to resistance and well-established long-term safety profiles, it has become feasible to expand antiviral therapy to a broader population. In addition, multiple studies have demonstrated that long-term antiviral therapy reduces the risk of HCC, supporting a shift in treatment goals from preventing cirrhosis to reducing HCC incidence.

The REVEAL study demonstrated a positive association between HBV DNA levels and HCC risk, suggesting a linear relationship between viral load and carcinogenesis. However, this study predominantly included hepatitis B e antigen (HBeAg)-negative patients and had limited representation of individuals with very high viral loads. More recent studies, particularly from Korean cohorts including both HBeAg-positive and -negative patients, have shown that the risk of HCC may be highest in patients with intermediate levels of viremia (HBV DNA 2,000–10⁴ IU/mL), while paradoxically lower in those with very

high viral loads. This observation may be explained by the dynamic interaction between viral replication and host immune responses. During the course of chronic HBV infection, immune-mediated hepatocyte turnover may promote HBV DNA integration into the host genome. Subsequent clonal expansion of hepatocytes that survive immune pressure may contribute to hepatocarcinogenesis. These processes may be particularly relevant in patients with intermediate levels of viremia, in whom ongoing immune activity and viral replication coexist. Based on these findings, a treatment-oriented framework based on HBV DNA levels is expected to be incorporated into the upcoming Korean Association for the Study of the Liver (KASL) clinical practice guidelines. This approach stratifies patients into high, intermediate, and low viremia groups, not as a linear representation of disease severity, but as a basis for treatment decisions.

In this framework, patients with intermediate viremia are considered a high-risk group for HCC and are recommended to receive antiviral therapy regardless of age or ALT levels. In contrast, patients with high viremia are not uniformly treated; instead, antiviral therapy is recommended when additional risk factors for disease progression are present, such as age ≥ 30 years, elevated ALT levels, or significant liver fibrosis. Patients with low viremia generally have a favorable prognosis, and antiviral therapy is reserved for those with cirrhosis, while others may be safely monitored. This HBV DNA-based treatment strategy represents a major paradigm shift by eliminating the grey zone and simplifying clinical decision-making. Notably, this approach differs from existing international guidelines, which continue to rely primarily on phase-based classifications and have not yet adopted a treatment-oriented framework centered on viral load.

Despite these advances, functional cure, defined as hepatitis B surface antigen (HBsAg) loss with or without seroconversion, remains rarely achievable with current NUC therapy. Therefore, the primary goal of treatment should be to reduce the risk of HCC through broader and more appropriate use of antiviral therapy. In the future, patients with sustained viral suppression and low HBsAg levels may achieve functional cure with the development of novel therapeutic agents targeting different stages of the HBV life cycle.

In conclusion, the management of CHB is evolving toward a simplified, treatment-oriented framework based on HBV DNA levels. By redefining treatment indications and eliminating the grey zone, this approach may improve the consistency and effectiveness of clinical practice and ultimately reduce the burden of HCC.

Keywords: Chronic hepatitis B; HBV DNA; Antiviral therapy; Hepatocellular carcinoma; Treatment strategy; Viremia

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6. Huang R, et al. HBV DNA levels and hepatocellular carcinoma risk: a nonlinear association. Hepatol Commun. 2024;8:e0357.



Beom Kyung Kim
Yonsei University

Self Introduction

Educational Background

- 1997-2003 Yonsei University College of Medicine, Seoul, Republic of Korea
- 2005-2007 Master Degree, Graduate School, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2010-2013 Ph.D., Graduate School, Yonsei University College of Medicine Seoul, Republic of Korea

Professional Experience

- 2003-2004 Internship: Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2004-2008 Residency: Severance Hospital, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2008-2011 Military Service as a Doctor
- 2011-2013 Fellowship: Severance Hospital, Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2013-2018 Gastroenterology Specialist: Severance Hospital, Seoul, Republic of Korea / Assistant Clinical Professor: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2018-2023 Assistant Professor/Associate: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
- 2023- Professor: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Research Interests

Viral Hepatitis, Liver Cirrhosis, and Hepatocellular Carcinoma,
Molecular Biology of Hepatitis B Virus

Representative Publications

1. Kim BK, Bernstein N, Huang DQ, Tamaki N, Imajo K, Yoneda M, Sutter N, Jung J, Nguyen K, Nguyen L, Le T, Madamba E, Richards L, Valasek MA, Behling C, Sirlin CB, Nakajima A, Loomba R. Clinical and histologic factors associated with discordance between steatosis grade derived from histology vs. MRI-PDFF in NAFLD. Aliment Pharmacol Ther. 2023 Jul;58(2):229-237. doi: 10.1111/apt.17564. Epub 2023 Jun 2.
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Assessing Disease Activity and Fibrosis in Chronic Hepatitis B: Non-Invasive Techniques and Beyond

Beom Kyung Kim Yonsei University

The clinical management of Chronic Hepatitis B (CHB) has undergone a paradigm shift, transitioning from reactive treatment to proactive, individualized risk stratification. Central to this evolution is the accurate assessment of liver fibrosis and necroinflammatory activity, which serve as the primary determinants for initiating antiviral therapy and predicting long-term outcomes such as cirrhosis and hepatocellular carcinoma (HCC). For decades, liver biopsy was the undisputed “gold standard”; however, its inherent limitations—including patient discomfort, rare but serious complications, and significant inter-observer variability due to sampling error—have necessitated the development of reliable non-invasive tests (NITs). This paper provides a comprehensive review of current NITs and explores the “beyond” landscape, where digital pathology, artificial intelligence (AI), and molecular profiling are redefining hepatology.

Current non-invasive methodologies are broadly categorized into biochemical “wet” markers and physical “dry” imaging techniques. Simple serum-based indices, such as the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and the Fibrosis-4 (FIB-4) index, remain indispensable in resource-limited settings due to their cost-effectiveness and high negative predictive value for excluding cirrhosis. However, their specificity often falters in the presence of acute inflammatory flares. To address this, specialized serum panels and novel biomarkers like Chitinase-3-like protein 1 (CHI3L1) and Mac-2 binding protein glycosylation isomer (M2BPGi) have emerged, offering superior accuracy in distinguishing intermediate stages of fibrosis.

Parallel to biochemical advances, elastography has revolutionized bedside assessment. Vibration-Controlled Transient Elastography (VCTE) is now globally integrated into clinical guidelines, providing rapid measurements of liver stiffness. More recently, Two-Dimensional Shear Wave Elastography (2D-SWE) and Magnetic Resonance Elastography (MRE) have pushed the boundaries further; MRE, in particular, overcomes the challenges of obesity and ascites, offering a volumetric map of liver stiffness that mitigates the sampling limitations of biopsy.

The “beyond” aspect of this review delves into the frontier of “Precision Hepatology.” As we move into 2026, the focus has shifted toward integrating multi-parametric data. Artificial Intelligence and Deep Learning (DL) algorithms are now being utilized to analyze ultrasound radiofrequency data and histo-

pathological slides with a level of granularity human eyes cannot achieve. Furthermore, the integration of “Omics”—including gut microbiome signatures and circulating microRNAs—is providing insights into disease activity at a molecular level, allowing clinicians to predict which patients are “fast-progres-sors” even when current stiffness scores appear stable.

In conclusion, while liver biopsy remains a valuable reference, the synergy between advanced imaging and molecular diagnostics is making a “biopsy-free” clinic a reality. The future of CHB management lies in the transition from static staging to dynamic monitoring, utilizing AI-driven integrated models to pro-vide a holistic view of liver health, optimize treatment timing, and ultimately reduce the global burden of hepatitis-related malignancy.

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**Ki Tae Yoon***Pusan National University*

Self Introduction

Prof. Ki Tae Yoon is a Professor of the Department of Internal Medicine, Pusan National University School of Medicine and is currently holding a position of Director of Clinical Trial Center in the Pusan National University Yangsan Hospital.

Prof. Yoon graduated from Yonsei University College of Medicine with his medical degree in 2000 and completed his internship and residency at the Department of Internal Medicine at Severance Hospital, receiving his diploma in Gastroenterology in 2008.

Now Prof. Yoon currently has several roles, including publication committee and research committee member of the Korean Association of the Study of the Liver (2026-2027).

Research Interests

Clinical Study for Hepatocellular Carcinoma, Chronic Hepatitis B, Chronic Hepatitis C

Interactions between HBV and Coexisting Liver Diseases: Clinical Implications in HCV and MASLD

Ki Tae Yoon*Pusan National University*

Introduction

With the advent of potent nucleos(t)ide analogues (NUCs), viral suppression in Chronic Hepatitis B (CHB) has become highly achievable; however, CHB remains a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC). In recent clinical practice, there has been a rapid increase in the proportion of CHB patients with coexisting liver diseases, such as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Hepatitis C Virus (HCV) infection, shifting the landscape away from pure, single-etiology hepatitis.

These comorbidities do not merely coexist; they amplify intrahepatic inflammatory responses, accelerate fibrosis, and ultimately worsen patient prognosis. This lecture aims to explore the clinical implications and management strategies for CHB patients with coexisting MASLD and HCV. It will focus on guideline recommendations for early treatment initiation and the early detection of clinical complications. Furthermore, it will outline when to suspect other frequently overlooked coexisting conditions, such as Autoimmune Hepatitis (AIH) and Hepatitis D Virus (HDV), and discuss their impact on patient outcomes.

Coexisting HBV and HCV (Dual Infection): Clinical Implications and Management Strategies

HBV and HCV dual infection is observed in approximately 1–10% of patients globally. The two viruses compete for replication space within the host hepatocytes. Generally, HCV exerts a dominant effect, suppressing HBV DNA replication. However, depending on the host's immune status, the two viruses may exhibit dynamic fluctuations, alternately dominating each other. Compared to mono-infection, dual infection is associated with a dramatically increased rate of progression to cirrhosis, a higher incidence of hepatic decompensation, and an elevated risk of HCC.

Because HCV can be cured using Direct-Acting Antivirals (DAAs), all patients with detectable HCV RNA should initiate DAA therapy without delay. Rapid HCV clearance via DAAs can lead to the explosive replication of previously suppressed HBV, potentially causing severe acute flare-ups and liver failure. The KASL guidelines strongly recommend that when initiating DAA therapy in HBV/HCV co-infected

patients, NUC therapy should be started concurrently if the HBsAg-positive patient meets the standard criteria for HBV antiviral treatment. Even if standard HBV treatment criteria are not fully met, prophylactic HBV antiviral therapy should be carefully considered concurrently with DAA initiation for any HBsAg-positive patient with detectable HBV DNA. If prophylaxis is not administered, close monitoring of ALT and HBV DNA every 4 weeks during DAA therapy and for at least 12 weeks post-treatment is mandatory to detect early signs of complications.

Coexisting HBV and MASLD: Clinical Implications and Management Strategies

Driven by an aging population and rising obesity rates, the prevalence of concurrent MASLD in CHB patients now reaches approximately 25–40%. When both diseases are present, the rate of fibrosis progression and the risk of HCC development are significantly higher compared to either disease alone. Metabolic abnormalities (e.g., diabetes, insulin resistance, obesity) independently induce oxidative stress within hepatocytes, thereby promoting HBV-driven oncogenesis. Patients with this dual etiology exhibit not only higher liver-related mortality but also elevated cardiovascular mortality. Therefore, moving beyond liver-directed therapy to prioritize the early detection and management of systemic metabolic complications is imperative.

According to the Korean Association for the Study of the Liver (KASL) and major global guidelines (AASLD, EASL), early and proactive initiation of antiviral therapy is recommended or strongly considered when concurrent MASLD suggests ‘significant fibrosis’ (≥F2) or in patients aged >30–40 years, even in the absence of cirrhosis. Although it is often clinically challenging to determine whether an elevated ALT is driven by MASLD or HBV, initiating NUCs early when HBV DNA is elevated is advantageous for improving prognosis by preventing cumulative liver damage. NUC therapy alone cannot halt the progression of MASLD. Therefore, rigorous patient education focusing on weight loss and dietary modification must be integrated into clinical practice. To achieve this, it is crucial to establish a long-term, continuous management system for metabolic syndrome by linking tertiary centers with primary care facilities and regional community medical networks. This holistic infrastructure is a core strategy for improving patient prognosis.

Other Coexisting Liver Diseases (AIH, HDV): Timing of Suspicion and Prognosis

AIH must be suspected when ALT/AST remains persistently elevated, or when unexplained acute flare-ups occur, despite successful suppression of HBV DNA by potent NUCs (e.g., Entecavir, Tenofovir). This is particularly relevant for female patients with hypergammaglobulinemia or a history of other autoimmune disorders. Screening for antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) should be performed to rule out an Overlap Syndrome. If concurrent AIH is missed and the patient is maintained solely on antiviral therapy, continuous immune-mediated liver injury will accelerate the progression to cirrhosis. Prompt initiation of combination immunosuppressive therapy (Corticosteroids ± Azathioprine) is essential to prevent liver failure and improve survival rates.

Because HDV utilizes the HBV surface antigen (HBsAg) as its envelope, it exclusively infects HBsAg-positive individuals. Screening for anti-HDV antibodies should be proactively performed in CHB patients presenting with severe acute exacerbations. Patients with high ALT and rapidly progressing liver disease despite low or undetectable HBV DNA levels. Migrants or travelers from regions with high HDV endemicity (e.g., Central Asia, Eastern Europe, Mongolia). HBV/HDV coinfection has the poorest prognosis among all viral hepatitis. Dual infection increases the risk of rapid progression to cirrhosis and HCC by 2-3 times compared to HBV mono-infection. Therefore, early diagnosis upon clinical suspicion is an absolute determinant of patient prognosis.

Conclusions

The clinical paradigm for managing Chronic Hepatitis B has evolved from the suppression of a single virus to the complex management of multiple coexisting liver pathologies. In patients with concurrent MASLD or HCV, the threshold for initiating HBV antiviral therapy should be lowered in accordance with current guidelines to proactively block the synergistic mechanisms that drive fibrosis and hepatocarcinogenesis. Furthermore, clinicians must remain vigilant for atypical clinical courses during treatment to ensure the timely diagnosis of hidden conditions such as AIH and HDV.

Ultimately, optimizing outcomes for patients with multifaceted liver diseases requires a holistic approach. This involves integrating specific antiviral and metabolic therapies with rigorous patient education, the early detection of clinical complications, and the establishment of robust regional medical networks for comprehensive, long-term care.

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PG COURSE 4

Chronic Hepatitis B

Chairs

Ming-Lung Yu (Kaohsiung Medical Univ., Taiwan)

Won Young Tak (Kyungpook National Univ.)



**Tetsuo Takehara***The University of Osaka, Japan*

Self Introduction

Tetsuo Takehara received his M.D. and Ph.D. from Osaka University. After a three-year postdoctoral fellowship at the Gastrointestinal Unit of Massachusetts General Hospital, he returned to Osaka University, becoming Associate Professor and later Professor of Gastroenterology and Hepatology. He also served as Director of Osaka University Hospital (2021–2023) and is currently Director General of Kansai Rosai Hospital.

He has led major basic and clinical research in hepatitis, cirrhosis, and liver cancer, publishing over 500 papers in leading international journals. His honors include the 2017 Oda Award of the Japan Society of Hepatology (JSH) and 2022 Scientific Research Award of the Japanese Society of Gastroenterology (JSGE). He has chaired annual meetings of JSH (2020, 2025), JSGE (2021), and the Japanese Society of Internal Medicine (2025). Since 2018, he has served as Director General of JSH.

Research Interests

Hepatitis, Cirrhosis, Liver Cancer

Representative Publications

1. Activation of the Integrin α V-YAP-CTGF Axis in Liver Sinusoidal Endothelial Cells Promotes Liver Fibrogenesis, Leading to Portal Hypertension and Liver Carcinogenesis in Congestive Hepatopathy. *Gastroenterology*. 2026 May;170(5):1000-1016.
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5. Hepatic Stellate Cells in Hepatocellular Carcinoma Promote Tumor Growth Via Growth Differentiation Factor 15 Production. *Gastroenterology*. 2021 Apr;160(5):1741-1754.e16.

Revisiting the Natural Course of Chronic Hepatitis B: Implications of the Indeterminate Phase

Tetsuo Takehara*The University of Osaka, Japan*

This lecture revisits the natural history of chronic hepatitis B, clarifies the concept of the indeterminate phase, and discusses its clinical implications, particularly regarding hepatocellular carcinoma (HCC) risk and antiviral therapy. I will also summarize how major guidelines approach treatment decisions for this heterogeneous patient group.

1. Natural History and Classical Phase Classification

Chronic hepatitis B has traditionally been described using the immune-tolerant, immune-active, inactive, and HBsAg loss phases, based on HBeAg, HBV DNA, ALT, and inflammatory activity. While useful, these phases are not static; ALT and HBV DNA fluctuate, and many patients do not fit neatly into the classical categories.

Thus, the key question is not whether a patient can be classified, but whether their long-term risk justifies antiviral therapy. The indeterminate phase should therefore be viewed as an issue of risk stratification rather than a classification gap.

2. What Is the Indeterminate Phase?

The indeterminate phase (grey zone) refers to patients whose HBV DNA and ALT levels do not meet the criteria for immune-tolerant, immune-active, or inactive phases. Approximately 28–55% of HBV-infected individuals fall into this category, reflecting a heterogeneous population with diverse risk profiles.

AASLD provides a clear definition, whereas other guidelines differ in how explicitly they address this group.

3. Clinical Significance of the Indeterminate Phase

Meta-analyses report annual incidences of ~0.32% for HCC, ~0.67% for cirrhosis, and ~0.34% for decompensation—risks that are not uniformly high but clinically meaningful. High-risk subgroups include HBeAg-positive patients, untreated individuals, older adults, men, and those with low platelet counts.

Observational studies suggest antiviral therapy may reduce HCC risk in indeterminate-phase patients without advanced fibrosis, with one study showing a ~70% reduction after IPTW adjustment. A recent

RCT in non-cirrhotic patients with moderate viremia also demonstrated that tenofovir alafenamide significantly reduced major liver-related outcomes.

4. Treatment Considerations in Clinical Practice

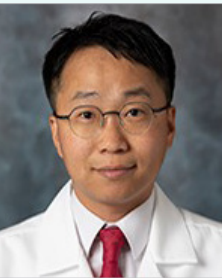
AASLD recommends considering antiviral therapy through shared decision-making, particularly in patients ≥40 years or with ≥F2 fibrosis. In HBeAg-negative patients, elevated ALT with low HBV DNA requires evaluation for alternative liver diseases, while high HBV DNA with ALT <2× ULN may justify treatment based on age, sex, and platelet count.

EASL 2025 adopts a phase-independent, risk-based algorithm integrating HBV DNA, ALT, fibrosis, age, HCC risk, and immunosuppression. JSH emphasizes HCC risk and recommends therapy when HBV DNA ≥2,000 IU/mL and ALT ≥31 U/L, while considering treatment in high-risk individuals regardless of ALT or HBeAg status. Future KASL guidelines is expected to be discussed in detail during the Day 3 session of this meeting.

Conclusion

The indeterminate phase is not benign but a heterogeneous group with incompletely defined long-term risks. Treatment decisions should incorporate age, fibrosis, viral activity, and HCC risk factors, and shared decision-making should be proactive and centered on HCC prevention.





Ju Dong Yang

Cedars-Sinai Medical Center, USA

Self Introduction

- 1999.03-2005.02 Medical School - Sungkyunkwan University School of Medicine, Seoul, Korea
- 2009.03-2011.05 Research Fellowship - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2009.09-2011.05 Master's Degree in Clinical and Translational Research - Clinical and Translational Science Activities, Mayo Graduate School
- 2011.06-2014.05 Residency - Internal Medicine, University of Arkansas for Medical Science, Little Rock, AR
- 2014.07-2017.12 Gastroenterology Fellowship, T32 Grant - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2018.01-2018.12 Transplant Hepatology Fellowship - Transplant Hepatology, Mayo Clinic, Rochester, MN
- 2023.01-Present Associate Professor of Medicine, Department of Medicine, Cedars-Sinai

Research Interests

The Yang Lab is dedicated to advancing the early detection and risk stratification of hepatocellular carcinoma (HCC) through the discovery and validation of circulating biomarkers, including circulating tumor cells and extracellular vesicles. By integrating these insights with predictive modeling and molecular profiling, the lab develops precision therapies tailored to individual patients and optimizes treatment responses. Leveraging population-based data, the Yang Lab also addresses global disparities in liver cancer care, guiding more equitable and effective clinical strategies.

Representative Publications

1. Antibiotic Use Linked to Worse Outcomes in Patients With Gastrointestinal and Liver Cancer on Immune Checkpoint Inhibitors: A Meta-Analysis. Rezaee-Zavareh MS, Karimi-Sari H, Parhizkar Roudsari P, Khattab O, Attia AM, Danpanichkul P, Hwang SY, Liu JS, Yalda T, Chen PJ, Gong J, Ferrone CR, Rich NE, Parikh ND, Pinato DJ, Singal AG, Yang JD. Am J Gastroenterol. 2026 Feb 12. doi: 10.14309/ajg.0000000000003956. Online ahead of print. PMID: 41677135.
2. Gastrointestinal cancer statistics in 2022 and projection to 2050: GLOBOCAN estimates across 185 countries. Danpanichkul P, Pang Y, Tothananunroj P, Dejvajara D, Kim D, Saokhieo P, Suparan K, Muthiah MD, Duangsonk K, Bernal DO, Lui RN, Wijarnpreecha K, Abou-Alfa GK, Wallace MB, Roberts LR, Singal AG, Yang JD. Cancer. 2026 Jan 1;132(1):e70245. doi: 10.1002/cncr.70245.
3. Impact of pre-transplant immune checkpoint inhibitor use on post-transplant outcomes in HCC: A systematic review and individual patient data meta-analysis. Rezaee-Zavareh MS, Yeo YH, Wang T, Guo Z, Tabrizian P, Ward SC, Barakat F, Hassanein TI, Dave S, Ajmera V, Bhoori S, Mazzaferro V, Chascsa DMH, Liu MC, Aby ES, Lake JR, Sogbe M, Sangro B, Abdelrahim M, Esmail A, Schmderer A, Chouik Y, Rudolph M, Sohal D, Giudicelli H, Allaire M, Akce M, Guadagno J, Tow CY, Massoumi H, De Simone P, Kang E, Gartrell RD, Martinez M, Paz-Fumagalli R, Toskich BB, Tran NH, Solino GA, Poltronieri Pacheco DM, Kalman RS, Agopian VG, Mehta N, Parikh ND, Singal AG, Yang JD. J Hepatol. 2025 Jan;82(1):107.

Risk Stratification and Surveillance Strategies for HCC in Chronic Hepatitis B

Ju Dong Yang

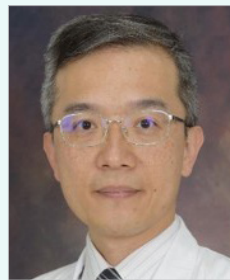
Cedars-Sinai Medical Center, USA

Chronic hepatitis B remains a leading cause of hepatocellular carcinoma (HCC) worldwide, contributing significantly to liver-related morbidity and mortality despite advances in vaccination and antiviral therapy. Although nucleos(t)ide analogue treatment reduces disease progression, it does not eliminate HCC risk, which persists even in treated patients and some individuals without cirrhosis. Early detection is essential, as it increases access to curative therapies and improves survival. However, variability in individual risk makes universal surveillance inefficient, particularly in resource-limited settings.

Recent data confirm a continued risk of HCC in HBV patients, with annual incidence ranging from 0.01% to 5.4% depending on cirrhosis and other factors. Risk prediction models such as PAGE-B, mPAGE-B, and REAL-B help identify patients exceeding the accepted surveillance threshold of 0.2% annual risk, enabling more targeted screening. Liver stiffness measurement further refines risk assessment by estimating fibrosis. In addition, biomarker-based models such as GALAD enhance detection sensitivity, especially when combined with imaging.

Ultrasound, with or without alpha-fetoprotein, remains the primary surveillance modality due to accessibility and cost-effectiveness. However, its limitations have prompted interest in alternative approaches. CT and MRI offer higher sensitivity but are less practical for routine use. Emerging tools, including liquid biopsies, circulating biomarkers, and artificial intelligence-based models, show promise for improving detection and personalizing surveillance. Virologic markers such as hepatitis B core-related antigen are also being explored as dynamic predictors of risk.

In summary, risk-based surveillance offers a more efficient, individualized approach to HCC screening in HBV. Combining risk scores, non-invasive fibrosis assessment, and novel biomarkers can improve early detection and resource allocation. Further validation and cost-effectiveness studies are needed to support broader implementation, particularly in diverse healthcare settings, with the goal of advancing early diagnosis and contributing to HBV elimination efforts.

**Tung-Hung Su***National Taiwan University, Taiwan*

Self Introduction

Dr. Tung-Hung Su earned his M.D. degree from the National Taiwan University College of Medicine in 2001 and his Ph.D. from the Graduate Institute of Clinical Medicine at the same university in 2015. He has been an attending physician specializing in Hepatology and a Clinical Professor in the Department of Internal Medicine at National Taiwan University Hospital since 2024. From 2017 to 2019, he was a visiting scholar at Stanford University. Dr. Su's research focuses on translational studies on liver fibrosis treatment, viral hepatitis B management, cirrhosis, and hepatocellular carcinoma, including disease prediction and outcome research using large-scale electronic medical records. Additionally, he applies artificial intelligence models to the study of liver diseases. He has published several research papers in these fields.

Research Interests

- Hepatitis B and MASLD
- HCC Surveillance
- AI applications in Hepatology

Representative Publications

1. Su TH, Wu CH, Kao JH. Artificial intelligence in precision medicine in hepatology. *J Gastroenterol Hepatol*. 2021 Mar;36(3):569-580
2. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liao SH, Hong CM, Liu CH, Lan TY, Yang HC, Liu CJ, Chen PJ, Kao JH. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. *Hepatol Int*. 2023 Oct;17(5):1139-1149.
3. Huang SC, Su TH, Tseng TC, Hsu SJ, Hong CM, Lan TY, Liu CH, Yang HC, Liu CJ, Kao JH. All-cause and cause-specific mortality in patients with chronic hepatitis B and concurrent steatotic liver disease. *J Hepatol*. 2025 Jul;83(1):43-51
4. Chang KC, Su TH, Wu CK, Huang SC, Tseng TC, Hong CM, Hsu SJ, Liu CH, Yang HC, Liu CJ, Kao JH. Metabolic dysfunction-associated steatotic liver disease is associated with increased risks of heart failure. *Eur J Heart Fail*. 2025 Mar;27(3):512-520
5. Su TH, Yang SS, Lee MH, Kao WY, Huang SC, Chen FF, Poon FS, Tsai LW, Chen YT, Lin C, Wang W, Kim WR, Kao JH. High SAFE scores predict hepatocellular carcinoma in viral and non-viral hepatitis and metabolic dysfunction associated steatotic liver disease. *Clin Mol Hepatol*. 2025 Jul;31(3):796-809

Clinical Course and Management Considerations after Antiviral Therapy Discontinuation in Chronic Hepatitis B

Tung-Hung Su*National Taiwan University, Taiwan*

Although antiviral therapy efficiently suppresses HBV replication, it cannot eradicate cccDNA from HBV-infected hepatocytes in a short course of treatment. Following the discontinuation of antiviral therapy, approximately 60–70% of patients experience a virological relapse (defined as HBV DNA > 2,000 IU/mL). Among them, roughly half will develop a clinical relapse (HBV DNA > 2,000 IU/mL, with ALT > 2x ULN). Conversely, 30–40% of patients who discontinue therapy will maintain low-level viremia and do not require further antiviral treatment. Because these patients have a higher likelihood of achieving a functional cure (HBsAg loss), finite therapy is a viable option for patients with low HBsAg levels at cessation and who can adhere to a strict monitoring schedule.

Following discontinuation, patients may experience a recurrence of viremia and hepatitis. Physicians must monitor viral activity closely and provide timely retreatment if a virus-dominant flare occurs. The most severe outcome is a severe hepatitis flare that leads to liver decompensation. These patients require prompt retreatment and close monitoring, with a small subset potentially requiring liver transplantation.

Due to the high potential for HBV relapse, disease activity must be monitored vigilantly, especially during the first year off-therapy. Patients should be evaluated monthly for the first 3 months, and then every 3 months until the 12-month mark. Relapse kinetics vary depending on the nucleos(t)ide analogue (NUC) used: patients discontinuing TDF or TAF typically relapse within the first 3 months, whereas those discontinuing ETV usually relapse 6–9 months post-cessation. Therefore, an individualized monitoring plan should be established based on the specific NUC. Regular assessment of ALT and HBV DNA is mandatory, while quantitative HBsAg monitoring may be necessary to differentiate between a virus-dominant and a host-dominant flare.

Ultimately, the decision to discontinue antiviral therapy must involve a shared decision-making process with the patient, emphasizing the critical need for ongoing monitoring of HBV activity, and that hepatitis B is not yet cured after NUC cessation.

**Edward Gane***University of Auckland, New Zealand*

Self Introduction

Dr. Gane trained in hepatology and liver transplantation at the King's College Institute of Liver Studies, London where he completed his doctoral thesis on pathogenesis of hepatitis C. In 1998, Dr Gane returned to New Zealand to set up the first national liver transplant unit. In 2007, Dr. Gane opened a dedicated Phase I research centre (Auckland Clinical Studies, now New Zealand Clinical Research) which helped develop the first oral cures for hepatitis C and is now focused on developing a finite cure for hepatitis B.

Dr. Gane is also the Government lead advisor for the New Zealand HBV and HCV elimination strategies. He is also assisting Pacific Island Governments with their HBV strategies

Research Interests

- Finite Cure for Hepatitis B
- New Therapies for HCC and NASH
- In vivo Gene Therapies for Inherited and Acquired Liver Diseases

Representative Publications

1. Lim SG, Baumert TF, Boni C, Gane E, Levrero M, et al. Scientific Basis of Combination Therapy for functional cure in Chronic Hepatitis B (CHB)" (reference number: NRGH-21-085V1B), Nature Reviews GH 2023; 20: 238-53.
2. Gillmore J, Gane E, Taubel J, Crispr/Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med 2021; 385(6):493-502.
3. Gane E, Verdon D, Brooks A, et al. Pilot study of anti-PD-1 blockade with and without therapeutic vaccination for chronic hepatitis B. J Hepatology 2019; 71: 900-907.
4. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir/Pibrentasvir for Patients with Hepatitis C and Severe Renal Impairment. N Engl J Med 2017;377:1448-55.
5. Gane E, Stedman C, Symonds W, et al. Once daily PSI-7977 plus RBV: pegylated interferon-alfa not required for sustained virologic response in treatment-naïve patients with HCV GT2 or GT3 N Engl J Med. 2013; 368: 34-44.

Innovative Therapeutic Strategies for Functional Cure in HBV

Edward Gane*University of Auckland, New Zealand*

The goal of therapy for chronic HBV infection is to improve quality of life and survival of the infected person by preventing progression to cirrhosis, decompensation and hepatocellular carcinoma (HCC). These endpoints can be partially achieved through maintained suppression of HBV replication with oral nucleot(s)ide (NUC) therapy, but this is usually lifelong and is associated with high cost, risk of break-through or nonadherence and potential toxicity. Also, NUCs reduce but do not remove the lifetime risk of HCC. Finally, most people who remain HBsAg positive continue to experience stigma and discrimination at home or in the workplace. Hence there is therefore great interest in developing a finite treatment strategy that will achieve durable off-treatment clearance of HBsAg and HBV DNA, so-called Functional Cure.

Recent advances in virology and immunology have identified many potential targets for new therapies. Current HBV Cure strategies target the high viral and antigen burden and inadequate host immune responses which characterise chronic HBV infection.

Pevifoscorvir is a new generation oral capsid assembly modulator. It is a potent inhibitor of HBV DNA and RNA at low concentrations through prevention of capsid formation. At higher concentrations, it can also depleted cccDNA through prevention of cccDNA disassembly – the so-called secondary mechanism of action. Current Phase II trials show pevifoscorvir monotherapy is safe and achieves rapid suppression of HBV DNA to below LOD, which may provide long-term benefits, in terms of more rapid reduction in integration burden and associated risk of hepatocarcinogenesis. Pevifoscorvir also does reduce HBsAg levels by 1-2 logs in HBeAg positive patients, presumably through the secondary mechanism of action. Longer term studies will determine whether it can lead to HBsAg loss.

Translation inhibitors can reduce HBV antigen production by intervening at the transcript level (mRNA). Translation inhibitors that been developed for HBV include siRNAs, antisense oligonucleotides (ASOs), PPAD5/7 inhibitors (RNA destabilisers), and transcription inhibitors.

Six PPAD5/7 inhibitors have been developed. All but one have been stopped for neurotoxicity either in preclinical or Phase I. GSK3965193 is still in clinical development in CHB patients.

Several siRNAs have entered clinical development. They achieve predictable 2-3 log reduction in HbsAg

but this effect plateaus after 4-6 month. HbsAg loss does not occur and rebound is universal. Their future role may be limited to reducing surface antigen burden to restore host immune responses prior to adding another novel therapy.

The first meaningful HBV Cure has been achieved with 24 weeks of antisense oligonucleotides, bepirovirsen and AHB-137, although efficacy is largely limited to patients with lower baseline HbsAg levels. The Phase II B-CLEAR study showed that 24 weeks of bepirovirsen 300mg could cure 10% of patients but this rate was increased in patients with baseline HBsAg levels below 3000 IU/mL. The Phase III has just completed and will be presented at EASL in May. Bepirovirsen is likely to be the first approved HBV Cure agent later this year. AHB-137 appears to be more potent than bepirovirsen in vitro and initial results from China Phase II studies reported higher HBsAg loss rates. AHB-137 is currently in phase III trials in China and Phase II in the rest of the world. HBsAg loss and cure following ASO therapy is associated with ALT flares, thought to reflect activation of the innate TLR-8 pathway. For this reason, ASOs are not recommended in cirrhotics.

CHB patients have poor humoral, and cell mediated immune responses to the virus, attributed to life-long high levels of HBV antigen and subsequent T-cell exhaustion. Vaccines that boost HBV-specific T or B cell immune responses could contribute to functional cure regimens but success in this approach has been sorely lacking. Over the last 30 years, multiple protein, peptide, DNA and viral vector-based vaccines have been developed but although these appear safe and immunogenic in healthy subjects, they have lacked efficacy in CHB patients. Two recent studies using GS-4774, a yeast-based vaccine, in NUC-naïve and NUC-experienced virally suppressed patients, showed minimal reduction in serum HBsAg levels] despite increased production of cytokines such as IFN γ by HBV-specific CD8 T cells. Recent approaches to therapeutic vaccines have focused on using viral vectors, inclusion of antigens from other regions of HBV such as core and polymerase instead of surface.

Restoration of T-cell responses has been observed without any shift in HBV DNA or HbsAg levels. However, animal studies have suggested that therapeutic vaccine (TherVacB) could achieve cure if preceded by lead-in siRNA (siHBV1/2) that lowers HBsAg levels to < 100 IU/mL (Michler T, et al. Gastroenterol 2020;158:1762–1775. This approach has now been evaluated in CHB patients without success (BR11-179/BR11-835 and AB-729/VTP-300). Combining therapeutic vaccines with anti-PD1 or pegylated interferon has also been disappointing with HBsAg loss only seen in patients with very low baseline HBsAg levels (<100 IU/mL).

Two novel immunogenic vaccines have recently entered clinical development, both incorporating two vaccines delivered by viral vectors in prime/boost to reduce neutralising antibodies. VRON-0200 expresses a genetically encoded checkpoint modifier (HSV1 glycoprotein D) fused with HBV core and pol (but not S) antigens, within chimpanzee adenoviral vector. VRON-0200 significantly increased T cell responses and reduced HBsAg levels in some CHB patients. GS-6779/GS-2829 encodes highly conserved regions of HBV Core, Pol and S delivered by 2 nonreplicating arenavirus vectors.

Other novel Immunotherapy approaches in HBV (TLR-7,8 and 9 agonists, checkpoint inhibitors) achieve variable suppression of HBsAg and restore HBV-specific immune responses but rarely achieve sustained HBsAg loss and only when the baseline HBsAg level is very low.

To date, enthusiasm for immunotherapies has been dampened by their associated toxicities, risk of flares and unpredictable antiviral effects.

In summary, initial HBV Cure regimens will combine multiple agents that inhibit replication, reduce HBV antigen burden and restore HBV-specific immune control. The successes to date of single agents in patients with chronic hepatitis B have been limited and in future, regimens containing multiple different classes of agents will be required. Initial HBV Cure regimens are likely to target patient populations most likely to respond (i.e., young patients without severe fibrosis or patients with low HBsAg levels). In the future, agents that direct eradicate or silence cccDNA may be able to achieve Complete or Sterilising Cure. However, gene editing approaches will need to overcome challenges of to deliver the drug efficiently to every infected hepatocyte and how to mitigate the long-term risks of chromosomal translocation in otherwise healthy young people.

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BASIC RESEARCH WORKSHOP 1

Viral Load-Based Immune Landscapes in Chronic Hepatitis B: From Tolerance to Cure

Chairs

Kyun-Hwan Kim (Sungkyunkwan Univ.)

Hyung Joon Yim (Korea Univ.)





Su-Hyung Park
KAIST

Self Introduction

Prof. Su-Hyung Park is a Professor and Department Chair at the Graduate School of Medical Science and Engineering (GSMSE), KAIST.

He received his Ph.D. from POSTECH in 2008 and subsequently completed postdoctoral training at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), USA, where he served as a postdoctoral fellow from 2008 to 2014. Following his postdoctoral training, he joined KAIST as an Assistant Professor in the Graduate School of Medical Science and Engineering.

Prof. Park leads the Laboratory of Translational Immunology and Vaccinology, where his research focuses on T cell immunity in a broad range of immune-related diseases, including cancer, autoimmune diseases, emerging infectious diseases, and viral hepatitis.

Research Interests

Prof. Su-Hyung Park's research focuses on T cell immunity in immune-related diseases, with the goal of translating fundamental immunological discoveries into improved therapeutic and preventive strategies. His laboratory investigates the mechanisms that regulate T cell responses in cancers, autoimmune diseases, emerging infectious diseases, and viral hepatitis. By integrating human immunology and translational research, his work aims to identify immune correlates of protection, disease progression, and treatment response. A major interest of the laboratory is understanding how T cell function can be modulated to enhance antiviral and antitumor immunity while controlling pathological immune activation in chronic inflammatory and autoimmune conditions.

Representative Publications

1. Robust effector memory features of human T-bethi B cells induced by repeated mRNA vaccination. *iScience* 29(2):114804 (2026)
2. Unique immune characteristics and differential anti-PD-1-mediated reinvigoration potential of CD8⁺ TILs based on BRCA1/2 mutation status in epithelial ovarian cancers. *Journal for ImmunoTherapy of Cancer* 12(7):e009058 (2024)
3. Anti-4-1BB×PD-L1 Bispecific Antibody Reinvigorates Tumor-Specific Exhausted CD8⁺ T Cells and Enhances the Efficacy of Anti-PD-1 Blockade. *Clinical Cancer Research* 30(18):4155-66 (2024)
4. A virtual memory CD8[±] T cell-originated subset causes alopecia areata through innate-like cytotoxicity. *Nature Immunology* 24(8):1308 (2023)
5. CEACAM1 marks highly suppressive intratumoral regulatory T cells for targeted depletion therapy. *Clinical Cancer Research* 29(9):1794 (2023)

Immune Dysfunction in Chronic Hepatitis B: Innate and Adaptive Perspectives

Su-Hyung Park KAIST

Chronic hepatitis B (CHB) is characterized by persistent hepatitis B virus replication, sustained antigen exposure, and broad dysregulation of antiviral immunity. This lecture will provide an overview of immune dysfunction in CHB, with emphasis on both adaptive and innate immune responses. In the adaptive immune compartment, prolonged antigen exposure contributes to functional impairment of HBV-specific CD8⁺ and CD4⁺ T cells, characterized by reduced cytokine production, impaired proliferative capacity, defective cytotoxicity, loss of polyfunctionality, and sustained expression of immune checkpoint receptors such as PD-1, CTLA-4, TIM-3, and LAG-3. Moreover, innate immune responses are quantitatively and qualitatively altered in CHB, involving attenuated pathogen recognition receptor signaling, suboptimal type I/III interferon induction, altered dendritic cell-mediated antigen presentation, dysregulated natural killer cell function, and aberrant inflammatory cytokine responses. These adaptive and innate immune alterations are further shaped by the tolerogenic intrahepatic microenvironment and collectively contribute to impaired antiviral control, viral persistence, and heterogeneous disease activity. This presentation will summarize the key immunologic features of CHB and provide an integrated perspective on how viral load and antigen burden shape antiviral immune dysfunction across innate and adaptive immune compartments.

**Sung-Gyoo Park***Seoul National University*

Self Introduction

Prof. Sung-Gyoo Park is a Professor at the College of Pharmacy, Seoul National University, and is currently serving as Associate Dean for Research & Planning Affairs at the same institution.

Prof. Park received his Ph.D. in Immunology from Seoul National University in 2003, following his M.S. (2000) and B.S. (1998) from the same institution.

After completing his doctoral training, Prof. Park pursued postdoctoral research at Yale Medical School and later at Columbia University under the mentorship of Sankar Ghosh. He subsequently held faculty positions at Gwangju Institute of Science and Technology, where he served in multiple leadership roles, including Dean of International and Public Affairs.

Since 2021, Prof. Park has been a Professor at Seoul National University, contributing to research and academic leadership in the fields of immunology and virology. His research focuses on molecular mechanisms of T cell activation, antigen receptor signaling, and viral infection-induced inflammatory diseases, utilizing both ex vivo systems and in vivo mouse models.

Research Interests

Prof. Sung-Gyoo Park has been interested in molecular mechanisms, especially T cell activation and regulations by using ex vivo cell systems and in vivo mouse model systems. In addition to T cell receptor signaling work, he is also working on inflammatory diseases induced by viral infections by identifying a new subset of T cells, viral protein-host responses, and new viral replication regulators. Based on this background in molecular mechanistic research, he also participated in a research program for immunological diseases caused by monogenic variation. These works identified the characteristics of many unresolved monogenic inflammatory diseases. Currently, Prof. Sung-Gyoo Park's lab focuses on viral infection-induced inflammatory diseases and monogenic factor-derived autoinflammatory diseases.

Representative Publications

1. Hyeong-Jin Cho, Sung-Gyoo Park. 2026. Regulation of Hepatitis B Virus cccDNA by Metabolic Pathways. *Clinical and Molecular Hepatology*. 32(1):381-384. 2026 Jan.
2. Jeong-Ryul Hwang, Chi Thi Ngoc Nguyen, Gwanghoon Ko, Jung-Ah Kang, Yeongseon Byeon, Seowoo Park, Ryunha Chang, Dawoon Jung, Mi Yeon Jeon, Young Hoon Sung, Cho-Rong Lee, Ki-Hoan Nam, Je Kyung Seong, Sankar Ghosh, Yun Pyo Kang*, Sung-Gyoo Park*. 2025. Pantothenate kinase 4 controls lipid synthesis for T-cell proliferation by modulating coenzyme A and glutaminolysis. *Signal Transduction and Targeted Therapy*. 10(1):302: 2025 Sep 18. *Co-correspondence.
3. So-Eun Bae, Sang-Heon Park, Chae Youn Kim, Cho-Rong Lee, Chanyeon Lee, Rosah May Payumo, So Yeon Kim, Kyu-Young Sim, Ho Jin Kim, Hyungseok Seo, Seong-Joon Koh, Seunghee Hong, Sung-Gyoo Park. 2025. Notch2-expressing CD4+ T cells attain immunoregulatory functions during autoimmune inflammation. *Cellular and Molecular Immunology*. 22(9):1077-1092. 2025 Sep.
4. Andrea Accogli[#], Saurabh Shaky^a, Taewoo Yang[#], ,,,, Sung-Gyoo Park* & Christopher J. Westlake*. 2024. Variants in the WDR44 WD40-repeat domain cause a spectrum of ciliopathy by impairing ciliogenesis initiation. *Nature Communications*. 15:365. 2024 Jan. *Co-correspondence.
5. WooChan Kim, Jung-Ah Kang, Minji Park, Pyeong-Hwa Jeong, Yoon Jun Kim, Yuri Cho*, Sung-Gyoo Park*, Yong-Chul Kim*. 2021. Discovery of Novel Pyrimidine-Based Capsid Assembly Modulators as Potent Anti-HBV Agents. *Journal of Medicinal Chemistry*. 64(9):5500-5518. 2021 May 13. *Co-correspondence.

Untreated Chronic HBV: Viremia-Dependent Immune States

Sung-Gyoo Park*Seoul National University*

Hepatitis B virus (HBV), a member of the Hepadnaviridae family, maintains its genome in the nucleus as covalently closed circular DNA (cccDNA), an episomal form that serves as the transcriptional template for viral RNAs. Although HBV is a DNA virus, it replicates through reverse transcription of a pregenomic RNA derived from cccDNA. A major clinical challenge of HBV infection is its strong association with the development of Hepatocellular carcinoma (HCC). Treatment with nucleos(t)ide analogues (NAs) effectively suppresses viral replication and reduces the risk of liver cirrhosis and HCC; however, complete cure remains difficult due to the persistence of cccDNA in the nucleus. Despite successful vaccination programs, a substantial number of chronic HBV carriers still exist worldwide.

HBV carriers can be broadly classified into three groups: inactive HBV, active HBV, and grey zone HBV. When focusing on exhausted T cell responses, accumulating evidence suggests that T cell dysfunction differs across these clinical states. In inactive HBV, HBV-specific T cells often exhibit a partially exhausted yet functionally recoverable phenotype, indicating that immune function is relatively preserved. In contrast, active HBV is associated with more profound T cell exhaustion, characterized by the co-expression of multiple inhibitory receptors and limited functional restoration even upon blockade of these pathways. Patients categorized as grey zone HBV, who do not fit classical clinical phases, display heterogeneous and dynamic exhaustion profiles, reflecting an intermediate and unstable immune state.

These observations suggest that T cell exhaustion in chronic HBV is not uniform but varies according to the clinical and virological state, which is closely linked to viral load. Indeed, therapeutic strategies aimed at reducing viral load, such as NA treatment, have been reported to partially improve T cell function. Furthermore, emerging approaches seek to reduce viral antigen burden, particularly hepatitis B surface antigen (HBsAg), which is not sufficiently controlled by NA treatment alone, in order to relieve exhaustion pressure and promote functional cure.

In conclusion, even in the absence of treatment, viral load varies among patients with chronic HBV infection and is closely associated with host immune responses. Among these, T cell exhaustion represents a key component of viremia-dependent immune regulation, and understanding how to effectively restore T cell function remains an important challenge in the pursuit of HBV cure.



Pil Soo Sung
The Catholic University of Korea

Self Introduction

Education and Training

- 2007.02 M.D., Medicine College of Medicine, The Catholic University of Korea, Seoul, Korea
- 2011.08 M.S., Internal Medicine (Hepatology), The Catholic University of Korea, Seoul, Korea
- 2016.02 Ph.D., Immunology, Graduate School of Medical Science & Engineering, KAIST, Daejeon, Korea

Positions and Honors

- 2007-2008 Rotating Internship, Catholic Medical Center, The Catholic University of Korea, Seoul, Korea
- 2008-2012 Residency, Department of Internal Medicine, Seoul St. Mary's hospital, The Catholic University of Korea, Seoul, Korea
- 2012-2016 Researcher and Teaching Assistant, Graduate School of Medical Science & Engineering, KAIST, Daejeon, Korea
- 2016-2018 Clinical Fellowship, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
- 2018-2020 Clinical Assistant Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
- 2020-2022 Assistant Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
- 2022-2025 Associate Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
- 2025-Present Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea

Professional Memberships

- 2007-Present The Korean Association of Medicine
- 2012-Present The Korean Association of Internal Medicine
- 2012-Present The Korean Association for the Study of the Liver
- 2013-Present The Korean Association of Immunologists
- 2014-Present The Korean Society of Biochemistry and Molecular Biology

Representative Publications

1. Kwon MH, Jang EJ, Tak KY, Cho HS, Han JW, Han ES, Kim Y, Lee H, Jang JW, Lee SH, Sung PS. Expanded but dysfunctional regulatory T cells in treatment-naïve autoimmune hepatitis. *Hepatology*. 2026 Feb;20(1):163-173.
2. Han JW, Kang MW, Lee SK, Yang H, Kim JH, Yoo JS, Cho HS, Jang EJ, Seo DH, Kwon JH, Nam SW, Bae SH, Jang JW, Choi JY, Yoon SK, Sung PS. Dynamic Peripheral T-Cell Analysis Identifies On-Treatment Prognostic Biomarkers of Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma. *Liver Cancer*. 2025;14(1):104-116.
3. Lee J, Cha JH, Cho HS, Yang K, Yang H, Nam H, Byun MY, Cho SK, Park J, Ko HW, Yang SW, Sung PS, Bae SH. The PNPLA3 I148M variant is associated with immune cell infiltration and advanced fibrosis in MASLD: a prospective genotype-phenotype study. *J Gastroenterol*. 2025 Oct;60(10):1284-1295.
4. Tak KY, Park MS, Sung PS. Plasma Exchange and Abrogation of Monocyte Activation in Wilson's Disease. *Clin Mol Hepatol*. 2025 Oct 13. doi:10.3350/cmh.2025.1039.
5. Kim JH, Han JW, Cho HS, Jang JW, Tak KY, Sung PS. Prognostic Significance of Glypican-3 Expression in Hepatocellular Carcinoma Treated with Atezolizumab-Bevacizumab. *Cancers (Basel)*. 2025 Dec 12;17(24):3967.

Immune Modulation Mechanisms during Antiviral Therapy

Pil Soo Sung The Catholic University of Korea

The therapeutic paradigm in chronic hepatitis B virus infection is moving from indefinite viral suppression toward functional cure, defined clinically as durable HBsAg loss with undetectable HBV DNA after treatment cessation. Current AASLD/IDSA guidance still positions entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide as preferred nucleos(t)ide analogues because of their potency and safety, while also emphasizing HBsAg loss as the desirable endpoint when achievable. The biological limitation of NA therapy is that it suppresses reverse transcription but does not directly eliminate cccDNA or integrated HBV DNA, allowing persistent HBV transcription, HBsAg production, and immune dysfunction.

Mechanistically, immune modulation during antiviral therapy should be understood as a sequence of events: viral suppression → antigen-load reduction → partial restoration of HBV-specific immunity → durable immune control. A particularly important axis is the HBx–SMC5/6 pathway. HBx promotes degradation of the host restriction factor SMC5/6, thereby maintaining active cccDNA transcription. RNAi or antisense-mediated depletion of HBV RNA reduces HBx expression, permits SMC5/6 reappearance, and may promote transcriptional silencing of cccDNA. This is not merely direct antiviral therapy; it is a form of molecular immune-environment remodeling that decreases antigenic pressure and may reopen the window for T-cell and B-cell recovery. The figures in the uploaded Science Translational Medicine review are useful for teaching: Fig. 1 shows why HBV RNAs from both cccDNA and integrants are targetable, Fig. 2 maps emerging antiviral classes across the HBV life cycle, and Fig. 3 illustrates how HBx depletion permits SMC5/6-mediated cccDNA repression.

The Korean immune-profiling study by Sung et al. provides an important clinical-immunologic bridge. In patients traditionally classified as “immune tolerant,” HBV-specific CD8⁺ T cells were detectable ex vivo using HBV core18–27 pentamer staining, despite weak immediate IFN-γ production. These cells showed a lower proportion of PD-1 positivity than HBV-specific CD8⁺ T cells in immune-active or anti-viral-treated phases, and some regained IFN-γ production after in vitro peptide stimulation. Thus, the “immune-tolerant” phase may not represent true deletional tolerance; rather, HBV-specific T cells may be present but functionally constrained and potentially inducible under appropriate stimulation. This supports the clinical rationale for early antigen-lowering or immune-modulatory strategies in selected

patients, particularly in East Asian genotype C–dominant populations.

Bepirovirsen, an antisense oligonucleotide targeting HBV RNA, is clinically important because it combines direct antiviral activity, HBsAg reduction, and intrinsic immunostimulatory potential. In the B-Clear phase 2b trial, bepirovirsen 300 mg weekly for 24 weeks achieved sustained HBsAg and HBV DNA loss in approximately 9–10% of participants, with higher response probability in those with lower baseline HBsAg. The B-Together study then tested a clinically attractive sequential strategy: bepirovirsen followed by pegylated interferon. In 108 NA-treated participants, the primary endpoint was achieved in 5 patients in Arm 1 and 8 patients in Arm 2, corresponding to 9% and 15%, and all responders had baseline HBsAg $\leq 3,000$ IU/mL. These results suggest that antigen knockdown alone may be insufficient for many patients, but it can prime a subset for subsequent immunomodulation with peg-IFN.

NA cessation represents another model of immune modulation, but with substantial clinical risk. In the RETRACT-B flare analysis, 1,552 HBeAg-negative virally suppressed patients stopped NA therapy; 350 developed ALT flares $\geq 5 \times$ ULN, 70.6% within the first year. Flares did not significantly increase HBsAg loss, and 13 patients developed decompensation after a flare, including 3 deaths. Older age, male sex, higher end-of-treatment HBsAg, prior TDF therapy, and early HBV DNA $> 5 \log_{10}$ IU/mL predicted flare risk. The 2026 long-term RETRACT-B follow-up of 2,029 patients showed a 10-year off-treatment HBsAg loss rate of 17%, but this rose to 52% when end-of-treatment HBsAg was < 100 IU/mL; by contrast, patients with HBsAg $\geq 1,000$ IU/mL had only 6% HBsAg loss, while 59% of the total cohort required retreatment.

Immune modulation in chronic HBV is not a single intervention but a staged therapeutic strategy. NA therapy suppresses replication; RNA-targeting agents such as bepirovirsen reduce antigen burden and may silence cccDNA transcription through HBx depletion; peg-IFN or future immunotherapies may then amplify host control. NA withdrawal can stimulate immunity, but RETRACT-B shows that this is safe only in carefully selected, non-cirrhotic, low-qHBsAg patients under strict monitoring. The emerging clinical algorithm is therefore: suppress HBV DNA, quantify antigen burden, select low-risk patients, lower HBsAg, add immunomodulation when appropriate, and monitor aggressively for flare and relapse.

THE
LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
in conjunction with EALA

June 11-13, 2026 | Conrad Seoul, Korea



Eui-Cheol Shin
KAIST

Self Introduction

Dr. Eui-Cheol Shin is a Professor at Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea. He received M.D. (1996) and Ph.D. (2001) from Yonsei University College of Medicine, Seoul, Republic of Korea, and was trained as a postdoctoral fellow at NIDDK, National Institutes of Health, Bethesda, Maryland, USA (2002 - 2007). Then he joined Graduate School of Medical Science and Engineering, KAIST in 2007, where he is currently a Professor. During the COVID-19 pandemic, he served as the director of the Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon, Republic of Korea (2021 - 2024). He was elected the Fellow of the Korea Academy of Science and Technology (2019) and the Fellow of the National Academy of Medicine of Korea (2024).

His lab investigates T cell responses in human viral disease and cancer with a focus on CD8+ T cells. In particular, his lab studies cytokine-mediated, TCR-independent activation of CD8+ T cells that contribute to host cell injury. A series of his studies has revived the research of bystander T cell activation in microbial infections as a cause of immunopathologic host injury (Nat Immunol 2022, 23:13).

Research Interests

Viral Immunology, Viral Hepatitis, Tumor Immunology, Immune Aging, and Human Immunology

Representative Publications

1. Lee et al. TCR signaling via NFATc1 constrains IL-15-induced NK-like activation of human memory CD8+ T cells. *Immunity* 58:2957-2971, 2025.
2. Kim et al. Epigenetic scars in regulatory T cells are retained after successful treatment of chronic hepatitis C with direct-acting antivirals. *J Hepatol* 81:806-818, 2024.
3. Koh et al. Identification of a distinct NK-like hepatic T-cell population activated by NKG2C in a TCR-independent manner. *J Hepatol* 77:1059-1070, 2022.
4. Jung et al. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. *Nat Microbiol* 7:909-917, 2022.
5. Lee et al. Significance of bystander T cell activation in microbial infection. *Nat Immunol* 23:13-22, 2022.

Functional Cure: Mechanisms of Sustained Immune Control

Eui-Cheol Shin KAIST

“Functional Cure” can be achieved among patients with chronic hepatitis B virus (HBV) infection even without complete eradication of the virus from the host. Functional cure is defined by sustained loss of hepatitis B surface antigen (HBsAg) and undetectable serum HBV DNA, which persist even after discontinuation of antiviral therapy. Accumulating evidence suggests that functional cure is largely mediated by immunological mechanisms. During chronic HBV infection, HBV-specific humoral and cellular immune responses are often exhausted or functionally impaired due to persistent antigen exposure. In individuals who achieve functional cure, these virus-specific immune responses appear to recover, leading to effective immune control of viral replication and antigen production. This lecture will discuss the immunological characteristics associated with functional cure in chronic HBV infection, with particular emphasis on the restoration of HBV-specific humoral and cellular immune responses and their potential roles in long-term viral control.

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BASIC RESEARCH WORKSHOP 2

Basic and Translational Research Methodologies in HBV Studies

Chairs

Eui-Cheol Shin (KAIST)

Jeong Won Jang (The Catholic Univ. of Korea)



**Kyun-Hwan Kim***Sungkyunkwan University*

Self Introduction

Kyun-Hwan Kim is a molecular virologist, currently a Professor of Precision Medicine at Sungkyunkwan University Medical School. He initially trained in Korea, obtaining a BS/MS from Seoul National University and a Ph.D. at Yonsei University, followed by postdoctoral studies at Brown University. He returned to Korea in 2005 to establish a Virology research laboratory at Konkuk University in Seoul. He moved to Sungkyunkwan University in Mar 2020. He serves as an academic editor at PLoS ONE, Frontiers in Immunology, and World Journal of Gastroenterology.

Research Interests

The Kyun-Hwan Kim's lab works in the fields of hepatitis B virus, influenza virus, coronavirus, and virus-related diseases, attempting to decipher the molecular and cellular mechanisms that control viral replication, life-cycle, and virus-induced diseases. Current interests and investigations include the viral evasion against host immune systems, drug resistance, and the development of antivirals.

Representative Publications

1. Dezhbord M, Kim SH, Park S, et al., & Kim KH*. Novel role of MHC class II transactivator in hepatitis B virus replication and viral counteraction. Clin Mol Hepatol. 2024. Jul 30;30(3):539.
2. Shin GC, Moon SU, Kang HS, et al., & Kim KH*. PRKCSH contributes to tumorigenesis by selective boosting of IRE1 signaling pathway. Nat. Commun. 2019. Jul 18;10(1):3185.
3. Park ES, Lee AR, Kim DH, et al., & Kim KH*. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. J Hepatol. 2019. Jun 70(6):1093-1102.
4. Park ES, Byun YH, Park S, et al., & Kim KH*. Co-degradation of interferon signaling factor DDX3 by PB1-F2 as a basis for high virulence of 1918 pandemic influenza. EMBO J. 2019. May 15;38(10).
5. Kim DH, Park ES, Lee AR, et al., & Kim KH*. Intracellular interleukin-32 γ mediates antiviral activity of cytokines against hepatitis B virus. Nat. Commun. 2018. Aug 16;9(1):3284.

Molecular Techniques for Analyzing HBV Replication and cccDNA Transcriptional Activity

Kyun-Hwan Kim*Sungkyunkwan University*

Chronic hepatitis B virus (HBV) infection is associated with significant morbidity and mortality, fibrosis, cirrhosis, end-stage liver diseases and primary hepatocellular carcinoma (HCC). More than 240 million people are chronically infected with HBV, with some 600,000 deaths per year attributed to the virus. The current antiviral drugs can efficiently control but not eliminate HBV in the carriers at risk to develop liver diseases and cancer. HBV patients often require lifelong therapies and cure is still a challenging goal because HBV establishes a stable nuclear persistence form, the so-called HBV cccDNA, in infected hepatocytes. Therefore, targeting HBV cccDNA is a critical issue if we want to cure HBV infection.

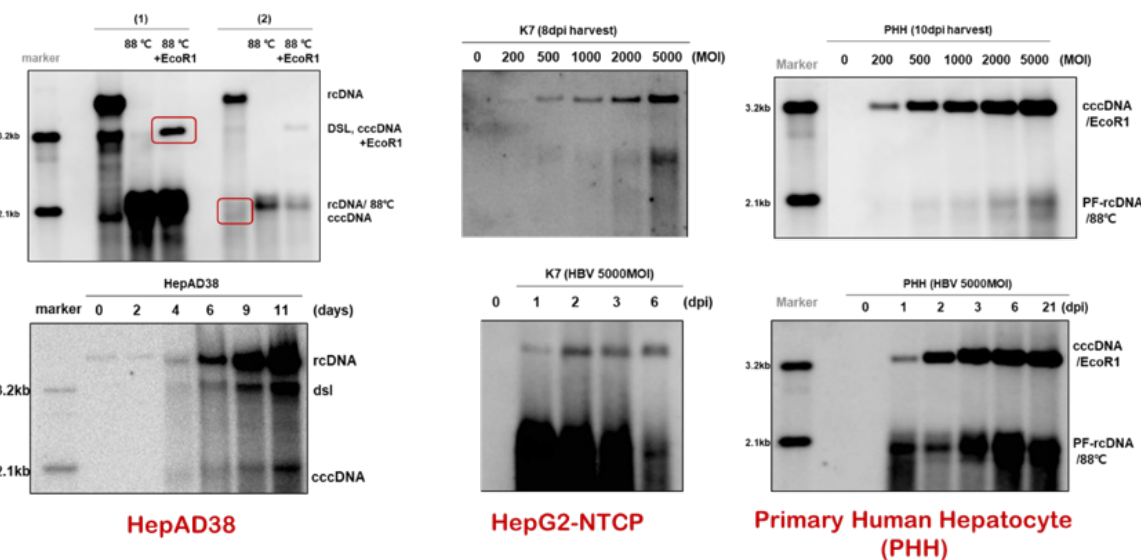
To study HBV using cell or animal models, it is essential to analyze HBV replication and cccDNA transcription activity. The gold standard for studying viral replication is the Southern blot. This method, which involves direct measurement without amplification, is the most accurate; however, it has the disadvantage of being highly complex and presenting significant technical barriers, resulting in poor reproducibility when first attempted. Another method involves the use of real-time PCR. Whilst this method is relatively simple and has low technical barriers, it involves amplification for detection, which carries the risk of yielding erroneous results.

The most accurate method for measuring cccDNA transcription is Northern blotting; other methods include enhancer activity assays, ChIP using transcription factors, and RNA-seq.

In this talk, I will review and introduce these molecular techniques for the study of HBV replication and cccDNA transcriptional activity.

Keyword: Hepatitis B virus (HBV), Covalently closed circular DNA (cccDNA), Replication, Transcription, Southern/Northern blot

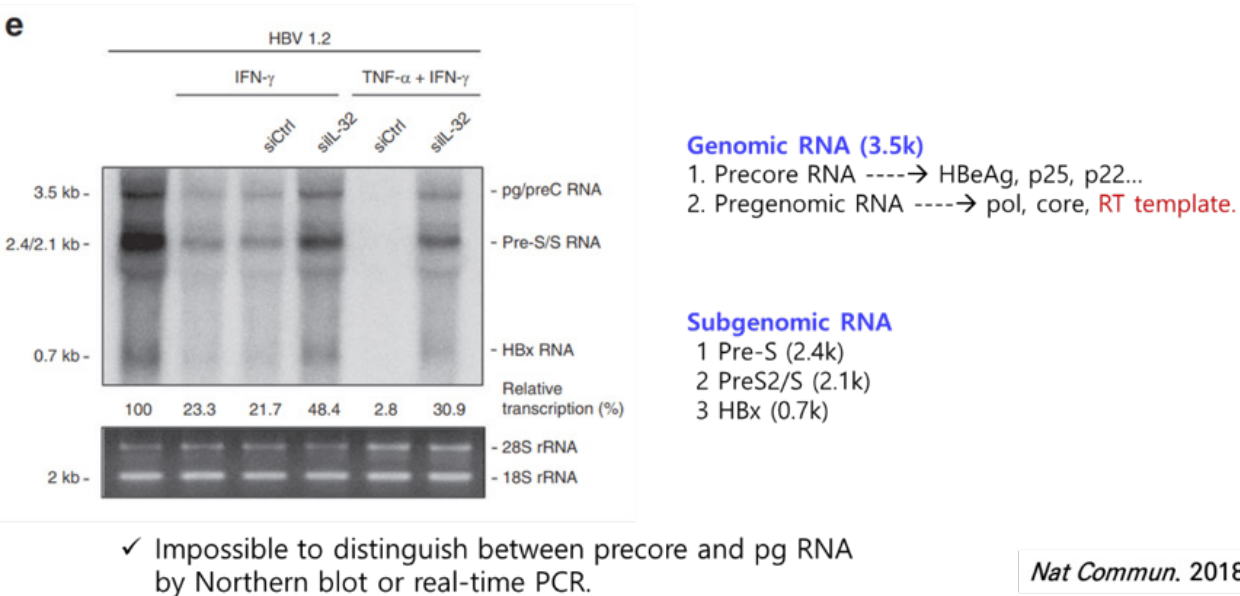
Detection of cccDNA by Southern Blot



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Detection of HBV RNAs by Northern Blot





Heeju Ryu
Sungkyunkwan University

Self Introduction

Prof. Heeju Ryu is an Assistant Professor of the Department of Immunology, School of Medicine at Sungkyunkwan University. Prof. Ryu graduated from the University of Michigan, Ann Arbor with her Bachelor of Science in Chemistry with Distinction in 2013 and received her Ph.D. in Pharmacy from the College of Pharmacy at Seoul National University in 2019. She completed her postdoctoral training at the Vaccine and Infectious Disease Division at the Fred Hutchinson Cancer Center from 2020 to 2024. Since 2024, Prof. Ryu has been recognized with a number of prestigious fellowships and honors, including the SITC Young Investigator Travel Award (2022), the Illumina Multi-omics Award (2024), and the AAI Early Career Faculty Travel Grant (2025).

Research Interests

The Ryu lab investigates how immune cell functional states drive disease progression and clinical outcomes, particularly in the contexts of cancer, viral infections, and liver transplantation. By employing high-dimensional immune profiling approaches, our goal is to uncover novel immunotherapeutic strategies and predictive biomarkers. Ultimately, we seek to translate mechanistic insights into clinically actionable models of anti-tumor immunity and allograft tolerance.

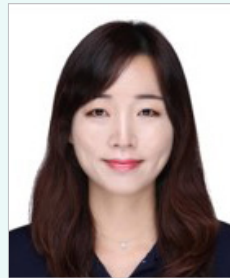
Representative Publications

1. Jones D, ..., Ryu H, Newell E. Cell simulation as cell segmentation. Nature Methods; 2025 May
2. Ye L*, Ryu H*, ..., Newell E, Redwood A. Stem-like exhausted CD8 T cells in pleural effusions predict improved survival in NSCLC and mesothelioma. Translational Lung Cancer Research; 2024 Sep; 13:2352 (*co-first authors)
3. Ryu H, ... , Newell E. Merkel cell polyomavirus-specific and CD39+CLA+ CD8 T cells as blood-based predictive biomarkers for PD-1 blockade in Merkel cell carcinoma; Cell Reports Medicine; 2024 Feb; 5:101390
4. Mayer-Blackwell K*, Ryu H*, ..., McElrath M, Newell E. mRNA vaccination boosts S-specific T cell memory and promotes expansion of unique CD45RAint TEMRA-like CD8+ T cells in COVID-19 recovered individuals. Cell Reports Medicine; 2023 Aug; 4:101149 (*co-first authors)
5. Ryu H, ..., Chung Y. Atherogenic dyslipidemia promotes autoimmune follicular helper T cell responses via IL-27. Nat Immunol. 2018 Jun; 19(6):583-593

Cell Culture, in vitro, and Animal Models

Heeju Ryu Sungkyunkwan University

The restricted host tropism of the Hepatitis B virus (HBV) presents a significant challenge in translational research, making the selection of appropriate experimental models critical. This session provides a focused overview of the core *in vitro* and *in vivo* methodologies utilized in current HBV studies. We will review the technical parameters, advantages, and limitations of established *in vitro* systems, spanning traditional immortalized hepatoma cell lines to more physiologically relevant platforms such as primary human hepatocytes and 3D liver organoids. Additionally, the session will examine key *in vivo* approaches, with a focus on the practical applications of humanized liver chimeric mice and surrogate hepadnaviral infection models. By systematically comparing these platforms, the presentation aims to guide researchers in selecting the most appropriate and robust models for their specific experimental objectives, including viral replication assays, host-pathogen interaction studies, and the preclinical evaluation of novel therapeutics.



Seunghee Hong
Yonsei University

Self Introduction

Prof. Seunghee Hong is a Principal Investigator in the Department of Biochemistry at Yonsei University, Republic of Korea. She has extensive expertise in immunology, molecular biology, and bioinformatics, with a particular focus on systems biology and multi-omics analysis of autoimmune and inflammatory diseases.

Prof. Hong received her B.S. in Biochemistry and Applied Statistics from Yonsei University in 2003, followed by a Ph.D. in Molecular Virology from Case Western Reserve University in 2010. She subsequently completed her postdoctoral training in Immunology at the Baylor Research Institute for Immunology in 2016.

Following her postdoctoral training, Prof. Hong served as a Research Associate at the Baylor Research Institute for Immunology (2016–2017), and later joined Weill Cornell Medicine as an Instructor (2017–2020) and Senior Bioinformatics Analyst (2020–2021). Since 2021, she has been leading her independent research as a Principal Investigator at Yonsei University. Her research integrates high-throughput transcriptomics, single-cell sequencing, and computational approaches to elucidate immune mechanisms and identify therapeutic targets in autoimmune diseases.

Research Interests

Prof. Seunghee Hong's research focuses on uncovering the molecular and cellular mechanisms of immune regulation in autoimmune and inflammatory diseases through integrative multi-omics approaches. Her work emphasizes systems immunology, particularly the use of bulk and single-cell transcriptomics to identify disease biomarkers and characterize immune cell heterogeneity.

She is also interested in developing and applying computational and bioinformatics methods, including longitudinal data analysis and machine learning, to interpret high-dimensional datasets. Through these approaches, her research aims to elucidate pathogenic immune networks and contribute to the discovery of novel therapeutic targets and precision medicine strategies.

Representative Publications

1. Banchereau, R.*, S. Hong*, B. Cantarel, N. Baldwin, J. Baisch, M. Edens, A. M. Cepika, P. Acs, J. Turner, E. Anguiano, P. Vinod, S. Khan, G. Obermoser, D. Blankenship, E. Wakeland, L. Nassi, A. Gotte, M. Punaro, Y. J. Liu, J. Banchereau, J. Rossello-Urgell, T. Wright, and V. Pascual. "Personalized Immunomonitoring Uncovers Molecular Networks That Stratify Lupus Patients." *Cell* 165, no. 6 (Jun 2 2016): 1548-50.
2. Hong, S.*, R. Banchereau*, B. L. Maslow, M. M. Guerra, J. Cardenas, J. Baisch, D. W. Branch, T. F. Porter, A. Sawitzke, C. A. Laskin, J. P. Buyon, J. Merrill, L. R. Sammaritano, M. Petri, E. Gatewood, A. M. Cepika, M. Ohouo, G. Obermoser, E. Anguiano, T. W. Kim, J. Nulsen, D. Nehar-Belaid, D. Blankenship, J. Turner, J. Banchereau, J. E. Salmon, and V. Pascual. "Longitudinal Profiling of Human Blood Transcriptome in Healthy and Lupus Pregnancy." *J Exp Med* 216, no. 5 (May 6 2019): 1154-69.
3. Nehar-Belaid, D.*, S. Hong*, R. Marches, G. Chen, M. Bolisetty, J. Baisch, L. Walters, M. Punaro, R. J. Rossi, C. H. Chung, R. P. Huynh, P. Singh, W. F. Flynn, J. A. Tabanor-Gayle, N. Kuchipudi, A. Mejias, M. A. Collet, A. L. Lucido, K. Palucka, P. Robson, S. Lakshminarayanan, O. Ramilo, T. Wright, V. Pascual, and J. F. Banchereau. "Mapping Systemic Lupus Erythematosus Heterogeneity at the Single-Cell Level." *Nat Immunol* 21, no. 9 (Sep 2020): 1094-106.
4. Jin, S. P., K. Lee, Y. J. Bang, Y. H. Jeon, S. Jung, S. J. Choi, J. S. Lee, J. Kim, E. Guttman-Yassky, C. G. Park, H. J. Kim*, S. Hong*, and D. H. Lee*. "Mapping the Immune Cell Landscape of Severe Atopic Dermatitis by Single-Cell Rna-Seq." *Allergy* 79, no. 6 (Jun 2024): 1584-97.
5. Yoon, S. H., C. Y. Kim, E. Lee, C. Lee, K. S. Lee, J. Lee, H. Park, B. Choi, I. Hwang, J. Kim, T. G. Kim, J. Son, Y. M. Hyun, S. Hong, and J. W. Yu. "Microglial Nlrp3-Gasdermin D Activation Impairs Blood-Brain Barrier Integrity through Interleukin-1beta-Independent Neutrophil Chemotaxis Upon Peripheral Inflammation in Mice." *Nat Commun* 16, no. 1 (Jan 15 2025): 699.

Sub-Cellular in Situ Profiling of Chronic Hepatitis B Liver Tissue Identifies Spatial Niches of Immune Tolerance in 'Grey Zone' Patients

Seunghee Hong Yonsei University

Hepatitis B virus (HBV) is a major cause of acute and chronic hepatitis B (CHB) and contributes significantly to mortality from chronic liver disease. After entering hepatocytes, HBV forms covalently closed circular DNA (cccDNA) in the nucleus, which persists as an episomal form indistinguishable from host DNA and serves as a stable template for viral replication.¹ Although elimination of cccDNA is essential for a complete cure, current treatments are limited to suppressing viral replication using nucleotide analogues (NAs) due to its persistence.² In addition, functional exhaustion of cytotoxic T cells in CHB patients is closely associated with high viral burden, making immune restoration a key therapeutic goal.³ In Asian populations, where vertical transmission predominates, strong immune tolerance is often established. While interferon therapy can epigenetically suppress cccDNA transcription and activate cytotoxic T cells, its clinical use is limited by significant side effects. Therefore, next-generation strategies focus on a multi-step approach combining antiviral suppression with immune modulation, such as therapeutic vaccines to enhance antibody and T-cell responses.⁴

HBV is a non-cytopathic virus, and liver damage primarily results from host immune responses rather than direct viral effects. During the immune-active phase, monocyte-derived macrophages infiltrate liver tissue and promote hepatocyte death and fibrosis through pro-inflammatory cytokines.⁵ The interplay between viral replication and host immunity results in diverse clinical phases, including inactive, active, and the poorly defined "Grey Zone".⁶ Conventional serum markers such as ALT and AST reflect overall liver injury but fail to capture localized immune evasion or viral activity within specific tissue niches.⁷ In Grey Zone patients, discordance between viral load and liver enzyme levels highlights the need for microenvironment-level analysis to better understand mechanisms regulating cccDNA.

To address these limitations, we applied Xenium, a next-generation spatial transcriptomics platform capable of detecting hundreds of genes at sub-cellular resolution [8]. Using a customized panel to detect multiple HBV subtypes and HDV RNA, we profiled liver tissues and classified Grey Zone patients into two subgroups: viral Grey (vGrey; high viral load with low liver enzymes) and Grey (lower viral load with relatively elevated liver enzymes). Increased immune cell infiltration and apoptosis were observed only in the Active group. However, cell-type composition alone could not explain suppressed apoptosis in

indeterminate groups.

Using scNiche, a spatial omics-based method for identifying shared cellular niches,⁹ we identified a conserved niche centered on HBV-infected hepatocytes present in both Active and indeterminate groups. Notably, hepatocyte apoptosis within this niche was significantly elevated only in the Active group. Spatial analysis revealed that infected hepatocytes were more frequently adjacent to T cells in the Active group, and these T cells showed higher expression of cytotoxic genes such as GZMA, along with enriched T-cell activation pathways.

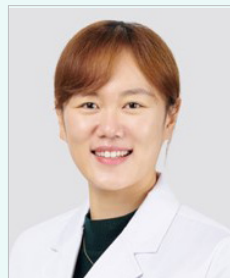
Overall, this study reveals that hepatocyte death in CHB is regulated by spatially organized immune interactions that are not captured by conventional single-cell analyses. The findings provide in situ validation of immune-mediated hepatocyte killing, demonstrating that effective T-cell engagement occurs specifically in the Active phase. In contrast, the vGrey condition is characterized by spatial exclusion of T cells or localized immunosuppression, explaining the lack of necroinflammation despite high viral load. These results highlight the importance of spatial immune niches in CHB pathogenesis and provide a foundation for early intervention and personalized therapeutic strategies targeting the vGrey phenotype.

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2. J. Chang, F. Guo, X. Zhao, J.-T. Guo, Therapeutic strategies for a functional cure of chronic hepatitis B virus infection, Acta Pharmaceutica Sinica B 4(4) (2014) 248-257.
3. B. Laupèze, V. Vassilev, S. Badur, A role for immune modulation in achieving functional cure for chronic hepatitis B among current changes in the landscape of new treatments, Expert Review of Gastroenterology & Hepatology 17(11) (2023) 1135-1147.
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5. Q. Bai, X. Hong, H. Lin, X. He, R. Li, M. Hassan, H. Berger, F. Tacke, C. Engelmann, T. Hu, Single-cell landscape of immune cells in human livers affected by HBV-related cirrhosis, JHEP Reports 5(11) (2023) 100883.
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7. M. Li, R. Sun, L. Xu, W. Yin, Y. Chen, X. Zheng, Z. Lian, H. Wei, Z. Tian, Kupffer Cells Support Hepatitis B Virus–Mediated CD8+ T Cell Exhaustion via Hepatitis B Core Antigen–TLR2 Interactions in Mice, The Journal of Immunology 195(7) (2015) 3100-3109.
8. S. Marco Salas, L.B. Kuemmerle, C. Mattsson-Langseth, S. Tismeyer, C. Avenel, T. Hu, H. Rehman, M. Grillo, P. Czarnewski, S. Helgadottir, K. Tiklova, A. Andersson, N. Rafati, M. Chatzinikolaou, F.J. Theis, M.D. Luecken, C. Wählby, N. Ishaque, M. Nilsson, Optimizing Xenium In Situ data utility by quality assessment and best-practice analysis workflows, Nature Methods 22(4) (2025) 813-823.
9. J. Qian, X. Shao, H. Bao, Y. Fang, W. Guo, C. Li, A. Li, H. Hua, X. Fan, Identification and characterization of cell niches in tissue from spatial omics data at single-cell resolution, Nature Communications 16(1) (2025) 1693.

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**Su Bin Lim***Ajou University*

Self Introduction

Prof. Su Bin Lim is an Associate Professor in the Department of Biochemistry & Molecular Biology at Ajou University School of Medicine, South Korea. She received her B.Eng. and Ph.D. from the National University of Singapore, followed by postdoctoral training at the Johns Hopkins University School of Medicine, USA. She joined Ajou University as an Assistant Professor in 2021 and was promoted to Associate Professor in 2025.

She has served as a Committee Member of the Korean Genome Organization (KOGO) and the Korean Society for Bioinformatics (KSBI). She is also an Editorial Board Member of Scientific Data and serves as an Associate Editor of Genomics & Informatics.

Prof. Lim leads an interdisciplinary research team focused on developing innovative approaches to precision medicine by integrating artificial intelligence with systems biology and multi-omics data analysis. Her research aims to extract clinically meaningful insights from large-scale genomic datasets and to identify novel therapeutic targets for cancer and neurodegenerative diseases.

Research Interests

AI Biology, Systems Biology, Single-Cell Analysis, Multi-Omics

Representative Publications

1. SB Lim et al. An extracellular matrix-related prognostic and predictive indicator for early-stage non-small cell lung cancer, *Nature Communications* 8 (1), 1-11, 2017
2. SB Lim et al. Addressing cellular heterogeneity in tumor and circulation for refined prognostication, *PNAS* 116 (36), 17957-17962, 2019
3. KY Goh et al. Matrisomal genes in squamous cell carcinoma of head and neck influence tumor cell motility and response to cetuximab treatment. *Cancer Communications* 42 (4), 2022
4. SB Lim et al. Macrophage-derived TNF-enriched tumor microenvironment shapes pancreatic ductal adenocarcinoma into the basal-like molecular phenotype through upregulating TAp63. *Clinical and Translational Medicine* 13(12), e1520, 2023
5. JW Hong et al. Multiomics profiling of buffy coat and plasma unveils etiology-specific signatures in hepatocellular carcinoma. *Clinical and Molecular Hepatology* 30(3), 2024

High-Dimensional and Multi-Omics Approaches in HBV Research

Su Bin Lim*Ajou University*

HBV infection drives complex molecular and immunological alterations across multiple cellular and spatial scales, necessitating integrative high-dimensional approaches to fully understand hepatocarcinogenesis and therapeutic vulnerabilities. In this lecture, we will discuss recent advances in multi-omics technologies applied to HBV research, including bulk and single-cell transcriptomics, spatial transcriptomics, proteogenomics, and sequencing-based integrative analyses. Representative recent studies will be highlighted to demonstrate how these approaches enable the characterization of tumor heterogeneity, immune exhaustion, stromal remodeling, and virus-associated oncogenic programs in HBV-related liver disease and hepatocellular carcinoma (HCC). In addition, we will share our recent translational research integrating plasma proteomics, single-cell and spatial transcriptomics, and tumor microenvironment analysis to identify a TREM2-driven macrophage program associated with immunosuppressive and aggressive HCC. Particular emphasis will be placed on how high-dimensional datasets can be translated into biologically and clinically meaningful insights, with practical perspectives on experimental design, computational analysis, biomarker discovery, and future precision medicine applications in HBV research.

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June 11-13, 2026 | Conrad Seoul, Korea



CAREER DEVELOPMENT FOR YOUNG INVESTIGATOR

Beyond the White Coat: Diverse Journeys in Modern Medicine

Chairs

So Young Kwon (Konkuk Univ.)

Hyung Joon Kim (Chung-Ang Univ.)



**Hyung Jin Choi**

Seoul National University

Self Introduction

Prof. Hyung Jin Choi is a Professor of the Department of Anatomy and Cell Biology, College of Medicine and the Department of Brain and Cognitive Science, College of Natural Sciences, Seoul National University.

Prof. Choi graduated from Seoul National University College of Medicine with his medical degree in 2002 and completed his internship, residency, and endocrinology fellowship at the Division of Endocrinology, Department of Internal Medicine at Seoul National University Hospital.

Research Interests

Prof. Choi is committed to advancing our understanding of the neural circuit mechanisms underlying motivated behaviors. His primary focus has been on the regulation of eating behavior, approached from both evolutionary biology and clinical medicine perspectives. As securing energy is fundamental to survival, his experience as an endocrinologist has highlighted the role of excessive eating drives in major health issues such as obesity and addiction.

Representative Publications

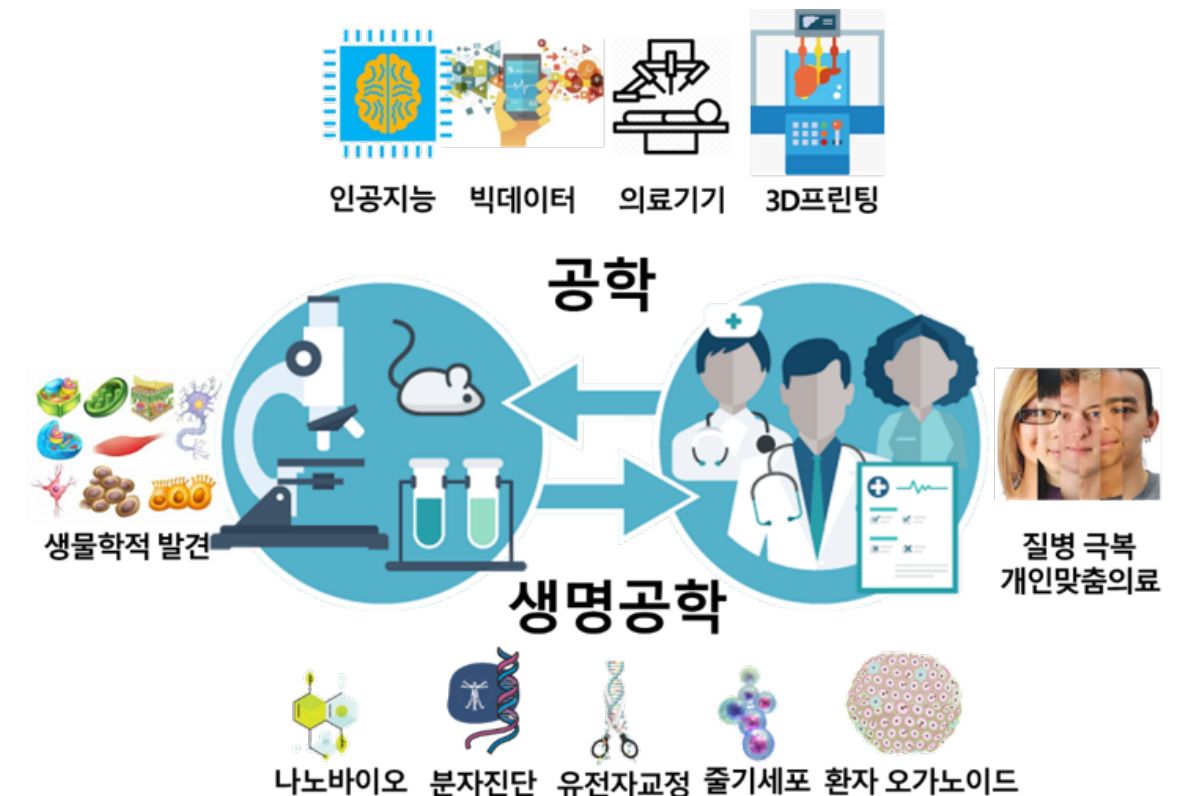
1. GLP-1 Increases Pre-ingestive Satiety via Hypothalamic Circuits in Mice and Humans. *Science*. 2024/7. Co-corresponding author. (IF=45.8)
2. Hypothalamic neuronal activation in non-human primates drives naturalistic goal-directed eating behavior. *Neuron*. 2024/4. Co-corresponding author. (IF=15.0)
3. Lateral Hypothalamic Leptin Receptor Neurons Drive Hunger-gated Food-seeking and Consummatory Behaviours. *Nature Communications*. 2023/2. Co-corresponding author. (IF=15.7)
4. AI-powered 3D pathology protocol enhances enteric nervous system visualization and quantification for clinical diagnostics. *Theranostics*. 2025/6. Co-corresponding author. (IF=13.3)
5. A Normative Framework Dissociates Need and Motivation in Hypothalamic Neurons. *Science Advances*. 2024/11. Co-corresponding author. (IF=12.5)

The Journey of a Physician-Scientist: Bridging the Bench and the Bedside

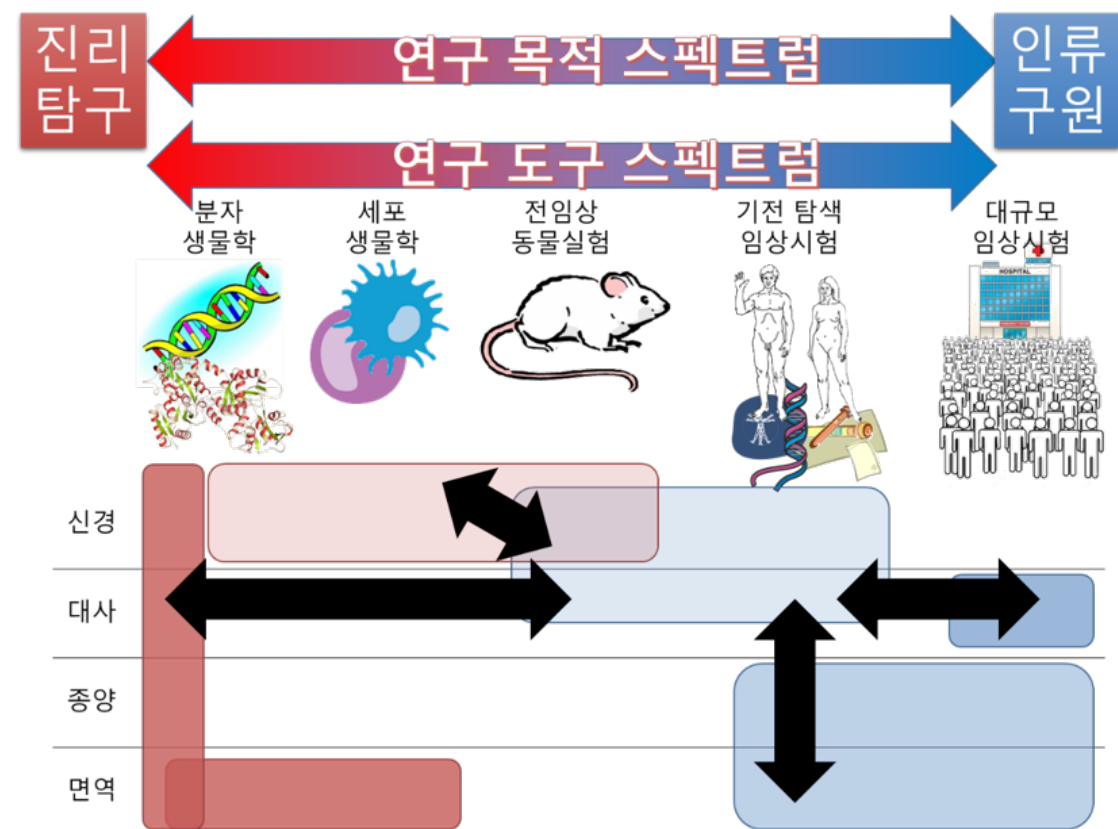
Hyung Jin Choi

Seoul National University

The physician-scientist occupies a singular vantage point in modern medicine, standing where laboratory discovery meets clinical care. This translational mission is being profoundly reshaped by the convergence, where biological discovery now meets a rapidly expanding ecosystem of enabling technologies. Engineering advances—artificial intelligence, big data, medical devices, and 3D printing—together with biotechnological breakthroughs in nanobiology, molecular diagnostics, gene editing, stem cells, and patient-derived organoids, are transforming how disease is understood, modeled, and treated. The result is a new era of precision and personalized medicine, in which the physician-scientist serves as the essential interpreter between molecular complexity and individual patient need.



Biomedical research unfolds along a continuous spectrum—from the pursuit of fundamental truth to the salvation of human lives, paralleled by a corresponding spectrum of tools that progress from molecular and cellular biology, through preclinical animal models, to mechanism-probing and large-scale clinical trials. Across disease domains such as neurology, metabolism, oncology, and immunology, the physician-scientist moves bidirectionally along this continuum, carrying unanswered clinical questions back to the bench and translating molecular insight forward to the bedside.



Yet the path remains demanding: failed experiments, clinical losses, funding pressures, and shrinking protected time threaten the pipeline. Sustaining this vocation requires deliberate mentorship, institutional support, and a renewed commitment to a simple promise—that what is learned at the bench finds its way, faithfully and without delay, to the bedside.

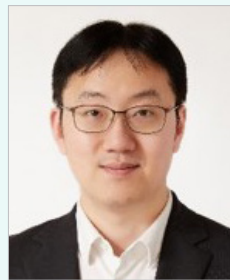
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Jeong Seok Lee
KAIST

Self Introduction

Prof. Jeong Seok Lee is an Associate Professor of the Graduate School of Medical Science and Engineering (GSMSE), Korea Advanced Institute of Science and Technology (KAIST) and is currently holding a position of Co-founder at Inocras Inc. simultaneously.

Prof. Lee graduated from Seoul National University College of Medicine with his medical degree in 2008 and completed his residency at the Department of Internal Medicine at Seoul National University Hospital, receiving his diploma in Internal Medicine in 2017.

Since 2022, Prof. Lee has been taking a number of distinguished roles and honors, including Ewon Endowed Assistant Professor at KAIST (2023–2025), recipient of the Young Investigator Award from the Korean College of Rheumatology (2024), and the Korean Association of Immunologists-Seegene Medical Foundation Excellence Award (2025).

Research Interests

His primary research interest lies at the fusion of human immunology and high-resolution genomics to crack the code of treatment-refractory inflammatory and autoimmune diseases. While his previous work extensively leveraged single-cell multi-omics to map pathogenic T cell dynamics and interferon signatures in ankylosing spondylitis and severe viral infections, his laboratory's future focus explores somatic evolution within non-malignant immune cells.

Representative Publications

1. Type 1 interferon signature and allograft inflammatory factor-1 contribute to refractoriness to TNF inhibition in ankylosing spondylitis. *Nat Commun.* 2025
2. NKG2D-mediated cytotoxicity of CD4 cytotoxic T cells in multiple myeloma. *Blood.* 2025
3. Therapeutic Single-Cell Landscape: Methotrexate Exacerbates Interstitial Lung Disease by Compromising the Stemness of Alveolar Epithelial Cells under Systemic Inflammation. *EBioMedicine.* 2024
4. Analysis of Single-Cell Transcriptome and Surface Protein Expression in Ankylosing Spondylitis Identifies OX40-Positive and Glucocorticoid-Induced Tumor Necrosis Factor Receptor-Positive Pathogenic Th17 Cells. *Arthritis Rheum.* 2023
5. Single-cell Transcriptome of Bronchoalveolar Lavage Fluid Reveals Sequential Change of Macrophages During SARS-CoV-2 Infection in Ferrets, *Nat Commun.* 2021

From Idea to Impact: The Doctor as an Entrepreneur

Jeong Seok Lee KAIST

For many physicians, daily clinical practice brings a profound “thirst”—a deep frustration with the structural boundaries of current treatments and the realization that standard protocols cannot save every patient. As a rheumatologist, this unmet clinical need became the catalyst for my own transformation. I stepped away from full-time clinical practice to pursue a Ph.D. in immunology at KAIST, seeking to decode disease pathogenesis through the lens of high-resolution genomics. However, I soon realized that true clinical impact requires moving beyond “papers in a journal” and into “diagnostic reports in a doctor’s hand”.

This realization gave birth to a unique fusion of academia and entrepreneurship. Co-founding Inocras taught me that doctors possess a distinct entrepreneurial edge: we do not just see data points; we see the human faces behind them. By translating advanced whole-genome sequencing into scalable, clinical-grade diagnostics, we bridged the critical gap between laboratory discovery and patient care.

In this presentation, I will share my 15-year journey of navigating the intersection of medicine, science, and business. I will challenge traditional professional boundaries and demonstrate how physician-led entrepreneurship can build a sustainable, data-driven ecosystem that accelerates true precision medicine from bench to bedside.



Chang Wook Kim
The Catholic University of Korea

Self Introduction

Chang Wook Kim is Professor in the Division of Gastroenterology and Hepatology, Department of Internal Medicine, at The Catholic University of Korea College of Medicine in Seoul, Korea. He received his medical training at The Catholic University of Korea College of Medicine. He has also previously held the positions of Clinical and Research Fellow, Instructor, Assistant Professor and Associate Professor at the same university. He completed an overseas assignment as a Postdoctoral researcher from 2009–2010, at Division of Gastroenterology, University of Pennsylvania, Philadelphia, USA. Currently, He is an international member of American Association for the Study of Liver (AASLD) and a regular member of Asia-Pacific Association for the Study of the Liver (APASL), The Korean Association for the Study of the Liver (KASL), The Korean Liver Cancer Association (KLCA) and The Korean Association of Internal Medicine. He was also a member of Scientific Committee of KASL and KLCA as one of the leading clinical hepatologists in South Korea.

Research Interests

Dr. Kim’s research interests include clinical aspects of chronic hepatitis, cirrhosis and hepatocellular carcinoma with immunologic background. He has authored or coauthored articles concerning these and related topics in internal medicine, with publications in Hepatology, Journal of Hepatology, Cancer, Journal of Gastroenterology and Hepatology, Clinical and Molecular Hepatology, Gut and Liver, and Korean J of Internal Medicine.

Representative Publications

1. Switching to besifovir in patients with chronic hepatitis B receiving tenofovir disoproxil fumarate: A randomized trial. Clin Mol Hepatol. 2025 Jul;31(3):810-822.
2. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patient with chronic hepatitis B. J Gastroenterol Hepatol. 2024 Aug;39(8):1673-1683.
3. Analysis of Immune-Related Adverse Events of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicentre Cohort Study. Liver Cancer. 2023 Dec 21;13(4):413-425.
4. Safety and effectiveness of direct-acting antivirals in patients with chronic hepatitis C and chronic kidney disease. Korean J Intern Med. 2022 Sep;37(5):958-968.
5. A Real-World Comparative Analysis of Atezolizumab Plus Bevacizumab and Transarterial Chemoembolization Plus Radiotherapy in Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombosis. Cancers (Basel). 2023 Sep 4;15(17):4423.

The Nature of Medicine as a Servant

Chang Wook Kim *The Catholic University of Korea*

1. The Nature of Medicine and the Meaning of Service

The essence of medicine lies beyond the technical act of treating disease; it lies in the practice of service and love toward patients who are physically and mentally frail. In particular, providing basic medical services to marginalized regions with poor medical environments is the most direct way to approach the true essence of medicine. Furthermore, education that goes beyond short-term treatment to cultivate high-quality medical personnel in these regions and establish a sustainable medical system can be considered the culmination of true service and dedication. This report aims to examine concrete practical methods for serving through medicine by examining various short-term medical ministries and training programs for local doctors that I have conducted for over 20 years.

2. Short-Term Medical Ministry: Providing Essential Medical Services in Poor Environments

Providing medical benefits to those suffering in regions with poor medical environments, who have never seen a doctor or received simple medical treatment in their lives, is a powerful act of love that opens closed hearts. While short-term overseas medical ministries face the limitation of treating a large number of patients with limited resources over a short period, they provide dramatic symptom relief and substantial assistance through immediate treatment for acute infectious diseases, skin conditions, musculoskeletal disorders, and nutritional deficiencies. The short-term ministry team examines patients with the eyes and hands of the Lord, maintaining an attitude of service to ensure that no soul is left behind. Beyond mere relief, this ministry serves as an exemplary model of spiritual service through physical healing, supporting the activities of local missionaries and laying the groundwork for church planting.

3. Local Mission Hospital Ministry: Improving Access to Medical Care and Continuous Service

To overcome the limitations of short-term ministries in managing chronic diseases, linkage with the local healthcare system and long-term hospital ministry are essential. The Hebron Medical Center in Phnom Penh, Cambodia, is an excellent example of such long-term medical service. A mission hospital

located in a medically underserved area serves as a channel for delivering tangible love to the local people simply through its very existence. This hospital has dramatically improved local patients’ access to medical care by lowering medical costs, and it serves as a leading example in the attitude of its medical staff toward patients and in the medical standards it provides.

4. Training and Education of Local Medical Personnel: The Core of Sustainable Medical Development

Beyond simply treating patients, training local doctors to become competent and morally mature medical professionals is the most valuable investment for fundamentally elevating the level of medical care in the region. I invited the young Cambodian doctor, whom I had trained during my visit to Cambodia, to Uijeongbu St. Mary’s Hospital, where I currently work, to conduct two months of intensive training in Hepatology (October–December 2025). Through this, the young Cambodian doctor received training in advanced medical techniques, including the early diagnosis of liver cirrhosis using liver ultrasonography and Fibroscan, the latest systemic chemotherapy for hepatocellular carcinoma (HCC), patient management after liver transplantation, and endoscopic hemostasis (EVL, EVO) for gastric and esophageal variceal bleeding. Furthermore, we aimed to provide holistic education that fosters growth into mature disciples who convey love and serve as physicians who deal with life, through not only medical knowledge but also daily morning Bible reading and meditation. Local doctor who receive this high-quality education return to their home countries to provide better medical services to the Cambodian people and make significant contributions to the development of hepatology in their nations. This represents the ultimate form of service that goes beyond one-time external support to help the local medical community become self-reliant and develop.

5. Conclusion: Realizing Healthcare as Service

Service through healthcare is not about lording over patients, but about standing in the position of a servant who thoroughly serves them, as stated in the scripture, “We proclaim that we are your servants” (2 Corinthians 4:5). The series of processes—treating acute diseases in medically underserved areas through short-term medical missions, lowering the barrier to medical care through local hospitals, and inviting local doctors to advanced hospitals in Korea for in-depth training—is not a series of disconnected activities. From serving directly in the clinical setting to “service through education” that fosters high-quality medical personnel to enable them to care for the lives of their own citizens, only when all these processes are combined can we truly approach the nature of medicine: “serving patients.” Now is the opportunity for Korean medicine to serve global medicine, and this has become its important role and holy calling.

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**Min Kyu Han***Kakao Healthcare*

Self Introduction

Dr. Han is a physician-executive specializing in digital health, preventive medicine, and AI-enabled healthcare innovation. He received his M.D. from Seoul National University College of Medicine (2005) and earned a Master of Public Health from Seoul National University (2014).

He has held leadership roles across academic medicine, international healthcare operations, and health technology companies in Korea and China. His previous appointments include Seoul National University Hospital, SK Hynix International Medical Center / Jiahui Health in China, and currently executive leadership at Kakao Healthcare.

His work focuses on translating medical knowledge into scalable digital platforms, particularly in chronic disease management, obesity care, continuous glucose monitoring (CGM), patient-generated health data, and AI-driven clinical workflows. He has extensive experience bridging medicine, business strategy, and technology commercialization across Asian healthcare markets.

Research Interests

- AI in Healthcare
- Continuous Glucose Monitoring (CGM)
- Obesity & Metabolic Disease
- Patient-Generated Health Data
- AI Native Healthcare, EMR, Clinical Intelligence

Representative Publications

1. Lowering Barriers to Health Risk Assessments in Promoting Personalized Health Management. *Journal of Personalized Medicine* · Mar 18, 2024
2. A Mobile-Based Comprehensive Weight Reduction Program for the Workplace (Health-On): Development and Pilot Study. *JMIR Mhealth Uhealth* · Nov 4, 2019
3. Importance of Active Participation in Obesity Management Through Mobile Health Care Programs: Substudy of a Randomized Controlled Trial. *JMIR Mhealth Uhealth*. · Jan 3, 2018
4. Assessment of Association between Metabolic Syndrome and Serum Uric Acid Level in Subjects Who Visited the Health Promotion Center. *Korean J Fam Pract.* · Jul 1, 2017
5. Correlation between Percent Body Fat and Fasting Blood Sugar in Korean Adult Women under the Age of 40. *Korean J Fam Pract.* · Jul 1, 201

On the Frontline of Digital Health: Redefining the Future of Care

Min Kyu Han*Kakao Healthcare*

This lecture will share my personal journey as a physician exploring different areas of healthcare beyond the traditional clinical setting. Throughout my career, I have had opportunities to work in academic medicine, public healthcare, international clinical practice, and most recently in the digital healthcare industry. Looking back, these experiences were connected by a common interest in how healthcare can evolve through prevention, chronic disease management, technology, and data.

My early experiences in university hospitals provided important foundations in clinical medicine and patient care, while also exposing me to the growing challenges of chronic diseases and population health management. Later, working in international healthcare environments offered opportunities to experience different healthcare systems and to participate in practical technology-driven healthcare initiatives in real-world clinical settings. These experiences gradually led me to become interested in digital health, sensor technologies, continuous monitoring, and data-driven approaches to healthcare delivery.

More recently, rapid advances in artificial intelligence and healthcare data infrastructure have created new possibilities for medicine. In particular, I have become increasingly interested in how AI, wearable sensors, and data-based clinical systems — including next-generation AI-enabled electronic medical records — may support physicians and improve patient care in the future. My current experience in the healthcare technology industry has allowed me to observe both the opportunities and the limitations of applying these technologies in real clinical practice.

Rather than presenting a single “correct” career path, this session is intended as a reflection on the experiences, transitions, and lessons I encountered while moving across different healthcare environments. I hope these stories may encourage young investigators and early-career physicians to remain open to new perspectives and to consider the many different ways physicians can contribute to the future of medicine.

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ULTRASOUND TRAINEE SESSION

Chair

Soo Young Park (Kyungpook National Univ.)





Seul Ki Han
Yonsei University Wonju

Self Introduction

Dr. Seul Ki Han is an Assistant Professor in the Division of Gastroenterology and Hepatology at Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, Republic of Korea. She specializes in hepatology with a clinical focus on liver cirrhosis, portal hypertension, acute-on-chronic liver failure (ACLF), and hepatocellular carcinoma. Her clinical expertise includes management of decompensated cirrhosis, endoscopic treatment of variceal bleeding, and abdominal ultrasonography including contrast-enhanced ultrasound.

Dr. Han is actively involved in both clinical and translational research. He currently participates in multicenter studies and clinical trials related to cirrhosis and regenerative medicine, including phase III studies using autologous bone marrow-derived mesenchymal stem cells in decompensated cirrhosis.

Research Interests

- Portal Hypertension and Hepatic Venous Pressure Gradient (HVPG)
- Noninvasive Prediction Models for Clinically Significant Portal Hypertension (CSPH)
- Artificial Intelligence and Multimodal Deep Learning in Hepatology
- Acute-on-Chronic Liver Failure (ACLF) and Decompensated Cirrhosis
- Alcohol-Associated Liver Disease and Systemic Inflammation
- Regenerative Medicine and Stem Cell Therapy for Liver Cirrhosis
- Big Data and Nationwide Cohort Studies Using National Health Insurance Service Databases
- Contrast-Enhanced Ultrasonography and Imaging Biomarkers in Chronic Liver Disease

Representative Publications

1. Han SK, Seo MJ, Lee T, Kim MY (2024) Effectiveness of the ALT/AST ratio for predicting insulin resistance in a Korean population: A large-scale, cross-sectional cohort study. PLoS ONE 19(5): e0303333.

2. SJ yoon, SK Han et al. (2025) The crosstalk between gut microbiota and microbiota-derived metabolites in hepatocellular carcinoma. Critical Reviews in Microbiology.

3. Seul Ki Han, Sung Hwa Kim, Sang Baek Koh, Moon Young Kim, Transplantation of Autologous Bone Marrow-Derived Mesenchymal Stem Cells for the Treatment of Decompensated Liver Cirrhosis: A Real-World Evidence Study in a Population-Based Cohort (Gut and Liver pISSN 1976-2283 eISSN 2005-1212)

4. Seul Ki Han, Soon Koo Baik, Moon Young Kim, Protein and Macronutrient Metabolism in Liver Cirrhosis: About Sarcopenia (Nutrients, 2025 doi: 10.3390/nu17213346)

5. Soonchang hone, Seul Ki Han et al. Preclinical Analysis of Bone Marrow-Derived Stem Cell Therapy Response and Transcriptomic Overlap Analysis in a Severe Alcoholic Hepatitis Mouse Model. (2026. Gut and Liver, doi.org/10.5009/gnl250425 pISSN 1976-2283 eISSN 2005-1212)

Getting Started with Upper Abdominal Ultrasonography

Seul Ki Han Yonsei University Wonju

Upper abdominal ultrasonography is a widely used, non-invasive imaging modality in gastroenterology. It enables real-time visualization of internal abdominal organs, facilitating early diagnosis and treatment planning. Due to its safety and accessibility, it is often the first-line imaging tool for evaluating liver, biliary disease and the presence of stone, ascites, and abdominal complaints.

Before performing the exam, patients should fast for at least 6 hours. This reduces gastric contents and air, and enables for detecting gallbladder contents (due to distension), allowing for clearer visualization. The exam is typically performed using a high-frequency (3.5–5 MHz) round convex transducer. For deeper structures or obese patients, lower-frequency probes may be utilized.

The examination usually begins with the patient in the supine position, but left and right lateral decubitus positions may be used if needed. The transducer should be manipulated using the principles of A-R-T: Alignment, Rotation, and Tilting, to optimize imaging planes and organ visualization.

Understanding liver anatomy is crucial for a complete and systematic evaluation. The liver is divided functionally according to the Couinaud classification, which is based on portal and hepatic vein anatomy. Key landmarks include:

- The middle hepatic vein, which divides the liver into right and left lobes.
- The left hepatic vein, which separates the medial (Segment IV) and lateral segments (II, III) of the left lobe.
- The right hepatic vein, dividing the right lobe into anterior (V, VIII) and posterior (VI, VII) segments.
- The portal vein, whose right and left branches define segmental borders.
- The falciform ligament, seen anteriorly, marking the boundary between anatomical lobes.
- The porta hepatis, where the portal vein, hepatic artery, and bile duct enter the liver, is a key reference point for segmental orientation.

Certain areas are frequently overlooked during routine scanning and require special attention. These include:

- Segment I (caudate lobe): Located posterior to the liver, it may be difficult to visualize but is clinically important, particularly in cirrhosis or hepatocellular carcinoma.

- Segment IV (quadrate lobe): Centrally located and sometimes obscured by surrounding structures.
- Right posterior segments (VI and VII): Deep and posterior under the ribs, often missed in tumor screening.
- Subdiaphragmatic surface: Close to the diaphragm and difficult to visualize due to limited acoustic windows.

In conclusion, proficiency in upper abdominal ultrasound relies on a solid understanding of hepatic anatomy and systematic scanning techniques. Awareness of commonly missed segments is key to improving diagnostic yield. Regular and repeated practice is essential for developing confidence and competence in abdominal ultrasonography.

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Hyun Yang
The Catholic University of Korea

Self Introduction

Prof. Hyun Yang is a Professor in the Division of Gastroenterology, Department of Internal Medicine at Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea. He is actively involved in the clinical management and research of chronic liver diseases and hepatocellular carcinoma.

Prof. Yang received his medical degree from the College of Medicine, The Catholic University of Korea. He completed his internship and residency in internal medicine at The Catholic University of Korea affiliated hospitals and subsequently pursued fellowship training in gastroenterology and hepatology. He obtained his Ph.D. in Internal Medicine from The Catholic University of Korea in 2023.

Prof. Yang has been engaged in both clinical practice and academic research, with particular interests in hepatocellular carcinoma and chronic liver diseases. He has a strong interest in healthcare policy and reimbursement systems, and since 2025, he has been serving as an Insurance Committee Secretary in both the Korean Association for the Study of the Liver (KASL) and the Korean Liver Cancer Association (KLCA), with a focus on liver disease-related policy and reimbursement issues.

Research Interests

Hepatocellular Carcinoma, Chronic Hepatitis B, Reimbursement Issues

Representative Publications

1. Yang H, Kim SS, Lee HW, Kim HJ. Expert survey on systemic therapy indications for hepatocellular carcinoma in Korea: bridging clinical practice and reimbursement criteria. *J Liver Cancer*. 2025;25(2):160-168.
2. Lee J, Yang H. Performance of Noninvasive Indices for Discrimination of Metabolic Dysfunction-Associated Steatotic Liver Disease in Young Adults. *Gut Liver*. 2025;19(1):116-125.
3. Lee J, Lee A, Yang H. Efficacy comparison of high-genetic barrier nucleos(t)ide analogues in treatment-naïve chronic hepatitis B patients: a network meta-analysis. *Korean J Intern Med*. 2024;39(4):577-589.
4. Yang H, Jang JW. A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance. *J Hepatol*. 2022;77(3):632-641.
5. Yang H, Yoon SK. Dexamethasone prophylaxis to alleviate postembolization syndrome after transarterial chemoembolization for hepatocellular carcinoma: a randomized, double-blinded, placebo-controlled study. *J Vasc Interv Radiol*. 2017;28(11):1503-1511.e2.

Ultrasound Scanning Techniques: Liver

Hyun Yang *The Catholic University of Korea*

Liver ultrasonography is a cornerstone imaging modality for the evaluation of hepatic disease, providing a non-invasive, radiation-free, and widely accessible method for assessing both diffuse liver conditions and focal hepatic lesions. It is commonly utilized as a first-line diagnostic tool and for longitudinal follow-up in clinical practice. However, its diagnostic performance is highly operator-dependent, emphasizing the need for a systematic and standardized scanning approach.

A thorough understanding of hepatic anatomy is essential for accurate image acquisition and interpretation. The Couinaud classification offers a practical framework for segmental localization based on the distribution of portal and hepatic veins. Hepatic veins delineate intersegmental planes, whereas portal veins run centrally within each segment, serving as key landmarks during ultrasonographic examination.

A structured and reproducible scanning protocol is crucial to ensure comprehensive evaluation and to minimize the risk of missed lesions. Liver ultrasonography typically incorporates multiple scanning planes, including transverse, longitudinal, subcostal, and intercostal approaches. These complementary views allow detailed assessment of hepatic parenchyma, vascular structures, and adjacent organs. Breathing maneuvers and positional adjustments further enhance visualization, particularly in regions that are difficult to access.

Certain anatomical areas, such as the hepatic dome and the inferior margin of the right lobe, are prone to suboptimal visualization and require careful probe manipulation and multiple acoustic windows. In addition, awareness of normal anatomical variants and common artifacts is essential to avoid diagnostic pitfalls. Integration of grayscale imaging with Doppler assessment further improves diagnostic confidence and accuracy.

Standardization of scanning technique and image acquisition is essential to improve reproducibility and reliability. A checklist-based approach that ensures adequate coverage of all hepatic segments and key vascular landmarks may be particularly useful in both routine clinical practice and training environments.

In conclusion, liver ultrasonography remains an indispensable diagnostic tool in hepatology. Mastery of

anatomical landmarks and adherence to a systematic scanning methodology are fundamental to optimizing image quality and ensuring accurate clinical interpretation.

References

1. Tsujimoto F, Ida M, Matsubara K. 복부초음파 아틀라스. 심찬섭 옮김. 북스메디칼; 2020.
2. Choong CC, Venkatesh SK, Siew EP. Accuracy of routine clinical ultrasound for staging of liver fibrosis. J Clin Imaging Sci. 2012;2:58.
3. 보건복지부. 영양급여의 적용기준 및 방법에 관한 세부사항(초음파 검사). 보건복지부 고시 제2023-293호; 2023.
4. 대한임상초음파학회. 복부초음파 표준영상 권고안(일반). 대한임상초음파학회; 2018.
5. 대한임상초음파학회. 복부초음파 표준영상 권고안(정밀). 대한임상초음파학회; 2018.

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Young Youn Cho
Chung-Ang University

Self Introduction

Educational

2010	Bachelor Degree, Seoul National University
2015	Master Degree, Seoul National University
2024	PhD Degree, Seoul National University

Current and Previous 4 Relevant Positions Including Academic Appointments

2011.03-2015.02	Resident, Seoul National University Hospital
2015-03-2016.07	Fellow, Seoul National University Hospital
2016-09-2018.01	Assistant Professor, Seoul National University Hospital
2018.03-2024.03	Assistant Professor, Chung-Ang University Hospital
2024.03-Current	Associate Professor, Chung-Ang University Hospital

Research Interests

Big Data Study, and Microbiome Study

Representative Publications

1. First / Gut Liver. 2020 Mar 15;14(2):225-231. / Long-term Nucleotide Analogue Treatment Has Higher Renal Toxicities than Entecavir in Patients with Chronic Hepatitis B / Cho YY, Chang Y, Nam JY, Cho H, Cho EJ, Lee JH, Yu SJ, Yoon JH, Kim YJ.
2. First/J Hepatocell Carcinoma. 2021 Jun 18;8:613-623./Clinical Characteristics of Long-Term Survivors After Sorafenib Treatment for Unresectable Hepatocellular Carcinoma: A Korean National Multicenter Retrospective Cohort Study./ Cho YY, Yu SJ, Lee HW, Kim DY, Kang W, Paik YH, Sung PS, Bae SH, Park SC, Doh YS, Kim KM, Jang ES, Kim IH, Kim W, Kim YJ.
3. Co-First/ Hepatol Int. 2021 Oct;15(5):1083-1092 /Impact of tenofovir alafenamide vs. entecavir on hepatocellular carcinoma risk in patients with chronic hepatitis B./Lee HW, Cho YY, Lee H, Lee JS, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK, Park SY.
4. Co-First / J Viral Hepat. 2021 Nov;28(11):1570-1578./ Effect of tenofovir alafenamide vs. tenofovir disoproxil fumarate on hepatocellular carcinoma risk in chronic hepatitis B. / Lee HW, Cho YY, Lee H, Lee JS, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK, Park SY.
5. Co-First / Clin Mol Hepatol. 2022 Jul;28(3):425-472. / Therapeutic mechanisms and beneficial effects of non-antidiabetic drugs in chronic liver diseases. / Lee HA, Chang Y, Sung PS, Yoon EL, Lee HW, Yoo JJ, Lee YS, An J, Song DS, Cho YY, Kim SU, Kim YJ.

Ultrasound Scanning Techniques: Pancreato-Biliary, Spleen, and Vascular

Young Youn Cho Chung-Ang University

Abdominal ultrasonography is the first-line imaging modality for the evaluation of gallbladder and biliary tract diseases because of its accessibility, noninvasiveness, cost-effectiveness, and high diagnostic accuracy. This lecture reviews the characteristic ultrasonographic findings of common gallbladder and biliary disorders and discusses practical diagnostic approaches through representative clinical cases.

Gallbladder stones are among the most frequently encountered biliary diseases and can usually be diagnosed with high sensitivity and specificity using ultrasonography. Typical sonographic findings include hyperechoic lesions with posterior acoustic shadowing and positional mobility. However, diagnostic pitfalls such as obesity, artifacts, and impacted stones should be recognized, and additional evaluation with endoscopic ultrasonography may occasionally be required. Biliary sludge and pseudo-sludge are also discussed, with emphasis on differentiation from true pathologic lesions and gallbladder neoplasms.

Gallbladder wall thickening is a common but nonspecific ultrasonographic finding that may result from acute cholecystitis, chronic cholecystitis, acute hepatitis, liver cirrhosis, or systemic conditions. Acute cholecystitis is characterized by gallstones, gallbladder distension, wall thickening, sonographic Murphy’s sign, pericholecystic fluid collection, and increased mural vascularity on Doppler imaging. In contrast, chronic cholecystitis often demonstrates a contracted gallbladder with fibrotic wall thickening and the characteristic wall-echo-shadow (WES) sign.

Gallbladder polyps are increasingly detected during routine health examinations. Differentiating neoplastic from non-neoplastic polyps is clinically important because malignant potential increases in lesions larger than 1 cm, solitary sessile lesions, and lesions occurring in older patients. Cholesterol polyps, adenomas, adenomyomatosis, and gallbladder carcinoma each exhibit distinctive sonographic features. Adenomyomatosis typically demonstrates gallbladder wall thickening with intramural cystic spaces and comet-tail artifacts related to Rokitansky–Aschoff sinuses. Gallbladder carcinoma presents in mass-forming, polypoid, or wall-thickening patterns, and differentiation from benign inflammatory disease may be challenging in some cases.

The lecture also addresses biliary tract diseases, including choledocholithiasis and cholangiocarcinoma. Ultrasonographic detection of common bile duct stones may be limited by small stone size, nondilat-

ed ducts, bowel gas, or pneumobilia. Nevertheless, careful tracing of the bile duct and recognition of indirect signs such as ductal dilatation are essential for diagnosis. Cholangiocarcinoma may present as hilar or extrahepatic disease, with sonographic findings including intrahepatic bile duct dilatation, ductal wall thickening, intraductal masses, or abrupt ductal narrowing. Because infiltrative lesions may not form discrete masses, meticulous evaluation of bile duct anatomy is critical.

In addition to pancreato-biliary imaging, this lecture reviews ultrasonographic evaluation of the spleen and intrahepatic vasculature. Splenic assessment includes evaluation of splenic size, echotexture, focal lesions, and associated signs of portal hypertension. Doppler ultrasonography plays a crucial role in evaluating portal venous flow direction, hepatic venous waveform, collateral circulation, portal vein thrombosis, and vascular complications associated with chronic liver disease. Recognition of hepatofugal flow, cavernous transformation, and altered hepatic venous waveforms provides important hemodynamic information in patients with portal hypertension and cirrhosis.

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THE
LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
in conjunction with EALA
June 11-13, 2026 | Conrad Seoul, Korea



Hyunwoo Oh
Sungkyunkwan University

Self Introduction

Prof. Hyunwoo Oh is a Clinical Assistant Professor of the Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine.

Prof. Oh graduated from Hanyang University College of Medicine with his medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at Hanyang University Medical center. And he received his Doctoral degree in Medicine in 2024 at Seoul National University.

Since 2026, Prof. Oh has been taking a role as a member of Education Committee of the Korean Association of the Study of the Liver.

Research Interests

Portal Hypertension, Hepatocellular Carcinoma, Metabolic Dysfunction-Associated Steatotic Liver Disease

Ultrasound Approaches to Common Diseases: A Practical Guide for Beginners

Hyunwoo Oh Sungkyunkwan University

The widespread use of screening abdominal ultrasonography (US) has increased the detection of incidental focal liver lesion in asymptomatic individuals. Because diffuse liver disease and hepatocellular carcinoma surveillance are addressed in parallel lectures and dedicated guidelines, this session focuses on common focal lesions encountered by beginning sonographers in routine screening practice.

The lecture is centered on four frequently encountered entities: simple hepatic cyst, hemangioma, focal nodular hyperplasia (FNH), and liver abscess, including eosinophilic abscesses that may mimic metastasis. Less common or more complex lesions, such as focal fat deposition or sparing, hepatic adenoma, and metastasis, are introduced briefly as important mimickers or lesions requiring further imaging evaluation. A consistent descriptive framework is proposed for every lesion: location, size, echogenicity, margin, internal architecture, posterior acoustic change, and Doppler vascularity when applicable. Each entity is anchored to practical sonographic clues: anechoic content, imperceptible wall, and posterior acoustic enhancement for a simple cyst; a homogeneous hyperechoic, sharply marginated lesion with posterior enhancement for a typical hemangioma, with the important caveat that hemangiomas may appear relatively hypoechoic in a fatty liver; a well-defined iso- or mildly hypoechoic/hyperechoic lesion, sometimes with a central scar or spoke-wheel vascularity, for FNH; and an irregular or thick-walled lesion with internal echoes, debris, septation, or dirty posterior shadowing/enhancement for liver abscess.

To facilitate understanding of ultrasound findings, selected histopathologic and CT correlations are briefly introduced for each lesion. Common diagnostic pitfalls are highlighted throughout the lecture, particularly situations in which benign lesions or pseudolesions may mimic malignant focal liver lesions on grayscale ultrasound.

The final part of the lecture presents a practical decision pathway. Typical simple cysts and typical small hemangiomas in a low-risk liver may often be diagnosed confidently by US. In contrast, non-typical, solid, enlarging, symptomatic, or indeterminate lesions — particularly in patients with chronic liver disease or a history of malignancy — should undergo further characterization with contrast-enhanced US, multiphasic dynamic CT, or contrast-enhanced MRI. The key message is that ultrasound is the starting point of focal liver lesion assessment, not always its endpoint; disciplined description and appropriate

escalation are the safest strategy for the beginning sonographer.

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ULTRASOUND TRAINER SESSION 1

Chair
Sang Gyune Kim (Soonchunhyang Univ.)





Tae-Suk Kim

Kangwon National University

Self Introduction

- 강원대학교 의학사
- 강원대학교 의학박사
- 강원대학교병원 의료혁신실장
- 보건복지부지정 강원대학교병원 지역환자안전센터장
- 대한간학회 교육위원회 간사
- 대한간학회 정책위원, 기획위원
- 대한임상초음파학회 진료지침이사

Research Interests

- Alcoholic Liver Disease
- Abdominal Ultrasound
- Patient Safety and Quality Improvement

Representative Publications

1. KIM, tae suk, et al. "The crosstalk between gut microbiota and microbiota-derived metabolites in hepatocellular carcinoma." *Critical Reviews in Microbiology* (2025): 1-15.
2. Kim, Tae Suk, et al. "Reappraisal of sepsis-3 and CLIF-SOFA as predictors of mortality in patients with cirrhosis and infection presenting to the emergency department: A multicenter study." *Clinical and molecular hepatology* 28.3 (2022): 540.
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Current Status and Future Directions for Maintaining Abdominal Ultrasound Certification Systems

Tae-Suk Kim

Kangwon National University

Ultrasound has become an essential diagnostic tool in hepatology, particularly for the diagnosis, monitoring, and management of liver diseases. As ultrasound training has become increasingly important in internal medicine residency, the Korean Association of Internal Medicine has established an accredited trainer system for abdominal ultrasound education. The Korean Association for the Study of the Liver (KASL) is one of the societies authorized to grant qualifications for abdominal ultrasound trainers under this system. In addition, KASL has independently operated an internal abdominal ultrasound certification system as a subordinate and complementary framework to recognize physicians with structured training and competency in abdominal ultrasound.

The abdominal ultrasound certification system of KASL was introduced to recognize physicians with appropriate clinical experience, education, and competency in abdominal ultrasound. This system aims not only to certify individual proficiency, but also to support the development of physicians who can contribute to resident education and quality control in clinical practice.

This system has contributed to the standardization of ultrasound education and to the recognition of abdominal ultrasound as a core competency for liver disease specialists. It has also established an operational cycle linking education, training, evaluation, certification, and recertification. In addition, it has provided a professional development pathway for young specialists who may later serve as ultrasound trainers for residents.

However, several limitations should be considered. Regional and institutional disparities remain in ultrasound training infrastructure, including differences in the availability of trainers, equipment, and educational opportunities. Maintaining the certification system also requires substantial administrative and educational resources, such as document review, credit management, renewal processes, and faculty participation in training programs. In addition, certification is not directly linked to reimbursement, hospital evaluation, or formal institutional incentives, which may reduce motivation for participation and renewal. The relationship between society-level certification and broader academic certification policies also requires careful review.

Therefore, the key question is not simply whether the current abdominal ultrasound certification system should be maintained or discontinued. Rather, the more important issue is how the system should

be redefined to better support resident education, trainer development, quality assurance, and clinical competency in abdominal ultrasound.

Future directions may include repositioning the system as a competency-based educational certification rather than a quasi-subspecialty qualification. The program should place greater emphasis on standardized curricula, hands-on training, objective assessment, faculty development, and regular re-certification. Closer alignment with the ultrasound trainer system of the Korean Association of Internal Medicine may also improve its relevance and sustainability.

In conclusion, the abdominal ultrasound certification system has played an important role in improving ultrasound education and clinical competency in Korea. However, its continued operation requires strategic reappraisal. The future goal should be to transform the system into a sustainable, quality-controlled educational platform aligned with internal medicine training requirements and broader academic certification policies.

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Yeowool Kang
Dong-A University

Self Introduction

2006.03-2011.02 Konkuk University, Department of Specialization Chemistry Bachelor of Science (B.Sc.)
2011.03-2015.02 Dong-A University Graduate School, Department of Medicine, Master of Medicine (M.D.)
2021.03-2023.02 Dong-A University Graduate School, Department of Medicine, Doctor of Medicine (Ph.D.)

Dr. Kang graduated from Dong-A University College of Medicine and completed her internship and residency at the Department of Gastroenterology & Hepatology at Dong-A university Hospital.

Since 2022, Dr. Kang has been taking a role in member of the Korean Association of the Study of the Liver.

Research Interests

- Viral Hepatitis
- Metabolic-Dysfunction Associated Steatotic Liver Disease
- Hepatocellular Carcinoma

Representative Publications

1. Kang YW, Son M, Lee JY, Moon SY, Koh M. Subtype-specific associations of steatotic liver disease with gastric and esophageal cancers: a nationwide cohort study. *Gastric Cancer*. 2026 Mar;29(2):365-375. doi: 10.1007/s10120-025-01711-w. Epub 2026 Jan 13. PMID: 41528661.
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Why Advanced Ultrasound Matters: Expanding the Role Beyond Screening

Yeowool Kang *Dong-A University*

Ultrasound has long been widely used as a primary screening tool for liver disease; however, its role in definitive clinical decision-making has been constrained by operator dependency and limitations in lesion characterization. With recent technological breakthroughs—including contrast-enhanced ultrasound (CEUS), elastography, and attenuation imaging—ultrasound is evolving beyond a simple screening modality into a pivotal platform that supports real-time, precision clinical decisions.

CEUS enables the dynamic assessment of microvascular patterns in hepatic lesions, facilitating the definitive differentiation of hepatocellular carcinoma (HCC) from benign nodules. By incorporating the latest CEUS LI-RADS algorithms, clinicians can achieve high diagnostic confidence while avoiding high-cost imaging or invasive procedures, particularly in patients with contraindications to CT/MRI contrast agents.

Furthermore, elastography and attenuation imaging provide reproducible, quantitative metrics for liver fibrosis and steatosis. These tools are now essential for staging and risk stratification in metabolic dysfunction-associated steatotic liver disease (MASLD), allowing for longitudinal monitoring of therapeutic efficacy and personalized HCC surveillance.

Beyond diagnosis, advanced ultrasound serves as an integrated guidance system for image-guided biopsy, local ablative therapies, and post-treatment response assessment. The synergy of fusion imaging and CEUS-based evaluation provides critical insights for tailoring personalized therapeutic strategies. Moreover, the integration of deep learning-based AI is poised to standardize ultrasound practice by enhancing objectivity and the detection of subtle lesions.

In this lecture, we will explore how these advanced technologies are transforming clinical pathways—from lesion characterization to treatment guidance—through practical, evidence-based scenarios. Ultimately, we aim to highlight the potential of advanced ultrasound as the most accessible and versatile tool in the era of precision hepatology.



Woo Sun Rou
Chungnam National University

Self Introduction

Prof. Woo Sun Rou is an Assistant Professor in the Division of Hepatology, Department of Internal Medicine, at Chungnam National University Sejong Hospital, Chungnam National University College of Medicine. He received his M.D. in 2006, M.S. in 2014, and Ph.D. in 2022 from Chungnam National University College of Medicine.

He completed his medical internship and residency in Internal Medicine at Inje University Ilsan Paik Hospital, receiving his diploma in Internal Medicine in 2011. He subsequently completed a fellowship in Gastroenterology and Hepatology in the Department of Internal Medicine at Chungnam National University Hospital (2014-2015).

He is currently a member of the Education Committee (2020-2023, 2026-) and the Insurance Committee (2026-) of the Korean Association for the Study of the Liver, and has been a member of the Editorial Board of the Korean Association of Clinical Ultrasound since 2023.

Research Interests

MASLD, Viral Hepatitis, Hepatocellular Carcinoma

Representative Publications

1. Woo Sun Rou, Hong Jae Jeon, Hyuk Soo Eun, et al. Association of Survival with Radiologic-Pathologic Discordance in Patients with Hepatocellular Carcinoma: A Nationwide Cohort Study Based on the Primary Liver Cancer Registry in Korea. Gut Liver. 2025;19(4):602-616.
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Mastering Advanced Ultrasound: From Stepwise Implementation to Clinical Pearls

Woo Sun Rou *Chungnam National University*

The Evolution of Advanced Ultrasound

Abdominal ultrasound (US) has played a pivotal role in the screening and initial evaluation of liver disease, owing to its inherent advantages of safety, accessibility, and real-time imaging. With the recent clinical adoption of various advanced US techniques, including Doppler US, shear wave elastography (SWE), US-based fat quantification, contrast-enhanced US (CEUS), microvascular imaging (MVI), and fusion imaging/navigation, abdominal US has evolved beyond simple morphological assessment into a quantitative, functional, and interventional imaging modality. These advanced US techniques are utilized in various clinical settings, including liver fibrosis assessment in chronic liver disease, quantitative evaluation of hepatic steatosis, hemodynamic assessment, characterization of focal liver lesions, and guidance for interventional procedures. This lecture focuses on how to implement these techniques stepwise in clinical practice, when to apply them selectively, and how to interpret their results appropriately.

Clinical Applications of Advanced US in Liver Disease

The clinical application of advanced US should begin with a clear definition of the clinical question to be addressed. In chronic liver disease, liver stiffness measurement using SWE is increasingly used not only for fibrosis assessment but also for risk stratification and follow-up of compensated advanced chronic liver disease (cACLD), clinically significant portal hypertension (CSPH), and liver-related events. In metabolic dysfunction-associated steatotic liver disease (MASLD), quantitative assessment of liver fat content can be performed using parameters such as the attenuation coefficient, backscatter coefficient, and speed of sound. More recently, viscosity-related parameters have also been investigated as potential biomarkers of inflammatory activity, although further validation is needed. In cirrhosis and vascular liver disease, hemodynamic assessment using Doppler US can support clinical decision-making. For focal liver lesions, Doppler US, MVI, and CEUS can assist in differential diagnosis by evaluating vascularity and dynamic enhancement patterns. In addition, when a lesion is poorly visualized on B-mode US or when accurate procedural targeting is difficult, CEUS-guided techniques or fusion imaging/navigation can improve the accuracy of interventional procedures such as biopsy and radiofrequency ablation.

Stepwise Implementation and Modality-Specific Considerations

During implementation, equipment performance, software options, image storage methods, examination protocols, reporting systems, and support staff should all be considered. SWE should be performed according to recommended protocols, including fasting and rest before the examination, right intercostal access, acquisition through an adequate B-mode acoustic window, appropriate region of interest (ROI) placement while avoiding blood vessels, bile ducts, and focal lesions, breath-holding at neutral respiration, and repeated measurements. Quality parameters such as SD/mean and IQR/M should also be verified. Because liver stiffness can be affected by acute hepatitis, ALT flares, cholestasis, hepatic congestion, and heart failure, the measured value should not be interpreted as an absolute indicator but should instead be assessed in the context of the patient’s clinical condition.

US-based fat quantification can also be influenced by ROI location, measurement depth, subcutaneous fat thickness, intrahepatic vessels, diaphragm-related artifacts, respiratory status, and differences in vendor-specific algorithms. Therefore, repeated measurements should be obtained using a standardized protocol within an appropriate acoustic window, and reliability indicators such as IQR/median and manufacturer-specific quality criteria should be checked. Although these quantitative parameters are useful for objectively assessing the longitudinal changes of hepatic steatosis, vendor-specific cut-off values have not yet been fully standardized. Therefore, when follow-up examinations are performed, the same device and protocol should preferably be used, and the equipment used should be specified in the report.

Doppler US and MVI are useful for evaluating blood flow, but their results may be affected by angle dependency, depth dependency, gain settings, motion artifacts, blooming artifacts, and low signal-to-noise conditions. Therefore, it is important to distinguish true vascular signals from artifacts during interpretation. The presence of flow on MVI should not be regarded as evidence of malignancy by itself; rather, vascular distribution, vascular pattern, B-mode morphology, and clinical background should be interpreted together.

CEUS can be useful for the characterization of focal liver lesions, as a contrast-enhanced imaging option in patients with impaired renal function, for further evaluation of indeterminate lesions on CT or MRI, and as a guidance tool for interventional procedures. CEUS-guided biopsy can be helpful when lesions are not visible or are poorly defined on B-mode US, when lesions contain necrotic areas, or when selective targeting of the viable portion is required. Before introducing CEUS into clinical practice, contrast agent preparation and injection methods, phase timing, cine-loop recording, and patient monitoring should be standardized. In addition, the patient’s clinical information, laboratory findings, and previous imaging studies should be reviewed before CEUS, and the location, size, and relationship of the lesion to vessels and surrounding structures should first be systematically evaluated using B-mode and Doppler US. Fusion imaging/navigation can assist with lesion localization and needle path planning when lesions visible on CT or MRI are poorly visualized on US; however, image registration error, respiratory

mismatch, differences in patient position, and organ deformation should always be considered.

Advanced US as a Clinical Problem-Solving Tool

In conclusion, reliable implementation of advanced US in clinical practice requires a stepwise approach: selecting the appropriate technique according to the clinical question, acquiring images using standardized methods, verifying image quality and reliability, interpreting results in light of equipment characteristics and patient factors, and finally linking the findings to clinical decision-making. Through this approach, advanced US can move beyond its traditional role as a screening tool and become a practical clinical problem-solving tool that connects diagnosis, risk assessment, treatment planning, and interventional procedures in the management of liver disease.

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2. Christoph F Dietrich, Christian Pállson Nolsøe, Richard G Barr, et al. Guidelines and Good Clinical Practice Recommendations for Contrast-Enhanced Ultrasound (CEUS) in the Liver-Update 2020 WFUMB in Cooperation with EFSUMB, AF-SUMB, AIUM, and FLAUS. *Ultrasound Med Biol.* 2020;46(10):2579-2604.
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7. Paul S Sidhu, Mustafa Secil, Dirke-Andre Clevert, et al. Non-invasive ultrasound assessment of chronic liver disease: current position and future directions for a “one-stop” liver ultrasound approach. *Insights Imaging.* 2026;17(1):120.



Young Chang

Soonchunhyang University

Self Introduction

Prof. Young Chang is an Assistant Professor of the Department of Internal Medicine, Soonchunhyang University College of Medicine.

Prof. Chang graduated from Seoul National University College of Medicine with her medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital, receiving his diploma in Internal Medicine in 2021.

Prof. Chang has been involved in a number of committees, and currently in Guideline Committee and Research Committee of the Korean Association of the Study of the Liver (2026-present), Publication Committee of the Korean Liver Cancer Association (2020-present).

Enhancing Diagnostic Clarity: Global Standard Lexicons for Professional Ultrasound Reporting

Young Chang

Soonchunhyang University

Abdominal ultrasound remains one of the most widely utilized imaging modalities in daily clinical practice because of its accessibility, safety, real-time capability, and diagnostic versatility. Nevertheless, considerable variability persists in the terminology and reporting style used among radiologists, institutions, and countries. Subjective expressions, inconsistent descriptors, and non-standardized interpretations may reduce diagnostic clarity and create challenges in communication between clinicians, follow-up assessment, and multidisciplinary patient management.

The adoption of standardized lexicons and structured reporting systems has become increasingly important in abdominal ultrasound practice. Consistent terminology improves reproducibility, facilitates clearer communication, and enhances diagnostic confidence across diverse clinical settings. Standardized descriptors for hepatic parenchymal echogenicity, focal liver lesions, biliary abnormalities, pancreatic findings, splenic lesions, renal abnormalities, and vascular structures contribute to more precise characterization and more uniform interpretation of ultrasound findings.

Recent developments in international reporting systems, including LI-RADS and other organ-specific structured lexicons, have demonstrated the clinical value of harmonized reporting language. Standardized categorization systems support risk stratification, improve interobserver agreement, and provide clearer recommendations for patient management and follow-up imaging. In chronic liver disease and hepatocellular carcinoma surveillance, structured lexicons have significantly improved consistency in lesion characterization and communication among radiologists, hepatologists, and surgeons.

The integration of structured lexicons into professional ultrasound reporting also plays an important role in education, quality assurance, clinical research, and artificial intelligence applications. Machine learning algorithms and natural language processing systems require standardized and machine-readable reporting formats to achieve reliable performance and interoperability across institutions. As ultrasound reporting becomes increasingly digitalized, globally harmonized terminology is expected to facilitate large-scale data integration and multicenter collaboration.

Practical considerations for implementation include balancing reporting standardization with workflow efficiency, adapting lexicons to regional clinical environments, and maintaining flexibility for complex or atypical findings. Educational initiatives and consensus-based guidelines from international societies

continue to support broader adoption of standardized abdominal ultrasound reporting systems in both academic and community practice settings.

Global standard lexicons in abdominal ultrasound reporting provide a common diagnostic language that enhances clarity, consistency, and clinical communication while supporting precision medicine, multidisciplinary collaboration, and future AI-driven imaging applications.

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ULTRASOUND TRAINER SESSION 2

Chair
Moon Young Kim (Yonsei Univ. Wonju)





Jae Seung Lee
Yonsei University

Self Introduction

Prof. Jae Seung Lee is a hepatologist from South Korea. He earned his medical degree and PhD from Yonsei University College of Medicine. He completed his residency in Internal Medicine at Severance Hospital, and after completing a two-year fellowship, he has been serving as a clinical assistant professor since 2020. His research encompasses a wide range of topics in hepatology, with a particular focus on developing predictive models for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B and metabolic dysfunction-associated steatotic liver disease (MASLD), as well as evaluating the diagnostic accuracy of non-invasive fibrosis measures.

His numerous publications focus on the treatment and prognosis of patients with liver-related diseases. Additionally, he explores experimental topics such as the mechanisms of drug resistance in HCC using HCC organoids. He is an active member of the Korean Association for the Study of the Liver and the Korean Liver Cancer Association.

Research Interests

Hepatitis B, Hepatitis C, Steatotic Liver Disease, Cirrhosis, Hepatocellular Carcinoma

Representative Publications

1. Lee JS, Jung CY, Lee JI, Ahn SH, Kim BS, Kim SU. Comparison of decline in renal function between patients with chronic hepatitis B with or without antiviral therapy. *Aliment Pharmacol Ther.* 2023 Jul;58(1):99-109.
2. Lee JS, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Jang JY, Park SY, Lee HW, Lee CK, Kim SU. Comparison of FibroScan-Aspartate Aminotransferase (FAST) Score and Other Non-invasive Surrogates in Predicting High-Risk Non-alcoholic Steatohepatitis Criteria. *Front Med (Lausanne).* 2022 Apr 14;9:869190.
3. Lee JS, Lee HW, Lim TS, Min IK, Lee HW, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK. External Validation of the FSAC Model Using On-Therapy Changes in Noninvasive Fibrosis Markers in Patients with Chronic Hepatitis B: A Multicenter Study. *Cancers (Basel).* 2022 Jan 29;14(3):711.
4. Lee JS, Sinn DH, Park SY, Shin HJ, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Oh JH, Lee JI, Kim SU. Liver Stiffness-Based Risk Prediction Model for Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. *Cancers (Basel).* 2021 Sep 11;13(18):4567.
5. Baatarkhuu O, Lee JS (Co-primary), Amarsanaa J, Kim DY, Ahn SH, Naranzul N, Enkhtuya D, Chojjamts N, Batbayar P, Otgonbayar R, Saruul BU, Gantuul C, Gegeebadrakh B, Tuvshinbayar N, Badamsuren D, Ulzmaa G, Otgonbold J, Han KH. Efficacy and safety of ledipasvir/sofosbuvir in 5,028 Mongolian patients infected with genotype 1 hepatitis C virus: A multicenter study. *Clin Mol Hepatol.* 2021 Jan;27(1):125-135.

Advanced Shear Wave Elastography (SWE): Multi-Vendor Comparison

Jae Seung Lee Yonsei University

Shear wave elastography (SWE) is a reliable, non-invasive method for assessing liver stiffness (LS) as a surrogate marker of liver fibrosis. By generating and measuring the propagation speed of shear waves through the liver parenchyma using internally directed acoustic radiation force impulse (ARFI), SWE enables quantitative estimation of liver stiffness in units of m/s or kilopascals (kPa). Meta-analyses across multiple etiologies have consistently reported AUROCs of 0.85–0.97 for significant fibrosis ($\geq F2$) and 0.91–0.98 for cirrhosis (F4), with intra- and inter-observer intraclass correlation coefficients exceeding 0.90. On this basis, major international societies including WFUMB, EFSUMB, SRU, and EASL have formally endorsed SWE as a first-line non-invasive modality for liver fibrosis evaluation. The 2024 WFUMB Multiparametric Ultrasound Guidelines (Part 1) recommend SWE to rule out advanced fibrosis (<8 kPa) and rule in advanced fibrosis (>12 – 15 kPa) in MASLD patients (LoE 1a, GoR A).

Technical Considerations and Measurement Reliability

SWE measurements are susceptible to several technical and physiological confounders. Reverberation artifacts from inadequate acoustic windows or rib shadowing can artificially elevate measured stiffness. Postprandial status, hepatic venous congestion, acute hepatic inflammation ($ALT >5 \times ULN$), and obstructive cholestasis all independently increase liver stiffness irrespective of fibrosis stage. High BMI and increased skin-to-capsule distance (>2.5 – 3 cm) reduce measurement reliability and amplify inter-system variability, particularly for point SWE systems. Measurement accuracy also tends to decline at depths beyond 5–6 cm.

To standardize acquisition across systems, EFSUMB (2017 update) and WFUMB (2024 update) recommend the following protocol: a minimum 2-hour fast prior to examination; right lobe measurement via intercostal approach in the supine or slight left lateral decubitus position with the right arm raised; ROI placement ≥ 1 cm diameter deep to the liver capsule, avoiding large vessels and artifacts; and acquisition of at least 5 to 10 valid measurements depending on the system (pSWE typically requires 10; 2D-SWE requires 5). A measurement session is considered reliable when the interquartile range-to-median ratio (IQR/median) is $\leq 30\%$. In some systems, the standard deviation-to-mean ratio (Std/Mean $\leq 30\%$) serves as an additional or alternative reliability index.

Beyond these common recommendations, each vendor provides system-specific quality control (QC) features to guide operators in real time. In 2D-SWE systems, these include visual shear-wave propagation maps, color confidence overlays, and reliability index maps, enabling operators to identify and exclude acquisitions compromised by artifacts or tissue motion before committing to a measurement. Familiarity with these vendor-specific tools is critical for reproducible results. The Canon Aplio i800 (Sound Touch Elastography) offers a real-time propagation wave map, allowing direct visualization of shear wave front quality prior to ROI placement. The Mindray Resona 7 (Sound Touch Elastography) provides a motion-stability index (M-STB, requiring ≥ 4 stars) alongside a reliability map (RLB map, requiring uniform green fill $\geq 95\%$) for each acquisition. Philips ElastQ (EPIQ series) displays a color confidence overlay and also offers Auto ElastQ, an automated frame-selection feature within a cine loop that achieves 99% reported reliability and up to a 60% reduction in examination time. GE HealthCare LOGIQ systems (E10/Fortis) use a comb-push multi-beam technique to generate a real-time 2D SWE color map with a confidence overlay, which automatically displays summary statistics upon completion of a measurement set. Siemens pSWE (VTQ, ACUSON Sequoia) does not display a visual propagation map but applies internal SNR-based rejection of low-quality acquisitions. SuperSonic Imagine Aixplorer (SSI), the earliest EFSUMB-recognized 2D-SWE system, provides a color SWE map and remains the most extensively validated platform in multicenter biopsy-controlled studies. Operators should ensure they are proficient in the specific QC workflow of their system before performing liver elastography in clinical practice.

Multi-Vendor Comparison: Variability and Clinical Implications

While all major SWE platforms demonstrate comparable overall diagnostic accuracy for liver fibrosis staging, direct comparison studies have consistently shown that absolute LSM values are not numerically interchangeable across vendor systems. Inter-system differences arise from vendor-specific implementation factors, including shear wave excitation frequency, beam geometry, ROI dimensions, frame rate, and signal reconstruction algorithms. These differences are most pronounced at higher stiffness values—precisely the range most relevant for diagnosing advanced fibrosis and cirrhosis.

The most comprehensive head-to-head comparison to date, assessed six systems simultaneously (Canon Aplio i800, GE LOGIQ E10, Mindray Resona 7, Philips EPIQ Elite, Siemens ACUSON Sequoia, and SuperSonic Aixplorer MACH 30) in both Phantoms and human livers. While intra-system repeatability was excellent ($ICC \geq 0.90$) across all platforms, inter-system agreement was limited, and absolute shear wave speed values differed significantly between systems, particularly at higher stiffness levels. An earlier study comparing Siemens, GE, Philips, and Canon systems in 318 healthy volunteers found that most systems performed equivalently at measurement depths of 3–5 cm, but agreement declined substantially beyond 5 cm.

System-specific validation data further underscore the non-interchangeability of cutoff values. For the Canon Aplio i800, Ferraioli et al. derived optimal cutoffs of >7 kPa for significant fibrosis and >9 kPa

for severe fibrosis using VCTE as reference ($n=367$), while Kovatsch et al. confirmed non-inferiority to FibroScan® with AUROCs of 0.852 ($\geq F2$), 0.868 ($\geq F3$), and 0.956 ($F4$) in a biopsy-proven cohort of 108 patients. For Philips ElastQ, Bauer et al. demonstrated in a prospective multicenter European study that ElastQ accurately rules out fibrosis (<8 kPa) and rules in compensated advanced chronic liver disease (cACLD, >13 kPa) across multiple etiologies, while noting that current EFSUMB/SRU guidelines do not yet incorporate ElastQ-specific data. For Mindray STE, Xiang et al. showed in 4,152 patients that STE measurements are systematically lower than SuperSonic SSI at higher stiffness values, with meaningful intersystem discordance when applying SRU “Rule of Four” thresholds. A recent study by Kapoor et al., directly comparing the Canon Aplio i800 (2D-SWE) and Siemens Sequoia (pSWE) in 89 obese patients, found an overall mean measurement difference of 1.44 kPa, widening to 5.79 kPa in $F4$ patients, with skin-to-capsule distance and shear wave dispersion identified as the principal determinants of inter-system discrepancy.

The RSNA Quantitative Imaging Biomarkers Alliance (QIBA) has worked to mitigate inter-system variability through standardized tissue-mimicking phantoms used by manufacturers for calibration. The SRU 2020 consensus statement acknowledged that QIBA efforts have reduced inter-system differences and introduced the vendor-neutral “Rule of Four” classification (thresholds: 5, 9, 13, 17 kPa) as a practical framework applicable across systems. However, its universal applicability, particularly in obese populations and for newer platforms, remains under investigation. Therefore, longitudinal monitoring of individual patients should be performed on the same system whenever possible, as the SRU 2020 guidelines explicitly recommend using delta changes from a system-specific baseline rather than absolute values for follow-up.

Conclusions

SWE is a well-validated, guideline-endorsed modality for non-invasive assessment of liver fibrosis, with a strong correlation with histopathology across major liver disease etiologies. Optimal measurement requires strict adherence to standardized acquisition protocols, active use of vendor-specific reliability tools, and awareness of physiological and technical confounders. Clinicians and sonographers must therefore apply system-specific reference ranges, utilize vendor-provided QC features, and maintain consistency in system use for longitudinal patient monitoring.

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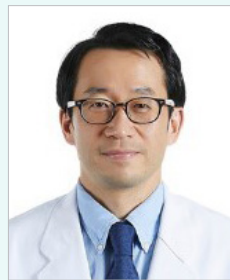
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Soung Won Jeong
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Self Introduction

Prof. Soung Won Jeong is a Professor of the Department of Gastroenterology, Soonchunhyang University Seoul Hospital and is currently holding a position of Chief of Internal medicine of Soonchunhyang University Seoul Hospital and Director of the Gastroenterology Center of Soonchunhyang University Seoul Hospital, simultaneously.

Prof. Jeong graduated from Soonchunhyang University College of Medicine with his medical degree in 1998 and completed his internship and residency at the Department of Internal Medicine at, Soonchunhyang University Seoul Hospital, receiving his diploma in Internal Medicine in 2003.

He is currently serving as the Executive Director of the KASL Cirrhosis Study Group (KCSG) and the Academic Director of the Korean Association of Clinical Ultrasound.

Research Interests

Abdominal US, HCC, LC

Current Role of Ultrasound and CEUS in the LI-RADS Framework

Soung Won Jeong Soonchunhyang University

The Liver Imaging Reporting and Data System (LI-RADS) was developed by the American College of Radiology to standardize imaging interpretation, reporting terminology, and management recommendations for patients at high risk for hepatocellular carcinoma (HCC).^{1,2} Initially centered on CT and MRI diagnosis, LI-RADS has evolved into a comprehensive multimodality framework encompassing surveillance ultrasound (US), contrast-enhanced ultrasound (CEUS), and treatment response assessment. Within this framework, conventional US and CEUS have distinct but complementary clinical roles.

US Surveillance

US remains the primary surveillance modality for patients at risk for HCC because of its accessibility, safety, and cost-effectiveness. LI-RADS US Surveillance Version 2024 standardizes surveillance interpretation by categorizing examinations as US-1 (negative), US-2 (subthreshold), or US-3 (positive) and separately assessing visualization quality using VIS-A, VIS-B, or VIS-C scores.³ This distinction is clinically important because a technically limited examination may reduce sensitivity even when no focal observation is identified. In clinical practice, surveillance US is not intended to establish a definitive diagnosis of HCC; rather, it identifies patients who require further evaluation with multiphasic CT, MRI, or CEUS and documents the adequacy of the examination for surveillance purposes.^{1,3}

Role of CEUS

CEUS LI-RADS uses intravascular microbubble contrast agents to evaluate arterial phase hyperenhancement, washout timing, and washout intensity in real time.^{4,5} A typical CEUS LR-5 observation measures at least 10 mm, demonstrates non-rim arterial phase hyperenhancement, and exhibits late, mild washout, findings that maintain high specificity for HCC in at-risk patients.^{4,6} In contrast, rim enhancement, early washout, or marked washout favors LR-M, indicating probable malignancy without HCC specificity, including intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma.^{4,5}

CEUS therefore functions not only as a lesion detection technique but also as a focused diagnostic and problem-solving modality that refines the probability of HCC versus non-HCC malignancy. Compared with CT or MRI, CEUS offers high temporal resolution, repeatability, lack of ionizing radiation, and feasi-

bility in patients with renal dysfunction or contraindications to iodinated or gadolinium-based contrast agents. However, CEUS is usually lesion-targeted and does not provide the same whole-liver or extrahepatic staging capability as CT or MRI. Acoustic window limitations, obesity, severe steatosis, and operator dependency may also affect diagnostic performance.

Treatment Response Assessment

More recently, CEUS has expanded into post-treatment evaluation through LI-RADS Contrast-Enhanced US Nonradiation Treatment Response Assessment Version 2024.⁷ This system categorizes treated lesions as LR-TR Nonviable, LR-TR Equivocal, or LR-TR Viable according to residual intralesional or perilesional enhancement after nonradiation locoregional therapy or surgical treatment. CEUS may be particularly useful after ablation or when CT/MRI findings remain indeterminate.

Conclusion

US and CEUS now occupy central positions within the LI-RADS framework. Surveillance US provides standardized recall recommendations and visualization assessment, while CEUS contributes real-time vascular characterization, targeted diagnostic clarification, and structured treatment response evaluation. Optimal implementation of LI-RADS requires understanding the strengths and limitations of each ultrasound modality and integrating imaging findings with CT, MRI, laboratory biomarkers, pathology, and multidisciplinary clinical decision-making.

Keywords: LI-RADS; Ultrasound; Contrast-enhanced ultrasound; CEUS; Hepatocellular carcinoma; Surveillance; Treatment response assessment

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Self Introduction

Prof. Hyun Jung Chung is a Clinical Professor of the Department of Gastroenterology & Hepatology, Yonsei University Wonju College of Medicine.

Prof. Chung graduated from Inha University College of Medicine with her medical degree in 2004 and completed his internship and residency at the Department of Internal Medicine at Inha University Hospital, receiving her diploma in Internal Medicine in 2011.

Since 2011, Prof. Hong has been taking a number of roles, including Chairman of the Korean Association of the Study of the Liver (2021-2022), Chairman of the Korean association of Gastroenterology (2022-2023), and currently as President of the Korean Association for Transplantation (2023-Present).

Research Interests

Portal Hypertension, Liver Cirrhosis, HCC, and Alcoholic Liver Disease

Mastering Doppler for Portal Hypertension: From Waveform Analysis to Clinical Decision Making

Hyun Jung Chung

Yonsei University Wonju

Doppler ultrasonography (US) is useful modality for evaluating blood flow in major hepatic vessels including portal vein (PV), hepatic vein (HV). As liver disease shows the characteristic waveforms based on each flow dynamics. Notably, because Doppler US allows for the non-invasive evaluation of portal hypertensive hemodynamics, it has been widely compared with the hepatic venous pressure gradient (HVPG), the gold standard for assessing portal hypertension (PH). This lecture introduce the clinical usefulness of hemodynamic evaluation by Doppler US through recently published data for Doppler US in PH and apply to clinical decision.

Blood Velocity and Flow in Vein

The portal vein velocity (PVV) in cirrhotic patient is considered relatively low compared to healthy subjects because of increased intrahepatic vascular resistance (outflow resistance). The cut-off value of 15cm/s showed a sensitivity and specificity of 88 and 96%. However, in cirrhotic patients with PH, various portosystemic shunts may develop; therefore, portal blood velocity and flow can differ among patients even when portal pressures are similar in clinical practice. Both splenic venous velocity and flow increase in PH associated dilated splenic vein (SV) and enlarged spleen. The SV flow exceeding PV flow is related to the portosystemic varices formation and a high risk of variceal bleeding.

Resistance by Measuring Resistive and Pulsatility Index in Artery

The resistances in the hepatic, splenic and renal artery can evaluated by measuring the resistive index (RI) and pulsatility index (PI) if the vessel is identified by color Doppler. With higher arterial resistance, there is increase in the peak systolic velocity and a decrease in the diastolic velocity. Therefore, RI and PI increase with higher arterial resistance, PI is different from RI in that it uses mean velocity as its denominator instead of the peak velocity like RI. PI is superior to RI when arterial resistance is extremely high that the end diastolic velocity is close to zero.

Hepatic Vein Waveform Analysis

In healthy individuals, the Doppler hepatic vein (HV) waveform exhibits a triphasic pattern comprising two negative waves and one positive wave, which reflects fluctuations in central venous pressure

during the cardiac cycle. In contrast, patients with liver cirrhosis characteristically display biphasic or monophasic HV waveforms. This alteration in the HV waveform serves as an effective parameter for predicting portal hypertension; specifically, it identifies a high HVPg (>12 mmHg) with a sensitivity of 76% and a specificity of 82%. Furthermore, the presence of a monophasic waveform correlates with higher Child-Pugh scores and a poorer prognosis in cirrhotic patients.

Doppler US Using Microbubble Contrast Agents

Contrast-enhanced ultrasound (CEUS) utilizes the intravenous administration of minute, gas-filled microbubbles that strongly amplify signal intensity from the intravascular flow. Hepatic vein arrival time (HVAT) is defined as the time interval (in seconds) from the peripheral injection of the contrast agent to its initial enhancement within the hepatic vein. With the advancement of liver fibrosis and cirrhosis, the progressive capillarization of hepatic sinusoids and the formation of intrahepatic arteriovenous or portovenous shunts induce profound hemodynamic alterations. In our previous study on compensated cirrhosis, HVAT demonstrated a significantly strong correlation with portal hypertension (PHT), where a shorter HVAT was associated with worse Child–Pugh scores and the presence of esophageal varices. In the derivation cohort, the mean values ($\pm$ standard deviation) for HVPg and HVAT were 11.4 ± 5.0 mmHg (range, 2–23) and 14.1 ± 3.4 seconds (range, 8.4–24.2), respectively. A statistically significant negative correlation was observed between HVPg and HVAT ($r^2 = 0.545$; $p < 0.001$). Therefore, HVAT serves as a valuable non-invasive indicator that correlates significantly with both the histological severity of liver fibrosis and the degree of portal hypertension.

Conventional Doppler US indices, including PVV and SVV, and arterial RI/PI, remain insufficient for the accurate diagnosis of PHT due to their conflicting results and the high variability in patient-specific portosystemic collateral pattern. To overcome these limitations, novel diagnostic characteristics such as the Doppler HV waveform have emerged, demonstrating that the extent of waveform flattening is closely correlated with the severity of HVPg via increased inflow through intrahepatic shunts. Furthermore, microbubble CEUS serves as another robust technique, where the detection of decreased HVAT provides valuable clinical insight into the severity of portal hypertension.

Although conventional Doppler US suffers from relatively poor reproducibility, the implementation of cooperative training programs alongside strict examination protocols can effectively reduce intra- and inter-observer variations. Overall, these ongoing developments in novel Doppler US indices and techniques hold significant potential to establish hemodynamic ultrasound evaluation as a reliable, non-invasive supplementary tool, particularly when invasive HVPg measurements are not feasible or adequate.

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Self Introduction

- 2011.02-2015.06 Assistant Professor, Internal Medicine, Department of Gastroenterology, Kyungpook National University Hospital
- 2015.06-2020.07 Associate Professor, Internal Medicine, Department of Gastroenterology, Kyungpook National University Hospital
- 2020.07-Present Professor, Internal Medicine, Department of Gastroenterology, Kyungpook National University Hospital
- 2018.08-2019.08 Visiting Scientist, UCSD, NAFLD Research Center

Research Interests

Translational Research, Biomarker Study, and Cancer Diagnostics, Chemotherapeutics, and Viral Hepatitis

Representative Publications

1. Endothelial RUNX3 Controls LSEC Dysfunction and Angiocrine LRG1 Signaling to Prevent Liver Fibrosis. *Hepatology*. 2025 Apr 1;81(4):1228-1243.
2. Early Antiviral Treatment with Tenofovir Alafenamide to Prevent Serious Clinical Adverse Events In Adults with Chronic Hepatitis B and Moderate or High Viraemia (ATTENTION): Interim Results from a Randomised Controlled Trial. *Lancet Gastroenterol Hepatol*. 2025 Apr;10(4):295-305.
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Deep Learning-Based Quality Control in Abdominal Ultrasound

Soo Young Park *Kyungpook National University*

Abdominal ultrasound is the most widely used imaging modality in hepatology practice, yet its diagnostic reliability is constrained by operator dependence, inter-examiner variability, and the absence of standardized real-time quality feedback. Significant discrepancies in image acquisition quality—affecting up to 40% of examinations—contribute to diagnostic inconsistency, repeat studies, and suboptimal trainee education. Deep learning (DL)-based quality control (QC) systems offer automated, objective, real-time assessment across multiple clinical dimensions, representing a transformative advance for hepatology practice.

This lecture reviews current evidence, key clinical applications, and future directions of DL-based QC in abdominal ultrasound, with emphasis on liver stiffness measurement, hepatic steatosis quantification, and focal liver lesion surveillance.

Introduction

Abdominal ultrasound occupies a central role in the investigation and surveillance of chronic liver disease, hepatocellular carcinoma (HCC), portal hypertension, and biliary pathology. Despite its widespread clinical adoption, the modality remains inherently susceptible to operator-dependent variation: inter-observer variability in liver size measurement has been reported to exceed 30%, the diagnostic accuracy gap between expert sonographers and trainees approximates threefold, and suboptimal image acquisition quality affects up to 40% of examinations in routine clinical practice.

Conventional quality control in ultrasound relies predominantly on retrospective image review, subjective expert assessment, and operator self-regulation—mechanisms that are inherently inconsistent and incapable of delivering real-time corrective feedback during examination. The rapid maturation of deep learning methodologies, particularly convolutional neural networks (CNNs) and, more recently, vision transformers, has created unprecedented opportunities to automate and standardize the quality assessment process. By training on large annotated datasets of labeled ultrasound examinations, DL models can learn the multidimensional features that characterize high-quality diagnostic images—including appropriate gain and depth settings, anatomical completeness, artifact profiles, and probe positioning—enabling consistent, examiner-independent quality evaluation at the point of acquisition.

This lecture provides a comprehensive overview of the current landscape, key clinical applications, and anticipated future directions of DL-based QC in abdominal ultrasound, with particular emphasis on hepatology-relevant use cases. We discuss the technical foundations, the principal QC domains amenable to DL automation, liver-specific applications of direct relevance to clinical hepatology, challenges pertaining to explainability and regulatory compliance, and the translational trajectory from research prototype to clinical deployment.

CNNs constitute the predominant architectural paradigm for ultrasound image analysis. These hierarchical feature extractors learn progressively abstract representations—from low-level edge and texture features to high-level structural configurations—through supervised training on paired image-label datasets. The ultrasound domain presents unique modeling challenges: speckle noise, acoustic shadowing, probe-dependent image characteristics, and real-time acquisition dynamics differ substantially from the properties of computed tomography or magnetic resonance imaging, necessitating domain-specific preprocessing strategies and data augmentation protocols. Vision transformers, which model long-range spatial dependencies through self-attention mechanisms, have more recently demonstrated competitive performance on ultrasound segmentation and classification tasks, often outperforming CNNs on larger datasets.

Five principal QC domains have been identified in the current literature, spanning the continuum from raw image acquisition to structured measurement (Table 1). Image quality assessment and standard plane detection are technically mature and have achieved clinical deployment; probe guidance and artifact detection are in active development; and automated measurement consistency represents an early-stage research frontier.

Table 1. Deep learning quality control domains in abdominal ultrasound, classified by function, clinical benefit, and developmental maturity.

QC Domain	Deep Learning Function	Clinical Benefit	Status
Image Quality Assessment	Automated gain/depth/focus scoring	Real-time suboptimal image detection	Established
Standard Plane Detection	CNN-based recognition of hepatic/biliary planes	Examination standardization	Established
Probe Guidance	Real-time transducer positioning feedback	Accelerated trainee education	Emerging
Artifact Detection	Shadowing/reverberation classification	Misinterpretation prevention	Emerging
Measurement Consistency	Liver size and parenchymal echogenicity quantification	Longitudinal follow-up reliability	Early

From the perspective of clinical hepatology, three DL-based QC applications are of particular immediate relevance. First, liver stiffness measurement (LSM) QC represents one of the most clinically mature applications. Automated elastography quality control—encompassing real-time IQR/median ratio assessment, region-of-interest positioning verification, and respiratory artifact detection—has demonstrated a 45% reduction in technical failure rates in prospective evaluations. DL models trained on sequential elastography acquisition data can identify suboptimal measurements before they are incorporated into clinical reports, directly reducing the need for repeat examination and improving LSM reliability in patients with chronic liver disease.

Second, hepatic steatosis quantification QC is increasingly recognized as a research priority. Automated hepatorenal echogenicity ratio measurement and controlled attenuation parameter (CAP) calibration QC substantially improve inter-observer reproducibility for NAFLD/MASLD grading—a critical need in both routine clinical assessment and interventional trial endpoint adjudication. Third, focal liver lesion surveillance QC addresses a core requirement of HCC surveillance programs: the reproducibility of standard cross-sectional planes across serial examinations. DL-guided plane reacquisition assistance reduces lesion measurement variability, supporting consistent LI-RADS categorization and enabling more reliable detection of interval growth.

A particularly noteworthy recent development is EchoNet-Liver, published in NEJM AI (2024), which demonstrated that a DL pipeline applied to routinely acquired echocardiographic subcostal views can opportunistically screen for cirrhosis (AUROC 0.837) and steatotic liver disease (AUROC 0.799) without additional imaging cost.

A fundamental barrier to DL clinical adoption is the interpretability deficit inherent to standard neural networks. Explainable AI (XAI) methods—principally Gradient-weighted Class Activation Mapping (Grad-CAM) and SHapley Additive exPlanations (SHAP)—address this through complementary mechanisms. Grad-CAM generates saliency heatmaps highlighting image regions most influential in a QC decision, enabling the sonographer to identify precisely which feature—such as posterior gain inadequacy or probe-rib artifact—triggered a quality alert and to take corrective action. SHAP values quantify each input feature’s marginal contribution to the QC score, providing a population-level model behavior framework. Both the Korean MFDS and the US FDA increasingly require explainability documentation in AI medical device submissions.

DL-based ultrasound QC is advancing from research to clinical deployment. Pilot programs at Korean tertiary centers have demonstrated significant improvements in examination standardization and trainee competency metrics. GE HealthCare’s Caption Guidance—the first FDA-cleared AI-guided ultrasound acquisition system—exemplifies real-time DL QC integration in commercial point-of-care hardware, enabling non-sonographer use without specialized training. Cumulative evidence associates DL QC implementation with approximately 25% reduction in examination time, 40% improvement in standard plane acquisition rates among trainees, and 15% reduction in repeat studies, though prospective ran-

domized evidence remains limited.

Despite promising early results, several substantive challenges require resolution. Dataset bias limits generalizability: models trained on single-institution data may underperform across different transducer platforms, body habitus distributions, or demographic groups. Real-time QC systems that influence clinical decisions are classified as Class II medical devices by the MFDS, requiring prospective clinical evidence for regulatory approval. The de-skilling risk—wherein automated feedback attenuates fundamental sonographic skill acquisition in trainees—necessitates structured educational integration. Edge deployment within ultrasound hardware requires significant model compression and latency optimization.

The next frontier encompasses multimodal integration of image quality signals with laboratory biomarkers and clinical metadata. Foundation models such as SAM and its medical adaptations offer robust QC systems from smaller labeled datasets, reducing annotation burden. Federated learning enables privacy-preserving multi-institutional model training, producing generalizable QC systems reflecting population heterogeneity. The proliferation of portable devices—Butterfly iQ+, Philips Lumify—creates urgency for effective DL QC systems capable of guiding non-expert operators in primary care and emergency settings.

Deep learning-based quality control represents a scientifically mature and clinically actionable advance in abdominal ultrasound practice. For clinical hepatologists, the most immediately applicable benefits lie in liver stiffness measurement QC and hepatic steatosis quantification, where automated assessment can directly reduce technical failure rates and improve diagnostic reproducibility in the management of chronic liver disease. AI-assisted QC systems function most effectively as intelligent assistants to skilled sonographers—augmenting human expertise and expanding the reach of high-quality hepatic ultrasound—rather than as autonomous replacements for examiner judgment. Successful adoption requires institutional attention to regulatory requirements, training program integration, and the sustained cultivation of foundational sonographic competence alongside AI-assisted workflows.

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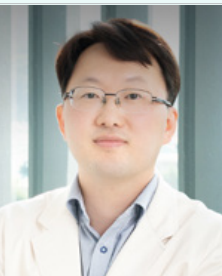
Expanding Horizons in Surgical Management of Hepatic Malignancies

Chairs

Jung-Hwan Yoon (Seoul National Univ.)

Deok-Bog Moon (Univ. of Ulsan)





Dong Hyun Sinn
Sungkyunkwan University

Self Introduction

Graduated Dankook Univ. in year 2001.
Received Doctor's degree in medicine from Sungkyunkwan Univ. in year 2013.
Trained at Samsung Medical Center from 2001 to 2012 as intern, resident (internal medicine), and fellow (gastroenterology).
Worked at Sanngye Paik Hospital, Inje Univ. from 2012 to 2014 as an assistant professor.
Working at Samsung Medical Center, Sungkyunkwan Univ. from 2012 to now as clinical assistant professor (2014-2016), associate professor (2016-2022) and professor (2022 to current)

Research Interests

Chronic Hepatitis, Liver Cirrhosis, Liver Failure, Hepatocellular Carcinoma

Representative Publications

1. Sinn DH, Kang D, Kang M, Guallar E, Hong YS, Lee KH, Park J, Cho J, Gwak GY. Nonalcoholic fatty liver disease and accelerated loss of skeletal muscle mass: A longitudinal cohort study. *Hepatology*. 2022 Dec;76(6):1746-1754.
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Expanding Indications for Surgery and Transplantation in Hepatic Malignancies: Ethics, Donor Considerations, and Future Perspectives

Dong Hyun Sinn Sungkyunkwan University

The expansion of surgical and transplant criteria for hepatic malignancies requires careful consideration of fundamental ethical principles, recurrence risk thresholds, and donor safety. This session examines the philosophical and practical frameworks that should guide decisions to extend treatment indications beyond established criteria. Deceased donor liver transplantation (DDLT) allocation is governed by three fundamental ethical principles: utility (maximizing overall benefit from scarce organs), justice (equitable distribution), and medical urgency (prioritizing those at highest risk of death). The Model for End-Stage Liver Disease (MELD)-based “sickest first” allocation system prioritizes patients with the highest short-term mortality from liver failure. For hepatocellular carcinoma (HCC), this creates inherent tension, as patients typically have preserved liver function but face mortality from tumor progression. MELD exception points address this by granting HCC patients competitive priority, balancing urgency against utility. The principle of utility becomes particularly critical when considering expanded criteria. While Milan criteria achieve 5-year survival exceeding 70% with recurrence rates below 15%, expanded criteria must demonstrate comparable outcomes to justify organ allocation. LDLT operates under fundamentally different ethical constraints. Unlike DDLT, LDLT does not compete for scarce deceased donor organs, theoretically allowing greater flexibility in recipient selection. However, this flexibility is constrained by the paramount principle of donor safety, introducing the concept of “double equipoise”—balancing recipient survival benefit against donor complication or death risk. The critical ethical question becomes: what recurrence risk and survival threshold justify exposing a healthy donor to surgical risk? International consensus demonstrates significant disagreement on this issue. Some experts prioritize donor protection by restricting LDLT to patients meeting DDLT criteria, while others support LDLT even for patients with poorer prognosis to maximize individual autonomy and benefit. The 2012 international consensus recommended that LDLT be acceptable only when expected 5-year survival is similar to comparably staged DDLT patients, and that institutions must establish clear positions with rigorous safeguards including full disclosure and prevention of donor coercion.

Determining acceptable recurrence risk for surgical resection requires balancing oncologic outcomes against treatment-related morbidity and mortality. For HCC resection, recurrence rates approach 50-

70% at 5 years, with most occurring within the first year. Despite this high recurrence rate, resection remains standard of care for appropriately selected patients, achieving 5-year survival exceeding 70% in patients with Child-Turcotte-Pugh class A cirrhosis, no portal hypertension, and adequate future liver remnant. The acceptability of this recurrence risk is justified by several factors: low perioperative mortality (3% in experienced centers), potential for salvage therapies including repeat resection or transplantation, and absence of superior alternatives for many patients. Extended indications beyond Barcelona Clinic Liver Cancer (BCLC) stage A, including multifocal disease and portal vein tumor thrombus, demonstrate 5-year survival of 52-77% in selected patients, supporting resection in high-volume centers after multidisciplinary discussion. The presence of microvascular invasion and/or satellitosis emerges as the strongest independent predictor of aggressive recurrence and mortality, with implications for patient counseling and consideration of adjuvant therapy or ab initio transplantation.

Expanding indications for surgery and transplantation in hepatic malignancies requires thinking about ‘resectability or transplantability’. Tumor might be technically resectable or transplantable, but this should be justified by oncological benefit.

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**Yun Bin Lee**

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Self Introduction

Prof. Yun Bin Lee is a Professor at the Department of Internal Medicine, Seoul National University Hospital. Prof. Lee graduated from Seoul National University College of Medicine in 2006 and completed her internship, residency, and fellowship at the Department of Internal Medicine at Seoul National University Hospital, receiving her diploma in Internal Medicine in 2018.

Since 2014, Prof. Lee has been taking on a number of roles in the Korean Association for the Study of the Liver and the Korean Liver Cancer Association. She is also serving as the Director of Academic Affairs of the Korean Radioembolization Association.

Research Interests

Prof. Yun Bin Lee is conducting translational and clinical research, including big data-based studies. In the clinical research domain, her team focuses on identifying risk factors for hepatocellular carcinoma development in patients with chronic liver diseases. In translational research, her current interest lies in regenerative medicine using stem cells. Her laboratory investigates the mechanisms of mitochondrial dysfunction and the therapeutic potential of various mesenchymal stem cells in metabolic dysfunction-associated steatotic liver disease (MASLD).

In addition, she is actively involved in investigator-initiated clinical trials—such as the SOLID trial and the DETECT trial—evaluating novel combinations of immunotherapy and locoregional treatments for unresectable hepatocellular carcinoma.

Representative Publications

1. A phase 1/2a trial of yttrium-90 radioembolization in combination with durvalumab for locally advanced unresectable hepatocellular carcinoma. *Clin Cancer Res.* 2023;29(18):3650-3658. (first author)
2. Association between daily aspirin therapy and risk of hepatocellular carcinoma according to metabolic risk factor burden in non-cirrhotic patients with chronic hepatitis B. *Aliment Pharmacol Ther.* 2023;58(7):704-714. (first & corresponding author)
3. Aspirin Use and Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B With or Without Cirrhosis. *Hepatology.* 2022;76:492-501. (first & corresponding author)
4. Association of Metabolic Risk Factors With Risks of Cancer and All-Cause Mortality in Patients With Chronic Hepatitis B. *Hepatology.* 2021;73:2266-2277. (first & corresponding author)
5. Association of Chronic Hepatitis B Infection and Antiviral Treatment with the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study. *J Clin Oncol.* 2022;40:3394-3405 (contributing author)

Downstaging and Conversion to Resection or Transplantation for Advanced HCC Using Systemic and Locoregional Therapies

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Introduction

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide, and the majority of patients present at an intermediate or advanced stage, rendering curative-intent surgery unfeasible at initial diagnosis. Only 15–30% of patients are eligible for resection or transplantation at the time of presentation.^{1,2} The concept of “conversion therapy”—the strategic use of systemic and/or locoregional therapies to render an initially unresectable or transplant-ineligible patient eligible for surgery—has gained substantial clinical traction over the past decade. This lecture reviews current practice-based strategies, encompassing neoadjuvant systemic therapy, locoregional modalities including transarterial radioembolization (TARE) with radiation segmentectomy or radiation lobectomy, and future liver remnant (FLR) augmentation via portal vein embolization (PVE), focusing on outcomes and patient selection principles.

Downstaging to Liver Transplantation

Liver transplantation offers the most durable oncologic outcome for cirrhotic patients with HCC, with post-transplant 5-year survival approaching 80% when strict selection criteria are applied. For patients presenting beyond Milan criteria, downstaging to within Milan criteria followed by transplantation has been validated as a robust strategy. A systematic review of 25 studies encompassing 3,997 patients demonstrated a pooled successful downstaging rate of 55.2%, with 31.5% ultimately receiving liver transplantation on an intention-to-treat basis, and a post-transplant HCC recurrence rate of 16.0%.³ The UNOS downstaging protocol, adopted nationally in 2017, established standardized entry and exit criteria, enabling patients who achieve successful downstaging to within Milan criteria to receive priority listing. Importantly, outcomes following successful downstaging are largely comparable to those of patients who were always within Milan criteria when prespecified upper limits of tumor burden are observed.⁴ The most widely employed downstaging modalities remain transarterial chemoembolization (TACE) and TARE, with prospective multicenter data confirming equivalent radiographic response and waitlist outcomes between these two approaches.⁴

TARE: Radiation Segmentectomy and Radiation Lobectomy in Conversion Therapy

TARE with yttrium-90 (Y90) microspheres has emerged as a versatile locoregional modality with the capacity to simultaneously achieve tumor control and augment the contralateral FLR. Radiation segmentectomy—the selective delivery of an ablative radiation dose to one or two hepatic segments—represents a curative-intent application of TARE for early-stage HCC and has been firmly established as an effective bridging and downstaging strategy to transplantation.⁵ Radiation segmentectomy is characterized by high local imaging response rates, long time to treated-tumor progression, and significant rates of complete pathological necrosis on explant.⁵ For patients with unresectable HCC beyond standard transplant criteria, boosted-dose TARE (>190 Gy) has demonstrated the ability to downstage tumors to within Milan or UCSF criteria; objective radiographic response by RECIST v1.1 is a positive predictive factor, while tumor size >7 cm portends lower conversion success.⁶ Radiation lobectomy—lobar TARE administration—provides a dual benefit of ipsilateral tumor control and contralateral hepatic hypertrophy, functioning concurrently as a bridge to resection and a biological test-of-time to assess tumor behavior and liver functional reserve.⁷ Recent Korean multicenter study further confirmed that TARE-based bridging/downstaging followed by surgical resection or living-donor liver transplantation achieved 76% disease-free survival at final follow-up, with efficient tumor necrosis and adequate remnant liver growth.⁸

Neoadjuvant and Conversion Systemic Therapy

The advent of effective systemic regimens—particularly combinations of immune checkpoint inhibitors (ICIs) with anti-angiogenic agents—has expanded the scope of conversion therapy for HCC. Neoadjuvant ICI-based therapy in resectable or locally advanced HCC is under active clinical investigation, with early-phase trials demonstrating encouraging objective response rates and feasibility of subsequent surgical resection.⁹ In the transplantation context, a prospective multicenter study evaluating neoadjuvant atezolizumab plus bevacizumab in 17 patients with HCC—predominantly beyond Milan criteria—reported that 82% achieved downstaging to within Milan criteria, with no severe post-transplant rejection or graft loss, provided that the drug was discontinued at least four weeks prior to transplantation.¹⁰ These preliminary data are encouraging, although ICI-associated immune-mediated rejection risk mandates cautious patient selection and strict washout protocols. Multimodal approaches combining systemic agents with locoregional therapies are increasingly being explored in prospective trials to optimize conversion rates and perioperative outcomes.

FLR Augmentation: Portal Vein Embolization and Beyond

For patients with adequate tumor biology but insufficient remnant liver volume, FLR augmentation is an indispensable prerequisite to safe major hepatectomy. Preoperative PVE—occlusion of ipsilateral portal vein branches to induce contralateral hypertrophy—remains the accepted standard, enabling 70–80% of selected patients to proceed to resection.¹¹ In cirrhotic patients with HCC, FLR thresholds are more stringent (≥40% standardized FLR) compared to non-cirrhotic livers. Liver venous deprivation (LVD), which

combines simultaneous portal and hepatic vein embolization, has demonstrated superior FLR hypertrophy kinetics and higher rates of successful resection compared to PVE alone in recent meta-analyses.¹² For HCC patients with unilateral disease and insufficient FLR, radiation lobectomy offers the unique advantage of concurrent tumor treatment and FLR growth over 3–6 months, embedding a test-of-time that may identify patients with favorable tumor biology who are most likely to benefit from curative resection.⁷

Conclusions

The successful conversion of initially unresectable or transplant-ineligible HCC patients to surgical candidacy requires a multidisciplinary, individualized approach integrating locoregional and systemic modalities with careful assessment of hepatic functional reserve. TARE-based radiation segmentectomy and radiation lobectomy, neoadjuvant ICI combinations, and PVE/LVD-based FLR augmentation constitute the current toolkit for this strategy. Patient selection guided by tumor burden, tumor marker kinetics, hepatic reserve, and underlying etiology remains paramount. Ongoing prospective trials combining systemic immunotherapy with locoregional approaches are anticipated to further define optimal sequencing and expand the boundaries of surgical candidacy in advanced HCC.

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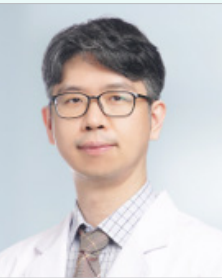
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Self Introduction

Prof. Sang Jin Kim is a Associate Professor of Division of Hepatobiliopancreas and Transplantation Surgery, Korea University Ansan Hospital. He graduated from Sungkyunkwan University with his medical degree in 2010. He completed his internship residency at the Department of Surgery and fellowship at the Transplantation division in Samsung Medical Center.

Prof. Kim has been serving as a faculty member in the Division of Hepatobiliary and Pancreatic Surgery at Korea University Ansan Hospital since 2021. His clinical expertise includes liver resection, liver transplantation, and kidney transplantation surgery. He is currently serving as a secretary and committee member in various divisions of the Korean Liver Cancer Association, The Korean Society for Transplantation, Korean Liver Transplantation Society, and Korean Society of Gastroenterology.

Research Interests

- Hepatocellular Carcinoma
- Liver Resection and Liver Transplantation
- Living Donor Safety and Psychiatric Management

Representative Publications

1. Kim SJ, Jeong WK, Han HJ, Choi GS, Kim KH, Kim J. Comparison of initial treatments for resectable hepatocellular carcinoma within Milan criteria: an observational study based on a nationwide survey. *Ann Surg Treat Res.* 2025 May;108(5):279-294.
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Surgical Management of Uncommon Hepatic Malignancies

Sang Jin Kim Korea University

Hepatic malignancies beyond hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA), and cystic neoplasms constitute a heterogeneous but clinically important group that every hepatobiliary surgeon must recognize. This presentation reviews the surgical approach, oncological principles, and tumor-specific considerations for uncommon primary hepatic malignancies, with the shared conviction that surgical resection — when feasible — remains the cornerstone of curative intent.

The tumors addressed in this presentation span a broad biological spectrum. Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor with an incidence below 1 per million per year, predominantly affecting young women without underlying liver disease and without a defined causative exposure. Imaging characteristically shows peripheral subcapsular lesions with capsular retraction and the lollipop sign on MRI — a hepatic vein drawn into a fibrous tumoral core — features that are highly suggestive of the diagnosis. Primary hepatic angiosarcoma (PHA) accounts for approximately 2% of all primary liver tumors and has been associated with prior exposure to thorotrast, vinyl chloride, and arsenicals, though most contemporary cases arise without an identifiable carcinogen. It presents as rapidly enlarging hypervascular lesions and may manifest as acute hemoperitoneum due to spontaneous tumor rupture. Fibrolamellar carcinoma (FLC) arises exclusively in adolescents and young adults without chronic liver disease, with an estimated incidence of 0.02 per 100,000 per year. On imaging, a calcified central scar without gadoxetate enhancement distinguishes it from focal nodular hyperplasia; serum AFP is typically normal. Undifferentiated embryonal sarcoma of the liver (UESL) is the third most common malignant liver tumor in children aged 6-10 years, with no established etiology. A characteristic imaging discordance exists: the tumor appears predominantly cystic on ultrasound yet predominantly solid on CT and MRI, a pattern that should prompt suspicion for UESL in a pediatric patient. Hepatic angiomyolipoma (HAML) is a mesenchymal tumor of perivascular epithelioid cell origin that is typically benign; the epithelioid variant harbors malignant potential. Diagnosis is supported by macroscopic fat on imaging combined with HMB-45 positivity on biopsy. Fat-poor epithelioid HAML may be indistinguishable from HCC on conventional imaging and frequently requires tissue confirmation. Primary hepatic lymphoma (PHL) accounts for less than 1% of all extranodal lymphomas, most commonly presenting as DLBCL in immunocompetent adults; chronic hepatitis C infection and immunosuppression are recognized predisposing factors. It is typically presented as a solitary or multifocal hepatic mass without

peripheral lymphadenopathy or systemic B symptoms, and diagnosis requires core-needle biopsy with immunohistochemical profiling. Primary hepatic neuroendocrine tumor (NET) is an exceedingly rare entity, requiring rigorous exclusion of all possible extrahepatic primary sites — including the gastrointestinal tract, pancreas, and lung — before the diagnosis can be established. No specific causative exposure has been identified. On imaging, hepatic NETs are hypervascular and somatostatin receptor-positive, and 68Ga-DOTATATE PET/CT is the modality of choice both for confirming the diagnosis and for excluding an occult extrahepatic primary. Sarcomatoid carcinoma of the liver is a dedifferentiated variant of HCC or CCA that presents as a rapidly enlarging, heterogeneous mass with central necrosis; serum tumor markers including AFP and CA19-9 are often disproportionately low relative to tumor burden, and biopsy revealing sarcomatoid morphology should significantly temper surgical expectations.

Among these uncommon malignancies, outcomes after surgical resection vary substantially. Tumors in which resection is associated with relatively favorable long-term survival — generally exceeding 50% at 5 years — include UESL, FLC, and HAML. For UESL, the introduction of neoadjuvant doxorubicin and ifosfamide chemotherapy prior to resection has transformed outcomes, with contemporary series reporting 5-year survival rates of 70–80%; complete resection remains the single most critical prognostic determinant. FLC, when resected with negative margins and thorough lymphadenectomy, achieves 5-year survival in the range of 50–70% in selected series, and even recurrent disease is amenable to repeat resection with meaningful benefit. HAML — particularly the conventional fat-containing variant — carries an excellent prognosis after resection, and the epithelioid subtype, while more aggressive, still permits durable control with complete excision and long-term surveillance. HEHE occupies an intermediate position; indolent cases managed with resection may achieve prolonged survival, though the multifocal nature of most presentations limits the proportion of patients eligible for curative surgery. Primary hepatic NET, when confirmed after thorough exclusion of an extrahepatic primary, is amenable to surgical resection with favorable outcomes; given the well-differentiated biology of most cases, 5-year survival following complete resection is reported in excess of 60% in the limited available series, and the indolent natural history supports an aggressive surgical approach in fit patients.

In contrast, primary hepatic angiosarcoma and sarcomatoid carcinoma represent tumors in which the prognosis remains poor even after surgical resection. Both entities frequently demonstrate resistance to postoperative chemotherapy, and although systemic treatment is attempted, it rarely translates into meaningful improvement in long-term survival. Honest prognostic communication and early multidisciplinary planning are therefore as important as technical surgical expertise in the management of these tumors.

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Self Introduction

Education

2007.3-2011.2 M.D., Jeonbuk National University Medical School, Jeonju
2015.3-2019.8 Ph.D., Graduate School of Medicine of Jeonbuk National University, Jeonju

Professional Experience

2014.5-2015.2 Internship, Jeonbuk National University Hospital, Jeonju
2015.3-2019.2 Residency, Department of Surgery, Jeonbuk National University Hospital, Jeonju
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2023.3-Present Clinical Assistant Professor, Division of Liver Transplantation and Hepatobiliary Surgery, Asan Medical Center, Seoul

Research Interests

His primary research interests lie in surgical oncology and transplant oncology for hepatocellular carcinoma, with a focus on improving surgical outcomes and expanding curative treatment options for patients with liver cancer. A core area of His work is living donor safety and long-term outcomes in living donor liver transplantation, including the identification of risk factors and the establishment of criteria that ensure safe and sustainable donor programs. He is also committed to advancing minimally invasive surgery and minimally invasive donor hepatectomy, exploring the clinical applicability and safety of novel surgical approaches to broaden their adoption while maintaining the highest standards of care for both donors and recipients.

Representative Publications

1. SH Kim, KH Kim, HD Cho, et al. Donor Safety and Risk Factors of Pure Laparoscopic Living Donor Right Hepatectomy: A Korean Multicenter Study. *Ann Surg.* 2023;278(6):E1198-E1203.
2. SH Kim, KH Kim, YI Yoon, et al. Feasibility of Pure Laparoscopic Donor Right Hepatectomy Compared to Open Donor Right Hepatectomy: A Large Single-Center Cohort Study. *Ann Surg.* 2025;281(5):823-833.
3. SH Kim, DH Jung, S Hwang, et al. Living right liver donation from donors aged 45 years and older: Outcomes for both donors and recipients. *Am J Transplant.* 2026;26:371-382
4. SH Kim, KH Kim, Hugo PM, João SC. Feasibility of robotic liver resection compared with laparoscopic and open liver resection for hepatocellular carcinoma: a network meta-analysis. *Int J Surg.* 2026;26:24-41.
5. SH Kim, KH Kim, S Sudhindran DC Broering. International Journal of Surgery Risk factors for morbidity in both donor and recipient following minimally invasive donor hepatectomy : A systematic review. *Int J Surg.* 2026;112:18-26.

Liver Transplantation for Uncommon Hepatic Malignancies: Beyond Current Criteria

Sang-Hoon Kim University of Ulsan

Background

Liver transplantation (LT) has traditionally been reserved for end-stage liver disease and hepatocellular carcinoma (HCC) within the Milan criteria. However, the transplant oncology landscape is rapidly evolving. Recent advances in surgical technique, systemic chemotherapy, and patient selection have expanded the potential indications of LT to a range of uncommon hepatic malignancies, including colorectal cancer liver metastases (CRLM), cholangiocarcinoma (CCC), neuroendocrine tumor liver metastases (NETLM), and hepatic epithelioid hemangioendothelioma (HEHE).

The 2024 EASL Clinical Practice Guidelines and the 2025 updated OPTN/UNOS allocation policies now formally recognize several of these entities as standard or non-standard exception indications, reflecting a paradigm shift in transplant oncology. Despite this progress, evidence remains largely limited to retrospective cohort studies and early-phase prospective trials, underscoring the critical importance of rigorous patient selection and multidisciplinary management.

Objectives

This lecture aims to:

- Review the current evidence base for LT in uncommon hepatic malignancies, including CRLM, perihilar and intrahepatic cholangiocarcinoma (pCCC, iCCC), NETLM, and HEHE.
- Summarize key clinical trials and landmark studies informing patient selection criteria.
- Present updated allocation policies in the United States and international consensus recommendations.
- Propose a systematic decision-making algorithm for each malignancy subtype.

Content

1. Colorectal Cancer Liver Metastases (CRLM)

CRLM represents the most extensively studied non-conventional LT indication. The Oslo SECA-I pilot

study (2013) demonstrated the feasibility of LT in patients with unresectable liver-only metastases, reporting a 5-year overall survival (OS) of 60%. The subsequent SECA-II study (2019) applied stricter selection criteria — including chemotherapy response $\geq 10\%$ and no lesion >10 cm prior to chemotherapy — and demonstrated markedly improved outcomes (5-year OS: 83%). Long-term follow-up of SECA-I confirmed durable benefit in patients with Oslo Score 0–1, with 10-year OS reaching 50%.

The landmark TransMet randomized controlled trial (Lancet, 2024) provided level-I evidence, demonstrating that combined LT with chemotherapy achieved a 5-year OS of 57% compared to 13% with chemotherapy alone. The 2025 OPTN/UNOS updated allocation policy now grants standard exception status for CRLM under strict criteria: prior primary resection, liver-only unresectable disease, stable or regressing disease for ≥ 6 months on systemic therapy, largest tumor <10 cm, and CEA <80 $\mu\text{g/dL}$.

Key selection parameters: Oslo Score 0–1, no BRAF mutation, CEA <80 $\mu\text{g/L}$, and disease stability ≥ 6 months on chemotherapy.

2. Cholangiocarcinoma (CCC)

Perihilar CCC (pCCC):

LT for pCCC was pioneered by the Mayo Clinic protocol, which established neoadjuvant chemoradiation (5-FU + radiation) followed by staging laparoscopy as a prerequisite to transplantation. Long-term outcomes with this protocol have been exceptional, with 5-year OS of 82% and a recurrence rate of 14.2%. The OPTN/UNOS now grants standard exception at MMat-3 for unresectable pCCC <3 cm, node-negative (confirmed by staging laparotomy), and following completion of neoadjuvant therapy. Ongoing prospective trials continue to refine patient selection, particularly focusing on response to chemoradiation as a stratification marker.

Intrahepatic CCC (iCCC):

LT for iCCC remains investigational. Meta-analysis of 18 studies ($n=385$) reported a 5-year OS of 42%, reaching 83.3% with neoadjuvant therapy in selected patients. Current EASL and AASLD guidelines recommend LT for iCCC only within the context of clinical trials. The 2025 US allocation policy grants exception for solitary tumors ≤ 3 cm in cirrhotic livers, or unresectable disease with ≥ 6 months of stability after neoadjuvant therapy.

3. Neuroendocrine Tumor Liver Metastases (NETLM)

NETLM represents a well-established indication for LT in highly selected patients. International multi-center data (Eshmuminov et al., Ann Surg, 2023; $n=455$) demonstrated superior OS and progression-free survival with LT compared to resection in patients meeting Milan criteria (G1–G2, Ki-67 $<5\%$, unresectable liver-only disease, stable for ≥ 6 months, hepatic volume $<50\%$, age <60). Single-institution data from the Milan group confirmed 5-year OS of 97.2% in transplanted patients vs. 50.9% in non-transplanted controls. Patient selection remains the critical determinant of outcome, with tumor grade and Ki-67 index serving as the most reliable prognostic biomarkers.

4. Hepatic Epithelioid Hemangioendothelioma (HEHE)

HEHE is an ultra-rare vascular sarcoma most commonly associated with WWTR1-CAMTA1 gene fusion, exhibiting highly variable biological behavior. LT is recommended by ESMO 2020 consensus for unresectable liver-confined HEHE in the absence of tumor rupture or macrovascular/hilar lymph node invasion, supported by Level V evidence. UNOS registry data ($n=121$) show post-LT median survival of 16.6 years for HEHE, comparable to HCC within Milan criteria. The HEHE-LT Score, derived from the ELTR-ELITA registry, provides a validated risk-stratification tool, with macrovascular invasion, hilar LN invasion, and waiting time ≤ 120 days identified as risk factors for recurrence. Asan Medical Center's institutional experience with living donor LT for HEHE ($n=4$) demonstrated 5-year OS and DFS of 75%.

Patient Selection: Key Criteria Summary

Across all uncommon malignancies, absence of extrahepatic disease and multidisciplinary tumor board evaluation are universal prerequisites. Disease-specific criteria are as follows:

- CRLM: Liver-only unresectable disease, no BRAF mutation, CEA <80 $\mu\text{g/L}$, stable on chemotherapy ≥ 6 months, Oslo Score 0–1 preferred.
- pCCC: Unresectable, tumor <3 cm, node-negative (confirmed by staging laparotomy), completion of neoadjuvant chemoradiation, specific institutional protocol mandatory.
- iCCC: Solitary ≤ 3 cm in cirrhotic liver OR unresectable disease stable after neoadjuvant therapy ≥ 6 months; investigational — clinical trial only.
- HEHE: Unresectable, liver-only, no tumor rupture, no macrovascular or hilar LN invasion, waiting time >120 days preferred.
- NETLM: G1–G2, Ki-67 $<10\%$, unresectable liver-only disease occupying $<50\%$ of liver volume, stable for ≥ 6 months, age <60 , no extrahepatic disease.

Conclusion

LT for uncommon malignancies represents one of the most rapidly evolving frontiers in transplant surgery. Accumulating evidence supports meaningful survival benefits in carefully selected patients with CRLM, pCCC, NETLM, and HEHE, while LT for iCCC remains investigational. Patient selection — guided by tumor biology, disease stability, and absence of extrahepatic spread — is the single most important determinant of post-transplant outcomes. Multidisciplinary evaluation, adherence to institutional protocols, and participation in prospective clinical trials are strongly encouraged to advance the evidence base and refine indications for this expanding field.

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KASL SYMPOSIUM 1

Redefining the Natural History of Chronic Hepatitis B: Expanding Treatment Paradigms

Chairs

W. Ray Kim (Mayo Clinic, USA)

Jaeyoun Cheong (Ajou Univ.)





Nina Le Bert

Duke-NUS Medical School, Singapore

Self Introduction

After her undergraduate degree in Berlin, Germany, Dr. Le Bert was awarded a Marie Curie Early-Stage Research Fellowship, which facilitated her pursuit of a Ph.D. from the Division of Infection & Immunity at University College London, UK.

In 2012, Dr. Le Bert relocated to Singapore, where she joined A/Prof Stephan Gasser's lab at the National University of Singapore as a Research Fellow. In 2014, she transitioned into Prof Antonio Bertoletti's lab, initially as a Research Fellow at the Singapore Institute for Clinical Sciences, A*STAR, and later as a Senior Research Fellow at Duke-NUS Medical School from 2017 onward.

Since 2023, Dr. Le Bert is an Assistant Professor at Duke-NUS Medical School within the Program in Emerging Infectious Diseases.

Research Interests

Dr. Le Bert's primary research interest is focused on the roles of antigen-specific T and B cells in the control and pathogenesis of chronic Hepatitis B virus (HBV) infection.

Representative Publications

1. Le Bert N et al. 2025. Rapid whole-blood immune profiling reveals heterogeneous HBV-specific T cell response patterns independent of clinical disease phases. *Journal of Hepatology* 83(6):1292-1304.
2. Le Bert N, Tan AT et al. 2020. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* 584:457-462.
3. Le Bert N, Gill US, Hong M et al. 2020. Effects of hepatitis B surface antigen on virus-specific and global T cells in patients with chronic HBV infection. *Gastroenterology* 159:652-664.
4. Le Bert N, Salimzadeh L et al. 2020. Comparative characterization of B cells specific for HBV nucleocapsid and envelope proteins in patients with chronic hepatitis B. *Journal of Hepatology* 72:34-44.
5. Salimzadeh L, Le Bert N et al. 2018. PD-1 blockade partially recovers dysfunctional virus-specific B cells in chronic hepatitis B infection. *The Journal of Clinical Investigation* 128:4573-4587.

Immunological Features of Chronic Hepatitis B: Stage-Independent Patterns of HBV-Specific T Cell Responses

Nina Le Bert

Duke-NUS Medical School, Singapore



Gi-Ae Kim
Kyung Hee University

Self Introduction

Dr. Gi-Ae Kim is an Associate Professor in the Department of Internal Medicine at Kyung Hee University School of Medicine, Seoul, Korea.

Dr. Kim completed her internship and residency in Internal Medicine at Asan Medical Center (2009–2013), followed by a clinical fellowship in Gastroenterology and Hepatology at the same institution (2013–2014).

Dr. Kim is a member of the Korean Association for the Study of the Liver and is actively involved in clinical research on liver diseases.

Research Interests

- Chronic Hepatitis B
- Metabolic Dysfunction–Associated Steatotic Liver Disease

Representative Publications

1. Multicenter Prospective Cohort Study on Clinical Outcomes and Fibrosis Patterns in Biopsy-Proven Steatotic Liver Disease Subtypes. Kim GA, Jang HJ, Kim MY, Park JH, Park JG, Cho EY, Jeong JY, Jeong S, Han SK, Kwon H, Jung Y, Hwang GW, Lee YR, Park SY, Kim SG, Kim W. Gastroenterology. 2026 Jan 29;S0016-5085(26)00030-2. doi: 10.1053/j.gastro.2026.01.007.

2. Viral Load-Based Prediction of Hepatocellular Carcinoma Risk in Noncirrhotic Patients With Chronic Hepatitis B: A Multinational Study for the Development and External Validation of a New Prognostic Model. Kim GA, Lim YS, Han S, Choi GH, Choi WM, Choi J, Sinn DH, Paik YH, Lee JH, Lee YB, Cho JY, Heo NY, Yuen MF, Wong VW, Chan SL, Yang HI, Chen CJ. Ann Intern Med. 2024 Oct;177(10):1308-1318. doi: 10.7326/M24-0384. Epub 2024 Sep 17.

3. Non-linear association between liver fibrosis scores and viral load in patients with chronic hepatitis B. Kim GA, Choi SW, Han S, Lim YS. Clin Mol Hepatol. 2024 Oct;30(4):793-806. doi: 10.3350/cmh.2024.0252. Epub 2024 Jul 19.

4. Metabolic Dysfunction-Associated Steatotic Liver Disease and Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake Increase the Risk of Developing Hepatocellular Carcinoma and Incident or Decompensated Cirrhosis: A Korean Nationwide Study. Kim GA, Jeong S, Jang H, Lee DH, Joo SK, Kim W. Liver Cancer. 2023 Dec 22;13(4):426-437. doi: 10.1159/000535943. eCollection 2024 Aug.

5. Moderate Levels of Serum Hepatitis B Virus DNA Are Associated With the Highest Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients. Kim GA, Han S, Choi GW, Choi J, Lim YS. Aliment Pharmacol Ther. 2020;51:1169–1179.

Clarifying the Indeterminate Phase in Chronic Hepatitis B: Defining Its Natural Course and Virological Characteristics

Gi-Ae Kim Kyung Hee University

Chronic hepatitis B (CHB) has traditionally been classified according to the immunological natural history, which categorizes patients into distinct phases based on hepatitis B e antigen (HBeAg), serum hepatitis B virus (HBV) DNA levels, and alanine aminotransferase (ALT) levels.¹⁻⁴ The immunological natural history consists of immune-tolerant, immune-active HBeAg-positive, immune-inactive, immune-active HBeAg-negative, and HBsAg loss phases.¹

Increasing evidence suggests that this framework has substantial limitations.⁵ Although ALT levels have long served as a surrogate marker of hepatic injury, their sensitivity and specificity for detecting histological liver injury are rather limited. Among patients with persistently normal ALT levels, approximately 18% have significant fibrosis and 34% demonstrate moderate-to-severe hepatic inflammation.⁶ In addition, the terminology and definitions across guidelines are inconsistent in which criteria used are heterogeneous and often overlapping.⁵ In particular, the definition of the immune-tolerant phase differs substantially among guidelines and the phase by guidelines does not reliably correspond to histological one.⁷ Most importantly, the immunological natural history has a large population of patients who cannot be clearly classified into any phase, commonly referred to as the indeterminate phase.¹

The indeterminate phase represents a clinically important yet poorly defined population in CHB, comprising approximately 30% of CHB patients.¹ A retrospective study involving 4,759 treatment-naïve CHB patients showed that about 29% were in the indeterminate phase, in which older age, HBeAg positivity, and higher ALT levels were independently associated with advanced liver disease.⁸ The indeterminate phase is quite heterogeneous, presenting a significant challenge for clinical decision-making. Notably, the clinical risk this phase carries is quite considerable. A meta-analysis showed that the patients in the indeterminate phase have a significant risk of hepatocellular carcinoma (HCC), cirrhosis, and hepatic decompensation.⁹ The 10-year HCC risk of the indeterminate phase was 14-fold higher than that of the inactive phase, which increased to 18-fold in those aged 45 years and older.⁹ Although antiviral treatment is generally not recommended, a study reported that treating the indeterminate phase lowered the risk of HCC, decompensation, liver transplantation, or death compared to those who were untreated.

To address the challenges of immunological natural history, attempts were made to redefine the natural history of CHB using viral load. Previously conflicting notions of a linear association of viral load with

HCC risk and low HCC risk at high viral load were integrated into a parabolic association where the HCC risk increases until the moderate viral load and decreases after that.¹⁰⁻¹¹ The highest HCC risk in moderate viral load was consistently observed in both treated and untreated patients.¹⁰⁻¹¹ Histological analysis showed highest liver inflammation in moderate viral load.¹² Potential biological mechanisms underlying the highest HCC risk in moderate viral load include clonal hepatocyte expansion, HBV DNA integration, and positive selection.¹³⁻¹⁴ The new natural history based on HBV DNA levels can eliminate the indeterminate phase and provide a more straightforward framework for clinical decision-making.

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4. Ghany MG, Pan CQ, Lok AS, Feld JJ, Lim JK, Wang SH, et al. AASLD/IDSA Practice Guideline on treatment of chronic hepatitis B. Hepatology 2026 Apr 1;83(4):974-997.
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6. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol 2007;47:760-767.
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8. Yao K, Liu J, Wang J, Yan X, Xia J, Yang Y, et al. Distribution and clinical characteristics of patients with chronic hepatitis B virus infection in the grey zone. J Viral Hepat 2021;28:1025-1033.
9. Lai JC, Wong GL, Tse YK, Hui VW, Lai MS, Chan HL, et al. Histological severity, clinical outcomes and impact of antiviral treatment in indeterminate phase of chronic hepatitis B: A systematic review and meta-analysis. J Hepatol 2025;82:992-1003.
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12. Liu J, Wang J, Yan X, Xue R, Zhan J, Jiang S, et al. Presence of Liver Inflammation in Asian Patients With Chronic Hepatitis B With Normal ALT and Detectable HBV DNA in Absence of Liver Fibrosis. Hepatol Commun 2022;6:855-866.
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Yao-Chun Hsu
I-Shou University, Taiwan

Self Introduction

Education

- 1996-2002 M.D., School of Medicine, National Taiwan University, Taiwan
- 2007-2009 MS.c., Graduate Institute of Clinical Medicine, National Taiwan University, Taiwan
- 2011-2014 Ph.D., Graduate Institute of Clinical Medicine, China Medical University, Taiwan

Professional Experience

- 2023-Present Director, Department of Medical Research, E-Da Hospital, Kaohsiung, Taiwan
- 2023-Present Director, Graduate Institute of Medicine, I-Shou University, Kaohsiung, Taiwan
- 2023-Present Professor, School of Medicine and Graduate Institute of Medicine, I-Shou University, Taiwan
- 2024-Present Vice Superintendent (Research Affairs), E-Da Hospital, Kaohsiung, Taiwan

Research Interests

Chronic Viral Hepatitis B, Liver Cirrhosis, Hepatocellular Carcinoma, Clinical Research Methodology, Meta-Research

Representative Publications

1. Pan DZ, Soulette CM, Aggarwal A, Han D, van Buuren N, Wu P, Feierbach B, Lin JT, Tseng CH, Chen CY, Downie B, Mo H, Diehl L, Li L, Fletcher SP, Balsitis S, Ramirez R, Suri V, Hsu YC*. Effects of Tenofovir Disoproxil Fumarate on Intrahepatic Viral Burden and Liver Immune Microenvironment in Patients with Chronic Hepatitis B. Gut. 2025 Mar 6;74(4):628-638.
2. Hsu YC, Chen CY, Tseng CH, Chen CC, Lee TY, Bair MJ, Chen JJ, Huang YT, Chang IW, Chang CY, Wu CY, Wu MS, Mo LR, Lin JT. Antiviral Therapy for Chronic Hepatitis B with Mildly Elevated Aminotransferase: A Rollover Study from the TORCH-B Trial. Clin Mol Hepatol. 2025 Jan;31(1):213-226.
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4. Hsu YC, Suri V, Nguyen MH, Huang YT, Chen CY, Chang IW, Tseng CH, Tseng, Wu CY, Lin JT, Pan DZ, Gaggar A, Podlaha O*. Inhibition of Viral Replication Reduces Transcriptionally Active Distinct Hepatitis B Virus Integrations with Implications on Host Gene Dysregulation. Gastroenterology. 2022;162(4):1160-1170.
5. Hsu YC, Chen CY, Chang IW, Chang CY, Wu CY, Lee TY, Wu MS, Bair MJ, Chen JJ, Chen CC, Tseng CH, Tai CM, Huang YT, Ku WH, Mo LR, Lin JT*. Tenofovir for Chronic Hepatitis B in Treatment-naïve Asian Patients with Minimally Raised Aminotransferase (TORCH-B): a multicenter randomized double-blind placebo-controlled trial. Lancet Infect Dis. 2021;21(6):823-833.

Impact of Antiviral Therapy in the Indeterminate Phase of Chronic Hepatitis B: Who Should Be Treated

Yao-Chun Hsu *I-Shou University, Taiwan*

The natural history of hepatitis B virus (HBV) infection has traditionally been categorized into distinct immune phases. While this classification provides a useful framework to appreciate the uniqueness of HBV infection, it does not fully capture the dynamic and heterogeneous nature of chronic hepatitis B (CHB). In daily practice, a substantial proportion of patients with CHB do not neatly fit into a predefined category. These “indeterminate” or “gray” zones inevitably arise due to the dynamic, fluctuating nature of host-virus interactions, the reliance on fixed cutoffs for ALT and HBV DNA, and the evolving definitions across major international guidelines. Importantly, the indeterminate phase should not be regarded as a uniformly benign state. Accumulating evidence demonstrates that these patients face a tangible, elevated risk of disease progression, particularly the development of hepatocellular carcinoma (HCC) and cirrhosis, if they are left untreated. Consequently, the traditional strategy of watchful waiting for these patients is being re-evaluated. This lecture will explore the prognostic implications of the indeterminate phase and assess the impact of antiviral therapy on long-term clinical outcomes. By synthesizing recent data, including evidence from randomized controlled trials, the presentation aims to provide practical, risk-stratified guidance on patient selection for antiviral treatment. Ultimately, refining our approach to identify and treat at-risk patients within the gray zone represents a vital step toward reducing the global burden of HCC.



Yasuhito Tanaka
Kumamoto University, Japan

Self Introduction

He is Chief Professor of the Department of Gastroenterology and Hepatology, Vice Dean of Kumamoto University, and Deputy Hospital Director and Director of the Liver Disease Center at Kumamoto University Hospital. He has worked as a gastroenterologist and hepatologist since 1991, with extensive clinical experience in Hepatology. His career integrates clinical hepatology with translational research in viral hepatitis, hepatocarcinogenesis, and host-virus interactions, through national research projects and international collaborations.

Research Interests

His research focuses on chronic viral hepatitis, molecular evolution of hepatitis viruses, hepatocarcinogenesis, host genetics, biomarker development, and HBV therapeutics. Since 2007, He has led national research projects, including GWAS that identified IL28B SNPs associated with response to pegylated interferon and ITPA SNPs related to treatment-associated adverse events. He has also collaborated internationally on HCV molecular evolution and HBV mutations associated with HCC development.

Using more than 8,000 human samples, we have conducted multi-omics analyses, including epigenomics, RNA sequencing, microRNA profiling, and gut microbiome studies. Recent work includes identifying a TLL1 variant associated with HCC after HCV eradication, developing RNA-destabilizing HBV therapeutics such as SAG-524, and establishing HBV marker monitoring strategies, including iTACT-HBcrAg, to prevent HBV reactivation-related hepatitis.

Representative Publications

1. Yucuma D, Rakover A, Tanaka Y, et al. Natural history of chronic hepatitis B in untreated adults without cirrhosis according to baseline hepatitis B virus DNA and alanine aminotransferase concentrations: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*, 2026 Online ahead of print.
2. Vincent JP, Ségéral O, Tanaka Y*, et al: Hepatitis B core-related antigen rapid test (HBcrAg-RDT) for point-of-care identification of women at high risk of hepatitis B vertical transmission in Cambodia, Cameroon, and Burkina Faso. *Lancet Gastroenterol Hepatol*, 2025. Online ahead of print.
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5. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon- α and ribavirin therapy for chronic hepatitis C. *Nature Genet.* 2009;41(10):1105-1109.

Latest Updates on Novel Biomarkers for Chronic Hepatitis B

Yasuhito Tanaka Kumamoto University, Japan

Hepatitis B core-related antigen (HBcrAg) is an established biomarker that reflects intrahepatic covalently closed circular DNA transcriptional activity and has become an important tool in the management of chronic hepatitis B (CHB). HBcrAg can be detected even in patients with undetectable serum HBV DNA or hepatitis B surface antigen. HBcrAg measurement has advanced along two major directions: the development of the fully automated, highly sensitive iTACT-HBcrAg assay and a rapid point-of-care testing system for use in resource-limited settings. iTACT-HBcrAg, together with iTACT-HBsAg, has improved monitoring of HBV reactivation, assessment of treatment response, and risk stratification for hepatocellular carcinoma, and is now available in routine clinical practice in Japan. Because HBV DNA quantification remains unavailable in many regions where most HBV-infected individuals live, HBcrAg-based point-of-care testing may provide a practical alternative for identifying patients who require antiviral prophylaxis or treatment, including pregnant women at risk of mother-to-child transmission.

Recent advances have also enabled component-specific HBcrAg assays, including assays for phosphorylated HBcAg (pHBcAg). Functional and biochemical analyses suggest that pHBcAg is a major component of circulating HBcrAg and is primarily associated with empty particles. Clinically, measurement of HBcrAg components may provide information on viral replicative activity that is not fully captured by conventional HBV DNA monitoring. In HBeAg-negative gray-zone patients, conventional HBV DNA and ALT criteria may be insufficient for stratifying disease-progression risk, whereas pHBcAg may provide additional information on transition risk. Larger studies and external validation are warranted to confirm its clinical utility.

This lecture summarizes recent advances in HBcrAg-based biomarkers, including iTACT-HBcrAg, point-of-care testing, and pHBcAg, and discusses their clinical utility in precision HBV management.

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KASL LEADING RESEARCH ACHIEVEMENT AWARD





Jeong-Hoon Lee
Seoul National University

Self Introduction

Professor Jeong-Hoon Lee earned his MD (2002), Master's (2007), and PhD (2009) from Seoul National University College of Medicine. Following his residency and fellowship at Seoul National University Hospital (SNUH), he joined the faculty in 2010 and currently serves as a Professor of Internal Medicine.

As a leading researcher, Professor Lee has spearheaded several high-impact national projects, including the development of HCC-specific aptamers, investigations into the brain-liver axis, and the implementation of AI-driven precision medical solutions. His leadership extends to key academic roles; since 2025, he has served as the Director of the Scientific Committee for the Korean Association for the Study of the Liver (KASL). He is also an active member of the Editorial Board for Hepatology (since 2024) and serves as an Associate Editor for Clinical and Molecular Hepatology (since 2026).

Research Interests

Professor Lee conducts comprehensive research in both clinical and translational hepatology. His expertise covers hepatocellular carcinoma (HCC) and chronic hepatitis B, supported by his active involvement in numerous clinical trials. His current research program emphasizes the application of artificial intelligence (AI) in clinical prediction models and the use of multiomics approaches to advance the understanding and treatment of HCC.

Representative Publications

1. Association of Chronic Hepatitis B Infection and Antiviral Treatment with the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study. *J Clin Oncol*. 2022 Oct;40(29):3394-3405. (first & corresponding author)
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4. AI model using CT-based imaging biomarkers to predict hepatocellular carcinoma in patients with chronic hepatitis B. *J Hepatol*. 2025 Jun;82(6):1080-1088 (corresponding author)
5. A machine learning model to predict liver-related outcomes after the functional cure of chronic hepatitis B. *J Hepatol*. 2025 Feb;82(2):235-244. (corresponding author)

Inspired to Question, Learning to Answer: A Physician-Scientist's Journey Through Hepatology

Jeong-Hoon Lee Seoul National University

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PRESIDENT'S CHOICE LECTURE

Chair
Young-Suk Lim (Univ. of Ulsan)





Chien-Jen Chen
Academia Sinica, Taiwan

Self Introduction

Professor Chien-Jen Chen received his Sc.D. majored in epidemiology and human genetics from the Johns Hopkins University. He was the founding director of Graduate Institute of Epidemiology and Preventive Medicine, and the Dean of College of Public Health of National Taiwan University. He is now a distinguished professor and president-elect of Academia Sinica in Taiwan. He is internationally well-known for his longitudinal REVEAL-HBV/HCV study, which pioneered the paradigm of viral load as well as molecular and genomic biomarkers in the long-term risk prediction and clinical management of end-stage liver diseases of patients with chronic viral hepatitis. He has been elected as an academician and council member of Academia Sinica, a member of World Academy of Sciences, an international member of US National Academy of Sciences, and an academician and council member of Pontifical Academy of Sciences.

Research Interests

- Chronic Viral Hepatitis and Liver Cancer
- Molecular and Genomic Biomarkers
- Risk Calculators, Precision Preventive Medicine

Representative Publications

1. Tseng TC, Huang SC, Pan MH, Liu CJ, Chen CJ, Yang WT, Tai CH, Su TH, Yang HC, Liu CH, Chen PJ, Yang HI*, Kao JH*. Hepatitis B surface antigen levels identifies patients with inactive chronic hepatitis B from Asia with HCC risk below surveillance threshold. Gut 2025; 74(11):1896-1904.
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From Clinical Research to Policy: An Epidemiologist's Journey toward Viral Hepatitis Elimination

Chien-Jen Chen *Academia Sinica, Taiwan*

The mortality from liver cancer and cirrhosis in Taiwan ranked among the highest in the world in 1980. Liver cancer remained the leading cause of cancer death in Taiwan in early 2000s.¹ The health insurance-based cohort (GECC) study in Taiwan showed chronic HBsAg carriers had 223-fold risk of developing hepatocellular carcinoma (HCC) than non-carriers.² The perinatal infection was the major route of HBV transmission in Taiwan.³ The clinical trial in neonates born to HBeAg-seropositive mothers showed a very high efficacy of HBV immunization with HBIG and vaccine to prevent transmission from mother to children.⁴ A national HBV immunization program was launched in 1984 in Taiwan,⁵ the HCC incidence was significantly reduced in vaccinated birth cohorts than unvaccinated ones.⁶ A community-based case-control study found several HCC risk factors including seropositivity of HBsAg and HBeAg, cigarette smoking, alcohol drinking, and family HCC history.⁷ The community-based REVEAL HBV/HCV cohort study has identified significant long-term risk predictors for HCC and cirrhosis in chronic hepatitis B and C patients.⁸⁻¹¹ Nomograms (risk prediction models) were developed and validated for the personalized long-term prediction of HCC and cirrhosis risk.¹²⁻¹³ These nomograms showed a high capability of discrimination and calibration. In order to validate the applicability of risk prediction models in East Asia, an international collaborative group had developed and validated the REACH-B Risk Estimator.¹⁴ Based on the risk stratification, the National Antiviral Therapy Program for patients with chronic viral hepatitis was launched in Taiwan in 2003.¹⁵ At the beginning, only chronic viral hepatitis patients with a high risk of developing cirrhosis and HCC were reimbursed for antiviral therapy. After 2009, patients with a moderate risk were also reimbursed for more potent antiviral agents. The national HCV elimination program was launched in 2017. Direct antiviral agent (DAA) was reimbursed for all HCV RNA-seropositive patients with chronic hepatitis C. There has been a significant reduction in mortality and incidence of HCC and cirrhosis since 2003 in Taiwan.¹⁶ The WHO's program targets of HCV elimination in 2030 were achieved in 2025 in Taiwan. The precision elimination of HBV and HCV is found cost-effective to reduce burden of cirrhosis and HCC.

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KASL-AASLD JOINT SYMPOSIUM

Beyond Steatosis: Metabolic, Muscular, and Oncologic Implications of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Chairs

Young-Suk Lim (Univ. of Ulsan)

Kathleen E. Corey (Harvard Medical School, USA)





Won Sohn
Sungkyunkwan University

Self Introduction

Dr. Won Sohn, M.D., Ph.D., is a Professor in the Department of Internal Medicine at Sungkyunkwan University School of Medicine and an attending physician in the Division of Gastroenterology at Kangbuk Samsung Hospital, Seoul, Republic of Korea.

He received his M.D. degree from Hanyang University, followed by a Master of Science and a Ph.D. in Internal Medicine from the same institution, respectively. His postgraduate training included an internship and residency in internal medicine at Hanyang University Medical Center, where he subsequently pursued fellowship training in gastroenterology.

Dr. Sohn has built extensive clinical and academic expertise in hepatology and gastroenterology through diverse clinical and research appointments. He served as an attending physician at Hanyang University Hospital, followed by a research fellowship at Samsung Medical Center. He later continued his clinical career at Bundang Jesaeng Hospital and Wonkwang University Sanbon Hospital, where he was appointed Assistant Professor. Since 2019, he has been serving as a Professor at Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine.

His research interests focus on metabolic dysfunction-associated steatotic liver disease (MASLD), liver fibrosis, hepatocellular carcinoma, viral hepatitis, and large-scale cohort studies, with a particular emphasis on risk prediction models and artificial intelligence applications in hepatology.

Dr. Sohn is an active member of several leading academic societies, including the Korean Association for the Study of the Liver, the Korean Liver Cancer Association, and the Korean Society of Gastroenterology. He has also played key leadership roles in national academic groups, serving as Director of the Research Committee and Scientific Committee of the Korean Steatotic Liver Disease Study Group, and currently as Director of the Committee for Primary Liver Cancer Registry of the Korean Liver Cancer Association.

He has an extensive publication record with numerous peer-reviewed articles in high-impact journals, contributing significantly to the understanding of liver disease epidemiology, risk stratification, and clinical outcomes. His work includes large-scale nationwide cohort studies, development of prediction models, and clinical practice guidelines, particularly in the fields of MASLD and hepatocellular carcinoma.

Public Health and Policy Implications in the Metabolic Era

Won Sohn *Sungkyunkwan University*

Over the past two decades, the epidemiology of chronic liver disease has undergone a profound global transition. While viral hepatitis, particularly hepatitis B and C, historically accounted for the majority of liver-related morbidity and mortality, the widespread implementation of vaccination programs and effective antiviral therapies has led to a substantial decline in viral liver disease. In contrast, metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading cause of chronic liver disease worldwide. Current estimates suggest that MASLD affects approximately one-quarter to one-third of the adult population, reflecting the global rise in obesity, type 2 diabetes, and metabolic syndrome. This shift has important implications for healthcare systems. Unlike viral hepatitis, which typically affects a more defined patient population and can be managed through targeted treatment strategies, MASLD is highly prevalent, heterogeneous, and largely asymptomatic. A substantial proportion of individuals with MASLD remain undiagnosed until advanced stages, including cirrhosis and hepatocellular carcinoma (HCC). As a result, MASLD is increasingly recognized not only as a liver disease but also as a systemic metabolic condition with significant implications for cardiovascular and overall mortality.

A central challenge in the metabolic era is that existing healthcare models are not designed to manage a disease of this scale. Traditional liver disease care has been largely specialist-centered and hospital-based, focusing on patients with established or advanced disease. This model is not sustainable for MASLD, given its high prevalence and the need for early identification and longitudinal management at the population level. Accordingly, a paradigm shift toward primary care-driven, population-based strategies is essential. Risk stratification has emerged as a cornerstone of this approach. Importantly, not all individuals with MASLD carry the same risk of disease progression. While most patients have a relatively indolent course, a smaller subset is at risk for advanced fibrosis, cirrhosis, and liver-related complications. Identifying this high-risk group is critical for efficient resource allocation. Noninvasive tests such as the fibrosis-4 (FIB-4) index provide simple, inexpensive, and scalable tools for initial risk assessment in primary care. Patients identified as low risk can be managed with lifestyle modification and periodic reassessment, whereas those at intermediate or high risk may require further evaluation using imaging-based modalities, including elastography, or referral to specialist care. This stepwise, risk-based model enables scalable and cost-effective management.

From a public health perspective, MASLD requires a shift from reactive to proactive strategies. Given its asymptomatic nature and high prevalence, reliance on symptom-driven diagnosis is insufficient. Instead, integrating MASLD risk assessment into routine healthcare encounters, particularly within primary care and general health evaluations, offers a practical pathway for early detection. Opportunistic screening using routinely available clinical and laboratory data represents a feasible and scalable approach. At the same time, prevention remains fundamental. Population-level interventions targeting obesity, unhealthy dietary patterns, and physical inactivity are essential and should be aligned with broader strategies addressing noncommunicable diseases.

Despite advances in risk assessment and growing awareness, major implementation gaps persist. Awareness among primary care providers remains variable, standardized care pathways are often lacking, and access to noninvasive diagnostic tools differs across regions and healthcare systems. In addition, care for MASLD is frequently fragmented across specialties, including hepatology, endocrinology, and primary care, limiting the effectiveness of coordinated management. Emerging technologies offer promising solutions. Digital health platforms can enable automated risk calculation and clinical decision support within electronic medical record systems, facilitating large-scale implementation of risk-based screening. Artificial intelligence-based models may further enhance risk prediction and patient stratification, particularly when applied to large population-level datasets. In parallel, there is increasing interest in developing low-cost, widely accessible screening tools that can be deployed beyond specialized centers, improving early detection and accessibility.

From a policy standpoint, several priorities should be emphasized. First, MASLD should be formally recognized as a major noncommunicable disease within national and global health strategies. Second, risk-stratified screening algorithms should be implemented at the primary care level to enable efficient allocation of healthcare resources. Third, multidisciplinary care models are needed to address the complex interplay between liver disease and metabolic disorders. Finally, sustained investment in prevention strategies and digital health infrastructure will be critical to mitigate the long-term burden of advanced liver disease and HCC.

In the Republic of Korea, this global transition is also evident. Notably, Korea has one of the most highly developed health screening systems in the world, encompassing both a nationwide government-led program and a highly active private screening sector. This unique infrastructure provides a strong platform for population-level risk stratification and early detection of MASLD using routinely collected clinical data. In addition, the Korean Association for the Study of the Liver recently developed the 2025 MASLD clinical practice guidelines, providing structured, evidence-based recommendations for clinicians. Importantly, these guidelines also facilitate close communication with government stakeholders, helping to align clinical practice with national health policy and supporting the integration of MASLD into broader public health strategies.

In conclusion, the metabolic era necessitates a fundamental rethinking of liver disease management.

MASLD is a population-level condition that cannot be effectively addressed through traditional specialist-based approaches alone. A coordinated strategy integrating risk stratification, primary care engagement, public health interventions, and policy support is essential to reduce the growing global burden of liver disease.

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Hye Won Lee
Yonsei University

Self Introduction

Dr. Hye Won Lee is an Associate Professor at Yonsei University College of Medicine and Severance Hospital. She graduated from Ewha Womans University College of Medicine and received her Ph.D. from Yonsei University College of Medicine. She completed her residency and fellowship training at Severance Hospital and later spent two years as a visiting scholar at The Chinese University of Hong Kong.

Her academic work has focused on chronic liver diseases, particularly MASH and HCC. Her research interests include disease progression, risk stratification, biomarker development, and integrated care strategies for patients with chronic liver disease. Dr. Lee has received multiple awards and research grants from academic institutions and professional societies in recognition of her contributions to hepatology research.

Research Interests

- Metabolic Dysfunction-Associated Steatohepatitis (MASH)
- Hepatocellular Carcinoma (HCC)

Representative Publications

1. Zhang Y, Lee HW, Lin H, Tsochatzis E, Petta S, Bugianesi E, Yoneda M, Zheng MH, Hagström H, Boursier J, Calleja JL, Goh GB, Chan WK, Gallego-Durán R, Sanyal AJ, de Lédinghen V, Newsome PN, Fan JG, Lai M, Fournier-Poizat C, Wong GL, Pennisi G, Armandi A, Nakajima A, Liu WY, Shang Y, de Saint-Loup M, Llop E, Teh KKJ, Lara-Romero C, Asgharpour A, Mahgoub S, Chan MS, Canivet CM, Romero-Gomez M, Kim SU, Wong VW, Castéra L, Yip TC. Head-to-head comparison between vibration-controlled transient elastography and histology in predicting liver-related events due to metabolic dysfunction-associated steatotic liver disease. *Hepatology*. 2025 Dec 24.
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Contemporary MASLD Management: Integrating Available Therapies, Metabolic Care, and Prevention of Sarcopenia

Hye Won Lee Yonsei University

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly understood as a systemic condition in which hepatic injury, cardiometabolic dysfunction, and skeletal muscle impairment interact to shape clinical outcomes. Contemporary management therefore needs to move beyond isolated steatosis reduction or drug-centered care, and toward a more integrated approach that incorporates available therapies, metabolic risk control, and preservation of muscle function according to patient phenotype.

A practical three-axis framework may help organize this approach. The hepatic axis includes MASH activity, lipotoxicity, and fibrosis; the metabolic axis reflects insulin resistance, adiposity, systemic inflammation, and cardiovascular risk; and the muscle axis includes sarcopenia, frailty, and physiologic reserve. These axes rarely act in isolation. Instead, they overlap and interact to create clinically relevant phenotypes, such as metabolic-dominant, hepatic-dominant, sarcopenic, and mixed forms of MASLD.

Available interventions can be viewed through the same framework. Liver-directed therapies mainly address hepatic risk, whereas incretin-based and obesity-directed treatments primarily target metabolic risk. Lifestyle intervention, particularly structured exercise combined with dietary modification, remains foundational because it can affect hepatic, metabolic, and muscle-related risks at the same time. In the era of potent weight-reducing therapies, sarcopenia should be considered more than a passive comorbidity. Muscle status may influence the risk–benefit balance of MASLD treatment, especially when weight loss is a major therapeutic goal.

Integrated MASLD care is not a matter of simply combining multiple interventions. It requires aligning treatment strategies with the patient’s dominant risks, while monitoring hepatic, metabolic, and functional outcomes over time. Such a phenotype-based approach may help clinicians select appropriate therapies, avoid weight-centric overtreatment, and preserve muscle and function. The next step in MASLD management is not only to add more therapies, but to build a care model that protects the liver, improves metabolic health, and maintains physical resilience.

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**Kathleen E. Corey***Harvard Medical School, USA*

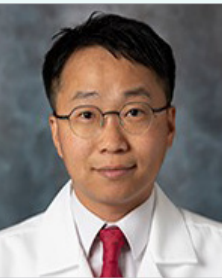
Self Introduction

Kathleen E. Corey, MD, MPH, MMSc is Associate Professor of Medicine at Harvard Medical School and Director of the MASLD Program at Massachusetts General Hospital. She is a transplant hepatologist and physician-scientist whose clinical and research interests focus on metabolic dysfunction-associated steatotic liver disease (MASLD/MASH), viral hepatitis, and liver transplantation. Dr. Corey leads several NIH-funded studies investigating the epidemiology, natural history, cardiovascular complications, and novel therapeutic approaches for MASLD. She has authored numerous influential publications in the field of hepatology and is internationally recognized for her contributions to metabolic liver disease research and clinical care.

Near-Future MASLD Therapies: Resmetirom, GLP-1 Receptor Agonists and Emerging Agents

Kathleen E. Corey *Harvard Medical School, USA*

Metabolic dysfunction associated steatotic liver disease (MASLD) is one of the leading causes of liver disease worldwide and can result in fibrosis, cirrhosis, liver-related complications and death. Until recently, treatment for MASLD was limited to lifestyle interventions and off label use of vitamin E and pioglitazone. However, over the last several years both metabolic therapy, in the form of glucagon like peptide 1 agonist semaglutide, and resmetirom, a MASLD specific therapy have emerged and are agency approved in several parts of the world for the treatment of MASLD with fibrosis stage 2-3. In addition, therapies including combination GLP1 RA with glucose dependent insulinotropic polypeptide (GIP), GLP1Ra with glucagon receptor agonists (GCGR) and fibroblast growth factor -21 analogs are in development for the treatment of not only MASLD and stage 2-3 fibrosis but MASLD cirrhosis as well. This talk will highlight semaglutide, tirzepatide and resmetirom that have received approval for MASLD in parts of the world and highlight emerging therapies.



Ju Dong Yang

Cedars-Sinai Medical Center, USA

Self Introduction

- 1999.03-2005.02 Medical School - Sungkyunkwan University School of Medicine, Seoul, Korea
- 2009.03-2011.05 Research Fellowship - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2009.09-2011.05 Master's Degree in Clinical and Translational Research - Clinical and Translational Science Activities, Mayo Graduate School
- 2011.06-2014.05 Residency - Internal Medicine, University of Arkansas for Medical Science, Little Rock, AR
- 2014.07-2017.12 Gastroenterology Fellowship, T32 Grant - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2018.01-2018.12 Transplant Hepatology Fellowship - Transplant Hepatology, Mayo Clinic, Rochester, MN
- 2023.01-Present Associate Professor of Medicine, Department of Medicine, Cedars-Sinai

Research Interests

The Yang Lab is dedicated to advancing the early detection and risk stratification of hepatocellular carcinoma (HCC) through the discovery and validation of circulating biomarkers, including circulating tumor cells and extracellular vesicles. By integrating these insights with predictive modeling and molecular profiling, the lab develops precision therapies tailored to individual patients and optimizes treatment responses. Leveraging population-based data, the Yang Lab also addresses global disparities in liver cancer care, guiding more equitable and effective clinical strategies.

Representative Publications

1. Antibiotic Use Linked to Worse Outcomes in Patients With Gastrointestinal and Liver Cancer on Immune Checkpoint Inhibitors: A Meta-Analysis. Rezaee-Zavareh MS, Karimi-Sari H, Parhizkar Roudsari P, Khattab O, Attia AM, Danpanichkul P, Hwang SY, Liu JS, Yalda T, Chen PJ, Gong J, Ferrone CR, Rich NE, Parikh ND, Pinato DJ, Singal AG, Yang JD. Am J Gastroenterol. 2026 Feb 12. doi: 10.14309/ajg.0000000000003956. Online ahead of print. PMID: 41677135.
2. Gastrointestinal cancer statistics in 2022 and projection to 2050: GLOBOCAN estimates across 185 countries. Danpanichkul P, Pang Y, Tothananunroj P, Dejvajara D, Kim D, Saokhieo P, Suparan K, Muthiah MD, Duangsonk K, Bernal DO, Lui RN, Wijarnpreecha K, Abou-Alfa GK, Wallace MB, Roberts LR, Singal AG, Yang JD. Cancer. 2026 Jan 1;132(1):e70245. doi: 10.1002/cncr.70245.
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Rethinking HCC Surveillance in the MASLD Era: From Non-Cirrhotic Risk to Global Strategies

Ju Dong Yang

Cedars-Sinai Medical Center, USA

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally and an increasingly important cause of hepatocellular carcinoma (HCC). Although cirrhosis remains the primary risk factor, up to 20–30% of MASLD-related HCC occurs in non-cirrhotic patients, highlighting gaps in current surveillance strategies. In addition to fibrosis, key risk factors include age, male sex, type 2 diabetes, obesity, and metabolic syndrome, all of which contribute to individual variability in HCC risk.

Risk stratification relies heavily on non-invasive fibrosis assessment tools such as FIB-4, NAFLD fibrosis score, and elastography-based liver stiffness measurement, given the strong association between fibrosis progression and HCC development. These tools enable identification of high-risk patients and guide surveillance decisions, with imaging-based methods offering improved accuracy over serum markers alone.

Additional layers of risk prediction include genetic variants (e.g., PNPLA3, TM6SF2, MBOAT7), though their clinical utility remains limited. Biomarker-based models, particularly the GALAD score, have demonstrated strong performance in early HCC detection, outperforming traditional markers like AFP. Other emerging biomarkers, including lipidomic signatures and inflammatory markers, show promise but require further validation.

Advances in technology are expanding detection capabilities. Machine learning models using clinical data have shown high predictive accuracy, while liquid biopsy approaches—such as circulating tumor DNA and extracellular vesicles—offer non-invasive options for early diagnosis and disease monitoring. Integrating clinical, molecular, and imaging data may enhance risk prediction and surveillance strategies.

From a global health perspective, scalable, risk-based surveillance strategies are essential given the high prevalence of MASLD and resource variability across regions. Prioritizing cost-effective tools such as non-invasive fibrosis scores and ultrasound, while reserving advanced diagnostics for higher-risk populations, can improve efficiency. Integration of these approaches into public health frameworks, alongside efforts targeting metabolic risk factors, will be critical to reducing the global burden of MASLD-related HCC.

In summary, improving HCC surveillance in MASLD will require a shift toward risk-based, multi-modal approaches that incorporate fibrosis assessment, biomarkers, and emerging technologies. While promising, these strategies need further validation before routine clinical adoption.

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KASL SYMPOSIUM 3

From Cure to Care: Remaining Challenges in HBV Management

Chairs

Jia-Horng Kao (National Taiwan Univ., Taiwan)

Sang Hoon Ahn (Yonsei Univ.)





Dong Hyun Sinn
Sungkyunkwan University

Self Introduction

Graduated Dankook Univ. in year 2001.
Received Doctor's degree in medicine from Sungkyunkwan Univ. in year 2013.
Trained at Samsung Medical Center from 2001 to 2012 as intern, resident (internal medicine), and fellow (gastroenterology).
Worked at Sanggye Paik Hospital, Inje Univ. from 2012 to 2014 as an assistant professor.
Working at Samsung Medical Center, Sungkyunkwan Univ. from 2012 to now as clinical assistant professor (2014-2016), associate professor (2016-2022) and professor (2022 to current)

Research Interests

Chronic Hepatitis, Liver Cirrhosis, Liver Failure, Hepatocellular Carcinoma

Representative Publications

1. Sinn DH, Kang D, Kang M, Guallar E, Hong YS, Lee KH, Park J, Cho J, Gwak GY. Nonalcoholic fatty liver disease and accelerated loss of skeletal muscle mass: A longitudinal cohort study. *Hepatology*. 2022 Dec;76(6):1746-1754.
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Expanding Indications for Nucleos(t)ide Analogue Therapy in Chronic Hepatitis B: Clinical Benefits and Long-Term Outcomes

Dong Hyun Sinn Sungkyunkwan University

Chronic hepatitis B virus (HBV) infection affects approximately 296 million people worldwide and remains a leading cause of cirrhosis, hepatocellular carcinoma, and liver-related mortality. The advent of nucleos(t)ide analogue (NA) therapy has fundamentally transformed the management of this disease, offering potent viral suppression and the potential to alter its natural history.

Nucleos(t)ide analogues are oral antiviral agents that inhibit HBV DNA polymerase by competing with endogenous nucleotide substrates, thereby terminating viral DNA chain elongation. Currently recommended first-line NAs include entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), all of which demonstrate high efficacy in achieving viral suppression (>95% of patients achieve undetectable HBV DNA), favorable safety profiles, and extremely low rates of drug resistance. The capacity of NAs to alter the natural history of chronic hepatitis B has been demonstrated through multiple lines of evidence. Long-term NA therapy leads to significant histological improvement, including regression of cirrhosis. More importantly, NAs reduce the incidence of cirrhosis complications (relative risk 0.51) and hepatocellular carcinoma (relative risk 0.37). NAs improve liver function in patients with decompensated disease, with a substantial proportion being delisted from liver transplantation. However, a critical limitation is that NAs rarely achieve HBsAg loss (functional cure), with annual rates of only approximately <1% and cumulative rates of 3-5% even after long-term treatment. Consequently, most patients require long-term or lifelong therapy. Hence, the indication of NA therapy is still a matter of balancing risk and benefit of treatment.

Current treatment indications for chronic hepatitis B vary across international guidelines, particularly regarding HBV DNA thresholds (ranging from 2,000 to 20,000 IU/mL), ALT cutoffs, and the role of fibrosis assessment. Controversy exists over managing CHB patients in “indeterminate” or “grey zone” phases that do not meet traditional treatment criteria, and a concept of simplified “treat-all” strategies. NA have fundamentally altered the natural history of chronic hepatitis B by preventing disease progression and reducing complications, though functional cure remains rare with current therapies. Treatment indications are expanding and the rationale will be discussed here.

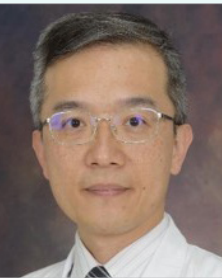
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Tung-Hung Su
National Taiwan University, Taiwan

Self Introduction

Dr. Tung-Hung Su earned his M.D. degree from the National Taiwan University College of Medicine in 2001 and his Ph.D. from the Graduate Institute of Clinical Medicine at the same university in 2015. He has been an attending physician specializing in Hepatology and a Clinical Professor in the Department of Internal Medicine at National Taiwan University Hospital since 2024. From 2017 to 2019, he was a visiting scholar at Stanford University. Dr. Su’s research focuses on translational studies on liver fibrosis treatment, viral hepatitis B management, cirrhosis, and hepatocellular carcinoma, including disease prediction and outcome research using large-scale electronic medical records. Additionally, he applies artificial intelligence models to the study of liver diseases. He has published several research papers in these fields.

Research Interests

- Hepatitis B and MASLD
- HCC Surveillance
- AI Applications in Hepatology

Representative Publications

1. Su TH, Wu CH, Kao JH. Artificial intelligence in precision medicine in hepatology. J Gastroenterol Hepatol. 2021 Mar;36(3):569-580
2. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liao SH, Hong CM, Liu CH, Lan TY, Yang HC, Liu CJ, Chen PJ, Kao JH. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. Hepatol Int. 2023 Oct;17(5):1139-1149.
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Personalizing Antiviral Therapy in Hepatitis B:
Balancing Safety, Efficacy, and HCC Prevention

Tung-Hung Su National Taiwan University, Taiwan

Managing chronic hepatitis B (CHB) requires balancing viral suppression, drug safety, and HCC prevention. First-line antiviral therapies include entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). In South Korea, besifovir dipivoxil maleate (BSV) is another widely approved first-line agent. Although all these oral medications target viral replication and have a high barrier to drug resistance, they still differ slightly in the speed of viral suppression and ALT normalization rates.

Long-term safety profiles are crucial for lifelong therapy. While TDF is associated with bone mineral density loss and renal tubule damage, newer agents such as TAF and BSV improve bone and kidney safety. However, metabolic issues such as lipid profiles should be monitored during treatment. Clinicians must also monitor unique drug side effects; for instance, long-term BSV use requires regular L-carnitine supplementation to prevent carnitine deficiency. Furthermore, specific safety evaluations are needed during pregnancy, in which TDF remains the primary standard.

Finally, reducing the incidence of primary and recurrent HCC remains a top priority. However, current real-world data comparing the cancer-preventing efficacy of ETV versus tenofovir formulations should be interpreted with caution. Reported differences in HCC risk are often skewed by selection, publication, or temporal biases.

In conclusion, modern hepatitis B management moves beyond simple viral suppression. Clinicians should use a patient-centric approach that carefully weighs baseline metabolic risks, renal and bone health, and drug-specific side effects to tailor the best long-term regimen.



Yao-Chun Hsu
I-Shou University, Taiwan

Self Introduction

Education

2011-2014	Ph.D., Graduate Institute of Clinical Medicine, China Medical University, Taiwan
2007-2009	MS.c., Graduate Institute of Clinical Medicine, National Taiwan University, Taiwan
1996-2002	M.D., School of Medicine, National Taiwan University, Taiwan

Professional Experience

2024-Present	Vice Superintendent (Research Affairs), E-Da Hospital, Kaohsiung, Taiwan
2023-Present	Director, Department of Medical Research, E-Da Hospital, Kaohsiung, Taiwan
2023-Present	Director, Graduate Institute of Medicine, I-Shou University, Kaohsiung, Taiwan
2023-Present	Professor, School of Medicine and Graduate Institute of Medicine, I-Shou University, Taiwan

Research Interests

Chronic Viral Hepatitis B, Liver Cirrhosis, Hepatocellular Carcinoma, Clinical Research Methodology, Meta-Research

Representative Publications

1. Pan DZ, Soulette CM, Aggarwal A, Han D, van Buuren N, Wu P, Feierbach B, Lin JT, Tseng CH, Chen CY, Downie B, Mo H, Diehl L, Li L, Fletcher SP, Balsitis S, Ramirez R, Suri V, Hsu YC*. Effects of Tenofovir Disoproxil Fumarate on Intrahepatic Viral Burden and Liver Immune Microenvironment in Patients with Chronic Hepatitis B. Gut. 2025 Mar 6;74(4):628-638.
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Discontinuation of Antiviral Therapy in Chronic Hepatitis B

Yao-Chun Hsu I-Shou University, Taiwan

Long-term nucleos(t)ide analogue (NA) therapy suppresses HBV replication, prevents fibrosis progression, and reduces hepatocellular carcinoma (HCC) risk; yet HBsAg seroclearance remains uncommon under continuous NA treatment. The concept of finite NA therapy thus emerged from observations that controlled treatment withdrawal may induce immune-mediated viral control and facilitate HBsAg seroclearance in selected patients. However, virological relapse commonly follows NA discontinuation, and clinical relapse with ALT flares occurs in 25–50% of patients, carrying tangible risks of hepatic decompensation and even death. This lecture will examine the evolving framework for NA discontinuation, emphasizing biomarker-guided patient selection and structured post-cessation monitoring. Conventional criteria based on HBeAg-negativity, non-cirrhotic status, and durable virological suppression identify candidates but do not adequately predict individual outcomes. Clinically actionable biomarkers, particularly quantitative HBsAg (qHBsAg), have been increasingly incorporated into stopping-rule algorithms. Other emerging biomarkers including HBV RNA, HBcrAg, and quantitative anti-HBc may further refine cccDNA-burden estimation and inform clinical decision making. Close monitoring is essential following NA discontinuation, mandating biochemical and virological surveillance every 1–3 months in the first year because most clinically significant flares occur during this period. Pre-specified retreatment thresholds are also crucial to mitigate severe hepatitis and decompensation. By integrating current evidence, the new guideline recommendations, and practical decision algorithms, this presentation aims to help clinicians refine patient selection, mitigate the risks of severe flare, and navigate the complexities of antiviral discontinuation.



Seng-Gee Lim

National University of Singapore, Singapore

Self Introduction

Professor Seng-Gee Lim is Director of Hepatology at the National University Health System and Professor of Medicine at the National University of Singapore. A leading hepatologist in Asia, his clinical and research interests focus on viral hepatitis, liver cirrhosis, hepatocellular carcinoma, liver failure, and liver transplantation. He has published over 250 peer-reviewed papers, secured more than SGD 48 million in research funding, and serves on the editorial boards of several leading hepatology journals. Professor Lim has held numerous international leadership roles, including Chairman of the Singapore Hepatitis Conference and former Congress Chairman of APASL Liver Week. He is internationally recognized for his contributions to HBV research and the development of curative strategies for chronic hepatitis B.

Immune Mechanisms Driving HBsAg Decrease with Various Anti-HBV Therapeutics

Seng-Gee Lim

National University of Singapore, Singapore

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KASL SYMPOSIUM 4

Management Strategies for Chronic Viral Hepatitis

Chairs

Man-Fung Yuen (The Univ. of Hong Kong, Hong Kong)

Hyung Joon Yim (Korea Univ.)



**Takumi Kawaguchi***Kurume University, Japan*

Self Introduction

Education and Employment

- 1995 M.D., Degree from Kurume University School of Medicine, Japan
- 1999 Ph.D., Degree in Kurume University Graduate School of Medicine, Japan
- 2000 Research Fellow, University of Texas, Southwestern Medical Center, Texas, USA
- 2012 Assistant Prof. Div. of Gastroenterology, Dept. of Medicine, Kurume Univ. School of Medicine, Japan
- 2022 Professor and Chairman, Div. of Gastroenterology, Dept. of Medicine, Kurume Univ. School of Medicine

Committee and Member

1. The Japan Society of Hepatology, International Committee Member
2. Evidence-Based Clinical Practice Guidelines for MASLD 2026, Committee Member
3. Clinical and Molecular Hepatology, Editorial Board Member
4. The Global MASH Council, Member

Research Interests

- Medication for MASLD
- Exercise Therapy for MASL

Representative Publications

1. Tsutsumi T, Tang NSY, Ng CH, Kawaguchi T et al. Comparative efficacy of phase 2-3 therapies for non-cirrhotic metabolic dysfunction-associated steatohepatitis: An updated network meta-analysis. Med. 2026 in press.
2. Younossi ZM, de Avila L, Kawaguchi T, et al. Predictors of fibrosis, clinical events, and mortality in MASLD: Data from the Global-MASLD study. Hepatology. 2026 in press.
3. Lim RY, Koh B, Ng CH, Kulkarni AV, Kawaguchi T, et al. Hepatocellular Carcinoma Surveillance and Survival in a Contemporary Asia-Pacific Cohort. JAMA Netw Open. 2025;8:e2520294.
4. Tsutsumi T, Nakano D, Kawaguchi M, Takahashi H, Kawaguchi T. Similar respiratory function including chronic obstructive pulmonary disease between non-alcoholic fatty liver disease and metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol. 2024;30:266-268.
5. Nakano M, Kawaguchi M, Kawaguchi T. Almost identical values of various non-invasive indexes for hepatic fibrosis and steatosis between NAFLD and MASLD in Asia. J Hepatol. 2024;80:e155-e157.

Beyond Cure: Practical Care for Hepatitis C Patients with MASLD

Takumi Kawaguchi *Kurume University, Japan*

Backgrounds

The advent of direct-acting antiviral agents (DAAs) has revolutionized the management of chronic hepatitis C virus (HCV) infection. However, eradication of HCV does not entirely eliminate the risk of liver-related events, particularly in the presence of metabolic dysfunction-associated steatotic liver disease (MASLD). Furthermore, a recent mortality survey revealed that extrahepatic events account for the majority of deaths after sustained virologic response (SVR).¹ In this symposium, I address four clinical questions regarding the practical care of patients with concomitant HCV and MASLD.

(1) Are There any Differences in HCV Treatment in Patients with Concomitant MASLD?

In the current DAA era, the antiviral regimen generally does not change for patients with MASLD. MASLD itself is not an independent predictor of DAA treatment failure.² Therefore, the most significant difference in managing these patients lies in the necessity for post-cure metabolic care and surveillance.

(2) Does Successful HCV Treatment Have a Favorable Impact on MASLD Itself?

The impact of HCV eradication on MASLD is mixed. We demonstrated that HCV directly induces hepatic insulin resistance by down-regulating insulin receptor substrates 1 and 2.³ Thus, viral clearance improves this HCV-induced insulin resistance and beta-cell function.⁴ However, viral clearance does not reliably improve metabolic steatosis. Steatosis often persists or worsens after SVR; one study noted that while significant fibrosis fell to 17% post-SVR, steatosis prevalence paradoxically rose from 47% to 61%.⁵ Progressive steatosis continues post-eradication, particularly among patients with metabolic derangements or PNPLA3 variants.⁶

(3) If MASLD is Left Untreated after HCV Cure, Does Fibrosis Progression Still Occur?

Fibrosis can still progress despite HCV cure. While SVR halts fibrogenesis for the majority, a minority experience worsening fibrosis driven by persistent metabolic injury. Follow-up cohorts confirm that fibrosis progression post-clearance occurs in approximately 4% of subjects and is significantly associated with higher BMI, smoking pack-years, and hepatic steatosis.⁷ With the viral driver eliminated, untreated MASLD perpetuates systemic and local inflammation, allowing chronic liver disease to progress and advanced fibrosis to persist despite virological cure.

(4) Can Prognosis be Further Improved by Actively Treating MASLD after HCV Cure?

Active MASLD treatment post-cure is essential. MASLD remains a significant determinant of liver-related events and de novo hepatocellular carcinoma (HCC) after viral clearance.⁸ In a multicenter study of elderly patients, MASLD at 24 weeks post-SVR was an independent HCC risk factor, serving as a critical classifier for HCC risk even with low alpha-fetoprotein levels (<7 ng/mL).⁹ Administering pioglitazone to HCV-infected diabetic patients after curative HCC treatment improved insulin resistance. Since insulin promotes growth, improving insulin resistance may suppress HCC in overweight patients.¹⁰ Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists reduce liver-related events, including HCC, in MASLD patients with type 2 diabetes.¹¹ In a nationwide medical claim database study in Japan, SGLT2 inhibitors also significantly suppressed extrahepatic cancers.¹² Thus, these agents are expected to improve overall prognosis through suppress both hepatic and extra-hepatic events after HCV cure.

Conclusion

Curing HCV is only the first step. The post-cure phase requires rigorous HCC surveillance and active management of metabolic dysfunction to prevent ongoing fibrosis progression, hepatocarcinogenesis, and extrahepatic events.

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Young Kul Jung
Korea University

Self Introduction

Prof. Young Kul Jung is a Professor in the Department of Internal Medicine at Korea University College of Medicine, Republic of Korea. He is a hepatologist specializing in hepatitis B virus, cirrhosis, alcohol-related liver disease, and hepatocellular carcinoma, with a strong focus on clinical outcomes and translational research.

He received his MD (1999), Master's degree (2004), and PhD (2012) from Korea University College of Medicine. He completed his internship and residency at Korea University Medical Center, followed by fellowship training in gastroenterology and hepatology.

Prof. Jung has held academic positions at Gachon University Gil Medical Center and Korea University Ansan Hospital, where he has been a Professor since 2019. He was a Visiting Professor at the Kyoto University Center for iPS Cell Research and Application (CiRA) from 2018 to 2019, where he expanded his research into regenerative medicine and cell-based therapies.

He recently served as Director of the Clinical Practice Guideline Committee of the Korean Association for the Study of the Liver (KASL) and is actively involved in multiple national academic societies. His research integrates multicenter clinical cohorts (KACLiF) with mechanistic studies, particularly focusing on hepatitis immune responses and prognostic modeling in alcohol-related liver disease and acute-on-chronic liver failure.

Research Interests

- Viral Hepatitis (HBV) and Antiviral Outcomes
- Alcohol-Related Liver Disease (ALD) and Acute-on-Chronic Liver Failure (ACLF)
- Liver Cirrhosis and Decompensation
- Hepatocellular Carcinoma (HCC)
- Immune Mechanisms and NK Cell Biology in Liver Disease
- Regenerative Medicine and iPS Cell-Based Therapy

Representative Publications

1. Lee JS, Lee SW, Lee HL, Yoo JJ, Seo YS, Yu SJ, Yim HJ, Jung YK, et al. Besifovir dipivoxil maleate versus other antivirals in reducing hepatocellular carcinoma in chronic hepatitis B. *Scientific Reports*. 2025 Aug 29;15(1):31879.
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5. Lim J, Kim S-E, Jo AJ, Kim JH, Han SK, Kim TH, Yim HJ, Jung YK, et al.; KACLiF Study Group. Effect of diabetes on mortality and liver transplantation in alcoholic cirrhosis with acute decompensation. *Hepatology International*. 2024 Jul 17;18(5):1579-1588.

The Need for Greater Awareness and an Evolving Treatment Landscape in Hepatitis D Infection

Young Kul Jung Korea University

Hepatitis D virus (HDV) infection represents the most severe form of chronic viral hepatitis, with rapid progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Despite its clinical significance, treatment options have historically been limited, and many patients remain undiagnosed or untreated. Increasing awareness of evolving therapeutic strategies is therefore essential to improve clinical outcomes.

For decades, pegylated interferon-alpha (PEG-IFN α) has been the only established therapy for chronic hepatitis D (CHD). Although PEG-IFN α can suppress HDV RNA and improve liver inflammation, sustained virologic response rates are modest and relapse frequently occurs after treatment discontinuation. In addition, its use is limited by significant adverse effects and contraindications in patients with advanced liver disease.

Recent advances in HDV virology have led to the development of novel targeted therapies that interfere with distinct stages of the viral life cycle. Bulevirtide, an entry inhibitor targeting the sodium taurocholate cotransporting polypeptide (NTCP), prevents viral entry into hepatocytes and has demonstrated meaningful reductions in HDV RNA and alanine aminotransferase levels. Lonafarnib, an oral prenylation inhibitor, disrupts viral assembly and has shown antiviral efficacy, particularly in combination with ritonavir and PEG-IFN α . In addition, nucleic acid polymers such as REP-2139 inhibit HBsAg secretion and indirectly suppress HDV replication. These emerging therapies represent a paradigm shift from nonspecific immune modulation to mechanism-based antiviral treatment.

However, important challenges remain, including the lack of curative therapy, optimal treatment duration, and limited accessibility of new agents in many regions. Sustained suppression of HDV RNA remains the primary therapeutic goal, as it is associated with improved clinical outcomes.

In conclusion, the treatment landscape of HDV infection is rapidly evolving. Enhanced awareness, early diagnosis, and integration of novel therapies into clinical practice are critical to improving the prognosis of this aggressive disease.

References

1. Hepatitis D virus; Chronic hepatitis D; Antiviral therapy; Bulevirtide; Lonafarnib

**Chun-Jen Liu***National Taiwan University, Taiwan*

Self Introduction

Chun-Jen LIU is a Professor at the Department of Internal Medicine, and Director of Clinical Trial Center and Division of Gastroenterology & Hepatology, National Taiwan University College of Medicine and Hospital. He achieved his MD and PhD at the National Taiwan University. He has been actively involved in clinical trials for the treatment of various liver diseases, and delivered the JGH Foundation Emerging Leader Lecture in APDW 2013. Recently, he received NTUH outstanding Research Award 2022. He is now the Immediate Past President of the Taiwan Association for the Study of the Liver, and the associate editor of the Journal of the Formosan Medical Association. He has authored 430 papers in international peer-reviewed journals.

Research Interests

Professor LIU's interests include chronic hepatitis B and C, HCC, and metabolic dysfunction-associated steatotic liver disease (MASLD), where his studies focus on the pathogenesis and the trial interventions for chronic viral hepatitis, MASLD and HCC.

Representative Publications

1. Liu CJ, Chuang WL, Sheen IS, et al. Efficacy of ledipasvir and sofosbuvir Treatment of HCV Infection in Patients Coinfected with HBV. *Gastroenterology* 2018;154:989-997.
2. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis C and B viruses. *Gastroenterology* 2009;136:496-504.
3. Liu CJ, Lee PH, Lin DY, et al. Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: A randomized phase II trial for safety and dose-finding. *J Hepatol* 2009;50:958-968.
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Low Level Viremia in Chronic Hepatitis B Patients Receiving Nucleos(t)ide Analogues: Clinical Impact and Management

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Low-level viremia (LLV), defined as persistent detectable HBV DNA below 2,000 IU/mL despite prolonged nucleos(t)ide analogue (NA) therapy, is increasingly recognized in chronic hepatitis B (CHB) management. With highly sensitive PCR assays, LLV is observed in approximately 20–40% of treated patients and remains a major clinical concern. Major determinants of LLV include high baseline HBV DNA, HBeAg positivity, advanced liver fibrosis, cirrhosis, and poor medication adherence. Persistent LLV is associated with increased risks of liver fibrosis progression, hepatic decompensation, and hepatocellular carcinoma (HCC). Patients with LLV have nearly a two-fold higher risk of HCC compared with those achieving complete virological response, particularly among individuals with cirrhosis. However, recent evidence suggests that in patients with excellent adherence ($\geq 90\%$), LLV itself may not independently predict adverse outcomes, highlighting medication adherence as a critical determinant of prognosis. Emerging biomarkers such as hepatitis B core-related antigen (HBcrAg) may further refine risk stratification and HCC prediction. Current management depends on underlying liver disease severity. In patients without advanced fibrosis, close monitoring and optimization of adherence and drug administration are generally recommended before modifying therapy. In contrast, patients with cirrhosis or advanced fibrosis require aggressive viral suppression, aiming for undetectable HBV DNA. Treatment modification, including switching to higher genetic barrier agents such as tenofovir alafenamide (TAF) or adding pegylated interferon-alpha, may improve virological outcomes in selected patients. Conclusions: LLV is a common and clinically important issue during long-term NA therapy in CHB patients. Persistent LLV is associated with worse liver-related outcomes, especially in cirrhotic patients. Careful assessment of adherence, individualized risk stratification, and timely treatment optimization are essential to minimize fibrosis progression and HCC development.



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Self Introduction

Prof. Moon Haeng Hur is a Clinical Assistant Professor in the Department of Gastroenterology at Seoul National University Hospital. He earned his B.S. in Electrical Engineering and Computer Science from Seoul National University in 2014, followed by his M.D. and Ph.D. from Seoul National University College of Medicine in 2018 and 2024, respectively. He completed his internship and residency in Internal Medicine at Seoul National University Hospital, followed by fellowship training in Gastroenterology at the same institution. Since 2023, he has been serving as a Clinical Assistant Professor in the Department of Gastroenterology, Seoul National University Hospital. His academic work focuses on chronic hepatitis B, hepatocellular carcinoma, MASLD, and the application of artificial intelligence and machine learning to liver disease risk prediction and personalized clinical decision-making.

Research Interests

Artificial Intelligence and Machine Learning in Hepatology, Clinical Prediction Models, Hepatocellular Carcinoma, Chronic Hepatitis B, MASLD

Representative Publications

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AI-Driven Strategies for Chronic Hepatitis B: From Prediction to Post-Cure Risk Stratification

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1. Persistent Hepatocarcinogenic Risk following HBsAg Seroclearance

HBsAg seroclearance is widely regarded as the optimal therapeutic endpoint — a functional cure — in chronic hepatitis B (CHB). Achieving seroclearance is associated with substantial reductions in the risk of hepatocellular carcinoma (HCC), hepatic decompensation, and liver-related mortality.¹ Nevertheless, this cure is incomplete. Long-term cohort data demonstrate that HCC risk persists after viral clearance, driven not by ongoing replication but by host- and liver-related factors including pre-existing fibrosis, age-related susceptibility, and metabolic comorbidities.² Importantly, the annual incidence of HCC after seroclearance has been reported at 0.86% in a Korean cohort — well above the 0.2% per year cost-effectiveness threshold for surveillance.³ As the number of patients achieving functional cure grows with novel therapeutic agents, determining who remains at risk has become a critical clinical imperative.

2. Conventional Prediction Models: Strengths and Limits

Regression-based models have provided the first frameworks for post-cure risk stratification. The Korean-derived model by Yang et al. identified age at seroclearance, cirrhosis, family history of HCC, and alcohol consumption as independent HCC predictors, yielding a C-index of 0.804 and time-dependent AUROCs of 0.799–0.835.³ The CAMP-B score was derived from over 8,700 patients across international centers and uses four readily available variables (cirrhosis, age ≥50, male sex, platelet count) to stratify HCC risk, with AUROCs approaching 0.80.⁴ These models are clinically accessible and simple to implement, but their reliance on static baseline variables and linear assumptions limits their capacity to support truly individualized surveillance strategies.

3. Machine Learning for Post-Cure Risk Prediction

To address these limitations, we developed and validated PLAN-B-CURE, a machine learning-based model designed to predict liver-related outcomes, comprising HCC, hepatic decompensation, and liver-related death, following HBsAg seroclearance.² Using a gradient boosting algorithm and seven routinely available clinical variables (age, sex, alcohol intake, diabetes, cirrhosis, serum albumin, and platelet count), the model was trained and validated in 4,787 patients from multinational cohorts in South Korea and Hong Kong. It demonstrated superior discriminative performance (C-index 0.82; AUROC 0.86)

compared with conventional models, which achieved AUROCs of 0.62–0.72 in the same cohort. Importantly, the inclusion of metabolic risk factors (diabetes and significant alcohol use) as model inputs underscores the host-driven nature of post-cure hepatocarcinogenesis. SHAP values were incorporated to enhance clinical interpretability, enabling individualized risk attributions for each patient.

4. Toward Risk-Adaptive Surveillance

Current guidelines recommend continued HCC surveillance for cirrhotic patients after seroclearance, but guidance for non-cirrhotic individuals remains heterogeneous and inconsistent across international recommendations.⁵ Machine learning-based risk stratification offers a foundation for shifting from uniform to risk-adaptive surveillance: high-risk patients may warrant close monitoring comparable to cirrhotic populations, while very-low-risk individuals may be candidates for less intensive follow-up. Such individualized strategies could improve cost-effectiveness and reduce patient burden while maintaining clinical safety. Nevertheless, prospective validation and formal cost-effectiveness analyses are prerequisite before routine clinical implementation.

5. Conclusion

Functional cure should be viewed not as the end of CHB, but as the beginning of a phase requiring personalized risk assessment. Machine learning models provide more precise, host-driven prognostication than conventional scores and support a transition from uniform surveillance to adaptive monitoring. As novel curative therapies enter practice, prospective validation of these tools in treatment-induced seroclearance populations will be an important next step toward precision hepatology.

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MINI SPECIAL INTEREST GROUP 1

The KASL Viral Hepatitis Study Group

Chair
Hyung Joon Yim (Korea Univ.)



**Janghan Jung***Hallym University*

Self Introduction

Prof. Janghan Jung is an Assistant Professor of the Department of Internal Medicine, Hallym University College of Medicine and is works in the division of Gastroenterology and Hepatology at Hallym Univeristy Dogtan Sacred Heart Hospital.

Prof. Jung graduated from Konyang University College of Medicine with his medical degree in 2006 and completed his internship and residency at the Department of Internal Medicine at Konyang University Hospital, receiving his diploma in Internal Medicine in 2011.

Prof. Jung completed fellowship in Gastroenterology & Hepatology at Severance Hospital, Yonsei University College of Medicine, and have been working at Hallym University Dongtan Sacred Heart Hospital since 2017.

Research Interests

- Chronic Viral Hepatitis
- Metabolic Dysfunction-Associated Steatotic Liver Disease
- Hepatocellular Carcinoma

Unmet Needs in the Clinical Practice of Chronic Viral Hepatitis: From Functional Cure to Personalized HCC Surveillance

Janghan Jung*Hallym University*

Viral hepatitis, particularly chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, remains a leading cause of cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Despite major advances in antiviral therapy, viral suppression or eradication does not fully eliminate long-term clinical risks. The key unmet needs have therefore shifted toward functional cure, finite therapy, refined treatment eligibility, and personalized HCC surveillance.

In chronic hepatitis B (CHB), potent nucleos(t)ide analogues effectively suppress HBV DNA and reduce liver-related complications, but they rarely eliminate the biological persistence of HBV maintained by intrahepatic covalently closed circular DNA and integrated HBV DNA. Consequently, functional cure, defined as sustained hepatitis B surface antigen loss, remains uncommon. Novel approaches such as small interfering RNA, antisense oligonucleotides, core protein allosteric modulators, therapeutic vaccines, and immune modulators are being investigated, but optimal combinations, patient selection, durability, and long-term safety remain unresolved.

A second unmet need in CHB is safe finite therapy. Many patients still require long-term or lifelong nucleos(t)ide analogue treatment, creating burdens related to adherence, cost, monitoring, comorbidities, and patient preference. Treatment discontinuation may be considered only in selected non-cirrhotic, HBeAg-negative patients with prolonged viral suppression and low quantitative HBsAg, but relapse, ALT flare, and hepatic decompensation remain concerns. Biomarkers such as quantitative HBsAg, hepatitis B core-related antigen, and serum HBV RNA may help predict sustained off-treatment control, but routine clinical use requires further standardization.

Current CHB treatment eligibility also remains limited by its reliance on alanine aminotransferase (ALT) and HBV DNA levels. These markers are essential but insufficient to reflect intrahepatic inflammation, fibrosis burden, and long-term HCC risk. Patients with normal ALT or low-level viremia may still have clinically relevant disease, particularly when older age, long infection duration, family history of HCC, metabolic dysfunction, or fibrosis is present. Therefore, treatment decisions should move beyond binary ALT/HBV DNA thresholds toward integrated assessment of fibrosis, host factors, metabolic risk, viral biomarkers, and individualized HCC risk.

In chronic hepatitis C, direct-acting antivirals (DAAs) have transformed HCV infection into a curable dis-

ease, with sustained virological response (SVR) rates exceeding 95%. However, SVR does not necessarily indicate complete reversal of liver disease or elimination of HCC risk. Patients with baseline cirrhosis, advanced fibrosis, high FIB-4 score, low platelet count, elevated liver stiffness, older age, male sex, diabetes, hepatic steatosis, alcohol use, or elevated alpha-fetoprotein may remain at risk for HCC for many years after viral cure. Thus, a central unmet need in the DAA era is to identify patients who remain biologically at risk despite virological cure.

Personalized HCC surveillance is a shared unmet need in CHB and post-SVR HCV. Current surveillance, usually based on cirrhosis or advanced fibrosis with semiannual ultrasonography $\pm$ alpha-fetoprotein, does not fully capture heterogeneous HCC risk. Risk models such as PAGE-B, REACH-B, aMAP, FIB-4, liver stiffness-based models, and AFP-based algorithms may support risk stratification, but require further validation, standardized cutoffs, and integration into routine practice.

Metabolic risk further modifies long-term outcomes in both diseases. MASLD, diabetes, obesity, hepatic steatosis, alcohol use, and smoking may accelerate fibrosis progression and increase HCC risk even after HBV suppression or HCV eradication. Therefore, post-antiviral care should include systematic management of modifiable metabolic and lifestyle risks, not merely confirmation of viral control.

In conclusion, the clinical unmet needs in chronic HBV and HCV now extend beyond viral suppression or cure. Future care should integrate fibrosis burden, viral and host biomarkers, metabolic and lifestyle risks, and validated prediction models to guide treatment decisions and personalize HCC surveillance, ultimately reducing residual liver-related morbidity and mortality.

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KASL SYMPOSIUM 2

Autoimmune Liver Diseases and Beyond

Chairs

Tetsuo Takehara (The Univ. of Osaka, Japan)

Sook-Hyang Jeong (Seoul National Univ.)





Ja Kyung Kim
Yonsei University

Self Introduction

Prof. Ja Kyung Kim is a Professor in the Division of Gastroenterology, Department of Internal Medicine at Yonsei University College of Medicine, and currently serves as the Vice Director of Yongin Severance Hospital.

Prof. Kim graduated from Yonsei University College of Medicine and subsequently obtained her Master’s and Ph.D. degrees from the same institution. She completed her internship and residency in Internal Medicine at Severance Hospital, followed by clinical and research fellowships in gastroenterology and hepatology.

Since 2019, Prof. Kim has been serving as Professor at Yongin Severance Hospital and has held several key leadership roles, including Chief of the Division of Gastroenterology (2019–2024), Vice Director of Yongin Severance Hospital (2022–2026) and currently Chief of Clinical Research Center in Yongin Severance Hospital and Vice Chief of Division of Medical Science Research Affaires in Yonsei University Health System. She is actively involved in multiple academic societies and editorial activities, contributing extensively to the field of hepatology with a focus on cell therapy and immunology in chronic liver disease.

Research Interests

- Cell Therapy in Liver Disease
- Immunology in Chronic Liver Disease
- Treatment for Hepatocellular Carcinoma
- Liver Cirrhosis and Portal Hypertension Complication
- MASLD and Clinical Implication

Representative Publications

1. Lim TS, Chung SJ, Jeon J, Kim JK, Kim J. The influence of metabolic dysfunction associated steatotic liver disease and body mass index on the incidence of Alzheimer disease: A nationwide cohort study. *Gut and Liver* 2025.

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Immunopathogenesis and Overlap Syndromes in Autoimmune Liver Diseases

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Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndromes (OS), represent a heterogeneous group of chronic immune-mediated hepatobiliary disorders characterized by loss of self-tolerance against hepatocytes and cholangiocytes. Recent advances in immunology, genetics, and microbiome research have substantially refined our understanding of the immunopathogenesis of these conditions, revealing shared and diseases-specific immune pathways across the spectrum of AILDs.¹

The healthy liver is intrinsically tolerogenic because of its continuous exposure to dietary antigens, microbial products, and gut-derived metabolites through the portal circulation. Hepatic immune homeostasis is maintained through coordinated interactions among Kupffer cells, liver sinusoidal endothelial cells, dendritic cells, regulatory T cells (Tregs), and anti-inflammatory cytokine networks. Breakdown of this tolerogenic environment in genetically susceptible individuals leads to aberrant activation of innate and adaptive immune responses, resulting in chronic hepatobiliary inflammation and fibrosis.²

AIH is considered the prototypic autoimmune liver disease and is characterized by a predominantly T-cell-mediated immune attack against hepatocytes. Strong associations with HLA-DR3 and HLA-DR4 suggest a major role for antigen presentation and adaptive immunity. Autoreactive CD4+ and CD8+ T cells targeting liver autoantigens such as CYP2D6 contribute to interface hepatitis and progressive parenchymal injury. Impaired Treg function, excessive Th1 and Th17 polarization, increased production of pro-inflammatory cytokines including IFN-γ, TNF-α, and IL-17, and activation of B cells and plasma cells collectively sustain hepatic inflammation. Although autoantibodies such as ANA, SMA, and anti-LKM1 are central diagnostic markers, increasing evidence indicates that cellular immunity rather than humoral immunity is the principal driver of hepatocellular injury.³

In contrast, PBC primarily targets small intrahepatic bile ducts and represents a unique interplay between cholangiocyte dysfunction and immune dysregulation. Anti-mitochondrial antibodies directed against PDC-E2 remain the serologic hallmark of the disease. Recent studies suggest that biliary epithelial cells are not merely passive victims but active participants in disease initiation. Epigenetic down-

regulation of the bicarbonate transporter AE2 and disruption of the “bicarbonate umbrella” increase cholangiocyte susceptibility to bile acid-mediated injury, apoptosis, and exposure of immunogenic mitochondrial antigens. This subsequently amplifies innate and adaptive immune activation involving NK cells, dendritic cells, autoreactive T cells, and B-cell responses.⁴

PSC exhibits distinct immunopathogenic features characterized by fibro-obliterative cholangiopathy and a strong association with inflammatory bowel disease. Gut-liver axis dysregulation, aberrant lymphocyte homing, microbial dysbiosis, and cholangiocyte senescence are considered central mechanisms. Compared with AIH and PBC, PSC demonstrates a less classical autoimmune phenotype and responds poorly to immunosuppression, suggesting a greater contribution of innate immunity, biliary injury, and environmental factors.¹

Overlap syndromes illustrate the immunologic continuum among AILDs and support the concept that these conditions share overlapping pathogenic mechanisms rather than existing as entirely separate diseases. AIH-PBC overlap syndrome is the most common form and combines hepatocellular and cholestatic immune injury. Patients frequently demonstrate simultaneous interface hepatitis, plasma-cell-rich infiltrates, AMA positivity, bile duct injury, and elevated IgG and IgM levels. AIH-PSC overlap is particularly common in younger individuals and may reflect combined hepatocyte-directed and cholangiocyte-directed immune responses. Current evidence suggests that environmental triggers, genetic susceptibility, defective immune tolerance, and microbiome-associated immune activation interact dynamically to produce these mixed phenotypes.⁵

Emerging evidence further highlights the importance of the gut microbiome, bile acid signaling, and sex-specific immune regulation in AILD pathogenesis. Dysbiosis may promote intestinal permeability, pathogen-associated molecular pattern signaling, and Th17 activation through the gut-liver axis. Furthermore, marked female predominance in AIH and PBC suggests a substantial role for sex hormones, X chromosome-associated immune regulation, and sexually dimorphic hepatic immunity.²

Collectively, contemporary understanding of AILD immunopathogenesis supports a multidimensional disease model involving genetic predisposition, environmental exposure, dysregulated innate and adaptive immunity, microbiome interactions, and impaired immune tolerance. Overlap syndromes further emphasize the shared immunologic architecture among autoimmune hepatobiliary diseases. Continued elucidation of these mechanisms is expected to facilitate precision medicine approaches and the development of targeted immunomodulatory therapies in the future.

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Soon Kyu Lee
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Self Introduction

Prof. Soon Kyu Lee is an associate professor in the Division of Gastroenterology and Hepatology at the Catholic University of Korea. He is actively conducting both basic and clinical research related to transplantation, autoimmune liver disease, hepatocellular carcinoma, metabolic dysfunction-associated steatotic liver disease, and gut microbiome.

Prof. Soon Kyu Lee graduated from the Catholic University of Korea, College of Medicine with his medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at The Catholic University of Korea, receiving his Ph.D. in Internal Medicine in 2022.

Prof. Soon Kyu Lee has been taking a number of roles in the Korean Association of the Study of the Liver, the Korean Society of Gastroenterology and the Korean Liver Transplantation Society.

He received Young Investigator Award, 2023 APPLE & 2023 APASL STC and Awarded the Deputy Prime Minister and Minister of Education Award, selected for the Top 50 Outstanding Outcomes in the Academic and Research Support Program by the Ministry of Education (2023).

Research Interests

Liver Transplantation, Hepatocellular Carcinoma, Autoimmune Liver Disease, Metabolic Dysfunction-Associated Steatotic Liver Disease, Gut Microbiome, Immunology

Representative Publications

1. Lee SK et al. Landscape of T-cell Exhaustion Heterogeneity and HBV Integration in Virus-related HCC Revealed by Whole Exome, Transcriptome, and Single-Cell Sequencing, JHEP reports (2025) <https://doi.org/10.1016/j.jhepr.2025.101518>.
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Hard-to-Treat Autoimmune Liver Diseases: Lessons from Clinical Cases

Soon Kyu Lee *The Catholic University of Korea*

Autoimmune hepatitis (AIH) is an inflammatory liver disease caused by autoimmune mechanisms, with an incidence rate of 1.07 per 100,000 population in Korea.¹ It shows a female predominance among adults and has the highest prevalence in the 60–69-year age group in Korea.^{1,2} Clinically, most patients present with chronic hepatitis, and approximately 30% have cirrhosis at the time of diagnosis. AIH can also manifest as acute hepatitis, acute severe AIH (AS-AIH), or even acute liver failure (AIH-ALF). For diagnosis, liver biopsy is recommended in patients with positive autoantibodies (ANA, AMA, anti-LKM1, or anti-SLA) and/or elevated serum IgG levels.^{3,4} Typical histopathological features of AIH include interface hepatitis, lymphoplasmacytic portal inflammation, hepatocyte rosettes, emperipolesis, and varying degrees of fibrosis.⁵ In addition to histological findings, diagnosis is supported using either the simplified or revised original diagnostic criteria.¹ The standard first-line treatment consists of prednisolone monotherapy (40–60 mg/day) or combination therapy with prednisolone (20–40 mg/day) and azathioprine (50 mg/day).¹ Although remission is achieved in approximately 65% of patients, a substantial proportion still experience difficult-to-treat or treatment-refractory AIH.

First, in the diagnosis of AIH, distinguishing it from drug-induced autoimmune-like hepatitis (DI-ALH) can be particularly challenging and difficult to treat. Several medications—such as nitrofurantoin, minocycline, alpha-methyldopa, and hydralazine—are known to trigger features resembling DI-ALH.⁶ To differentiate AIH from DI-ALH, the Roussel Uclaf Causality Assessment Method (RUCAM) score, along with the simplified or revised original diagnostic criteria, may be applied.^{5,6} Although liver biopsy plays a critical role in the diagnostic workup, it may not definitively distinguish between the two, as both conditions can present with overlapping histologic features such as interface hepatitis. Given this overlap, when liver biopsy findings suggest “probable” or “possible” AIH, immunosuppressive therapy may be initiated in patients with ongoing liver injury. Following clinical and biochemical resolution, an attempt to withdraw immunosuppressive therapy can aid in differentiating AIH from DI-ALH, as relapse is common in true AIH.⁶

Second, acute presentations of AIH—including acute AIH, acute severe AIH (AS-AIH), and AIH-associated acute liver failure (AIH-ALF)—must also be considered, as they account for approximately 10–40% of all AIH cases.⁷ In acute AIH, serum IgG levels and autoantibody titers may be normal or only mildly

elevated.⁸ AS-AIH is defined by the presence of jaundice, a prothrombin time-international normalized ratio (PT-INR) ≥ 1.5 , absence of hepatic encephalopathy, and no history of pre-existing liver disease. AIH-ALF is characterized by jaundice, PT-INR ≥ 1.5 , the development of hepatic encephalopathy within 26 weeks of symptom onset, and no prior liver disease.⁹ In addition to typical histological features of AIH, AS-AIH and AIH-ALF may present with central perivenulitis, centrilobular hemorrhagic necrosis, portal lymphoplasmacytic infiltration, and minimal or absent fibrosis/cirrhosis.. For AS-AIH, early evaluation of treatment response—typically within 3–7 days of initiating corticosteroid therapy—is recommended. The SURFASA score, which incorporates day 0 INR, day 3 INR, and day 3 bilirubin levels, may assist in predicting treatment response.^{8,10} In patients with AS-AIH who do not improve, or in cases of AIH-ALF with high MELD scores, liver transplantation should be considered.⁷

Third, treatment failure following first-line therapy and relapse after remission remain major challenges in the management of AIH. In first-line therapy, steroid-based induction therapy followed by azathioprine-based maintenance therapy is commonly used.^{1,8} Treatment response is typically evaluated after 1 month (to assess response vs. non-response) and again at 6 months (to assess complete biochemical response vs. incomplete response).^{4,11,12} For patients with an incomplete response, second-line therapies such as mycophenolate mofetil (MMF) or tacrolimus are preferred, while cyclosporine, 6-mercaptopurine (6-MP), and 6-thioguanine (6-TG) are also recommended alternatives.^{4,11,12} In cases of relapse following remission, re-initiation of first-line therapy is generally advised, along with consideration for long-term treatment.^{5,11} Recently, several novel therapeutic candidates for AIH have been studied, including tofacitinib, infliximab, tocilizumab, IL-2 mutein, and ustekinumab, which target the JAK/STAT, TNF- α , IL-6, IL-2, and IL-12/IL-23 pathways, respectively.^{13,14} In addition, cell-based therapies are under investigation, such as regulatory T cell (Treg) infusion, anti-BAFF receptor antibody targeting B cells, and therapies targeting natural killer cells.^{13,14}

In conclusion, AIH presents with a broad clinical spectrum, including chronic hepatitis, AS-AIH, and AIH-ALF, posing diagnostic and therapeutic challenges for clinicians. In addition, DI-ALH should be carefully differentiated from AIH, with relapse following treatment withdrawal serving as a key distinguishing feature of true AIH. Despite the generally favorable prognosis, the high relapse rate and potential for incomplete response remain major challenges in AIH management. Several second-line therapies have been introduced, and novel therapeutic candidates are currently under investigation to improve clinical outcomes in affected patients.

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**Atsumasa Komori***Nagasaki University, Japan*

Self Introduction

Atsumasa Komori is the director of Clinical Research Center, and a senior staff member of Hepatology division, NHO Nagasaki Medical Center (NHO-NMC), Japan. After graduation of Kyushu University School of Medicine, followed by the training in the field of cancer research at National Cancer Center/Saitama Cancer Center in Japan and of B cell immunology at Weill Medical School of Cornell University in USA, he joined in NHO-NMC to study clinical hepatology in 2003. Since 2020, to promote clinical and translational research in primary biliary cirrhosis (PBC), He has been organizing the nationwide multicenter observational studies, as well as the nationwide PBC surveys in Japan, as the head of PBC division in the Intractable Hepato-Biliary Diseases Study Group for Research on Measures for Intractable Disease, which is supported by Health Labor Science Research Grants in Japan. He is also the chief of Division of International Medical Cooperation in NHO-NMC, whose continuing clinical mentorship in the Republic of Kazakhstan was awarded as an honorary professor of Kazakhstan National Medical University in 2015. He is a board certified hepatologist and member of the board of trustees of the Japan Society of Hepatology. With two-decade-long collaboration with KASL colleagues, he is served as a section editor of Clinical and Molecular Hepatology.

Research Interests

Autoimmune Liver Disease, Cholestatic Liver Disease, Steatotic Liver Disease, Viral Hepatitis, Hepatocarcinogenesis

Representative Publications

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Treatment Optimization in Autoimmune Hepatitis: When First-Line Therapy Fails

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Introduction

The aim of the treatment of autoimmune hepatitis (AIH) is a prevention of disease progression from liver-related outcomes, ensuring healthy quality-of life. To this end, it is necessary to attain biochemical, clinical, and histological remission of the disease. According to the report by International Autoimmune Hepatitis Group, complete biochemical response, a surrogate primary endpoint of remission, was defined as normalization of serum transaminases and IgG below the upper limit normal no later than 6 months ($CBR \leq 6M$) after the initiation of de facto first-line combination therapy with prednisolone (PSL) and azathioprine (AZA). As the combination of AZA or mycophenolate mofetil (MMF) with PSL is to spare corticosteroid (CS) from maintenance therapy, that is, secondary endpoint of treatment, early combination is recommended. In ordinary clinical practice of AIH, intolerance or insufficient response to AZA, the latter of which could otherwise be resolved by the dose-optimization of AZA, with the aid of measurement of the active drug metabolite 6-thioguanine nucleotides (6-TGN), are the main indication of second-line therapy.

Treatment Optimization in AIH by Second-Line Therapy

High discontinuation rate of AZA during the first 6 months of therapy (30 %<), that clearly impacts CBR status, was reported by the prospective multicentre European registry. Gastrointestinal side effects are common, while myelotoxicity occur at a low frequency, once patients with NUDT15 risk allele are excluded (in Asian countries). Treatment options for individuals who are intolerant or insufficient response to AZA included MMF, 6-mercaptopurine (6-MP, the first metabolite of AZA), or calcineurin inhibitors (tacrolimus [TAC]>cyclosporin A).

MMF is now regarded as a potential second-line drug, mainly due to its safer and more tolerable profile than AZA, with fewer discontinuation rate: a meta-analysis revealed that the combination of MMF+CS was the most widely prescribed second-line therapy.

Evidence regarding the efficacy of TAC as second-line drug in AZA insufficient responders is limited. An ongoing TAILOR study, an open-label phase IIIb RCT (NCT05221411) comparing the effectiveness and safety of TAC and MMF as second-line drug for AIH patients who failed to reach $CBR \leq 6M$ should provide

practical insights.

Future Direction

Optimization of first-line therapy for AIH is further warranted; MMF+PSL achieved higher rate of the primary endpoint CBR≤6M-ALT/IgG than AZA+PSL in an open-label RCT (CAMARO trial), while allopurinol with low-dose thiopurines that leads to relative increase in the ratio of 6-TGN/toxicity-associated 6-methylmercaptopurine was reported to improve chance of CBR.

Meanwhile, we are expecting progress in ongoing/future clinical trials of novel B cell-targeted Immuno-therapeutics as second-line drug to AIH.

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Yu Jun Wong
Duke-NUS Medical School, Singapore

Self Introduction

Dr. Wong is a Senior Consultant Gastroenterologist at the Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore, and Clinical Associate Professor at Duke-NUS Medical School. He graduated from the National University of Malaysia and completed hepatology fellowship training at the University of Alberta, Edmonton, Canada.

His clinical and research interests focus on chronic liver disease, particularly the development of non-invasive risk stratification of portal hypertension and risk stratification in cirrhosis. He also conducts research in viral hepatitis C and metabolic dysfunction-associated steatotic liver disease. Dr. Wong has authored more than 100 peer-reviewed publications and regularly speaks at regional and international scientific meetings.

Dr. Wong’s research contributions have been recognized with several awards, including the AASLD Early Career Investigator Award in Clinical/Translational Science (2022) and the AASLD Foundation Healthcare Disparities Research Award (2024). He is also a recipient of the Nurturing Clinician Scientist Scheme (NCSS) from SingHealth and has received multiple Best Oral Presentation Awards at GIHEP (2018, 2021, 2023). He currently serves as an editorial board member of Hepatology and is a member of the AASLD Portal Hypertension Special Interest Group. His contributions to peer review were recognized with the Outstanding Reviewer Award from Hepatology in 2024 and 2025.

In addition to research, Dr. Wong leads industry-sponsored clinical trials and was awarded the Clinical Trialist Award in 2025. He is actively involved in mentoring medical students and trainees, receiving the Outstanding Mentor Award from the Singapore Medical Association in 2023 and 2025. Dr. Wong also contributes to regional professional societies and currently serves as a member of the APAGE Emerging Leaders Committee and an Executive Committee member of the Chapter of Gastroenterology, Academy of Medicine, Singapore.

Research Interests

Cirrhosis and Portal Hypertension, Viral Hepatitis, Autoimmune Liver Disease, Steatotic Liver Disease

Representative Publications

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Beyond Ursodeoxycholic Acid: The Next Chapter in Primary Biliary Cholangitis Treatment

Yu Jun Wong
Duke-NUS Medical School, Singapore

Despite Ursodeoxycholic acid remaining first-line therapy, up to 40% of patients with Primary Biliary Cholangitis have an incomplete biochemical response. This talk explores the evolving second-line landscape, including fibrates, PPAR agonists, and emerging agents, while critically examining the limitations of surrogate endpoints such as ALP reduction. Drawing on real-world data and trial evidence, we will discuss treatment sequencing, patient selection, and the gap between biochemical response and meaningful clinical outcomes. The session highlights how future strategies must integrate efficacy, safety, and cost to deliver truly patient-centred, outcome-driven care.

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SPECIAL INTEREST GROUP 1. KCSG & CHES JOINT SYMPOSIUM

Leading the Frontiers of Cirrhotic Portal Hypertension in East Asia

Chairs

Won Hyeok Choe (Konkuk Univ.)

Tengfei Si (Zhejiang Univ., China)





Seong Hee Kang
Korea University

Self Introduction

Educational Background

Bachelor, Korea University, College of Medicine
Master's Degree of Medicine, Korea University, Graduate School of Medicine
Doctor's Degree of Medicine, Korea University, Graduate School of Medicine

Professional Experience

Assistant Professor, Wonju Severance Christian Hospital
Associate Professor, Korea University Ansan Hospital

Research Interests

Liver Cirrhosis, Alcoholic Hepatitis, MASLD, Hepatocellular Carcinoma

Representative Publications

1. SH Kang et al. Tenofovir Alafenamide vs. Tenofovir Disoproxil Fumarate in Lowering the Risk of HCC Development in Patients With CHB. J Gastroenterol Hepatol. 2026 Mar 8
2. SH Kang et al. Association Between SGLT2 Inhibitor Use and Reduced Risk of Liver-Related Events, Including Hepatocellular Carcinoma, in Diabetic Patients with Viral Hepatitis: A Nationwide Cohort Study. Cancers 2026,18(1), 120
3. SH Kang et al. Need of Treatment Modification During Entecavir Therapy in Patients with Chronic Hepatitis B: Long-Term Follow-Up Results for 120 Months. Microorganisms 2025,13(2), 218
4. SH Kang et al. Subclinical diabetes confirmed by 75-g OGTT influence on the prognosis of decompensated cirrhosis. J Gastroenterol Hepatol. 2024 Jan;39(1):172-179
5. SH Kang et al. Outcome of Intermittent Thoracentesis versus Pigtail Catheter Drainage for Hepatic Hydrothorax. Journal of Clinical Medicine. 2022

Emerging Evidence: Ongoing Prospective Trials in Cirrhosis from Korea

Seong Hee Kang Korea University

This report summarizes three landmark prospective clinical trials in South Korea aimed at optimizing liver cirrhosis management. In the first study regarding acute variceal bleeding, researchers demonstrated that continuous infusion of terlipressin offers comparable efficacy to the traditional bolus approach, with both methods yielding high success rates. Notably, the continuous infusion regimen was significantly safer, associated with a reduced incidence of gastrointestinal, cardiovascular, and ischemic adverse events. The second trial on Branched-Chain Amino Acid (BCAA) supplementation showed a significant elevation in serum albumin levels, particularly among patients with over 80% adherence, highlighting the critical role of therapeutic compliance. The final study evaluated the efficacy of autologous bone marrow-derived mesenchymal stem cell therapy for refractory ascites. At the one-year follow-up, treated patients exhibited a significant mean reduction in total ascites volume. Furthermore, clinical responders showed marked improvements in MELD scores, indicating that biomarker-driven personalized selection could further enhance treatment outcomes in the future.



Xiaolong Qi
Liver Health Consortium in China (CHESS), China

Self Introduction

Educational Background

2007-2013 Tongji University, Clinical Medicine (Eight-year Program), Bachelor
2013-2015 Tongji University, Clinical Medicine (Eight-year Program), Doctor of Medicine (M.D.)
2017-2019 Harvard Medical School, Postdoctoral Fellow

Professional Experience

2016-2019 Nanfang Hospital, Southern Medical University, Liver Disease Center, Associate Researcher
2019-2022 Lanzhou University First Hospital, Institute of Portal Hypertension, Principal Investigator / Researcher
2022-Present Zhongda Hospital, Southeast University, Professor

Research Interests

Focused on the research and transformation of new technologies for the diagnosis and treatment of major chronic liver diseases, published SCI papers with a cumulative impact factor of 1998.9 points, cited 10123 times, and an H-index of 55 (Google scholar), 51 (Scopus).

Representative Publications

1. Yuping Chen; Xinrui Jin; Chuan Liu; Ming-Hua Zheng; Xiao Liang; Yameng Sun; Hye Won Lee; Huapeng Lin; Emmanuel Tsochatzis; Salvatore Petta; Elisabetta Bugianesi; Masato Yoneda; Hannes Hagstrom; Jerome Boursier; Jose Luis Calleja; George Boon-Bee Goh; Wah-Kheong Chan; Rocio Gallego-Duran; Arun J. Sanyal; Victor De Ledinghen; Philip N. Newsome; Jian-Gao Fan; Laurent Castera; Michelle Lai; Celine Fournier-Poizat; Grace Lai-Hung Wong; Grazia Pennisi; Angelo Armandi; Atsushi Nakajima; Wen-Yue Liu; Ying Shang; Marc De Saint-Loup; Elba Llop; Kevin Kim Jun Teh; Carmen Lara-Romero; Amon Asgharpour; Sara Mahgoub; Mandy Sau-Wai Chan; Adrien Lannes; Manuel Romero-Gomez; Airong Hu; Yiling Li; Qing-Lei Zeng; Wei Gou; Hua Bian; Xiao Han; Chenlin Sun; Seung Up Kim; Terry Cheuk-Fung Yip; Gao-Jun Teng; Vincent Wai-Sun Wong; Xiaolong Qi; Two-step clinical care pathway to predict MASLD-related advanced fibrosis and long-term outcomes in type2 diabetes, Gut, 2026 (Co-corresponding author)
2. Chenyan Wang; Eric Felli; Jonathan A Fallowfield; Christoph F Dietrich; Don C Rockey; Jürgen Hennig; Gao JunTeng; Jordi Gracia-Sancho; Xiaolong Qi; Vasomics of the Liver, Gut, 2025 (sole corresponding author)
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5. Xiaolong Qi; Weimin An; Fuquan Liu; Ruizhao Qi; Lei Wang; Yanna Liu; Chuan Liu; Yi Xiang; Jialiang Hui; Zhao Liu; Xingshun Qi; Changchun Liu; Baogang Peng; Huiguo Ding; Yongping Yang; Xiaoshun He; Jinlin Hou; JieTian; Zhiwei Li; Virtual Hepatic Venous Pressure Gradient with CT Angiography (CHESS 1601): A Prospective Multicenter Study for the Noninvasive Diagnosis of Portal Hypertension, Radiology, 2019 (sole corresponding author).

LiverRCT: CHESS Ongoing Randomized Controlled Trials of Cirrhotic Portal Hypertension

Xiaolong Qi Liver Health Consortium in China (CHESS), China

Introduction: The Rationale for Investigator-Initiated RCTs in Portal Hypertension

Investigator-initiated clinical research refers to studies conducted by healthcare institutions that focus on individuals or groups as research subjects, covering a wide range of dimensions such as disease diagnosis, treatment, rehabilitation, prognosis, etiology, prevention, and health maintenance.¹ Among these, investigator-initiated trials (IITs), particularly randomized controlled trials (RCTs), serve as a crucial complement to pharmaceutical company-initiated drug clinical trials. Unlike industry-sponsored studies, IITs typically do not focus on profit-making or drug registration. Instead, they primarily involve clinical researches on already marketed drugs, medical devices, or diagnostic reagents, aiming to expand and optimize existing clinical practices with evidence-based medical support.

China is the country with the highest burden of liver disease globally. Chronic liver conditions can progress to cirrhosis and hepatocellular carcinoma, imposing a substantial economic and healthcare burden. In an effort to reduce this burden, Chinese researchers have conducted a considerable number of investigator-initiated clinical studies; however, a review of international databases reveals a notable dearth of investigator-initiated RCTs in liver disease led by Chinese researchers, particularly in high-impact journals.

Methodological Benchmarks from Representative Multicenter RCTs

By contrast, scholars in other fields have initiated numerous internationally leading, high-quality IITs. For instance, in 2023, researchers published landmark multicenter RCTs in prestigious journals such as *BMJ*, *JAMA*, *The Lancet*, and *N Engl J Med*.²⁻⁸ These studies encompass diverse clinical scenarios and methodological designs, including open-label randomized trials for antihypertensive treatment in acute ischemic stroke,² surgical intervention trials,³ dual antiplatelet therapy trials,⁴ combination thrombolytic therapy trials,⁵ tenecteplase versus alteplase non-inferiority trials,⁶ and stepped wedge cluster randomized controlled trials.⁷

CHESS Ongoing RCTs in Cirrhotic Portal Hypertension

In light of these challenges, the Liver Health Consortium in China (CHESS) has initiated a series of ongoing RCTs focusing on key clinical issues in the prevention and treatment of cirrhotic portal hypertension.

The objective of this initiative is to support the initiation of high-quality investigator-led RCTs in liver disease in China. These ongoing trials address critical unmet needs across the spectrum of portal hypertension management, including acute variceal bleeding, secondary prophylaxis of variceal rebleeding, and primary prevention of hepatic decompensation in compensated cirrhosis with clinically significant portal hypertension. This project aims to provide funding and academic platforms for researchers dedicated to improving liver disease management practices both in China and globally. Additionally, the CHESS collaborative network will establish quality control assistance, offering methodological education and technical guidance to overcome existing barriers and advance the development of RCTs in the liver disease field within China.

Challenges and Collaborative Framework

Despite the urgent need for high-quality RCTs in cirrhotic portal hypertension, the number of such trials remains limited in China. The main challenges include: (1) Limited funding for researchers; (2) Difficulty in multi-center collaboration; (3) Quality control challenges; (4) Suboptimal team structure; and (5) Lack of experience and training. There is a scarcity of institutions or training programs that provide systematic methodological training for conducting RCTs, which hinders the development of investigator-initiated trials. The CHESS ongoing RCTs aim to address these gaps by implementing collaborative networks and rigorous methodological standards comparable to those established in recent landmark multicenter trials.²⁻⁸

Conclusion

The CHESS ongoing RCTs in cirrhotic portal hypertension represent a critical step toward generating high-quality, investigator-initiated evidence for liver disease prevention and treatment. By leveraging collaborative networks and adhering to rigorous methodological frameworks, these trials aim to refine clinical guidelines and improve patient outcomes both in China and globally.

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Tom Ryu
Soonchunhyang University

Self Introduction

Prof. Tom Ryu is an Assistant Professor in the Department of Internal Medicine at Soonchunhyang University College of Medicine, Seoul, Korea, and a faculty member of the Institute for Digestive Research and Digestive Disease Center. He received his M.D. from Soonchunhyang University College of Medicine and completed his internship and residency in Internal Medicine at Soonchunhyang University Hospital. He subsequently obtained his Ph.D. in Medical Science and Engineering from the Korea Advanced Institute of Science and Technology (KAIST).

Prof. Ryu completed his clinical fellowship in Gastroenterology and Hepatology at Soonchunhyang University Hospital and was appointed as a Clinical Assistant Professor before assuming his current position as Assistant Professor in 2025. He is actively involved in academic societies, serving as Academic Secretary of the Korean Association of Clinical Ultrasound, Academic Committee Member of the Korean Liver Cancer Association, and Public Relations Committee Member of the Korean Association for the Study of the Liver.

Research Interests

- Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)
- Hepatocellular Carcinoma (HCC)
- Cardio-Hepatic Interactions and Arrhythmia in Liver Disease
- Real-World Evidence Using Large-Scale Cohort Databases
- Translational Research on Inflammation and Immune Mechanisms in Liver Disease

Representative Publications

1. Ryu T*, Chung BS*, Lee J, Han JW, Yang H, Yang K. Protective effects of Ginkgo biloba supplementation on clinical outcomes in metabolic dysfunction-associated steatotic liver disease. *Phytomedicine*. 2025 May 21;143:156889.
2. Ryu T, Chang Y, Yoo JJ, Lee SH, Jeong SW, Kim SG, Kim YS, Kim HS, Yang K, Jang JY. Glucosamine supplementation attenuates progression of metabolic dysfunction-associated steatotic liver disease and related comorbidities. *Clin Nutr*. 2025 Feb 14;47:119-128.
3. Ryu T*, Chang Y*, Jeong SW, Yoo JJ, Lee SH, Kim SG, Kim YS, Kim HS, Kim SU, Jang JY. Adverse impact of metabolic dysfunction on fibrosis regression following direct-acting antiviral therapy: A multicenter study for chronic hepatitis C. *Clin Mol Hepatol*. 2025 Jan 9. doi: 10.3350/cmh.2024.0904. Online ahead of print.
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Clinical Insights from the Korean Multicenter HVPG Cohort

Tom Ryu Soonchunhyang University

The hepatic venous pressure gradient (HVPG) remains the gold standard for assessing portal hypertension and provides a direct hemodynamic measure of disease severity in patients with chronic liver disease. Defined as the difference between wedged and free hepatic venous pressure, HVPG reflects portal pressure in a quantitative manner and has long been recognized as a key prognostic indicator in cirrhosis. Increasing HVPG levels are closely associated with the development of major clinical complications, including variceal bleeding, ascites, hepatic encephalopathy, and ultimately mortality.

The Korean multicenter HVPG cohort was established to evaluate the clinical role of HVPG in a real-world setting and to identify prognostic factors associated with long-term outcomes in patients with portal hypertension. This cohort includes a broad spectrum of cirrhotic patients with diverse etiologies, providing a valuable opportunity to examine the natural history of portal hypertension under contemporary management strategies.

Consistent with prior studies, HVPG demonstrated a strong association with clinical outcomes. A threshold of 10 mmHg has been widely accepted as the point at which clinically significant portal hypertension (CSPH) develops, marking the stage when complications begin to emerge. Beyond this threshold, further increases in HVPG were associated with progressively worse outcomes. In particular, stratification based on HVPG levels allowed for clear differentiation of long-term survival, with higher HVPG values corresponding to increased risks of decompensation and mortality.

Analyses from the Korean cohort have also suggested that refined HVPG cutoffs may further improve prognostic discrimination. Patients with HVPG values above 16 mmHg, for example, showed significantly reduced long-term survival compared with those in lower classification, highlighting the value of more granular risk categorization. These findings reinforce the importance of HVPG not only as a diagnostic tool but also as an important marker for risk stratification in cirrhosis.

Importantly, the prognostic value of HVPG is further enhanced when integrated with established clinical scoring systems such as the Model for End-Stage Liver Disease score or the Child–Turcotte–Pugh classification. While biochemical scores present liver function and systemic impact, HVPG provides complementary information by directly reflecting portal hemodynamics. This combined approach allows for a more comprehensive assessment of disease severity and patient prognosis.

In addition to its role as an invasive measurement, efforts have been made to identify non-invasive surrogates of HVPg. Emerging evidence suggests that liver stiffness measurement, serum biomarkers, and machine learning–based models would offer alternative approaches to estimating portal pressure. However, despite these advances, HVPg remains the reference standard, particularly in research settings and in cases where precise hemodynamic assessment is required.

The Korean multicenter HVPg cohort is notable for its large sample size and real-world design, demonstrating the heterogeneity of cirrhotic patients encountered in routine clinical practice. Findings from this cohort have consistently presented that HVPg-based stratification effectively predicts clinical outcomes, supporting its continued use in both clinical and research settings.

In addition to its established role, recent findings from the Korean multicenter cohort suggest that HVPg may offer clinically actionable stratification beyond conventional thresholds. While CSpH (HVPg ≥ 10 mmHg) remains a key milestone, further subdivision at higher ranges appears to provide incremental prognostic value, particularly in identifying patients at high risk of decompensation and mortality. Importantly, these findings position HVPg not only as a static diagnostic metric, but also as a dynamic tool that can inform clinical decision-making. In real-world practice, HVPg-guided stratification would help refine risk assessment, guide surveillance strategies, and potentially identify patients who could benefit from earlier or more intensive therapeutic interventions.

At the same time, the growing interest in non-invasive surrogates, including liver stiffness and machine learning–based prediction models, highlights an evolving landscape. While these approaches show promise, they should currently be viewed as complementary rather than substitutive, particularly in settings where precise hemodynamic evaluation remains critical.

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Ling Yang
Southeast University, China

Self Introduction

Ling Yang focuses her research on non-invasive diagnosis and treatment of liver diseases through vasomics. She was graduated from Southeast University and has published 9 academic papers, including 7 SCI-indexed papers with a total impact factor of 79.3. She has led two university-level projects to completion. She holds one registered computer software copyright (as the primary contributor) and three national invention patents under review. She was awarded the First Prize of the Ruihua Clinical Research Innovation Award in 2025. Her research findings have been accepted four times at the Annual Meetings of the American Association for the Study of Liver Diseases (AASLD) and the Asian Pacific Association for the Study of the Liver (APASL) as first author. She delivered an oral presentation at the Second China Medical Imaging Fusion Innovation and Development Conference in 2024, where she also won the Second Prize in the “YOUNG Sail Away” Youth Chinese Forum Competition.

Research Interests

Non-invasive diagnosis and treatment of liver diseases through vasomics, with a focus on integrating multimodal imaging, artificial intelligence, and vascular biology to advance precision medicine in hepatology.

Representative Publications

1. Yang, Ling et al. “Editorial: Non-selective beta-blockers: A lifesaving shield for critically ill patients with acute decompensation of cirrhosis?” *Alimentary pharmacology & therapeutics* vol. 60,7 (2024): 965-966. doi:10.1111/apt.18207
2. Liu, Chuan et al. “Correspondence to editorial on “Carvedilol to prevent hepatic decompensation of cirrhosis in patients with clinically significant portal hypertension stratified by new non-invasive model (CHESS2306)”.” *Clinical and molecular hepatology* vol. 31,2 (2025): e155-e157. doi:10.3350/cmh.2024.0723
3. Xiang, Yi et al. “Post-TIPS Overt Hepatic Encephalopathy Increases Long-Term but Not Short-Term Mortality in Cirrhotic Patients With Variceal Bleeding: A Large-Scale, Multicenter Real-World Study.” *Alimentary pharmacology & therapeutics* vol. 61,7 (2025): 1183-1196. doi:10.1111/apt.18509
4. Wang, Tianqi et al. “A Multi-Scale Computational Model of the Hepatic Circulation Applied to Predict the Portal Pressure After Transjugular Intrahepatic Portosystemic Shunt (TIPS).” *International journal for numerical methods in biomedical engineering* vol. 41,1 (2025): e3908. doi:10.1002/cnm.3908

Vasomics: CHESS Emerging Technologies of Cirrhotic Portal Hypertension

Ling Yang Southeast University, China

The vascular system, composed of arteries, veins, and capillaries, serves as the core architecture of the body’s circulatory network, performing essential functions including oxygen transport, nutrient distribution, waste removal, and immune surveillance. Pathological changes in the vasculature are closely associated with the development and progression of many major diseases, such as cardiovascular and cerebrovascular diseases, liver disease, malignant tumors, diabetes, and kidney disease. These conditions collectively account for more than 30 million deaths annually worldwide, representing a substantial global health burden.

Focusing initially on the liver, this lecture introduces Vasomics as an emerging omics discipline that takes multimodal, cross-scale vascular characterization as its research object.¹ By integrating biology, basic medicine, clinical medicine, computer science, and artificial intelligence, Vasomics establishes interpretable models of the associations among vascular structure, function, and dynamic changes in disease, thereby promoting the prevention, diagnosis, and treatment of vascular-related diseases.

The liver serves as the initial model organ for Vasomics research, with several key innovations developed in recent years. These include an AI-based Hepatic Vasomics Analysis System, jointly developed with SenseTime Healthcare, which automatically generates 64 geometric vascular parameters, performs three-dimensional liver reconstruction including the eight liver segments and intrahepatic vascular system, and provides quantitative analysis of fatty liver and cirrhosis risk.²

Another major advancement is the virtual portal pressure gradient (vPPG), a non-invasive technique based on three-dimensional model reconstruction and computational fluid dynamics, first reported in *Gut* (2015)³ and further developed in subsequent *Radiology* (2019).⁴ World-first discoveries have also emerged from this research program, including the finding that the neurotoxin phenethylamine, produced by the gut bacterium *Ruminococcus gnavus*, is significantly enriched in liver cirrhosis and serves as an important biochemical characterization factor in the context of vascular remodeling.⁵ Additionally, ROCK2 expression levels have been found to be significantly upregulated in liver vascular endothelial cells and perivascular hepatic stellate cells of patients with liver fibrosis, leading to dysfunction of the vascular microenvironment, and a highly selective inhibitor (TDI01) has been developed providing a new avenue for the treatment of liver fibrosis.⁶

Vasomics is structured around four methodological pillars: radiology-based Vasomics (rVasomics), ultrasound-based Vasomics (uVasomics), biomarker-based Vasomics (bVasomics), and pathology-based Vasomics (pVasomics). The methodological framework includes vascular status data collection integrating multimodal data, data preprocessing to standardize multi-source data, high-throughput feature extraction from each modality, Vasomics model construction using multimodal alignment techniques, and model validation with product translation through internal and external validation as well as biological validation including in vitro experiments and animal models. Beyond the liver, Vasomics is expanding to other organs, including the heart, brain, eye, kidney and the maternal-fetal unit. A bibliometric analysis retrieved 24,258 vascular-organ related studies, showing that the heart, brain, and liver are the organs most closely associated with vascular system research.

The Vasomics Consortium was established in 2025, bringing together experts from 21 academician teams to jointly advance the field. Future research frontiers in Vasomics include novel non-invasive measurement methods, foundation models for Vasomics, digital twin simulation systems, macro-micro correlation analysis, biological pathway analysis, multi-organ interaction analysis, disease biomarkers, vascular organoid models, and panvascular aging research.

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3. Qi, Xiaolong et al. "Virtual portal pressure gradient from anatomic CT angiography." Gut vol. 64,6 (2015): 1004-5. doi:10.1136/gutjnl-2014-308543

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Il Han Song (Dankook Univ.)
Hee Bok Chae (Chungbuk National Univ.)





Byeong Geun Song
Sungkyunkwan University

Self Introduction

Prof. Byeong Geun Song is an Associate Professor of the Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine.

Prof. Song graduated from Sungkyunkwan University School of Medicine with his medical degree in 2013 and completed his residency in Internal Medicine and fellowship in Gastroenterology at Samsung Medical Center. He received his Master's degree in Medicine from the same institution in 2018.

Since 2018, Prof. Song has served in various roles at Samsung Medical Center, including Clinical Instructor, Clinical Fellow, and Clinical Assistant Professor.

Prof. Song currently serves as a member of the Scientific Committee of the Korean Association for the Study of the Liver (KASL), the Scientific Committee of the Korean Liver Transplantation Society (KLTS), and the Scientific Committee of the Korean Society of Clinical Ultrasound (KSCU).

Research Interests

- Steatotic Liver Disease
- Hepatocellular Carcinoma (HCC) Risk Stratification and Biomarker Discovery
- Portal Hypertension and Non-Invasive Diagnosis of CSPH
- Population-Based Cohort Studies Using Health Screening and Claims Data

Representative Publications

1. Song BG, Goh MJ, Kang W, et al. Serum ferritin levels and liver-related events in individuals with steatotic liver disease: A longitudinal cohort study. *Aliment Pharmacol Ther.* 2024. <https://doi.org/10.1111/apt.18402>
2. Song BG, Kim A, Goh MJ, et al. Risk of hepatocellular carcinoma by steatotic liver disease and its newly proposed subclassification. *Liver Cancer.* 2024. <https://doi.org/10.1159/000538301>
3. Song BG, Choi SC, Goh MJ, et al. Metabolic dysfunction-associated fatty liver disease and the risk of hepatocellular carcinoma. *JHEP Rep.* 2023. <https://doi.org/10.1016/j.jhepr.2023.100810>
4. Song BG, Goh MJ, Kang W, et al. Validation of non-invasive diagnosis of CSPH in patients with compensated advanced chronic liver disease according to Baveno VII. *Liver Int.* 2023;43:1966–74. <https://doi.org/10.1111/liv.15632>
5. Song BG, Sinn DH, Kang W, et al. Changes in the prevalence of hepatitis B and metabolic abnormalities among young men in Korea. *Korean J Intern Med.* 2022;37(5):1082–7. <https://doi.org/10.3904/kjim.2021.452>

Evaluation and Management of Abnormal Liver Function Tests in Clinical Practice

Byeong Geun Song *Sungkyunkwan University*

Abnormal liver biochemical tests are one of the most common reasons for referral to gastroenterology and hepatology clinics, affecting approximately 8% of the general population in reported series. Although conventionally referred to as liver function tests (LFTs), only total bilirubin, prothrombin time, and albumin truly reflect hepatic synthetic and excretory function, whereas aminotransferases (AST, ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) indicate hepatocellular injury or cholestasis. Because each of these parameters can also be influenced by extrahepatic conditions such as hemolysis, vitamin K deficiency, malnutrition, muscle injury, bone disease, or thyroid disorders, their interpretation requires an appropriate clinical context.

A structured approach begins with a detailed history and physical examination. Key elements include risk factors for viral and metabolic liver disease, alcohol intake, prescription and over-the-counter medications, herbal and dietary supplements, recent infections, and family history. Physical findings are often normal but may reveal jaundice, muscle wasting, ascites, splenomegaly, palmar erythema, spider angiomas, or hepatomegaly; asterixis or altered mental status mandates immediate evaluation for acute liver failure and prompt referral to a transplant center. Initial laboratory re-testing with a complete liver panel, supplemented by liver, gallbladder, and pancreas ultrasonography, is essential to confirm abnormalities and characterize the pattern of injury. The R ratio ($[ALT/ULN] \div [ALP/ULN]$) helps classify injury as hepatocellular ($R > 5$), cholestatic ($R < 2$), or mixed ($R 2\text{--}5$), and aminotransferase elevations are further stratified by magnitude: borderline (<80 IU/L), mild (80–200), moderate (200–600), severe (>600), and massive ($>10,000$).

Hepatocellular injury is evaluated according to the degree of aminotransferase elevation. Borderline and mild elevations commonly reflect metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease, or chronic viral hepatitis, and initial work-up should include HBsAg/anti-HBs/anti-HBc, anti-HCV with reflex HCV RNA, and discontinuation of potential hepatotoxins; persistent elevation prompts testing for autoimmune hepatitis, ceruloplasmin, thyroid and muscle studies, and consideration of liver biopsy. Moderate elevations warrant assessment for acute liver failure and additional work-up including HAV IgM, anti-HBc IgM, and autoimmune markers. Severe elevations require evaluation for drug-induced liver injury (including acetaminophen with N-acetylcysteine when indicat-

ed), viral causes such as HSV, EBV, and CMV, and Doppler ultrasonography to exclude vascular disorders. Massive elevations (>10,000 IU/L) are almost always attributable to ischemic hepatitis, toxic or drug-induced injury, or rhabdomyolysis.

A cholestatic pattern is suggested by isolated or predominant elevation of ALP. Because ALP is also expressed in bone, placenta, intestine, and kidney, GGT should be measured to confirm hepatobiliary origin. Hepatic causes include extrahepatic biliary obstruction, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury, infiltrative diseases (sarcoidosis, tuberculosis, lymphoma, amyloidosis), sepsis, heart failure, total parenteral nutrition, and postoperative or ICU-related cholestasis. Non-hepatic causes include bone disease, hyperthyroidism, pregnancy, and chronic kidney disease. In adult patients with unexplained cholestasis and negative autoimmune markers, monogenic disorders such as ABCB4 (MDR3) deficiency and other variants of progressive familial intrahepatic cholestasis should be considered, as they may be misclassified as seronegative PBC or small-duct PSC.

For hyperbilirubinemia, fractionation into direct and indirect components is the first diagnostic step. Unconjugated hyperbilirubinemia is most often caused by Gilbert syndrome, hemolysis, ineffective erythropoiesis, large hematoma resorption, hyperthyroidism, or certain medications. Conjugated hyperbilirubinemia reflects hepatocellular or cholestatic disease and requires systematic assessment for biliary obstruction, drug-induced injury, and parenchymal liver disease, often in combination with imaging and contextual laboratory data.

Beyond the initial panel, phosphatidylethanol (PEth) can document recent alcohol use within 30 days when concealment is suspected, and ferritin with transferrin saturation may identify hereditary hemochromatosis, although elevated ferritin is more commonly explained by alcohol or MASLD (dysmetabolic iron overload syndrome). Noninvasive assessment of fibrosis and steatosis using vibration-controlled transient elastography or shear wave elastography has largely replaced liver biopsy for staging. Liver biopsy nevertheless retains an important role in selected settings, including persistently unexplained abnormalities, confirmation of MASH when clinically relevant, suspected overlap conditions (e.g., MASH with autoimmune hepatitis), and specific diagnoses such as alpha-1 antitrypsin deficiency, Wilson disease, and hemochromatosis. Extrahepatic mimics—rhabdomyolysis, congestive hepatopathy, ischemic hepatitis, and cholestasis of sepsis—should be recognized to avoid unnecessary evaluation.

Key take-aways include a thorough history and physical examination with careful review of supplements and over-the-counter medications, recognition of MASLD and MetALD, prompt imaging when biliary obstruction is suspected, and awareness of atypical viral hepatitis and drug-induced liver injury.

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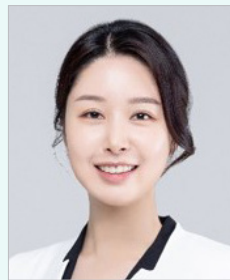
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Hyo Jung Park
University of Ulsan

Self Introduction

Prof. Hyo Jung Park graduated from University of Ulsan College of Medicine with her medical degree in 2013 and completed her internship and residency at Asan Medical Center, receiving her diploma in Radiology in 2018. She obtained a master's degree in 2022 and a doctoral degree in 2022. She is an Assistant Professor of the Department of Radiology, University of Ulsan College of Medicine.

Research Interests

Liver Imaging, Biliopancreatic Imaging, Cancer Imaging, Personalized Medicine

Representative Publications

1. Jeong B, Park HJ, Choi WM, Choi SH, Kim KW, Kim SY, Lee SS. Radiologic Response Assessment With RECIST 1.1 and mRECIST in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab. *Korean J Radiol.* 2026 May;27(5):428-439.
2. Park HJ, Shin K, You M-W, et al. Deep Learning-based Detection of Solid and Cystic Pancreatic Neoplasms at Contrast-enhanced CT. *Radiology* 2023 Jan 306(1):140–149.
3. Park HJ, Kim SY, Singal AG, Lee SJ, Won HJ, Byun JH, Choi SH, Yokoo T, Kim MJ, Lim YS. Abbreviated magnetic resonance imaging vs ultrasound for surveillance of hepatocellular carcinoma in high-risk patients. *Liver Int.* 2022 Aug;42(9):2080-2092.
4. Park HJ, Seo N, Kim SY. Current Landscape and Future Perspectives of Abbreviated MRI for Hepatocellular Carcinoma Surveillance. *Korean J Radiol.* 2022 Jun;23(6):598-614.
5. Park HJ, Kim KW, Won SE, et al. Definition, Incidence, and Challenges for Assessment of Hyperprogressive Disease during Cancer Treatment with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2021; 4(3) e211136.

Assessing Tumor Response in HCC: RECIST and mRECIST

Hyo Jung Park University of Ulsan

HCC treatments often induce tumor necrosis without significant anatomical size reduction, which fundamentally limits the utility of the traditional size-based RECIST 1.1. To address this, the modified RECIST (mRECIST) criteria, which exclusively measure contrast-enhancing viable tumor, were developed. Currently, mRECIST stands as the definitive gold standard for assessing response and predicting overall survival (OS) in locoregional therapies such as TACE and local ablation.

In the realm of systemic therapy, however, the predictive performance of these criteria shifts significantly depending on the drug's mechanism of action. While mRECIST is superior in capturing objective responses and predicting survival for anti-angiogenic targeted therapies (TKIs), the landscape has changed with immune checkpoint inhibitors (ICIs). In ICI-based combinations (e.g., Atezolizumab + Bevacizumab), immune-mediated cell death frequently leads to actual tumor shrinkage, allowing RECIST 1.1 to reclaim its strong prognostic value for OS. Consequently, major clinical guidelines, including AASLD, EASL, and KLCA-NCC, reflect this paradigm by recommending the parallel or selective use of both criteria in advanced HCC.

This lecture explores the differential performance of RECIST 1.1 and mRECIST across diverse treatment modalities and reviews current guideline recommendations. Furthermore, it addresses clinical unmet needs in the modern immunotherapy era, highlighting emerging alternative tools such as the attenuation-based Choi criteria, the biomarker-integrated alpha-RECIST, and 3D volumetrics to optimize personalized response evaluation in HCC.

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3. Gordic S, Corcuera-Solano I, Stueck A, et al. Evaluation of HCC response to locoregional therapy: Validation of MRI-based response criteria versus explant pathology. *J Hepatol.* 2017;67:1213-1221.
4. Gillmore R, Stuart S, Kirkwood A, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. *J Hepatol.* 2011;55:1309-1316.
5. Yu H, Bai Y, Xie X, et al. RECIST 1.1 versus mRECIST for assessment of tumour response to molecular targeted therapies

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**Ha Il Kim***Hanyang University*

Self Introduction

Professor Ha Il Kim is a Professor in the Department of Gastroenterology and Hepatology at Hanyang University College of Medicine and currently serves as a practicing hepatologist at Hanyang University Guri Hospital.

He obtained his M.D. from Hanyang University College of Medicine in 2013, followed by internship, residency, and fellowship training in gastroenterology at Asan Medical Center. In 2020, he was awarded a Ph.D. in Internal Medicine from the University of Ulsan College of Medicine.

His clinical and research interests include steatotic liver disease, hepatocellular carcinoma, and big data-driven analysis in hepatology.

Research Interests

Steatotic Liver Disease, Hepatocellular Carcinoma, Big Data-Driven Analysis

Representative Publications

1. Association of comorbidity duration with the occurrence and prognosis of steatotic liver disease, Digestive Diseases and Sciences, 2025.
2. Impact of metabolic risk factors on the hepatic and cardiac outcomes in patients with alcohol- and non-alcohol-related fatty liver disease, 2023, JHEP Reports.
3. Loco-regional therapies competing with radiofrequency ablation in potential indications for hepatocellular carcinoma: a network meta-analysis, 2023, Clin Mole Hepatol.
4. Postresection Period-Specific Hazard of Recurrence as a Framework for Surveillance Strategy in Patients with Hepatocellular Carcinoma: A Multicenter Outcome Study, Liver Cancer, 2022.
5. Incidence and management patterns of alcohol-related liver disease in Korea: A nationwide standard cohort study, Scientific Report, 2021.

Practical Approaches to Metabolic Dysfunction-Associated Steatohepatitis (MASH) Therapy and Complication Management

Ha Il Kim*Hanyang University*

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive and heterogeneous liver disease that has emerged as a leading cause of cirrhosis, hepatocellular carcinoma, and liver-related mortality worldwide. Despite recent therapeutic advances, including the approval of liver-targeted agents and the increasing use of incretin-based therapies, a substantial proportion of patients fail to achieve meaningful histological or clinical improvement. This phenomenon, commonly referred to as treatment non-response or resistance, represents a major challenge in the management of MASH.

One of the key determinants of treatment response is disease stage. Patients with advanced fibrosis or cirrhosis consistently demonstrate lower response rates across various therapeutic modalities, likely due to the limited reversibility of established fibrotic changes. In addition, metabolic dysfunction plays a central role in treatment resistance. Persistent insulin resistance, poorly controlled diabetes, and inadequate weight reduction are strongly associated with poor histological outcomes. Clinical studies have shown that metabolic improvement, particularly weight loss exceeding 7–10%, is closely linked to MASH resolution and fibrosis regression. Conversely, failure to achieve meaningful metabolic improvement often leads to histological non-response, even in the presence of pharmacologic therapy. In this context, lifestyle intervention remains a cornerstone of MASH management; however, it is often insufficient when used alone, and adherence remains a major barrier.

Among emerging strategies to overcome treatment resistance, combination therapy has gained increasing attention. Given the multifactorial pathogenesis of MASH, simultaneous targeting of multiple pathways—including steatosis, inflammation, and fibrosis—represents a rational approach. Early clinical data suggest that combining metabolic agents, such as GLP-1 receptor agonists, with liver-directed or anti-fibrotic therapies may provide additive or synergistic benefits. However, as combination therapy becomes more widely used, the risk of adverse effects may increase. Complications associated with MASH treatment vary according to drug mechanisms and individual patient characteristics. Liver-directed agents may cause gastrointestinal symptoms, endocrine alterations, or hepatobiliary complications, while incretin-based therapies are frequently associated with gastrointestinal intolerance and may increase the risk of gallstone formation due to rapid weight loss. In some cases, these adverse effects may overlap with disease progression, complicating clinical interpretation. Therefore, careful monitoring is

essential during treatment. Notably, as therapeutic strategies evolve toward combination regimens, the risk of cumulative or overlapping adverse effects may increase, necessitating more comprehensive safety assessment and individualized risk management.

In summary, treatment resistance in MASH reflects both the biological heterogeneity of the disease and the limitations of current therapeutic approaches. Addressing this challenge requires a paradigm shift toward integrated and individualized management strategies. Combination therapy, precision medicine, lifestyle optimization, and early intervention represent the most promising approaches to improving treatment response and long-term outcomes. At the same time, careful monitoring and proactive management of treatment-related complications are essential, particularly in the era of combination therapy.

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Taekeun Park
Seoul National University

Self Introduction

Education

- 2022- Seoul National University Graduate School, Seoul, South Korea (Ph.D. Candidate)
- 2012-2016 Seoul National University Graduate School, Seoul, South Korea (M.S.)
- 2012-2016 Seoul National University, College of Medicine, Seoul, Korea (M.D.)
- 2008–2012 Seoul National University, College of Natural Sciences (Biological Sciences), Seoul, Korea (B.S.)

Professional Experience

- 2024- Clinical Assistant Professor, Seoul National University Hospital, Seoul, Korea
- 2023-2024 Clinical Fellow, Seoul National University Hospital, Seoul, Korea
- 2020-2023 Residency, Seoul National University Hospital, Seoul, Korea
- 2017-2020 Medical Officer, Republic of Korea Army
- 2016-2017 Internship, Seoul National University Hospital, Seoul, Korea

Qualifications

- 2016 Korean Medical License. Medical License / ID Number: 122731
- 2023 Korean Board Certification of Internal Medicine / ID Number: 20742

Societies/Professional Affiliations

- Korean Society of Medical Oncology
- Korean Cancer Study Group
- Korean Society of Hematology
- Korean Society of Hematopoietic Stem Cell Transplantation
- Korean Society of Internal Medicine

How to Report Complications: CTCAE and SUSAR

Taekeun Park Seoul National University

Background

Clinical trials in hepatology are expanding rapidly across therapeutic areas including metabolic dysfunction-associated steatohepatitis (MASH), hepatocellular carcinoma (HCC), and chronic viral hepatitis. As hepatologists increasingly assume roles as principal or co-investigators in interventional studies, accurate and timely adverse event reporting has become an essential clinical competency. However, unlike medical oncologists who engage with clinical trial infrastructure as a routine part of practice, many hepatologists have limited formal exposure to the standardized reporting frameworks mandated by international and domestic regulatory bodies.

This gap creates practical challenges in day-to-day trial conduct, particularly given the inherent complexity of grading adverse events in patients who already carry a burden of chronic liver disease. Cirrhotic patients enrolled in clinical trials frequently present with baseline laboratory abnormalities, ongoing complications such as ascites or encephalopathy, and altered drug metabolism — all of which can confound the attribution and severity grading of trial-related adverse events. Without a firm grounding in the applicable regulatory tools, hepatologists risk either under-reporting clinically significant events or generating inconsistent documentation that undermines trial integrity.

Objectives

This lecture aims to provide hepatologists with a practical, working understanding of two core regulatory tools in clinical trial safety reporting: the Common Terminology Criteria for Adverse Events (CTCAE) and the Suspected Unexpected Serious Adverse Reaction (SUSAR). The session is designed for clinicians who may be new to trial conduct, with emphasis on immediate applicability to real-world practice rather than regulatory theory. By the end of the lecture, participants should be able to accurately apply CTCAE grading to liver-related adverse events, correctly identify when an event meets SUSAR criteria, understand the relevant reporting timelines and role-specific responsibilities, and communicate effectively with sponsors and regulatory authorities in the context of hepatic safety events.

Content

The first part of the lecture covers the principles of CTCAE v5.0, with particular focus on hepatology-relevant adverse event terms including aminotransferase elevation, hepatic failure, ascites, and hepatic encephalopathy. The grading structure — from Grade 1 (mild, no intervention required) through Grade 5 (death) — is reviewed with emphasis on the clinical decision points that define each threshold. Special attention is given to a challenge that is frequently underappreciated in the hepatology setting: the application of CTCAE grading in patients with pre-existing liver dysfunction. Since standard CTCAE criteria are anchored to the upper limit of normal (ULN), grading can be misleading when baseline laboratory values or clinical status are already abnormal at enrollment. Many trial protocols include provisions for baseline-adjusted grading in this population, and practical guidance is provided on how to identify and apply these provisions consistently throughout the course of a trial.

The second part addresses the classification hierarchy of adverse events — from Adverse Event (AE) to Serious Adverse Event (SAE) to SUSAR — and the regulatory obligations associated with each level. The six seriousness criteria that define an SAE are reviewed, followed by a detailed discussion of the three additional conditions required for SUSAR designation: the event must be serious, unexpected relative to the safety profile described in the current Investigator’s Brochure (IB), and at least possibly causally related to the investigational product. A key practical point is that “unexpected” is defined with reference to the IB, not to published literature or the investigator’s personal clinical experience — a distinction that frequently causes confusion in practice. Reporting timelines are outlined, including the 7-day expedited reporting requirement for fatal or life-threatening SUSARs and the 15-day requirement for all others. The respective responsibilities of the investigator and the sponsor are clearly delineated, as misunderstanding this division of roles is a common source of reporting delays. Domestic requirements under the Korean Ministry of Food and Drug Safety (MFDS) are discussed in the context of ICH E2A guidelines.

The lecture concludes with two case-based scenarios drawn from a hepatology trial context. The first case involves CTCAE grading in a patient with Child-Pugh B cirrhosis and HCC receiving an immune checkpoint inhibitor, in whom aminotransferase levels rise from an already-elevated baseline and new ascites develops during treatment — raising questions about grading, SAE determination, and causality assessment. The second case involves SUSAR identification in a patient with MASH-related cirrhosis enrolled in an antifibrotic trial who develops acute hepatic decompensation not described in the current IB, prompting a step-by-step review of the reporting process. Both cases are designed to encourage audience interaction and to illustrate how the regulatory framework applies in situations that hepatologists are likely to encounter in actual clinical trial practice.

Conclusion

Accurate adverse event reporting is a fundamental responsibility of any clinical trial investigator, and one that carries direct implications for patient safety, trial validity, and regulatory compliance. For hepa-

tologists, the intersection of complex baseline liver pathology with trial-related toxicity demands a higher level of nuance in applying standard reporting frameworks. Errors in CTCAE grading — whether from misapplication of grading thresholds or failure to account for pre-existing disease — can lead to under-recognition of clinically meaningful events. Delays or omissions in SUSAR reporting, meanwhile, can compromise both patient safety and the broader scientific integrity of the trial.

This lecture provides a concise, practice-oriented foundation in CTCAE grading and SUSAR reporting, equipping hepatologists with the knowledge to fulfill their regulatory obligations with confidence. As the role of hepatologists in clinical research continues to grow, familiarity with these tools is no longer optional — it is an integral part of responsible and effective trial conduct.

Keywords

CTCAE; SUSAR; Adverse event reporting; Clinical trials; Hepatology; Liver disease; Good clinical Practice; MFDS; ICH E2A

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KLCA SYMPOSIUM 1

From Detection to Prevention: Evolving Strategies in Hepatocellular Carcinoma (HCC) Diagnosis and Chemoprevention

Chairs

Yong-Han Paik (Sungkyunkwan Univ.)

Seok Hyun Kim (Chungnam National Univ.)





Hyo Jung Park
University of Ulsan

Self Introduction

Prof. Hyo Jung Park graduated from University of Ulsan College of Medicine with her medical degree in 2013 and completed her internship and residency at Asan Medical Center, receiving her diploma in Radiology in 2018. She obtained a master's degree in 2022 and a doctoral degree in 2022. She is an Assistant Professor of the Department of Radiology, University of Ulsan College of Medicine.

Research Interests

Liver Imaging, Biliopancreatic Imaging, Cancer Imaging, Personalized Medicine

Representative Publications

- 1. Jeong B, Park HJ, Choi WM, Choi SH, Kim KW, Kim SY, Lee SS. Radiologic Response Assessment With RECIST 1.1 and mRECIST in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab. *Korean J Radiol.* 2026 May;27(5):428-439.
- 2. Park HJ, Shin K, You M-W, et al. Deep Learning–based Detection of Solid and Cystic Pancreatic Neoplasms at Contrast-enhanced CT. *Radiology* 2023 Jan 306(1):140–149.
- 3. Park HJ, Kim SY, Singal AG, Lee SJ, Won HJ, Byun JH, Choi SH, Yokoo T, Kim MJ, Lim YS. Abbreviated magnetic resonance imaging vs ultrasound for surveillance of hepatocellular carcinoma in high-risk patients. *Liver Int.* 2022 Aug;42(9):2080-2092.
- 4. Park HJ, Seo N, Kim SY. Current Landscape and Future Perspectives of Abbreviated MRI for Hepatocellular Carcinoma Surveillance. *Korean J Radiol.* 2022 Jun;23(6):598-614.
- 5. Park HJ, Kim KW, Won SE, et al. Definition, Incidence, and Challenges for Assessment of Hyperprogressive Disease during Cancer Treatment with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2021; 4(3) e211136.

Controversies in Imaging-Based Diagnosis of HCC: Revisiting Major Features and Regional Differences

Hyo Jung Park *University of Ulsan*

The imaging-based non-invasive diagnosis of HCC is a cornerstone of HCC management, yet significant international variations persist regarding the criteria for a “definite HCC” diagnosis. This lecture aims to dissect the heterogeneous landscape of major imaging features as defined by leading global guidelines, including the KLCA-NCC, APASL, LI-RADS, AASLD, and EASL. By comparing these frameworks, we will identify how the definition of “major features”, specifically arterial phase hyperenhancement (APHE) and washout, diverges across different geographic and clinical contexts.

A primary focus will be placed on the technical and interpretive controversies surrounding gadoxetic acid (EOB-MRI). We will examine the ongoing debate over the temporal boundaries of “washout”, whether it should be restricted to the portal venous phase or extended to the transitional phase or hepatobiliary phase (HBP), and discuss the diagnostic weight assigned to HBP hypointensity. While some guidelines incorporate HBP findings as a major feature to enhance sensitivity for early-stage HCC, others maintain a more conservative stance to protect specificity.

This lecture will further evaluate the clinical implications of these regional differences. Eastern guidelines often prioritize high sensitivity for early detection and local intervention, whereas Western criteria typically emphasize high specificity to ensure transplant eligibility and avoid false positives. We will discuss which criteria are most appropriate for specific clinical scenarios, considering the local prevalence of HCC and available therapeutic options. Finally, to address current academic and clinical confusion, key recommendations include the adoption of a shared lexicon to unify terminology, phase-specific reporting to reduce inter-observer variability, and the implementation of purpose-specific thresholds.

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Hyunjae Shin
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Self Introduction

2012-2016	Master's Degree of Medicine, Seoul National University
2023-2025	Doctor's Degree of Medicine, Seoul National University (Advisor : Prof. Jung-Hwan Yoon)
2020-2023	Residency in Internal Medicine, Seoul National University Hospital
2023-2024	Research and Clinical Fellow in Gastroenterology, Seoul National University Hospital
2024-2024	Clinical Assistant Professor in Center for Liver and Pancreatobiliary Cancer, Research Institute and Hospital, National Cancer Center
2024-Present	Clinical Assistant Professor in Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital

Research Interests

Hepatocellular Carcinoma, MASLD, AI Use in Hepatology

Representative Publications

1. AI model using CT-based imaging biomarkers to predict hepatocellular carcinoma in patients with chronic hepatitis B. J Hepatol. 2025 Jun. (Impact Factor: 33.0)
2. Aspirin and HCC risk in MASLD: Nationwide cohort study with genetic risk analysis. Clin Mol Hepatol. 2026 Jan. (Impact Factor: 16.9)
3. Inhibition of sodium-glucose cotransporter-2 and liver-related complications in individuals with diabetes: A mendelian randomization and population-based cohort study. Hepatology. 2024 Sep. (Impact Factor: 13.5)

AI-Driven Prediction and Risk Stratification for HCC Surveillance

Hyunjae Shin Seoul National University

Introduction

Hepatocellular carcinoma (HCC) remains one of the few solid malignancies for which surveillance is both routinely recommended and frequently inadequate. The classical definition of surveillance — periodic application of a sensitive test in a defined high-risk population — assumes that risk is binary and that the test interval is fixed. In practice, HCC risk is continuous, heterogeneous across etiologies, and changes over time within the same patient. The next generation of surveillance must therefore be personalized along three axes simultaneously: who is monitored, with which modality, and at what interval. Artificial intelligence (AI) and machine learning (ML) have moved this aspiration from rhetoric to a feasible operational framework.

Traditional Risk Scores and Their Structural Limits

The PAGE-B score, derived in 1,325 Caucasian patients with chronic hepatitis B from eight European centers and externally validated in 490, established the value of structured risk stratification on antiviral therapy and remains a useful benchmark; its modified counterpart, mPAGE-B, extended this framework to Asian cohorts and improved discrimination in non-cirrhotic patients. Both, however, are built on a linear regression backbone that forces additive, monotonic effects and cannot capture biologically plausible non-linear thresholds — most notably the U-shaped relationship between serum HBV DNA and HCC incidence quantified in long-term registry cohorts. This structural ceiling, rather than insufficient sample size, is the chief reason their AUROC has plateaued near 0.78 across multiple validation studies.

The First Generation of ML-Based Scores

The first wave of ML-based scores — PAGED-B, PLAN-B, PLAN-B-CURE, and SMART — was designed explicitly to relax this constraint. PLAN-B, trained with random survival forests on 6,051 Korean anti-viral-treated patients and externally validated in 5,817 additional Asian and 1,640 Caucasian patients, achieved a Harrell's C-index above 0.79 and outperformed PAGE-B and mPAGE-B in head-to-head validation. PLAN-B-CURE, focused on patients who have achieved functional HBV cure, was derived in

2,046 Korean patients and validated in 2,741 Hong Kong patients, providing a tool calibrated for the increasingly large post-cure population in which baseline risk distributions differ markedly from those of patients on continuous antiviral therapy. Across these scores, gradient boosting and random survival forests reproducibly delivered C-indices in the 0.78–0.82 range and — crucially — separated minimal-risk subgroups whose 10-year cumulative HCC incidence approached zero, a stratification depth unobtainable with the older scores and one with direct implications for de-escalating or even safely discontinuing semi-annual surveillance.

Recent Advances (2024–2026)

Between 2024 and 2026, the field has expanded along four parallel directions.

First, imaging-AI scores have matured. The ALARM model (Guo et al., eClinicalMedicine 2024), trained on 1,858 cirrhotic adults from eleven multinational centers (88% HBV-related), combined six radiomic features, seventeen deep-learning features from a fine-tuned 3D-ResNet50 applied to triple-phase CT, and the clinical aMAP score; it achieved AUROCs of 0.929, 0.902, and 0.918 in discovery, internal, and external validation, respectively, with a 58-fold gradient in 3-year HCC incidence (24.3% vs. 0.42%) between high- and low-risk strata and captured 94% of all HCC events. aMAP-CT (Hepatology 2025) reported an AUC of 0.85 by fusing CT radiomics with the clinical aMAP score, and a separate multiphasic CT/MRI deep-learning model (Hui RW et al., Hepatology 2025; n = 1,231) achieved AUROCs of 0.77–0.86 across external sites.

Second, etiology has expanded beyond viral hepatitis. A multinational MASLD-HCC model (Clin Gastroenterol Hepatol 2025; n = 77,677) reported C-indices of 0.83–0.93 across geographically diverse validation sites; a 16-center MASLD risk-based score (Lai JC et al., Gut 2025; n = 12,950) refined surveillance entry criteria for the fastest-growing at-risk population; and a Chinese XGBoost HBV-HCC model (Lin Y et al., Cancer Med 2026; n = 3,568) reached an external AUC of 0.94.

Third, liquid biopsy and dynamic trajectories are replacing single-timepoint snapshots with continuously updated risk. The longitudinal aMAP-2 and aMAP-2 Plus scores (J Hepatol 2024) incorporated repeated measurements and cfDNA fragmentomics; the MAPLE cfDNA methylation panel (2025; n ≈ 1,500) demonstrated competitive discrimination at substantially lower invasiveness; and emerging biomarker panels such as CELiver (2026; n = 180) point toward feasible blood-only surveillance pathways.

Fourth, foundation and population-scale models are addressing the transferability problem that has long limited the adoption of single-center scores. LIRIC (2024), trained on the electronic health records of approximately 500,000 patients, achieved an AUROC of 0.84 with minimal manual feature engineering; the Texas Risk score (2026; n = 1,560) and the Nahon et al. ML benchmark (J Hepatol 2026; n = 4,867) further demonstrate that federated, population-level approaches now match or exceed traditional sin-

gle-center models in discrimination and calibration.

Our Contribution: PLAN-B-DF and a CT Imaging Biomarker Pipeline

Within this landscape, we developed PLAN-B-DF, which integrated transient elastography into a deep-learning risk score for entecavir- and tenofovir-treated patients with chronic hepatitis B and improved discrimination over the original PLAN-B without requiring additional invasive testing. More recently, we built a CT-based quantitative imaging biomarker pipeline (J Hepatol 2025) using fully automated DeepFore segmentation of the liver, spleen, skeletal muscle, and visceral and subcutaneous adipose compartments. A gradient boosting machine of 50 sequential trees (10-fold cross-validation tuning: learning rate 0.07, maximum depth 5, sample and variable fractions 0.7) combining CT-derived volumetric and density features with routine clinical variables — including age, platelet count, HBeAg status, HBV DNA, antiviral agent, diabetes mellitus, and hypertension — achieved a Harrell’s C-index of 0.89 (95% CI 0.87–0.90) in external validation, exceeding contemporary regression-based and imaging-only models. The model stratified patients into four risk groups with 10-year cumulative HCC incidences of 0.0%, 0.4%, 16.0%, and 46.2% — a discrimination gradient comparable to ALARM but achieved using a single CT examination that is often already available in the patient’s chart. The pipeline is now being adapted for opportunistic surveillance, in which abdominal CT performed for unrelated indications is repurposed for HCC risk assessment without additional cost or radiation exposure.

Future Directions and Remaining Challenges

Several caveats deserve emphasis. AUROC ceilings in many Western validation cohorts still hover near 0.78; prospective deployment data are scarce; and most published models are static, whereas real patients are not. The most promising directions for the next three years are (i) multimodal fusion combining imaging, omics, and cfDNA into a single risk engine; (ii) federated learning that allows international cohorts to contribute without sharing raw data; (iii) joint prediction of HCC together with hepatic decompensation, liver-related death, and overall survival, so that a single risk output drives multiple downstream decisions; and (iv) genuinely dynamic models that re-score patients at every clinical encounter rather than at fixed enrollment. Equally critical is the unglamorous infrastructure layer: explainability sufficient for regulatory approval, seamless EMR integration, prospective cost-effectiveness studies, and equitable data access across regions and etiologies. In our experience, the bottleneck for the field is no longer algorithmic capacity but data accessibility — the willingness of institutions and consortia to share standardized, longitudinally annotated cohorts.

Conclusion

In this lecture, I will summarize where AI-driven HCC risk prediction currently stands, outline where the

field is heading, and identify the gaps that must close before personalized surveillance — continuous, etiology-aware, and dynamic — can become the new standard of care.

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Hye Won Lee
Yonsei University

Self Introduction

Dr. Hye Won Lee is an Associate Professor at Yonsei University College of Medicine and Severance Hospital. She graduated from Ewha Womans University College of Medicine and received her Ph.D. from Yonsei University College of Medicine. She completed her residency and fellowship training at Severance Hospital and later spent two years as a visiting scholar at The Chinese University of Hong Kong.

Her academic work has focused on chronic liver diseases, particularly MASH and HCC. Her research interests include disease progression, risk stratification, biomarker development, and integrated care strategies for patients with chronic liver disease. Dr. Lee has received multiple awards and research grants from academic institutions and professional societies in recognition of her contributions to hepatology research.

Research Interests

- Metabolic Dysfunction-Associated Steatohepatitis (MASH)
- Hepatocellular Carcinoma (HCC)

Representative Publications

1. Zhang Y, Lee HW, Lin H, Tsochatzis E, Petta S, Bugianesi E, Yoneda M, Zheng MH, Hagström H, Boursier J, Calleja JL, Goh GB, Chan WK, Gallego-Durán R, Sanyal AJ, de Lédinghen V, Newsome PN, Fan JG, Lai M, Fournier-Poizat C, Wong GL, Pennisi G, Armandi A, Nakajima A, Liu WY, Shang Y, de Saint-Loup M, Llop E, Teh KKJ, Lara-Romero C, Asgharpour A, Mahgoub S, Chan MS, Canivet CM, Romero-Gomez M, Kim SU, Wong VW, Castéra L, Yip TC. Head-to-head comparison between vibration-controlled transient elastography and histology in predicting liver-related events due to metabolic dysfunction-associated steatotic liver disease. *Hepatology*. 2025 Dec 24.
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Biomarkers for HCC Diagnosis and Surveillance:
Beyond AFP

Hye Won Lee Yonsei University

Surveillance for hepatocellular carcinoma (HCC) is intended to find tumors early enough for curative treatment. Alpha-fetoprotein (AFP) has long been the most widely used serum biomarker, but its limitations are well recognized, including modest sensitivity for early-stage HCC and false-positive elevations related to hepatic inflammation or regeneration. The question is not whether AFP should simply be discarded, but how additional biomarkers can be used to improve surveillance and diagnostic decision-making.

Biomarkers need to be interpreted within the broader context of HCC surveillance, where imaging remains central and clinical risk varies by liver disease etiology, tumor biology, and patient background. AFP-L3 and des-gamma-carboxy prothrombin, also known as DCP or PIVKA-II, provide information that differs from total AFP and are generally more useful when interpreted together rather than in isolation. Panel-based models such as GALAD and GAAD reflect this shift from single-marker interpretation toward risk estimation using both clinical and biological variables. Their growing evidence base is encouraging, although their role in routine surveillance still depends on assay availability, cost, target population, and downstream imaging strategy.

Liquid biopsy approaches, including circulating tumor DNA, DNA methylation markers, microRNAs, extracellular vesicles, and multi-omics assays, may further expand the biomarker landscape for HCC detection. Yet good diagnostic performance in studies does not automatically mean that a test is ready for routine surveillance. A useful surveillance biomarker must not only distinguish HCC from chronic liver disease, but also help detect tumors earlier, avoid unnecessary imaging, and fit into a workable clinical pathway.

The future use of HCC biomarkers will likely be risk-adapted, longitudinal, and closely linked to imaging. Biomarker results should be read in relation to baseline HCC risk, liver disease etiology, ultrasound visualization quality, and changes over time. Rather than replacing imaging or clinical judgment, biomarkers beyond AFP should help identify patients who need diagnostic imaging, closer surveillance, or alternative surveillance strategies. The goal is not to find a perfect single biomarker, but to make HCC surveillance more accurate, timely, and clinically useful.

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**Jeong Eun Song***Daegu Catholic University*

Self Introduction

Prof. Jeong Eun Song graduated from Daegu Catholic University School of Medicine with her medical degree in 2009 and completed his internship at Seoul Asan Medical Center and residency at the Department of Internal Medicine at Daegu Catholic University Medical Center, receiving her diploma in Internal Medicine in 2015.

Prof. Jeong Eun Song is a Professor of the Department of Internal Medicine, Daegu Catholic University School of Medicine.

Since 2019, Professor Song has been active as a committee member in various organizations such as the Korean Association for the Study of the Liver, the Korean Liver Cancer Association, and the Korean Society of Clinical Ultrasound.

Research Interests

Viral Hepatitis, Liver Cirrhosis, Autoimmune Liver Disease, Hepatocellular Carcinoma

Representative Publications

1. Jeong J, Lee CH, Kim BS, Jeong Eun Song. In-Hospital Hepatitis C Alarm System: A Strategy to Enhance Linkage to Care for Hepatitis C Virus Infection. *Gut Liver*. 2025 Sep 17. doi: 10.5009/gnl250170. Online ahead of print.
2. Yu Rim Lee, Jeong Eun Song, Hyun Young Woo, et al. Liver Stiffness Measurements After Oral Antivirals Effectively Predict the Risk of HCC in Patients With Chronic Hepatitis C. *J Gastroenterol Hepatol*. 2025 Oct;40(10):2568-2579.
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4. Min Kyu Kang, Jeong Eun Song, Rohit Loomba, Soo Young Park, Won Young Tak, Young Oh Kweon, Yu Rim Lee, Jung Gil Park. Comparative associations of MASLD and MAFLD with the presence and severity of coronary artery calcification. *Sci Rep*. 2024 Oct 2;14(1):22917
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Chemoprevention in MASLD: Can We Reduce the Risk of HCC?

Jeong Eun Song*Daegu Catholic University*

Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality worldwide. As viral hepatitis is increasingly controlled and metabolic disease becomes more prevalent, metabolic dysfunction-associated steatotic liver disease (MASLD) is emerging as an increasingly important contributor to HCC, including in Korea.^{1,2} MASLD-related hepatocarcinogenesis is driven by insulin resistance, lipotoxicity, chronic inflammation, and progressive fibrosis, providing multiple potential targets for risk reduction.³

Several cardiometabolic drugs have shown signals of HCC risk reduction. Metformin and sodium-glucose cotransporter-2 inhibitors have been associated with lower HCC incidence in patients with type 2 diabetes, although evidence remains largely observational studies.⁴⁻⁶ Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are of particular interest because of their effects on weight loss, insulin resistance, and liver histology. Population-based data suggest a reduced risk of HCC among patients treated with GLP-1 RA.⁷ In the phase 3 ESSENCE trial, semaglutide 2.4 mg significantly improved MASH resolution and fibrosis endpoints in patients with noncirrhotic F2–F3 MASH, leading to accelerated FDA approval for this indication and subsequent practice guidance updates.^{8,9} However, whether these histologic benefits translate into reduced HCC incidence requires long-term outcome data. Aspirin and statins represent another major area of interest. Low-dose aspirin has been associated with reduced hepatic fat in a randomized trial and with lower HCC risk in a large Korean MASLD cohort supported by genetic analysis.^{10,11} Statins have the most consistent observational evidence, with meta-analyses and nationwide cohort data suggesting dose-dependent reductions in HCC incidence and liver-related mortality.^{12,13} Ongoing biomarker-driven trials, such as TORCH, are testing whether atorvastatin can modulate validated molecular signatures of HCC risk, but prospective evidence demonstrating a reduction in incident HCC is still lacking.

A broader paradigm is also emerging: disease modification of MASH as a route to HCC prevention. Resmetirom, the first FDA-approved MASH-directed therapy, and emerging agents such as FGF21 analogues may reduce long-term carcinogenic risk by improving steatohepatitis and fibrosis.^{14,15} Nevertheless, no pharmacologic agent has yet been validated in an adequately powered HCC-outcome trial in MASLD.

In summary, pharmacologic chemoprevention of MASLD-related HCC is promising but not yet ready for firm recommendation as a stand-alone strategy. For now, HCC risk reduction in MASLD should be framed as a secondary benefit of evidence-based cardiometabolic and MASH-targeted therapy, while comprehensive metabolic risk-factor control remains the foundation of prevention.

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2026 KLCA-NCC PRACTICE GUIDELINES

Hepatocellular Carcinoma

Chair
June Sung Lee (Inje Univ.)





Bo Hyun Kim
National Cancer Center

Self Introduction

Prof. Bo Hyun Kim is a Senior Scientist and Head of the Division of Gastroenterology at the Center for Liver and Pancreatobiliary Cancer, National Cancer Center, and is currently holding a position of Adjunct Professor at the Department of Public Health & AI, National Cancer Center Graduate School of Cancer Science and Policy.

Prof. Kim graduated from Hanyang University College of Medicine with her medical degree in 2002 and completed her internship at Asan Medical Center and her residency in Internal Medicine at Seoul National University Hospital. She then continued as a Clinical and Research Fellow at the Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, and received her Master's and Doctoral degrees in Medicine from Seoul National University in 2009 and 2011, respectively. She has been working as a hepatology specialist at the National Cancer Center since 2012.

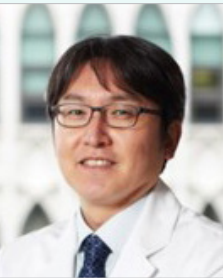
Prof. Kim has been actively involved in the Korean Association for the Study of the Liver (KASL), serving as Treasurer (2024–2026) and currently as Director of the Committee for Practice Guidelines (2026–Present), and has previously served on its Scientific, Publication, and Clinical Practice Guideline Committees. She has also been engaged in the activities of the Korean Liver Cancer Association (KLCA), serving as Director of the Committee for Primary Liver Cancer Registry (2022–2025), Treasurer (2025–Present), and Vice Chair of the HCC Guideline Committee (2025–Present).

Research Interests

Hepatocellular Carcinoma, Systemic Therapy, Combined-Modality Treatment, HCC Epidemiology and Nationwide Registry, Clinical Practice Guideline Development

Representative Publications

1. An J, Chang Y, Choi GH, Sohn W, Song JE, Shin H, Yoon JH, Yoon JS, Jang HY, Cho EJ, Han JW, Hong SK, Cho J-Y, Jung K-W, Park EH, Kim E, Kim BH. Hepatocellular carcinoma in Korea: an analysis of the 2016-2018 Korean Nationwide Cancer Registry. J Liver Cancer 2025;25(1):109-122.
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5. Kim BH, Lee D, Jung KW, Won YJ, Cho H. Cause of death and cause-specific mortality for primary liver cancer in South Korea: a nationwide population-based study in hepatitis B virus-endemic area. Clin Mol Hepatol 2022;28(2):242-253.



Do Young Kim
Yonsei University

Self Introduction

Do Young Kim is now a professor of Internal Medicine at Yonsei University College of Medicine, Seoul, Korea, and a hepatologist in the Severance Hospital where he has been a faculty member since 2007. He graduated Yonsei University at 1996, and completed training course in Severance Hospital from 1996 to 2001. He studied proteomics and microRNA in hepatocellular carcinoma (HCC) at Fred Hutchinson Cancer Research Center as a research associate between 2011 and 2012.

Research Interests

HCC, Hepatitis C

Representative Publications

1. Rhee H, Kim M-J, Kim DY, et al. [Co-corresponding author] Noncontrast magnetic resonance imaging vs ultrasonography for hepatocellular carcinoma surveillance: A randomized, single-center trial. Gastroenterology 2025;168:1170-1177.
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2026 KLCA-NCC Practice Guidelines: Hepatocellular Carcinoma

Bo Hyun Kim

Do Young Kim

National Cancer Center

Yonsei University

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KLCA-ILCA JOINT SYMPOSIUM

Who Is the Best Partner for Anti-PD-1/
PD-L1 in Advanced HCC: VEGF Inhibition
vs. CTLA-4 Blockade

Chairs
June Sung Lee (KLCA)
Stephen Lam Chan (ILCA)





Eui-Cheol Shin
KAIST

Self Introduction

Dr. Eui-Cheol Shin is a Professor at Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea. He received M.D. (1996) and Ph.D. (2001) from Yonsei University College of Medicine, Seoul, Republic of Korea, and was trained as a postdoctoral fellow at NIDDK, National Institutes of Health, Bethesda, Maryland, USA (2002 - 2007). Then he joined Graduate School of Medical Science and Engineering, KAIST in 2007, where he is currently a Professor. During the COVID-19 pandemic, he served as the director of the Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science (IBS), Daejeon, Republic of Korea (2021 - 2024). He was elected the Fellow of the Korea Academy of Science and Technology (2019) and the Fellow of the National Academy of Medicine of Korea (2024).

His lab investigates T cell responses in human viral disease and cancer with a focus on CD8+ T cells. In particular, his lab studies cytokine-mediated, TCR-independent activation of CD8+ T cells that contribute to host cell injury. A series of his studies has revived the research of bystander T cell activation in microbial infections as a cause of immunopathologic host injury (Nat Immunol 2022, 23:13).

Research Interests

Viral Immunology, Viral Hepatitis, Tumor Immunology, Immune Aging, and Human Immunology

Representative Publications

1. Lee et al. TCR signaling via NFATc1 constrains IL-15-induced NK-like activation of human memory CD8+ T cells. Immunity 58:2957-2971, 2025.
2. Kim et al. Epigenetic scars in regulatory T cells are retained after successful treatment of chronic hepatitis C with direct-acting antivirals. J Hepatol 81:806-818, 2024.
3. Koh et al. Identification of a distinct NK-like hepatic T-cell population activated by NKG2C in a TCR-independent manner. J Hepatol 77:1059-1070, 2022.
4. Jung et al. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. Nat Microbiol 7:909-917, 2022.
5. Lee et al. Significance of bystander T cell activation in microbial infection. Nat Immunol 23:13-22, 2022.

Evolving Landscape of Immunotherapy in HCC: Finding the Optimal Partner

Eui-Cheol Shin KAIST

Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis are now widely used in the treatment of multiple cancers, including hepatocellular carcinoma (HCC). However, current therapeutic strategies for HCC primarily rely on combination regimens. In particular, ICIs are used together with VEGF inhibitors or CTLA-4 inhibitors. The tumor microenvironment of HCC is characterized by profound immunosuppression, chronic inflammation, and aberrant angiogenesis. VEGF signaling contributes to immune evasion by promoting abnormal tumor vasculature and suppressing antitumor immune responses, while CTLA-4 blockade enhances T-cell priming and activation. Consequently, combining PD-1/PD-L1 inhibitors with VEGF or CTLA-4 blockade can enhance antitumor immunity through complementary mechanisms. In this lecture, we will examine the immunological mechanisms underlying the combination of ICIs with VEGF blockers or CTLA-4 inhibitors in the treatment of HCC. In addition, considering the unique biological and immunological characteristics of HCC, we will discuss potential therapeutic targets beyond VEGF and CTLA-4 that may exhibit synergistic effects with ICIs.



Antonio D'Alessio
King's College Hospital, UK

Self Introduction

Consultant Medical Oncologist and Honorary Clinical Senior Lecturer with specialist expertise in hepatocellular carcinoma, hepatobiliary malignancies, and immunotherapy. He completed his PhD at Imperial College London, focusing on biomarker discovery in neoadjuvant immunotherapy for hepatocellular carcinoma. He is currently a Consultant Medical Oncologist at King's College Hospital, leading a translational research programme embedded in the largest UK centre for treatment of hepatocellular carcinoma. His clinical practice integrates complex hepatobiliary oncology care with early-phase clinical trials and translational research. He previously completed specialty training in Medical Oncology at Humanitas University (Italy), graduating with honours.

Research Interests

His research focuses on immunotherapy in hepatocellular carcinoma, particularly in early-stage and neoadjuvant settings. He is interested in predictive biomarkers of response and resistance to immune checkpoint inhibitors, mechanisms of T-cell exhaustion, and translational integration of spatial transcriptomics, circulating tumour DNA, immune phenotyping, and microbiome profiling. His work aims to bridge early-phase clinical trials with mechanistic immune profiling to improve patient selection and therapeutic strategies in liver cancer.

Representative Publications

- 1. D'Alessio A et al. Pathological response following neoadjuvant immunotherapy in hepatocellular carcinoma: a cross-trial, patient-level analysis. *Lancet Oncology*. 2024.
- 2. D'Alessio A et al. Safety and preliminary efficacy of pembrolizumab following trans-arterial chemoembolization for hepatocellular carcinoma: the PETAL Phase 1b study. *Clinical Cancer Research*. 2024.
- 3. D'Alessio A, Pinato DJ et al. Integrated phenotyping of the anti-cancer immune response in HIV-associated hepatocellular carcinoma. *JHEP Reports*. 2023.
- 4. Cortellini A, D'Alessio A, et al. Type 2 Diabetes Mellitus and Efficacy Outcomes from Immune Checkpoint Blockade in Patients with Cancer. *Clin Cancer Res*. 2023;29 (14), 2714-2724.
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Anti-VEGF as a Partner to PD-L1 Blockade

Antonio D'Alessio *King's College Hospital, UK*

This lecture will review the biological and clinical rationale for combining anti-VEGF therapy with PD-(L)1 blockade in hepatocellular carcinoma (HCC). We will discuss preclinical evidence supporting the immunomodulatory role of VEGF signalling, including translational data demonstrating associations between VEGF-related signatures and response to immunotherapy.

The presentation will also focus on key clinical trials establishing the role of VEGF inhibition in combination strategies, including IMbrave150, CARES-310, and EMERALD-1. Finally, the lecture will cover the use of immunotherapy combinations in the adjuvant setting across tumour types, where bevacizumab-containing strategies have not consistently translated into improved outcomes.

Overall, the talk will examine the role of VEGF inhibition as a key partner for optimising immune checkpoint blockade in HCC.



Bo Hyun Kim
National Cancer Center

Self Introduction

Prof. Bo Hyun Kim is a Senior Scientist and Head of the Division of Gastroenterology at the Center for Liver and Pancreatobiliary Cancer, National Cancer Center, and is currently holding a position of Adjunct Professor at the Department of Public Health & AI, National Cancer Center Graduate School of Cancer Science and Policy.

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Research Interests

Hepatocellular Carcinoma, Systemic Therapy, Combined-Modality Treatment, Hcc Epidemiology and Nationwide Registry, Clinical Practice Guideline Development

Representative Publications

1. An J, Chang Y, Choi GH, Sohn W, Song JE, Shin H, Yoon JH, Yoon JS, Jang HY, Cho EJ, Han JW, Hong SK, Cho J-Y, Jung K-W, Park EH, Kim E, Kim BH. Hepatocellular carcinoma in Korea: an analysis of the 2016-2018 Korean Nationwide Cancer Registry. *J Liver Cancer* 2025;25(1):109-122.
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3. Kim BH, Park HC, Kim TH, Koh Y-H, Hong JY, Cho Y, Sinn DH, Park B, Park J-W. Concurrent nivolumab and external beam radiation therapy for hepatocellular carcinoma with macrovascular invasion: a phase II study. *JHEP Reports* 2024;6:100991.
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Dual Immune Blockade in HCC

Bo Hyun Kim National Cancer Center

First-line systemic therapy for unresectable HCC now centers on two distinct combination strategies: anti-PD-1/PD-L1 combined with anti-VEGF, and anti-PD-1/PD-L1 combined with anti-CTLA-4. Each offers a different therapeutic profile rather than a clear hierarchy of efficacy.

The mechanistic rationale for adding CTLA-4 blockade is complementary to PD-1/PD-L1 inhibition. Anti-CTLA-4 antibodies enhance T-cell priming in lymphoid tissues, broaden the T-cell receptor repertoire, and deplete intratumoral regulatory T cells via Fcγ receptor-dependent ADCC. This dual engagement of non-overlapping immune pathways underlies the deep and durable responses observed in a subset of patients.

Clinical data support this rationale. In the phase III HIMALAYA trial, the STRIDE regimen achieved a 5-year overall survival rate of 19.6% versus 9.4% with sorafenib, the longest follow-up reported in any phase III HCC trial to date. In CheckMate 9DW, nivolumab plus ipilimumab demonstrated a median OS of 23.7 months versus 20.6 months with lenvatinib or sorafenib, with an objective response rate of 36%. HIMALAYA also showed that even modest tumor shrinkage translated into meaningful OS benefit, suggesting that conventional RECIST criteria may underestimate the clinical impact of dual checkpoint blockade.

The benefit of dual IO blockade comes with considerations that inform patient selection. Grade 3-4 immune-related adverse events are more frequent with CTLA-4 containing regimens, and the depth and durability of response are not uniformly observed across the treated population. Dual IO blockade is therefore best suited to patients with contraindications to anti-VEGF therapy, those with adequate performance status and liver function to tolerate immune-related toxicity, and those for whom durable, treatment-free survival is a primary therapeutic goal.

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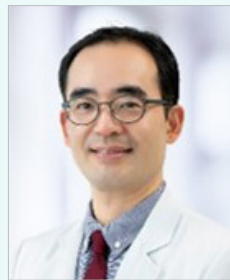


KLCA SYMPOSIUM 2

Managing MASLD-HCC: A Comprehensive Overview of Treatment Modalities and Strategies

Chairs
Antonio D'Alessio (King's College Hospital, UK)
Arndt Vogel (Univ. of Toronto, Canada)



**Su Jong Yu**

Seoul National University

Self Introduction

Dr. Su Jong Yu is a Professor in the Department of Internal Medicine and the Liver Research Institute at Seoul National University College of Medicine, and a hepatologist at Seoul National University Hospital. He graduated from Seoul National University College of Medicine in 2001 and went on to earn his Master's degree (2006) and Doctorate (2012) in Medicine from the same institution.

He completed his medical internship (2001–2002) and residency in Internal Medicine (2002–2006) at Seoul National University Hospital, followed by a research and clinical fellowship at the Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine (2009–2011). From 2016 to 2018, he conducted research as a Research Fellow at the National Cancer Institute (NCI), National Institutes of Health (NIH), in Bethesda, MD, USA. He has served as a faculty member at Seoul National University Hospital since 2011.

Dr. Yu has taken on a number of leadership roles in the field. Within the Korean Liver Cancer Association (KLCA), he served as Academy Affairs Director (2022.07–2025.06). In the Korean Association for the Study of the Liver (KASL), he served as Vice Secretary General and Director of the Liaison Committee (2019.12–2021.12) and as Director of the Planning Committee (2023.12–2025.11). He has also served as an Associate Editor of Gut and Liver since 2021.

Research Interests

Hepatocellular Carcinoma, Immunotherapy, Gut Microbiome, Biomarker

Representative Publications

1. Kim SC, Kim DW, Cho EJ, Lee JY, Kim J, Kwon C, Kim-Ha J, Hong SK, Choi Y, Yi NJ, Lee KW, Suh KS, Kim W, Kim W, Kim H, Kim YJ, Yoon JH, Yu SJ, Kim YJ. A circulating cell-free DNA methylation signature for the detection of hepatocellular carcinoma. *Mol Cancer*. 2023 Oct 6;22(1):164.
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MASLD-HCC Carcinogenesis: Genetics and Metabolic Drivers

Su Jong Yu

Seoul National University

Hepatocellular carcinoma (HCC) is no longer predominantly a viral disease. As hepatitis B and C decline and obesity and type 2 diabetes continue to rise, an increasing share of new HCC arises in patients with metabolic dysfunction–associated steatotic liver disease (MASLD).^{1,2} The 2023 nomenclature change reframed the disease around positive metabolic criteria rather than exclusion of alcohol, placing insulin resistance, lipotoxicity, and host susceptibility at the center of how we think about progression to cancer.¹ One of the most challenging features of MASLD-HCC is that a substantial proportion of cases occur in patients without cirrhosis, often presenting late with larger tumors—populations who fall outside cirrhosis-based surveillance.³ Two questions follow: why do some patients with apparently similar metabolic profiles develop cancer while others do not, and which mechanisms upstream of fibrosis actually drive transformation? This lecture addresses both, focusing on inherited genetic susceptibility and on the metabolic processes that translate steatosis into malignancy.

Genetic Susceptibility

Among common variants, *PNPLA3* rs738409 (I148M) is the strongest and most consistently replicated. In Newcastle–Bern case-control data, each G allele conferred an adjusted odds ratio of about 2.3 for NAFLD-HCC, and GG homozygotes had roughly a five-fold increase over CC, independent of cirrhosis.⁴ A recent reassessment of 19 candidate variants in 3,094 biopsied MASLD patients reinforced this point: only variants at the *PNPLA3*–*SAMM50*–*PARVB* locus showed reproducible association with histologic severity, and a previously validated three-SNP genetic risk score was driven almost entirely by *PNPLA3* rs738409.⁵ *TM6SF2* rs58542926 (E167K) acts independently by impairing hepatic VLDL secretion and trapping lipid in hepatocytes, increasing risk of MASH, advanced fibrosis, and HCC after adjustment for age, BMI, diabetes, and *PNPLA3* genotype.⁶ The protective side is dominated by *HSD17B13* rs72613567:–TA, a loss-of-function splice variant first reported in DiscovEHR to reduce risk of alcoholic and non-alcoholic chronic liver disease and to attenuate the effect of *PNPLA3* I148M.⁷

More clinically useful than any single variant is the additive picture. Gellert-Kristensen and colleagues combined *PNPLA3*, *TM6SF2*, and *HSD17B13* into a 0–6 risk score in 110,761 Copenhagen residents and 334,691 UK Biobank participants; individuals with the highest scores had a 12-fold higher odds of cirrhosis and substantially elevated risk of HCC compared with those carrying no risk alleles.⁸ A subsequent polygenic risk score combining *PNPLA3*–*TM6SF2*–*GCKR*–*MBOAT7* (adjusted for *HSD17B13*) predicted

HCC in NAFLD cohorts more robustly than any single variant and improved discrimination in patients without severe fibrosis.⁹ On the somatic side, MASLD-HCC shares the core driver mutations (*TERT* promoter, *TP53*, *CTNNB1/AXIN1*) but Pinyol and colleagues showed it carries its own signature—*ACVR2A* mutations in 10% of NASH-HCC (vs 3% in viral/alcoholic HCC), a novel MutSig-NASH-HCC mutational signature, lower *TP53* mutation rate (18% vs 32%), and enrichment of the Wnt/TGF- β proliferation subclass rather than the canonical *CTNNB1* subclass.¹⁰

Metabolic Drivers

If genetics defines who is susceptible, the metabolic milieu defines how transformation proceeds. Lipotoxicity from excess fatty acid delivery and insulin resistance drives ER stress, oxidative stress, inflammatory activation, and hepatocyte death; from the standpoint of carcinogenesis, these responses generate oxidant-induced DNA damage and the accumulation of somatic mutations in metabolic genes such as *FOXO1*, *CIDEB*, and *GPAM*.¹¹ Consistent with the central role of metabolic risk, type 2 diabetes is the strongest independent metabolic risk factor for NAFLD-HCC.¹¹ The clinical consequence is visible at population scale: in a Korean NHIS analysis of 2.4 million adults with type 2 diabetes, MASLD was associated with an adjusted hazard ratio of 1.38 for incident HCC, rising to 5.02 when MASLD coexisted with another liver disease and further amplified by alcohol intake.¹² At the cellular level, what kills hepatocytes is not bulk triglyceride but lipid species accumulating when handling is overwhelmed—saturated fatty acids, ceramides, lysophosphatidylcholines, and diacylglycerols generated by excess FFA delivery, SREBP-1c/ChREBP-driven de novo lipogenesis, and impaired β -oxidation. These intermediates trigger ER stress, mitochondrial dysfunction, and oxidative injury; the resulting cycle of cell death, regeneration, and damage-associated molecular pattern release sustains the inflammatory milieu in which DNA damage accumulates.¹³ Nakagawa's recent re-evaluation of SREBPs in MASLD adds a nuance worth noting: SREBP activity is high in early MASLD as expected, but human transcriptomic data show it is markedly downregulated in advanced “burned-out” MASH, where SREBP loss disrupts phospholipid homeostasis and, in murine models, accelerates carcinogenesis—a caution against assuming broad lipogenesis inhibition is therapeutically safe at every disease stage.¹⁴

Lipotoxic lipids also modify mitochondrial function and generate oxidative stress, contributing to the hepatocellular injury and oxidant-induced DNA damage that precede transformation.¹³ Patients with NASH-HCC carry higher levels of hepatic oxidative DNA damage than those with other aetiologies.¹¹ The most striking recent advance in this area is the work of Gu, Zhu, and Karin on fructose-1,6-bisphosphatase 1 (FBP1) in MASH-driven HCC: MASH-inducing diets cause DNA breaks that engage a p53-dependent senescence program in which FBP1 is paradoxically elevated and acts as a brake on tumorigenesis. Cancer emerges when this brake fails—FBP1 declines first in metabolically stressed pre-malignant hepatocytes and is suppressed in most human HCC through promoter hypermethylation and proteasomal degradation, releasing AKT and NRF2 to drive proliferation.¹⁵ Senescence in fatty liver is therefore not a benign endpoint but a reversible checkpoint, and the metabolic factors that erode it are themselves drivers of HCC. Metabolic stress also reshapes the epigenome: altered one-carbon metabolism,

acetyl-CoA, and α -ketoglutarate availability link metabolism to DNA methylation and histone modification, with hypermethylation of tumor suppressors such as *RASSF1* and *DACT2* reinforcing aberrant Wnt/ β -catenin signaling in MASLD-HCC.¹⁶ Taken together, MASLD-HCC arises at the meeting point of inherited susceptibility (*PNPLA3*, *TM6SF2*, *MBOAT7*, and protective *HSD17B13*) and chronic metabolic injury (insulin resistance, lipotoxicity, mitochondrial dysfunction, senescence escape).

The clinical agenda that follows is straightforward to state if difficult to implement: identify high-risk non-cirrhotic patients earlier through combined genetic, metabolic, and noninvasive fibrosis assessment, and pursue metabolic therapy—GLP-1 receptor agonists, the THR- β agonist resmetirom, and pathway-targeted agents now in trials—with the expectation that what reduces MASH activity will, over time, reduce MASLD-HCC.

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Arndt Vogel
University of Toronto, Canada

Self Introduction

Prof. Vogel is a clinician scientist at the rank of a full professor at the University of Toronto, Canada. He is appointed as the Longo Family Chair in Liver Cancer Research and is leading a multi-pronged research program in basic and clinical science at the Toronto General Hospital and the Princess Margarete Cancer Center. Before joining UNH, he worked as senior consultant at Hannover Medical School for more than 20 years and still holds a research position there.

Prof. Vogel's scientific focus is the translational and clinical research in gastrointestinal cancer. Since 2004, he is leading a translational research group interested in the pathogenesis of hepatobiliary cancers and in precision medicine. Arndt Vogel is a clinical investigator in oncology since 2006 and has served as principal investigator on numerous clinical trials. He is author or co-author of more than 400 articles published in peer-reviewed journals including Lancet, Lancet Oncology, Cancer Cell, and Gastroenterology among others with an H-index of 93.

Prof. Vogel is member of societies including ESMO, ASCO, and EASL. He is member and chairman of Hepatobiliary Cancer Study Group of the AIO, a collaborative group in clinical oncology in Germany. Within ESMO, he is member of the ESMO Guidelines Steering Committee. He has responsibilities in the establishment of the national guideline and is the coordinator of the ESMO clinical practice guideline on the management of hepatocellular carcinoma and biliary tract cancer

Research Interests

Liver Cancer, Precision Oncology

Representative Publications

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Immunity and Resistance in MASLD-HCC: Strategies for Immune Checkpoint Inhibitor Therapy

Arndt Vogel
University of Toronto, Canada

MASLD-HCC is rapidly emerging as a major subtype of hepatocellular carcinoma and differs biologically and immunologically from viral HCC. Chronic metabolic inflammation, lipotoxicity, and immune dysregulation create a pro-tumorigenic microenvironment characterized by dysfunctional and exhausted CD8+ T cells that may impair effective anti-tumor immunity.

Emerging data suggest that immune checkpoint inhibitors may be less effective in some patients with MASLD-HCC compared with viral HCC, potentially because of chronic immune exhaustion, altered macrophage populations, and abnormal tumor vasculature. However, MASLD-HCC remains insufficiently captured in most phase 3 studies and is frequently grouped under the broader category of “non-viral HCC,” limiting definitive conclusions regarding the true impact of MASLD on immunotherapy outcomes. In addition, the substantial overlap of metabolic, viral, alcohol-related, and other risk factors further complicates interpretation of currently available clinical data.

Recent studies also demonstrate substantial heterogeneity within MASLD-HCC, highlighting that etiology-specific immune profiling and biomarker development will likely become increasingly important. Single-cell analyses identified endothelial FABP4 as a potential biomarker associated with improved immune cell infiltration and better immunotherapy outcomes in MASLD-related HCC. These findings support the concept that additional biomarkers may help to better stratify patients and tailor immunotherapy approaches in MASLD-HCC.

Overall, future therapeutic strategies will likely focus on combining immune checkpoint inhibition with anti-angiogenic and metabolic-targeted approaches to overcome resistance and improve immune activation in MASLD-HCC



Sunyoung Lee
Yonsei University

Self Introduction

2007.02	Korean Board Certificate of Medical Doctor
2012.02	Korean Board of Internal Medicine
2016.02	Korean Board of Radiology
2016.03-2017.02	Clinical Fellow, Department of Radiology, Samsung Medical Center
2017.03-2018.02	Clinical Fellow, Department of Radiology, Asan Medical Center
2018.03-2024.02	Assistant Clinical Professor, Department of Radiology, Severance Hospital, Yonsei University College of Medicine
2024.03-Present	Associate Clinical Professor, Department of Radiology, Severance Hospital, Yonsei University College of Medicine

Research Interests

Liver Imaging

Representative Publications

1. US Liver Imaging Reporting and Data System Version 2017: A Systematic Review and Meta-Analysis. Radiology. 2025 Mar;314(3):e240450.

2. Percentages of Hepatocellular Carcinoma in LI-RADS Categories with CT and MRI: A Systematic Review and Meta-Analysis. Radiology. 2023 Apr;307(1):e220646.

3. Effect of Microvascular Invasion Risk on Early Recurrence of Hepatocellular Carcinoma after Surgery and Radiofrequency Ablation. Ann Surg. 2021 Mar;273(3):564-571.

4. Radiofrequency ablation vs. surgery for perivascular hepatocellular carcinoma: Propensity score analyses of long-term outcomes. J Hepatol. 2018 Jul;69(1):70-78.

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Prognostic Imaging: Assessing Risk and Predicting Outcomes in MASLD-HCC

Sunyoung Lee Yonsei University

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a rapidly growing etiology of hepatocellular carcinoma (HCC) worldwide. As the incidence of MASLD-related HCC (MASLD-HCC) continues to rise, there is an increasing need for robust prognostic tools that can guide risk stratification, treatment planning, and surveillance strategies.

Imaging plays a pivotal role beyond diagnosis, serving as a noninvasive biomarker for tumor biology and patient outcomes. This lecture will provide a comprehensive overview of prognostic imaging in MASLD-HCC.



Takahiro Kodama
The University of Osaka, Japan

Self Introduction

He is a physician-scientist specializing in hepatology, gastroenterology, and oncology. He obtained his M.D. from Osaka University in 2002 and completed his Ph.D. in the Department of Gastroenterology and Hepatology at the same institution in 2011. Following a postdoctoral fellowship at the Houston Methodist Research Institute in Texas (2012-2016), he returned to Osaka University, where he currently serve as a Professor and Chairman at the Department of Gastroenterology and Hepatology. He is an editorial board member of Hepatology and serve as an associate editor of Scientific Reports, Frontiers in Oncology, and Annals of Hepatology. He is a councilor of JSH and JCA. He is an expert panelist of the Pan-Asia Adapted ESMO HCC Guidelines.

Research Interests

His research focuses on liver cancer biology, cancer immunotherapy, and biomarker development. He has published over 160 peer-reviewed papers, including first or senior author publications in J Clin Invest, Hepatology, Gastroenterology, J Hepatology, Clin Cancer Res, J Immunother Cancer, and PNAS. He holds seven patents related to diagnostic biomarkers and therapeutic stratification methods in cancer. He integrates genomic technologies, advanced animal models, and clinical cohorts to drive precision medicine in liver diseases and cancer. His work has contributed to understanding immune resistance in HCC and developing biomarker-guided therapeutic strategies.

Representative Publications

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Tailoring Immunotherapy for MASLD-HCC: Challenges and Emerging Strategies

Takahiro Kodama *The University of Osaka, Japan*

Recent advances in immune checkpoint inhibitor (ICI)-based therapies have improved outcomes in hepatocellular carcinoma (HCC); however, their efficacy remains limited in metabolic dysfunction-associated steatotic liver disease-related HCC (MASLD-HCC). Emerging evidence indicates that the etiology of HCC critically shapes the tumor immune microenvironment (TME) and therapeutic responsiveness.

In MASLD-HCC, tumor-intrinsic metabolic and stress signaling pathways play a central role in driving immune evasion. Notably, activation of the NRF2–COX2–PGE2 axis promotes the development of an immune “cold” TME characterized by reduced cytotoxic T-cell infiltration, increased regulatory T cells, and resistance to combination immunotherapy such as atezolizumab plus bevacizumab. This mechanism highlights how metabolic stress adaptation rewires tumor–immune interactions, leading to primary and acquired resistance in a substantial subset of patients.¹

In contrast, MASLD-HCC also exhibits marked intratumoral heterogeneity, and a subset of tumors displays an immune “hot” phenotype. Multiomics analyses have revealed that intratumoral lipid accumulation defines a distinct immunological subtype characterized by immune cell enrichment but functional exhaustion, including PD-L1 upregulation, M2 macrophage polarization, and T-cell dysfunction. Importantly, this steatotic, immune-enriched TME may retain susceptibility to ICI-based therapies, suggesting that lipid metabolism-driven tumor states can paradoxically shape both immune activation and suppression.²

Together, these findings underscore a dual paradigm in MASLD-HCC: metabolic stress pathways such as NRF2 drive immune exclusion and resistance, whereas intratumoral steatosis can define an immune-infiltrated yet exhausted niche with potential therapeutic vulnerability. Tailoring immunotherapy for MASLD-HCC therefore requires precise stratification of tumor metabolic and immune states, integrating biomarkers of immune coldness and lipid-driven immune remodeling. Such approaches may enable the development of rational combination strategies to overcome resistance and improve clinical outcomes in this increasingly prevalent HCC subtype.

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KASL BRANCH EARLY MORNING
WORKSHOP 1

[Gyeonggi-Incheon]

Chair
Jung Hyun Kwon (The Catholic Univ. of Korea)





Jong-Hon Kang

Teine Keijinkai Hospital, Japan

Self Introduction

Education and Qualifications

- 1977-1983 Bachelor of Medicine, Hokkaido University School of Medicine, Sapporo, Japan
- 1983 Physician's License, Ministry of Health, Labour and Welfare, Japan
- 1993 Ph.D., Hokkaido University School of Medicine, Sapporo, Japan

Professional Work Experience

- 1983-1985 Resident of Internal Medicine, Hospital of Jichi Medical College, Tochigi Prefecture, Japan
- 1985-1986 Clinical Fellow, Third Department of Internal Medicine, Hokkaido University College of Medicine, Sapporo, Japan
- 1987-1997 Physician, Department of Internal Medicine, Teine Keijinkai Hospital, Sapporo, Japan
- 1987- Physician, Center for Gastroenterology Teine Keijinkai Hospital I, Sapporo, Japan

Research Interests

Viral Hepatitis, Autoimmune Liver Diseases, Acute Liver Failure

Representative Publications

1. Takahashi A, Ohira H, Abe K, Zeniya M, Abe M, Arinaga-Hino T, Torimura T, Yoshizawa K, Takaki A, Kang JH, Suzuki Y, Nakamoto N, Inui A, Tanaka A, Takikawa H. Increasing incidence of acute autoimmune hepatitis: a nationwide survey in Japan. *Sci Rep*. 2020 Aug 28;10(1):14250.
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Clinical and Epidemiological Analysis of HEV Infection Based on the Nation-Wide Surveillance of Hepatitis E in Japan

Jong-Hon Kang

Teine Keijinkai Hospital, Japan

Background and Aims

In November 2011, assay of IgA class antibody for hepatitis E virus (HEV) was covered by the public medical insurance in Japan, and then, the diagnosis of hepatitis E has rapidly expanded in clinical practice throughout the country. Changing circumstances have encouraged us to conduct a nationwide investigation of HEV infection.

Method

To 525 medical facilities in Japan, we requested a survey to investigate the medical record for the patients with HEV infection diagnosed from 2012 to 2017. The questionnaire included baseline characteristics, clinical course and virologic aspects of the patients.

Results

A total of 503 cases (407 males, average age of 56.6 years) were registered from 156 medical facilities across Japan during Dec 2018 to 2022. In Eastern Japan, 347 cases were collected from 68 facilities (5.1cases/facility), and 156 cases were gathered from 88 (1.8 cases/facility) in Western Japan. Among them, 169 patients had habitual alcohol consumption; 20 g/day or more in 15 female, 30 g/day or more in 154 male patients. Pre-existing liver disease was present in 93 patients, hypertension in 86, diabetes mellitus in 84, and dyslipidemia in 93, respectively. The average Body Mass Index (BMI) at onset was 23.3 ± 3.8 kg/m². Except for 4 cases, none had travel history to endemic areas during latent period. Ninety patients had consumed pork meat within the past two months, 48 had ingested pork offal, 13 had consumed venison, and 18 had eaten wild boar meat. Transfusion transmission of HEV was suspected in 4 patients. For the diagnosis of HEV infection, 468 (98.5%) patients were positive among 499 patients underwent an anti-HEV IgA test, certified by insurance in Japan. HEV RNA was detected in 203 of 223 patients using PCR. Among 178 patients whose HEV genotypes were determined, genotype 3 was identified in 123 patients (69.1%), genotype 4 in 51 (28.7%), and genotype 1 in 4 (2.2%) patients who had traveled to endemic areas. Of the 503 total patients, 346 (68.8%) were hospitalized, and 52 (10.3%) developed liver failure (LF). Five patients (1.0%) out of 503 patients presented with hepatic coma, 2 (0.4%)

received liver transplantation, and 5 (1.0%) deceased. LF was associated with male gender, alcohol consumption, BMI, genotype 4, and pre-existing liver disease or diabetes. AHE shifted to chronic hepatitis in 6 patients (1.2%). They had undergone organ transplantation or had underlying diseases including hematological disorders, respectively. Extrahepatic manifestations such as neurological disorders including Guillain-Barré syndrome, were observed in 6 patients.

Conclusion

AHE in Japan was autochthonous with rare exceptions, and genotype 3 of HEV was the dominant strain. A higher incidence in Eastern Japan might be observed compared to the Western area. Whereas AHE was self-limited in almost 90% of patients, LF developed in 10%, and 1 % had a fatal course. This may be the first nationwide study to examine the clinical picture of HEV infection throughout Asian countries including Japan.

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TRANSLATIONAL RESEARCH 1

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Pathogenesis and Metabolic-Immune Cross-Talk

Chairs

Won Kim (Seoul National Univ.)

Wonhyo Seo (Ewha Womans Univ.)





Stefano Romeo
Karolinska Institutet, Sweden

Self Introduction

Stefano Romeo is a Professor of Clinical Diabetology at Karolinska Institutet (Department of Medicine, Huddinge) and leads the Human Translational Genetics research group. His work focuses on how human genetic variation drives metabolic disease, with a main emphasis on metabolic dysfunction-associated steatotic liver disease (MASLD), and links to diabetes and cardiovascular disease.

He earned his medical degree in 2001 (Campus Bio-Medico University of Rome), became a specialist in Endocrinology and Metabolic Diseases in 2006, and completed a PhD in 2009 from Sapienza University of Rome that was carried out at UT Southwestern in Dallas, TX, USA. He later held a Clinical lectureship in Endocrinology at the University of Cambridge (2009 to 2011) and he became a Professor at the University of Gothenburg in 201, and was appointed professor at Karolinska Institute in September 2024.

Research Interests

Human and Molecular Genetics of Steatotic Liver Disease

Representative Publications

1. Mureddu M, Pelusi S, Jamialahmadi O, Vujkovic M, Miano L, Eidgah Torghabehei H, Ronzoni L, Malvestiti F, Saracino M, Periti G, Moretti V, Teerlink CC, Lynch JA, Tsao PS, Johnson JP, La Mura V, Dilella R, Alqahtani SA, Cherubini A, Russo FP, D'Ambrosio R, Fraquelli M, Petta S, Miele L, Vespasiani-Gentilucci U, Bugianesi E, Mancina RM, Parini P, Prati D, Chang KM, Schneider CV, Romeo S*, Valenti LV.* Carriage of rare APOB variants predisposes to severe steatotic liver disease and hepatocellular carcinoma. J Clin Invest. 2026 Feb 10:e201762. doi: 10.1172/JCI201762. Online ahead of print. PMID: 41665936 *Corresponding IF: 13.6;

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MASLD Phenotypic Diversity. From Genetic Discovery to Precision Medicine Stratification

Stefano Romeo *Karolinska Institutet, Sweden*

The lecture will present PNPLA3 as a paradigm for how human genetics has clarified the pathogenesis and prognosis of steatotic liver disease. Starting from a common variant encoding for the I148M substitution that was found associated with increased liver fat across ancestry groups. The lecture will then discuss how subsequent studies extended PNPLA3 from steatosis to clinically relevant outcomes. The I148M variant has been associated with steatohepatitis, fibrosis progression, cirrhosis and hepatocellular carcinoma, indicating that PNPLA3 influences both fat accumulation and liver disease progression. Mechanistically, the lecture will address how I148M promotes accumulation of mutant PNPLA3 on lipid droplets, impairing lipid remodeling and triglyceride mobilization. Effects on retinyl-palmitate metabolism in hepatic stellate cells may also link PNPLA3 to fibrogenesis. Finally, the lecture will consider translational implications. PNPLA3 genetics can support disease stratification, prognostic assessment and target discovery. Therapeutic strategies aimed at reducing PNPLA3 expression are being investigated, raising the possibility of genotype-directed treatment for MASLD.



Yong-Hyun Han
Kangwon National University

Self Introduction

Prof. Yong-Hyun Han is Associate Professor of the College of Pharmacy at Kangwon National University and is currently member of Scientific Committee of the Korean Association for the Study of the Liver. Also, he is member of Young Korean Academy of Science and Technology(Y-KAST) and got Lim Sung Ki Young Research Award from Hanmi Lim Sung Ki Foundation.

Prof. Yong-Hyun Han graduated from Kangwon National University College of Pharmacy with his BS degree in 2011 and completed his PhD degree at the College of Pharmacy at Seoul National University in 2018. Currently, he is Associate Editor of the Gut and Liver Journal (2024-).

Research Interests

- Identification of Roles of Liver Macrophage Heterogeneity in Liver Disease
- Novel Findings of Functional Endotoxin Neutralizer in Portal Vein Such as Immune Cell, Lipid Metabolites and Microbiome
- Deciphering Roles of Immunosenescence to Modulate Liver Pathology
- Finding Drug Candidates Targeting NLRP3 Inflammasome

Representative Publications

1. Kim DH*, Choi G*, Song EB*, Lee H*, Kim J*, Jang YS, Park J, Chi S, Han J, Kim SM, Kim D, Bae SH, Lee HW, Park JY, Kang SG#, Cha SH#, Han YH#. Treatment of IL-18 binding protein biologics suppresses fibrotic progression in metabolic dysfunction-associated steatohepatitis. Cell Rep Med. (2025) Apr 15;6:102047 [IF=10.6]

2. Kim DH, Lee KJ, Park J, Chi S, Han J, Bang Y, Kim SM, Kang SG#, Cha SH#, Han YH#. Disruption of IL-18 signaling via engineered IL-18BP biologics alleviates experimental cholestatic liver disease. Biomed Pharmacother. (2023) Nov;167:115587 [IF=7.5]

3. Han YH*, Onufer EJ, Huang LH, Sprung RW, Davidson WS, Czepielewski RS, Wohltmann M, Sorci-Thomas MG, Warner BW, Randolph GJ*. Enterically derived high-density lipoprotein restrains liver injury through the portal vein. Science, (2021) July 23;373:eabe6729 [IF=44.8]

4. Han YH, Shin KO, Khadka D, Kim JY, Kim HJ, Cho WJ, Cha JY, Lee YM, Lee BJ, Lee MO. A maresin 1/ROR α /12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. J Clin Invest, (2019) Mar 11;130:1684-1698 [IF=13.3]

5. Han YH, Kim DK, Na TY, Ka NL, Choi HS, Lee MO. ROR α switches transcriptional mode of ERR γ that results in transcriptional repression of CYP2E1 under ethanol-exposure. Nucleic Acids Res, (2016) Feb 18;44:1095-1104 [IF=16.7]

When Blood Ages Badly: Pathological Impact of Clonal Hematopoiesis on Advanced Aging–Driven MASH

Yong-Hyun Han Kangwon National University

Clonal hematopoiesis of indeterminate potential (CHIP) has emerged as a hallmark of aging and is increasingly recognized as a contributor to systemic chronic inflammation and age-associated diseases. Beyond its established association with hematologic malignancies and cardiovascular disorders, CHIP may also reflect broader processes of immune aging, or immunosenescence that influence the progression of chronic metabolic diseases. Immunosenescence is characterized by skewed myeloid differentiation, persistent low-grade inflammation, impaired immune regulation, and maladaptive tissue remodeling, all of which are highly relevant to the pathogenesis of MASH. However, the mechanistic links between age-related hematopoietic alterations and hepatic disease remain incompletely understood. In this study, we aim to investigate how immunosenescence-associated hematopoietic remodeling contributes to MASH development and progression, with particular focus on age-driven changes in innate immune cell function and inflammatory responses. Furthermore, we plan to define the molecular and histopathological mechanisms underlying the crosstalk between senescent immune systems and the liver microenvironment. By integrating hematopoietic aging with hepatic pathophysiology, this study is designed to provide new insights into the role of immunosenescence in the initiation and progression of MASH. These findings may offer a conceptual framework for the development of therapeutic strategies targeting immune aging to prevent or treat chronic liver disease.



Tatsuya Kanto

Japan Institute for Health Security, Japan

Self Introduction

Tatsuya Kanto is a researcher and hepatologist/physician with expertise in immunology in liver diseases. He earned a PhD at Osaka University and worked as a research associate in dendritic cell biology at the University of Pittsburgh, USA, from 1998 to 2001. He worked as an Associate Professor at Osaka University from 2003 to 2013 and moved to the National Center for Global Health and Medicine (NCGM). His current position is Director General at the Research Center for Hepatitis and Immunology, Japan Institute for Health Security (JIHS).

He has been working with the Ministry of Health, Labor, and Welfare to promote the Hepatitis Action Plan in Japan. His field of interest is the exploration of the pathogenesis of liver disease to develop immune-based therapies against viral hepatitis, liver cirrhosis, and cancer. He has published more than 260 papers and invited review articles in peer-reviewed journals, such as Hepatology, Journal of Hepatology, Immunity, Journal of Immunology, and Gastroenterology.

Research Interests

- Immunopathogenesis of Viral Hepatitis, MASLD/MASH, and Liver Cancer
- Development of Immune Modulators for the Treatment of Chronic HBV Infection
- Establishment of a Therapeutic Strategy for Congestive Liver Disease, Such as FALD
- Promotion of Hepatitis Countermeasures in Japan

Representative Publications

1. Yamazoe T, Kanto T, et al. Genomic and transcriptomic profiling of hepatocellular carcinoma in patients with Fontan-associated liver disease. Hepatology 2026; in press.
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5. Mori T, Yoshio S, Kakazu E, Kanto T. Active role of the immune system in metabolic dysfunction-associated steatotic liver disease. Gastroenterol Rep (Oxf). 2024 Oct 15;12:goae089. doi: 10.1093/gastro/goae089. eCollection 2024.PMID: 39411101

The Metabolic Triad in MASLD-MASH: Glucose, Lipid, and Amino Acid Dysregulation

Tatsuya Kanto

Japan Institute for Health Security, Japan

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its relatively advanced form, metabolic dysfunction-associated steatohepatitis (MASH), are becoming increasingly prevalent world-wide, making their prevention and management an urgent global health priority. Central to their development are key metabolic defects, including abnormal concentrations of monosaccharides, fatty acids, and amino acids, but the complex relationships between these substances within the hepatic microenvironment remain only partially understood. Dysregulated glucose metabolism and selective insulin resistance (IR) promote hepatic gluconeogenesis, glycolysis, and de novo lipogenesis (DNL), and excessive concentrations of free fatty acids from the diet and adipose tissue drive steatosis. Emerging evidence also implies that amino acid metabolism affects mitochondrial function and redox balance. Dysfunctional mitochondrial oxidative phosphorylation and the associated increase in reactive oxygen species production further exacerbate the cellular stress, inflammation, and fibrosis. However, compared with monosaccharide and fatty acid metabolism, the role of amino acid metabolism in MASLD/MASH remains less well understood.

Recently, it was revealed that dimethyl fumarate (DMF), a precursor of fumarate, regulates metabolism by inhibiting GAPDH, a glycolytic enzyme, in immune cells. We thus aimed to verify the therapeutic effects of DMF on MASH and clarify how metabolic reprogramming via GAPDH affects glucose/lipid metabolism and VLDL particle formation. Eight-week-old male C57BL/6 mice were divided into three groups: normal chow (NC), high-fat/high-fructose/high-cholesterol (FFC) diet, and FFC + DMF (DMF) for a 20-week intervention. The DMF group significantly improved MASH pathologies caused by FFC. Hepatic multi-omics and transcriptomic analyses showed that DMF suppressed hepatic GAPDH activity, increased metabolites downstream of 3-phosphoglycerate during fasting, and significantly restored TCA cycle intermediates and ATP levels depleted in the FFC group. DMF also suppressed the upregulation of genes related to gluconeogenesis and DNL. Lipidomic analysis revealed that in the DMF group, palmitic acid/oleic acid accumulation in the TG fraction decreased, while linoleic acid increased in the free fatty acid and phospholipid fractions. Furthermore, substrates for phosphatidylcholine (PC) synthesis (methionine and choline) required for VLDL synthesis increased, and these changes were linked to VLDL particle size. Furthermore, in human hepatocytes, MMF administration suppressed GAPDH activity, increased VLDL-TG secretion, and reduced oxidative stress. To verify clinical significance in humans, we analyzed

blood lipoprotein fractions and VLDL particle size using a biobank general population cohort of 28,823 cases and liver biopsy-diagnosed cases (54 MASH/MASLD, 65 other chronic liver diseases). In human MASH cases, blood linoleic acid and the Large/Small VLDL ratio decreased as steatosis progressed, and blood linoleic acid levels showed a significant positive correlation with the number of Large VLDL particles.

In summary, DMF improved MASH progression by inhibiting hepatic gluconeogenesis and DNL through metabolic reprogramming initiated by GAPDH inhibition. It also matured VLDL by adjusting lipid composition, including linoleic acid. A better understanding of the role of such metabolic dysfunction in liver pathobiology should aid the identification of more useful biomarkers and precision therapies for MASLD/MASH.

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TRANSLATIONAL RESEARCH 2

Cutting-Edge Technologies in Liver
Research: From Spatial Omics to
Precision Therapeutics

Chairs
Si Hyun Bae (The Catholic Univ. of Korea)
Won-Il Jeong (KAIST)





David A. Brenner
Sanford Burnham Prebys, USA

Self Introduction

He received extensive training in clinical medicine and biomedical research at Yale, NIH, and UCSD, resulting in Board certification in Internal Medicine and Gastroenterology. He is a physician scientist, dedicated to using state-of-the-art technology to translate biomedical research into improving health. He has taken leadership positions as Chief of Gastroenterology at UNC, Chapel Hill, Chairman of Medicine at Columbia University, Vice Chancellor of Health Sciences and Dean of the Medical School at UCSD, and now President and CEO of Sanford Burnham Prebys Medical Discovery Institute. He has more than 200 peer reviewed publications, two patents, and recognition among Highly Cited Researchers by Web of Science and Clarivate Analytics.

Research Interests

He directs a laboratory Studying Chronic Liver Disease, Hepatocellular Cancer, Pancreatic Cancer, and Aging.

Representative Publications

1. Kim HY, Mizrahi O, Lee W, Rosenthal SB, Han C, Yee BA, Blue SM, Diaz J, Jonnalagadda J, Hokutan K, Jang H, Ma CT, Bobkov A, Sergienko E, Jackson MR, Stefanovic B, Kisseleva T, Yeo GW, Brenner DA. LARP6 regulates the mRNA translation of fibrogenic genes in liver fibrosis. *bioRxiv*. 2025 Jan 18; PubMed Central PMCID: PMC11761402.

2. Parsons CJ, Stefanovic B, Seki E, Aoyama T, Latour AM, Marzluff WF, Rippe RA, Brenner DA. Mutation of the 5'-untranslated region stem-loop structure inhibits α 1(I) collagen expression in vivo. *J Biol Chem*. 2011 Mar 11;286(10):8609-8619. PubMed Central PMCID: PMC3048743.

3. Lindquist JN, Parsons CJ, Stefanovic B, Brenner DA. Regulation of alpha1(I) collagen messenger RNA decay by interactions with alphaCP at the 3'-untranslated region. *J Biol Chem*. 2004 May 28;279(22):23822-9. PubMed PMID: 14973140.

4. Stefanovic B, Schnabl B, Brenner DA. Inhibition of collagen alpha 1(I) expression by the 5' stem-loop as a molecular decoy. *J Biol Chem*. 2002 May 17;277(20):18229-37. PubMed PMID: 11889120.

5. Stefanovic B, Brenner DA. 5' stem-loop of collagen alpha 1(I) mRNA inhibits translation in vitro but is required for triple helical collagen synthesis in vivo. *J Biol Chem*. 2003 Jan 10;278(2):927-33. PubMed PMID: 12419812.

Hepatic Stellate Cell Activation and Fibrosis Reversal Mechanisms

David A. Brenner *Sanford Burnham Prebys, USA*

Liver fibrosis of different etiologies is a serious health problem worldwide. There is no effective therapy available for liver fibrosis except the removal of the underlying cause of injury or liver transplantation. Development of liver fibrosis is caused by fibrogenic myofibroblasts that are not present in the normal liver but rather activate from liver resident mesenchymal cells in response to chronic toxic or cholestatic injury. The major source of myofibroblasts in hepatotoxic liver injury such as MASH is the activation of hepatic stellate cells. Epigenetic changes in quiescent hepatic stellate cells lead to multiple phenotypes in the diseased livers. Many studies indicate that liver fibrosis is reversible when the causative agent is removed. Regression of liver fibrosis is associated with the disappearance of activated myofibroblasts and resorption of the fibrous scar. The disappearance of myofibroblasts results from both cell death by apoptosis as well as the change to an inactivated phenotype. Inactivated hepatic stellate cells are similar to, but distinct from, quiescent hepatic stellate cells. Genetic tracing and cell fate mapping of hepatic stellate cells and portal fibroblasts have demonstrated the origin and fate of myofibroblasts. More recently, single nucleus multi-omics have provided new insights into the transcriptional changes that induce the myofibroblast phenotype and the regression to a quiescent phenotype.

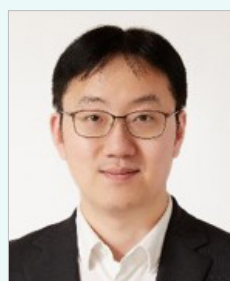
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2. The Origin and Fate of Liver Myofibroblasts. Kim HY, Sakane S, Eguileor A, Carvalho Gontijo Weber R, Lee W, Liu X, Lam K, Ishizuka K, Rosenthal SB, Diggle K, Brenner DA, Kisseleva T. *Cell Mol Gastroenterol Hepatol*. 2024;17(1):93-106. doi: 10.1016/j.jcmgh.2023.09.008. Epub 2023 Sep 22. PMID: 37743012.

3. Heterogeneity of HSCs in a Mouse Model of NASH. Rosenthal SB, Liu X, Ganguly S, Dhar D, Pasillas MP, Ricciardelli E, Li RZ, Troutman TD, Kisseleva T, Glass CK, Brenner DA. *Hepatology*. 2021 Aug;74(2):667-685. doi: 10.1002/hep.31743. Epub 2021 Aug 10. PMID: 33550587.

4. Identification of Lineage-Specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution. Liu X, Xu J, Rosenthal S, Zhang LJ, McCubbin R, Meshgin N, Shang L, Koyama Y, Ma HY, Sharma S, Heinz S, Glass CK, Benner C, Brenner DA, Kisseleva T. *Gastroenterology*. 2020 May;158(6):1728-1744.e14. doi: 10.1053/j.gastro.2020.01.027. Epub 2020 Jan 23. PMID: 31982409.



Jeong Seok Lee
KAIST

Self Introduction

Prof. Jeong Seok Lee is an Associate Professor of the Graduate School of Medical Science and Engineering (GSMSE), Korea Advanced Institute of Science and Technology (KAIST) and is currently holding a position of Co-founder at Inocras Inc. simultaneously.

Prof. Lee graduated from Seoul National University College of Medicine with his medical degree in 2008 and completed his residency at the Department of Internal Medicine at Seoul National University Hospital, receiving his diploma in Internal Medicine in 2017.

Since 2022, Prof. Lee has been taking a number of distinguished roles and honors, including Ewon Endowed Assistant Professor at KAIST (2023–2025), recipient of the Young Investigator Award from the Korean College of Rheumatology (2024), and the Korean Association of Immunologists-Seegene Medical Foundation Excellence Award (2025).

Research Interests

His primary research interest lies at the fusion of human immunology and high-resolution genomics to crack the code of treatment-refractory inflammatory and autoimmune diseases. While his previous work extensively leveraged single-cell multi-omics to map pathogenic T cell dynamics and interferon signatures in ankylosing spondylitis and severe viral infections, his laboratory's future focus explores somatic evolution within non-malignant immune cells.

Representative Publications

1. Type 1 interferon signature and allograft inflammatory factor-1 contribute to refractoriness to TNF inhibition in ankylosing spondylitis. *Nat Commun.* 2025
2. NKG2D-mediated cytotoxicity of CD4 cytotoxic T cells in multiple myeloma. *Blood.* 2025
3. Therapeutic Single-Cell Landscape: Methotrexate Exacerbates Interstitial Lung Disease by Compromising the Stemness of Alveolar Epithelial Cells under Systemic Inflammation. *EBioMedicine.* 2024
4. Analysis of Single-Cell Transcriptome and Surface Protein Expression in Ankylosing Spondylitis Identifies OX40-Positive and Glucocorticoid-Induced Tumor Necrosis Factor Receptor-Positive Pathogenic Th17 Cells. *Arthritis Rheum.* 2023
5. Single-cell Transcriptome of Bronchoalveolar Lavage Fluid Reveals Sequential Change of Macrophages During SARS-CoV-2 Infection in Ferrets, *Nat Commun.* 2021

Multi-Omics and Single-Cell Spatial Insights for HCC Target Discovery

Jeong Seok Lee KAIST

Hepatocellular carcinoma (HCC) is characterized by profound intratumoral heterogeneity and a highly complex tumor microenvironment (TME), posing significant challenges for discovering effective targeted and immunotherapies. Conventional bulk omics analyses lack the resolution to capture individual cellular phenotypes and their physical, spatial interactions. This presentation explores how the integration of single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics into a multi-omics framework is redefining the HCC TME and shifting the paradigm of novel therapeutic target discovery.

Advanced single-cell and spatial multi-omics technologies enable high-resolution mapping of the dynamic interplay among malignant, immune, and stromal cells within their spatial context. This approach goes beyond observing cellular composition to decoding immune evasion mechanisms and intercellular crosstalk localized in specific spatial niches.

A compelling demonstration of this strategy's utility is a recent landmark study published in *Nature Medicine* (2024). Leveraging spatial multi-omics, the research elegantly delineated distinct multicellular neighborhoods and immunosuppressive spatial architectures within the HCC ecosystem. By mapping how spatially restricted intercellular communication networks drive tumor progression, the study highlighted previously hidden regulatory elements as novel, actionable therapeutic targets. This serves as a powerful proof-of-concept of how spatial biology directly translates into target discovery. Building on this, the presentation will discuss broader pipelines utilizing spatial insights to uncover synergistic target combinations.

The integration of single-cell and spatial multi-omics is essential for decoding the complexity of the HCC ecosystem beyond mere cell-centric views. These spatial insights provide a robust framework for targeting critical microenvironmental hubs, thereby advancing next-generation precision oncology and the development of novel therapeutics for HCC.



Wonseok Lee
Gachon University

Self Introduction

Dr. Wonseok Lee is an Assistant Professor at the College of Pharmacy, Gachon University. He received his Pharm.D. and Ph.D. in Preventive Pharmacy from Seoul National University College of Pharmacy, where he studied the molecular mechanisms of drug-induced liver injury and hepatic lipid metabolism.

After completing his doctoral training, Dr. Lee conducted postdoctoral research at the University of California San Diego School of Medicine, focusing on liver fibrosis, metabolic dysfunction-associated steatotic liver disease, hepatocellular carcinoma, and human liver spheroid/organoid-based disease modeling.

Since March 2025, Dr. Lee has been leading the Molecular Toxicology Laboratory at Gachon University. His current research focuses on elucidating the molecular mechanisms of drug-induced liver injury, MASLD/MASH, liver fibrosis, and hepatocellular carcinoma, with the goal of identifying novel therapeutic targets using human liver organoid and spheroid platforms.

Research Interests

- Molecular Mechanisms of MASLD/MASH, Liver Fibrosis, and Hepatocellular Carcinoma
- Human Liver Organoid and Spheroid-Based Disease Modeling
- Identifying Transcription Factors that Promote MASH and Liver Fibrosis

Representative Publications

1. W Lee, X Liu, S.B. Rosenthal, et al., ETS1 suppresses hepatic stellate cell activation and liver fibrosis, JCI insight. (2025) 10(24):e195242
2. W Lee, HY Kim, YJ Choi, et al., SNX10-mediated degradation of LAMP2A by NSAIDs inhibits chaperone-mediated autophagy and induces hepatic lipid accumulation, Theranostics. (2022) 12(5):2351
3. W Lee, Y Mun, KY Lee, et al., Mefenamic acid-upregulated Nrf2/SQSTM1 protects hepatocytes against oxidative stress-induced cell damage, Toxics. (2023) 11(9):735
4. HY Kim, O Mizrahi, W Lee, et al., RNA-binding protein LARP6 coordinates hepatic stellate cell activation and liver fibrosis, The Journal of Clinical Investigation. (2026) 136(8):e197923
5. HY Kim, W Lee, X Liu, et al., Protocol to generate human liver spheroids to study liver fibrosis induced by metabolic stress. (2024) 5(2):103111

Transcriptional Regulation of Hepatic Stellate Cell Phenotypes during Liver Fibrosis Resolution

Wonseok Lee Gachon University

Liver fibrosis is a pathological wound-healing response to chronic liver injury and is characterized by excessive accumulation of extracellular matrix, tissue remodeling, and progressive loss of liver function. Hepatic stellate cells (HSCs) are the central effector cells in this process. In the healthy liver, quiescent HSCs store vitamin A and contribute to liver homeostasis. Upon liver injury, however, HSCs become activated and acquire a myofibroblast-like phenotype, producing collagen and other extracellular matrix proteins that drive fibrosis progression.

Importantly, liver fibrosis is now recognized as a dynamic and potentially reversible process. Upon removal of the underlying injury, activated HSCs either undergo apoptosis or transition into an inactivated, quiescent-like phenotype. This plasticity suggests that transcriptional programs determine whether HSCs remain activated or revert toward a less fibrogenic state. However, the key transcription factors governing HSC inactivation and fibrosis resolution remain poorly understood.

Recent single-cell and epigenomic analyses of mouse and human HSCs have identified lineage-associated transcription factors, including ETS, GATA, and IRF family members, as potential regulators of HSC phenotype. Among these candidates, ETS1 emerged as a transcription factor enriched in quiescent HSCs and reduced in disease-associated HSCs. Based on these findings, we investigated whether ETS1 regulates HSC activation and fibrosis regression.

Using HSC-specific Ets1 knockout mice, we found that deletion of Ets1 accelerated carbon tetrachloride-induced liver fibrosis and impaired fibrosis regression during the recovery phase. Even in naïve mice without experimental liver injury, loss of Ets1 in HSCs promoted basal fibrogenic and inflammatory gene expression, suggesting that ETS1 is required to maintain HSC homeostasis.

To validate these findings in a human multicellular system, we used primary human liver spheroids composed of hepatocytes, HSCs, and nonparenchymal cells. Under MASH-like culture conditions, ETS1 knockdown exacerbated fibrogenic responses. During the recovery phase, ETS1 knockdown suppressed the induction of inactivated HSC markers, including BAMBI, GABRA3, and PPAR γ , suggesting that ETS1 is required for activated HSCs to transition toward an inactivated, quiescent-like phenotype.

Mechanistically, our data suggest that ETS1 maintains quiescent and inactivated HSC phenotypes

through the CRTC2–PPAR γ regulatory axis. ETS1 knockdown reduced CRTC2 and PPAR γ -related signaling, whereas activation of PPAR γ partially suppressed fibrogenic responses induced by CRTC2 knockdown. Together, these findings identify ETS1 as a critical transcriptional regulator that restrains HSC activation and promotes fibrosis resolution. Targeting ETS1-dependent transcriptional programs may provide a promising therapeutic strategy to enhance liver fibrosis regression in chronic liver diseases, including MASH-associated fibrosis.

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2. X Liu, J Xu, S.B. Rosenthal, L-J. Zhang, R. McCubbin, et al. Identification of lineage-specific transcription factors that prevent activation of hepatic stellate cells and promotes fibrosis resolution. Gastroenterology 2020; 158(6):1728-1744
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4. HY Kim, S. Sakane, A. Eguileor, R. Carvalho Gontijo Weber, W Lee, X Liu, et al. The origin and fate of liver myofibroblasts. Cellular and Molecular Gastroenterology and Hepatology 2024; 17:93-106.

THE

LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
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June 11-13, 2026 | Conrad Seoul, Korea



Hyun Young Kim
Dankook University

Self Introduction

Prof. Hyun Young Kim is a professor at Dankook University College of Pharmacy. She received her Pharmacy degree from Seoul National University in 2017 and earned her Ph.D. in Pharmacology from Seoul National University in 2022. She then worked as a postdoctoral scholar at the University of California, San Diego School of Medicine until 2025. Prof. Kim has been an assistant professor at Dankook University College of Pharmacy since 2025.

Research Interests

The major interest of Prof. Hyun Young Kim’s research is the identification of therapeutic targets for metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated alcohol-related liver disease (MetALD)-associated liver fibrosis.

- 1. Liver Fibrosis: Validation of therapeutic targets for metabolic dysfunction-associated liver fibrosis
- 2. Hepatic Stellate Cells (HSCs): Phenotypic changes of HSCs in MASLD progression
- 3. Human Liver Organoids: Generation of 3D human liver spheroids to study liver fibrosis induced by metabolic stress

Representative Publications

- 1. Kim, H. Y., Mizrahi, O., Lee, W., Rosenthal, S. B., . . . Kisseleva, T., Yeo, G. W., and Brenner, D. A. (2026) RNA-binding protein LARP6 coordinates hepatic stellate cell activation and liver fibrosis. *The Journal of Clinical Investigation*, 136(8):e197923.
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Multi-Modal Analysis of Human Stellate Cells Identifies Novel Therapeutic Targets for MASLD

Hyun Young Kim Dankook University

Metabolic dysfunction-associated steatotic liver disease ranges from metabolic dysfunction-associated steatotic liver (MASL) to metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis.¹ Trans-differentiation of hepatic stellate cells (HSCs) into fibrogenic myofibroblasts plays a critical role in the pathogenesis of MASH liver fibrosis.² We compared transcriptome and chromatin accessibility of human HSCs from NORMAL, MASL, and MASH livers at single-cell resolution. We identified a set of concurrently upregulated and more accessible core genes that drive activation of HSCs, including SERPINE1. The pathological relevance of the selected targets, such as SERPINE1 (PAI-1), was demonstrated using dsRNA-based HSC-specific gene knockdown or pharmacological inhibition of SERPINE1 in 3D human MASH liver spheroids,³ and HSC-specific Serpine1 knockout mice.⁴

We also demonstrated that LARP6, an RNA-binding protein, coordinates HSC activation and liver fibrosis.⁵ By using single-nucleus RNA-seq and assay for transposase-accessible chromatin sequencing, we showed that JUNB upregulated LARP6 expression in activated HSCs. Moreover, LARP6 knockdown in human HSCs suppressed fibrogenic gene expression. By integrating enhanced crosslinking and IP analysis and ribosome profiling in HSCs, we showed that LARP6 interacted with mature mRNAs comprising more than 300 genes, including RNA structural elements within COL1A1, COL1A2, and COL3A1 to regulate mRNA expression and translation. IP–mass spectrometry analysis demonstrated LARP6 protein–protein interactions with mRNA translation components and the actin cytoskeleton. Furthermore, Dicer substrate siRNA-based HSC-specific gene knockdown or pharmacological inhibition of LARP6 attenuated fibrosis development in human MASH and MetALD liver spheroids. Our results suggest LARP6 plays a key role in fibrogenic gene regulation and that targeting LARP6 in human HSCs may represent a therapeutic approach for liver fibrosis.

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JiYeon Choi
Yonsei University

Self Introduction

JiYeon Choi, PhD, RN is an Associate Professor at Yonsei University College of Nursing in Seoul, South Korea. She completed her BSN from Yonsei University, an MSN from the University of Washington, and completed her PhD and postdoctoral fellowship at the University of Pittsburgh School of Nursing.

Her research has been supported by the National Institutes of Health, the Rehabilitation Nursing Foundation, the American Nurses Foundation, the International Society of Heart and Lung Transplantation, and the National Research Foundation of Korea.

Internationally, she has maintained long-standing engagement with the American Thoracic Society (ATS), serving in leadership roles within the Nursing Assembly, including Program Committee Member (2009–2019; 2023–present) and Program Committee Chair (2016–2017), as well as session chair and moderator at ATS International Conferences. She was inducted as an ATS Fellow in 2021 and received the ATS Nursing Assembly Early Career Achievement Award (2015) and Mentoring Award (2025).

In Korea, Dr. Choi served as the founding chair of the conference committee of the Korean Society of Nursing Industry (2022.8 -2026.2) and as treasurer of the Korean Society of Adult Nursing (2020-2021). She currently serves as chair of the Conference Committee of the Korean Society of Critical Care Nursing (2026.2–present) and as vice president of the Korean Society of Nursing Industry (2026.3-Present).

Research Interests

Dr. Choi’s research focuses on improving care for individuals with complex acute and chronic conditions, including ICU survivors, solid organ transplant recipients, and family caregivers, with an emphasis on family-centered communication in critical care, digital literacy and the digital divide, and data-driven approaches to self-management and mental health.

Representative Publications

1. Kang H, Kim B, Hyun J, Chu SH & Choi J. (2026). Relative Importance of Social Connectedness Indicators for Depression and Suicidal Ideation Among Urban and Rural Older Adults in South Korea. *Journal of Affective Disorders*. 404:121536. doi: 10.1016/j.jad.2026.121536.

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Analysis of Symptoms in Liver Transplant Recipients and Living Donors

JiYeon Choi Yonsei University

Background

Liver transplantation (LT) has achieved steadily improving survival, shifting the focus of care and re- search beyond graft survival to long-term quality of life and patient- and donor-centered outcomes. Nevertheless, many LT recipients experience persistent symptoms—including fatigue, sleep distur- bance, pain, gastrointestinal discomfort, and psychological distress—that continue despite clinical sta- bility and substantially affect daily functioning.

Living liver donors, although generally healthy, may also experience meaningful symptom burden during recovery. Accumulating evidence suggests that donor recovery is not uniform; while many re- cover as expected, some experience prolonged physical or emotional symptoms beyond the typical postoperative period.

Objectives

- (1) To summarize current research trends in symptom assessment and analysis after LT
- (2) To illustrate these trends through three complementary studies conducted by our research team—a scoping review of symptom measurement tools, a symptom network analysis among Korean LT recipients, and a longitudinal analysis of symptom trajectories among Korean living liv- er donors
- (3) To discuss future research directions and clinical implications.

Overview of Research Trends and Illustrative Studies

(1) Symptom Measurement in LT Recipients: Scoping Review

Recent transplant research has increasingly emphasized patient-reported outcomes to capture recov- ery experiences not reflected in laboratory or imaging findings. Our scoping review revealed substan- tial heterogeneity in symptom domains, instruments, assessment timing, and recall periods. Although gastrointestinal symptoms and fatigue were most frequently assessed, no measure comprehensively captured all core symptom attributes, highlighting the absence of standardized, patient-centered mea-

surement frameworks tailored to LT populations.

(2) Symptom Interrelationships in LT Recipients: Network Analysis

Beyond symptom prevalence, emerging research has examined how symptoms interact. Using a symptom network approach, our analysis identified fatigue as the most central and highly interconnected symptom, closely linked to muscle weakness, sleep disturbance, and emotional symptoms. Associations with depressive symptoms and steroid-containing immunosuppressive regimens underscore the multidimensional nature of symptom burden and support integrated approaches to symptom assessment and management.

(3) Symptom Trajectories among Living Liver Donors

Symptom research has also expanded to living donors, though evidence remains limited. Our longitudinal analysis demonstrated heterogeneous recovery trajectories. Emotional symptoms improved rapidly, whereas fatigue, physical functioning, pain interference, and social role participation showed more prolonged changes. While most donors returned to baseline quality of life by six months, a subset did not, with early divergence associated with baseline depressive symptoms rather than demographic or donation-related factors.

Future Directions and Clinical Implications

Together, these studies reflect key directions in contemporary symptom research: increased use of patient-reported measures, growing attention to symptom interrelationships, and expanding focus on living donor outcomes. Future research should prioritize longitudinal designs, harmonized measurement strategies, and analytic approaches that capture symptom dynamics rather than static severity.

For clinicians, symptom-informed care can complement traditional clinical indicators by facilitating early identification of individuals at risk for prolonged recovery, guiding anticipatory education, and supporting timely referral. Integrating symptom data into routine transplant coordination may enhance patient- and donor-centered outcomes across the transplant continuum.

Conclusion

Symptom analysis has emerged as a central component of modern LT research and care. By presenting current research trends alongside illustrative findings from symptom measurement, network analysis, and donor recovery trajectories, this presentation highlights the clinical relevance of symptoms as indicators of recovery beyond graft function alone. Strengthening symptom-informed transplant coordination represents a critical step toward more comprehensive, responsive, and person-centered post-transplant care.

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Sunyoung Son
Gangnam Severance Hospital

Self Introduction

Prof. Son is a Transplant Coordinator at the Transplantation Center of Gangnam Severance Hospital and currently serves as President of the Korean Organ Transplant Coordinator Organization. She is also Chair of the Coordinator Committee of the Korean Liver Transplantation Society, an Adjunct Professor at Yonsei University College of Nursing, and a long-standing member of the IRB Committee at Gangnam Severance Hospital.

Prof.Son earned her PhD in Nursing from Yonsei University Graduate School in 2007, where she completed her dissertation on “The Experiences of Adolescents with Hematologic Malignancies.” She also received her M.S. in Nursing in 2002 with a thesis on “Self-Image of Adolescents with Cancer,” and obtained her B.S. in Nursing from Yonsei University College of Nursing in 1996.

Since 2010, she has served as a Transplant Coordinator at Gangnam Severance Hospital. Her previous roles include Full-time Instructor at the Red Cross College of Nursing, Transplant Coordinator at Myongji Hospital, Child Hospice Nurse at Yonsei University Medical Center, and Teaching Assistant at both Yonsei University and Red Cross College of Nursing. She has also been actively involved in academic and professional leadership, including serving on the Board of Education for the Korean Society for Transplantation since 2017.

Research Interests

Patient Education and Self-Care Improvement in Transplantation, Donor Follow-Up and Health Management, Clinical Communication, Curriculum Development and Professional Competency of Transplant Coordinators, Ethical Decision-Making in Clinical Settings

Representative Publications

1. Son, S., Min, D., & Kim, S. (2025). Effectiveness of a simulation programme with lectures about end-of-life care using a standardised patient. *BMC Nursing*, 24, 371.
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Physical and Psychosocial Experiences of Living Liver Donors in Korea: A Qualitative Systematic Review

Sunyoung Son *Gangnam Severance Hospital*

Background

South Korea is one of the leading countries in living donor liver transplantation worldwide; however, standardized psychosocial support and long-term follow-up systems for living liver donors remain insufficient. This study aimed to review the physical and psychosocial experiences of living liver donors in Korea and provide foundational evidence for donor-centered management strategies.

Methods

A qualitative systematic review with thematic synthesis was conducted, with supplementary quantitative studies reviewed to support contextual interpretation of donor experiences. Literature searches were performed using RISS, KISS, DBpia, KMBase, and PubMed. Studies focusing on Korean living liver donors and donor-related family experiences were included. Study selection was conducted according to PRISMA guidelines.

Results

A total of 29 studies were identified through database searching. After screening based on PRISMA guidelines, 10 studies were preliminarily included in the review.

Preliminary screening identified recurrent themes including family-centered responsibility and sacrifice, physical recovery burden, psychological distress such as anxiety and regret, and the need for continuous psychosocial support and follow-up care.

Conclusions

Living liver donors in Korea experience complex physical and psychosocial burdens within family-centered sociocultural contexts. These findings suggest the need for standardized donor follow-up systems and donor-centered support strategies.



Seo Ha Jung
Yonsei University

Self Introduction

Ms. Seoha Jung is a doctoral student at the College of Nursing, Yonsei University, Seoul, Korea. Ms. Jung has approximately 7 years of clinical experience as a staff nurse in nephrology and endocrinology wards at Asan Medical Center, Seoul. She holds certifications in nephrology nursing and cardiovascular nursing (ANNA; ANCC). Her PhD training is currently supported by the Brain Korea 21 Four Scholarship and the Kyu-Hee Bae Endowed Scholarship. She is a research assistant on a project entitled “Determinants of Clinical Outcomes and Quality of Life Trajectories after Solid Organ Transplantation: A Prospective Study” (NRF, RS-2022-NR075577) and Science and Technology in Aging at Yonsei University (NRF, RS-2020-NR049581).

Research Interests

Heath and Quality of Life among Solid Organ Transplant Recipients

Representative Publications

- 1. Jung, S., Hyun, J., Lee, H., Chu, S., Joo, D., Lee, J., Kim, D., Min, E., & Choi, J. (Under review). Mapping modifiable pathways to alcohol use after liver transplantation: Loneliness, depression, and physical symptom burden: A path analysis. *Journal of Psychiatric and Mental Health Nursing*.
- 2. Jung, S., & Roh, Y. (In revision). Health literacy and self-care maintenance in post-transplantation diabetes mellitus among kidney transplant recipients: The mediating role of self-care confidence. *Research and Theory for Nursing Practice*.
- 3. Jung, S., Hyun, J., Lee, H., & Choi, J. (2026). Depressive symptoms and self-care among liver transplant recipients: Exploring the roles of self-efficacy and social support [Poster presentation]. *East Asian Forum of Nursing Scholars*, Singapore.

Depressive Symptoms and Self-Care in Liver Transplant Recipients

Seo Ha Jung Yonsei University

Background

As of 2024, liver transplantation accounts for approximately 24.5% of all solid organ transplants world-wide, making it the second most common transplant after kidney transplantation.¹ According to a recent report from the United States, approximately 30% of liver transplant recipients have a psychiatric diagnosis, with about one-fifth receiving no treatment.² Although the association between psychiatric diagnoses and survival remains inconclusive, substantial evidence links them to poorer quality of life and treatment adherence.³⁻⁵

Depressive symptoms, distinct from clinical depression, are transdiagnostic features observed across multiple psychiatric conditions and have gained attention as early intervention targets with potential broad benefits.⁶ In the post-transplant context, where patients must navigate complex medication regimens, frequent treatment adjustments, and multiple comorbidities, depressive symptoms may be particularly detrimental to effective self-management.⁷⁻⁸

A key mechanism linking emotional states to self-management behavior is self-efficacy—an individual’s belief in their capacity to carry out and sustain health-related actions.⁹ Self-efficacy may also serve as a pathway through which social support exerts its influence; however, despite its perceived importance in transplant care, the role of social support in explaining post-transplant outcomes remains inconsistent and poorly understood.¹⁰⁻¹²

Previous research has largely focused on medication adherence rather than broader self-care processes. Therefore, this study investigates how depressive symptoms relate to self-care via self-efficacy as a mediating mechanism, and whether social support moderates this pathway. Identifying these modifiable targets may inform early detection and intervention strategies aimed at improving self-care outcomes in liver transplant recipients.

Objectives

- (1) To describe the levels of depressive symptoms and self-care among liver transplant recipients; and
- (2) To examine the mediating role of self-efficacy and the moderating effect of social support in the re-

lationship between depressive symptoms and self-care.

Method

This study involved a secondary analysis of data collected from a single tertiary academic hospital in Seoul, South Korea, between September 2023 and February 2024. As a convenience sample drawn from one institution, the sample consisted of adult liver transplant recipients aged 19 years or older who were within five years of transplantation.

Self-care was measured using the Korean version of the Self-Care of Chronic Illness Inventory,¹³ which consists of three independently scored subscales: self-care maintenance (8 items), self-care monitoring (6 items), and self-care management (6 items) (Cronbach’s $\alpha = 0.70, 0.90,$ and $0.77,$ respectively). Self-efficacy was evaluated using the 10-item Self-Care Self-Efficacy Scale ($\alpha = 0.921$).¹³ Depressive symptoms were assessed using the Korean version of the Patient Health Questionnaire-9,¹⁴ a 9-item scale (Cronbach’s $\alpha = 0.83$). Social support was measured using the Korean version of the Multidimensional Scale of Perceived Social Support,¹⁵ a 12-item scale (Cronbach’s $\alpha = 0.938$).

Conditional process analyses using Model 59 of the PROCESS Macro (version 4.2) with the HC3 estimator and 5,000 bootstrap resamples were performed to test self-efficacy as a mediator and social support as a moderator in the relationship between depressive symptoms and each self-care subscale.

Results

Among 200 participants, 69% were male, with a mean age of 56.57 years ($SD = 9.17$), and 84% had received living-donor liver transplantation. Time since transplantation was 24.91 ± 18.02 months (range: 1–60). The most common indication for transplantation was hepatitis B- or C-related liver cirrhosis or hepatocellular carcinoma ($n = 80, 40\%$), followed by alcohol-related liver cirrhosis or hepatocellular carcinoma ($n = 66, 33\%$), with the remaining 27% presenting with combined or other etiologies.

A total of 74 (37.0%) had a history of at least one mental health diagnosis (excluding delirium) based on ICD-10 records, and 92 (46.0%) reported mild or greater depressive symptoms, of whom 48 (52.2%) also had a documented mental health diagnosis.

After adjustment for sociodemographic and clinical covariates, depressive symptoms were statistically significantly associated with lower self-efficacy ($B = -1.078, p = .001, 95\% \text{ CI } [-1.717, -.439]$), whereas neither the main effect of social support nor its interaction with depressive symptoms reached statistical significance. Across self-care maintenance, monitoring, and management, depressive symptoms showed no statistically significant direct effects at any level of social support. In contrast, statistically significant indirect effects through self-efficacy were consistently observed across all three domains.

Clinical Impression

In our sample, self-efficacy serves as a consistent mechanism linking depressive symptoms to self-care

across all three domains, independent of social support. Given the transdiagnostic nature of depressive symptoms, routine screening in the post-transplant setting may also facilitate early identification of broader psychiatric conditions. Clinically, integrating standardized depressive symptom screening into post-transplant follow-up is warranted, as compromised self-efficacy may represent the pathway through which psychological distress translates into poorer self-care. Interventions targeting self-efficacy—such as psychoeducation or motivational support—may therefore be particularly beneficial, even when social support appears adequate.

Conclusion

Self-efficacy is a key modifiable target for improving self-care in liver transplant recipients with depressive symptoms, underscoring the value of early psychological screening and efficacy-focused interventions in post-transplant care.

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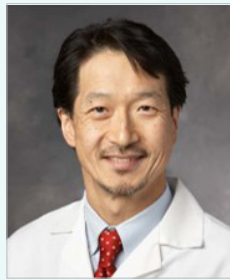
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W. Ray Kim
Mayo Clinic, USA

Self Introduction

Dr. Kim earned his medical diploma at Seoul National University.

After moving to the US, he received his GI and hepatology training at Mayo Clinic Minnesota, where he rose through the ranks to be a Professor of Medicine. In 2013, he moved to Stanford University to lead the Division of Gastroenterology and Hepatology. In 2024, he returned to Mayo Clinic to found and direct the Center for Policy and Outcomes Research in Transplant (CPORT) and continue his research and mentorship.

He has served on the boards of the American Association for the Study of Liver Disease (AASLD) and AASLD Foundation, culminating as President of the society in 2024.

Research Interests

Dr. Kim's research interest has been in prognostication in chronic liver disease. His research accomplishments include development of the Model for End Stage Liver Disease (MELD) and the Steatosis-Associated Fibrosis Estimator (SAFE) score.

Representative Publications

1. W. Ray Kim, Ajitha Mannalithara, Vivek Charu, Nakia Chung, Allison Kwong, Paul Y. Kwo, Natalie J. Torok, Steven M. Asch, Sun H. Kim. Optimal Population Screening Strategies for Liver Fibrosis Associated With Metabolic Dysfunction-Associated Steatotic Liver Disease. *American Journal of Gastroenterology*. 2025 October. DOI:10.14309/ajg.0000000000003268
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Principles of Cohort Study Design: From Question to Data

W. Ray Kim

Mayo Clinic, USA



Jeong-Hoon Lee
Seoul National University

Self Introduction

Professor Jeong-Hoon Lee earned his MD (2002), Master's (2007), and PhD (2009) from Seoul National University College of Medicine. Following his residency and fellowship at Seoul National University Hospital (SNUH), he joined the faculty in 2010 and currently serves as a Professor of Internal Medicine.

As a leading researcher, Professor Lee has spearheaded several high-impact national projects, including the development of HCC-specific aptamers, investigations into the brain-liver axis, and the implementation of AI-driven precision medical solutions. His leadership extends to key academic roles; since 2025, he has served as the Director of the Scientific Committee for the Korean Association for the Study of the Liver (KASL). He is also an active member of the Editorial Board for Hepatology (since 2024) and serves as an Associate Editor for Clinical and Molecular Hepatology (since 2026).

Research Interests

Professor Lee conducts comprehensive research in both clinical and translational hepatology. His expertise covers hepatocellular carcinoma (HCC) and chronic hepatitis B, supported by his active involvement in numerous clinical trials. His current research program emphasizes the application of artificial intelligence (AI) in clinical prediction models and the use of multiomics approaches to advance the understanding and treatment of HCC.

Representative Publications

1. Association of Chronic Hepatitis B Infection and Antiviral Treatment with the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study. *J Clin Oncol.* 2022 Oct;40(29):3394-3405. (first & corresponding author)
2. Adjuvant Immunotherapy with Autologous Cytokine-induced Killer Cells for Hepatocellular Carcinoma. *Gastroenterology.* 2015 Jun;148(7):1383-1391. (first author)
3. Discontinuation of Nucleos(t)ide Analogues Is Not Associated with A Higher Risk of HBsAg-Seroreversion after Antiviral-Induced HBsAg-Seroclearance: A Nationwide Multicenter Study. *Gut.* 2020 Dec;69(12):2214-2222. (corresponding author)
4. AI model using CT-based imaging biomarkers to predict hepatocellular carcinoma in patients with chronic hepatitis B. *J Hepatol.* 2025 Jun;82(6):1080-1088 (corresponding author)
5. A machine learning model to predict liver-related outcomes after the functional cure of chronic hepatitis B. *J Hepatol.* 2025 Feb;82(2):235-244. (corresponding author)

How to Conduct Successful Multinational Cohort Studies

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1. Introduction

Hepatology, like other areas of contemporary clinical science, has increasingly moved toward large multinational cohort studies. Single-center or even single-country datasets are often insufficient to answer important modern clinical questions, particularly when investigators want to determine whether a prediction model performs consistently across different populations and healthcare systems. Multinational cohorts help address these issues by increasing sample size, improving external validation, and incorporating broader clinical diversity. Studies involving international collaboration also tend to receive greater academic attention and are often perceived as having stronger generalizability.^{1,2}

The challenges, however, are substantial. Multinational studies are often slow and organizationally demanding. Differences in variable definitions, ethical approval processes, authorship expectations, and local regulations can easily complicate collaboration. In our experience, the main difficulties are usually not scientific, but practical and organizational. Coordinating multiple centers across different countries and time zones requires sustained communication and considerable trust between investigators.²

2. Why Researchers Participate: The Psychology of Joining a Multinational Cohort

Why do investigators participate in multinational cohort studies despite the additional workload and the absence of guaranteed academic return? The reasons might be diverse.

First, there is genuine scientific idealism. Many researchers are genuinely motivated by scientific interest. Investigators often want to determine whether findings from one country can be validated in different populations and clinical environments. Previous studies on international collaboration have consistently shown that shared scientific interest and the opportunity to contribute to globally relevant questions are major motivating factors.^{2,3}

Second, multinational studies create valuable academic networks. Collaborators may establish long-term relationships with investigators at other institutions, including senior opinion leaders and researchers with complementary expertise. These relationships frequently lead to future collaborations, visiting opportunities, grant partnerships, and joint publications.¹⁻³

Third, participation in one multinational project often facilitates future collaborations in the opposite direction. Investigators who contribute data to other groups are generally more likely to receive support when they later organize their own international studies. In relatively small academic fields such as hepatology, this type of reciprocity is common and often helps sustain long-term research networks.

3. Realistic Challenges: Effort, Authorship, and the Limits of Goodwill

In practice, however, participation is not always equally rewarding, and authorship is often the most sensitive issue. Large multinational studies may involve dozens of contributing centers while assigning only one or two first or senior authorships. As a result, investigators who invested substantial effort in extracting and harmonizing data may ultimately receive only middle authorship or consortium acknowledgment. For junior and mid-career investigators this can be an important concern because promotion and grant evaluation systems still strongly emphasize first or corresponding authorship positions. The workload required for local data cleaning and harmonization may take weeks or months, whereas academic recognition can sometimes be limited.

Another practical issue is that reciprocity is never formally guaranteed. Contributing data to one multinational study does not necessarily ensure access to external datasets in future projects. Some investigators may therefore hesitate to participate unless the collaboration structure appears fair and sustainable.

4. Practical Tips: Designing Studies that Are Easy to Join and Fair to Contributors

4.1. Leverage data that contributors have already collected.

In our experience, the practical effort required to extract and harmonize data is one of the strongest determinants of whether a center will participate. Studies that require entirely new prospective data collection across multiple countries are usually slow and difficult to coordinate. By contrast, projects using variables that are already available in existing institutional databases are much easier to organize.

An illustrative example is the wave of validation studies following the report by Choi and colleagues in JAMA Oncology, which suggested a differential hepatocellular carcinoma (HCC) risk between entecavir (ETV) and tenofovir disoproxil fumarate (TDF) in chronic hepatitis B.⁴ In response to this finding, many tertiary referral centers worldwide undertook their own validation studies and, in doing so, assembled structured datasets on patients receiving ETV or TDF. Subsequent multinational projects could therefore be organized with relatively limited additional effort on the part of contributing centers, since the necessary variables had already been curated as a by-product of these institutional validation efforts. Building on this accumulated body of data, our group developed and externally validated PLAN-B, a gradient-boosting machine-learning model for HCC prediction in antiviral-treated chronic hepatitis B, using a Korean derivation cohort and independent Korean and Caucasian validation cohorts.⁵ The same framework later supported the development of PLAN-S, a personalized antiviral selection model validat-

ed across South Korea, Hong Kong, and Taiwan.⁶ In these studies, the burden on participating centers was relatively modest because the required variables were already available in existing databases.

A similar pattern emerged after the publication of MELD 3.0 by Kim and colleagues in Gastroenterology,⁷ which generated broad international interest in validating the new score. As in the ETV/TDF example, many liver transplant centers worldwide conducted their own validation studies of MELD 3.0 and, in the process, assembled the requisite variables into structured, research-ready datasets. This accumulated body of data subsequently served as the foundation for the APEX study (Artificial Intelligence Priority Expert System for Liver Transplant), an XGBoost-based waitlist mortality prediction model to be presented as a plenary session at The Liver Week 2026.⁸ Numerous centers contributed precisely because the marginal data-extraction burden was minimal.

The broader principle illustrated by both examples is to design multinational studies around data that contributing centers have already curated through recent independent validation work in the same field. When a landmark publication generates a wave of such validation efforts, the resulting structured datasets become readily available for follow-on multinational projects, and the marginal effort required to participate is correspondingly low.

4.2. Use authorship as a deliberate reward mechanism.

The International Committee of Medical Journal Editors (ICMJE) criteria require substantial intellectual contribution, manuscript revision, final approval, and accountability for the integrity of the work.⁹ Within these principles, however, coordinating investigators still retain flexibility regarding authorship structure. In our multinational projects, we have generally tried to recognize collaborators as generously as possible when they clearly meet ICMJE criteria. This includes the use of co-first authorship or co-corresponding authorship when appropriate. Even when principal authorship is not feasible, maintaining visible and meaningful middle-author positions may still provide academic value for collaborators. In practice, a more flexible and inclusive authorship policy often improves long-term collaboration and encourages participation in future projects.

4.3. Choose intellectually compelling questions and innovative methodologies.

Beyond data burden and authorship, the scientific appeal of the study itself is a major determinant of recruitment. Investigators are generally more inclined to join multinational studies that address clinically important questions and that employ methodologies capable of generating evidence beyond what conventional cohort analysis can provide. In particular, quasi-experimental approaches such as regression discontinuity design (RDD), instrumental variable analysis, and target-trial emulation have gained increasing traction in hepatology because they can approximate randomized controlled trials (RCTs) using observational data and provide causal estimates that conventional cohort comparisons cannot deliver.

A recent example is the multinational RDD study by Shin and colleagues to be presented at The Liver

Week 2026, which exploits the ALT 80 U/L treatment threshold recommended in several Asian practice guidelines as a natural experiment to estimate the causal effect of early antiviral therapy on HCC risk in chronic hepatitis B.¹⁰ The study applied a fuzzy RDD framework to 10,776 patients from 19 centers across eight countries in Asia, Europe, and the United States, effectively mimicking a randomized comparison among patients with baseline ALT marginally below versus above the treatment threshold. Both the clinical importance of the question and the methodological novelty of the design were instrumental in recruiting a geographically diverse international network, including centers in Europe and North America well beyond the original Korean cohort.

In practice, methodological ambition functions as a second axis of attraction, complementary to low contributor burden. Studies that combine manageable data requirements with a clinically important question and a distinctive analytic framework are particularly likely to draw sustained international participation.

5. Realistic Limits: Data Use Agreements and Federated Analysis

Even with thoughtful study design and fair authorship policies, some barriers cannot easily be resolved. Data use agreements (DUAs), institutional review board policies, and national privacy regulations may prohibit the transfer of patient-level data across institutions or countries.¹¹ In some national registries, exporting raw data outside the country is not permitted under any circumstances.

For these situations, federated analysis has become an increasingly useful approach. Instead of transferring raw datasets, the coordinating center distributes standardized analytic scripts to participating sites. Local investigators run the analyses using their own data and return only aggregated results.¹¹ This approach improves privacy protection and is generally compatible with most DUAs. The main limitation is reduced flexibility for exploratory or post hoc analyses. Nevertheless, for external validation studies and confirmatory analyses, federated approaches are often sufficient.

6. Conclusion

Successful multinational cohort studies in hepatology depend less on grand design than on the following practical principles: (i) selecting questions for which contributing centers already possess the data, so that the effort required to join is minimal; (ii) treating authorship as a meaningful reward and applying ICMJE criteria liberally rather than restrictively; (iii) offering a clinically important question together with a methodologically distinctive design—particularly approaches that approximate randomized trials through quasi-experimental methods; and (iv) when data cannot cross borders, bringing the analysis to the data through federated approaches. Ultimately, multinational collaboration depends heavily on trust and long-term relationships between investigators. Studies that minimize contributor burden, recognize collaborators fairly, and offer scientifically distinctive opportunities are more likely to sustain productive international research networks over time.

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Sehee Kim

University of Ulsan

Self Introduction

Dr. Sehee Kim is a Research Associate Professor in the Department of Clinical Epidemiology and Biostatistics at the University Ulsan College of Medicine and Asan Medical Center.

She received her PhD in Biostatistics from the University of North Carolina and subsequently worked as a research fellow at the Harvard School of Public Health from 2010 to 2012. From 2012 to 2020, she served as a professor of Biostatistics at the University of Michigan, before joining the Asan Medical Center in 2020.

Research Interests

Dr. Kim’s research focused on developing statistical methods for joint modeling of longitudinal and time-to-events data and complicated time-to-event outcomes (including recurrent events, left-truncated data, cure-rate models, and competing risks analyses, etc). She also works on risk score development and evaluation.

Through collaborative research, Dr. Kim seeks to advance biological and public health science by bridging the gap between researchers, statistical methodologies, and the effective communication of results.

Representative Publications

1. Kim J, Kim JH, Im BS, Kim GH, Chu HH, Gwon DI, Shin JH, Shim JH, Yoon SM, Kim S. (2026). Atezolizumab Plus Bevacizumab for Advanced Hepatocellular Carcinoma with Macroscopic Vascular Invasion: An Inverse Probability of Treatment Weighted Analysis. *Cancers*, 18(1):33.

2. Chung SW, Kim YJ, Lim J, Choi J, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Kim S*, Choi WM*. (2025). Risk of extrahepatic malignancies in patients with Autoimmune Hepatitis: A nationwide cohort study. *Am J Gastroenterology*, 120(10):2302-2311. (* Co-corresponding author)

3. Lim J, Kim YJ, Kim S*, Choi J*. (2025). Risk of hepatocellular carcinoma in Asian patients with primary biliary cholangitis: A nationwide and hospital cohort study. *JHEP Rep.*, 7(2):1-11. (*Co-corresponding author)

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5. Hartman N#, Kim S, He K, Kalbfleisch JD. (2023). Pitfalls of the concordance index for survival outcomes. *Statistics in Medicine*, 42(13):2179-2190. (#Student under my supervision)

From Statistical Associations to Causal Inference: The Role of Regression and Propensity Score Methods

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Observational evidence is central to hepatology because randomized trials may be unavailable, infeasible, delayed, or ethically constrained. Yet many clinical questions in liver-disease research are implicitly causal: Does statin initiation reduce hepatic decompensation? Are albumin-treated inpatients dying because albumin is harmful, or because albumin is more commonly administered to patients with acute kidney injury, infection, hypotension, or high MELD? These questions cannot be answered adequately by statistical association alone. They require explicit attention to the target population, treatment or exposure definition, comparator group, timing of eligibility and treatment assignment, outcome definition, and clinically relevant confounders.

This seminar will review the conceptual distinction between statistical association and causal effect estimation in observational hepatology research. Regression adjustment will be discussed as an outcome-modeling approach for estimating exposure–outcome associations conditional on measured covariates. Propensity score methods will be presented as design-oriented approaches that aim to balance measured baseline covariates between exposed and unexposed groups, while emphasizing their limitations in the presence of unmeasured confounding, poor covariate overlap, immortal time bias, or misspecified time zero. Clinical examples from liver disease, including statin use in cirrhosis, albumin therapy, and liver transplantation, will be used to illustrate common threats to causal interpretation.

The seminar introduces the potential-outcomes framework, in which causal effects are conceptualized as comparisons between alternative outcomes under different treatment strategies in the same eligible population. In this framework, the observed outcome is only one of several possible counterfactual outcomes. For example, the causal question is not simply whether statin users have lower rates of decompensation than non-users, but what the outcome would have been in the same well-defined population under a strategy of statin initiation compared with no initiation. This distinction helps clinicians recognize why an adjusted hazard ratio or odds ratio should not automatically be interpreted as a causal effect.

Regression adjustment and propensity score methods will be presented as complementary approaches rather than competing techniques. Regression models condition on covariates in the outcome model, whereas the propensity score, $e(L)=Pr(A=1|L)e(L) = Pr(A = 1 \mid L)e(L)=Pr(A=1|L)$, models the probability

of treatment or exposure conditional on measured baseline covariates. Propensity scores may be used for matching, stratification, weighting, or covariate adjustment. A central theme is that propensity score methods reduce bias from measured baseline confounding; they do not create randomization. They cannot address unmeasured clinical judgment, poorly measured covariates, inappropriate outcome definitions, misspecified time zero, or exposure definitions that depend on future follow-up.

The seminar closes with a target-trial checklist for evaluating observational hepatology studies. The checklist asks whether eligibility criteria, treatment strategies, assignment time, follow-up, outcome definition, confounder measurement, and analysis plan are aligned with the causal question. The goal is to help clinicians interpret regression-adjusted and propensity score analyses more critically, recognizing when these methods strengthen causal interpretation and when important threats to validity remain.

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Dong Keon Yon
Kyung Hee University

Self Introduction

Prof. Dong Keon Yon is a Professor in the Department of Digital Health at Kyung Hee University College of Medicine and currently serves as Deputy Director of Center for Digital Health, Kyung Hee University Medical Center.

He received his undergraduate degree from Korea University College of Life Sciences and his medical degree from CHA University School of Medicine in 2013. He completed his internship and pediatric residency at CHA University Bundang Medical Center. He earned his PhD in Software Engineering in 2022.

Prof. Yon is a pediatrician and physician-scientist specializing in respiratory and allergic diseases, with a strong focus on big data analytics and artificial intelligence.

Research Interests

- AI
- Big-Data

Representative Publications

1. JAMA 2026, Prenatal Exposure to Acid-Suppressive Medications and Risk of Neuropsychiatric Disorders in Children
2. Nature Medicine 2026, Global burden of amphetamine, cannabis, cocaine and opioid use in 204 countries, 1990-2023: a Global Burden of Disease Study
3. Nature Medicine 2026, Global, regional, and national burden of chronic respiratory diseases and impact of the COVID-19 pandemic, 1990-2023: a Global Burden of Disease study
4. Nature Medicine 2026, Global, regional and national burden of ischemic heart disease attributable to suboptimal diet, 1990–2023: a Global Burden of Disease study
5. Nature Medicine 2025, Global, regional and national burden of dietary iron deficiency from 1990 to 2021: a Global Burden of Disease study

Applying Survival and Multivariable Analysis in Clinical Research: Interpreting the Results

Dong Keon Yon *Kyung Hee University*

Survival analysis and multivariable modeling are fundamental tools in clinical research, enabling investigators to evaluate time-to-event outcomes and adjust for complex confounding structures. However, misinterpretation of these methods remains common, particularly in the distinction between association and causation, and in the interpretation of hazard ratios under non-proportional hazards.

This lecture, “Applying Survival and Multivariable Analysis in Clinical Research: Interpreting the Results,” provides a practical and conceptually grounded framework for interpreting results from commonly used methods, including Kaplan–Meier curves, Cox proportional hazards models, and alternative approaches such as restricted mean survival time (RMST). Emphasis is placed on understanding key assumptions (e.g., proportional hazards), identifying non-linearity, and appropriately handling time-dependent variables, competing risks, and censoring. In addition, the lecture highlights the roles of confounders, mediators, colliders, and effect modifiers in multivariable analysis, offering guidance on model construction and interpretation to avoid biased estimates. Real-world examples from high-impact clinical studies are used to illustrate common pitfalls and best practices.

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DATA SCIENCE CAMP 2

Chairs

Oh Sang Kwon (Gachon Univ.)

Tae-Hee Lee (Konyang Univ.)





Kyunga Kim
Sungkyunkwan University

Self Introduction

Prof. Kyunga Kim is a Professor and Director of the Biomedical Statistics Center, Research Institute for Future Medicine, Samsung Medical Center, and is concurrently serving as Adjunct Professor at the Department of Digital Health, SAIHST (Samsung Advanced Institute for Health Sciences & Technology) and the Department of Data Convergence & Future Medicine, School of Medicine, Sungkyunkwan University.

Prof. Kim received her B.S. in Computer Science and Statistics and M.S. in Statistics from Seoul National University, followed by a Ph.D. in Statistics from Purdue University, USA. After completing her Postdoctoral Research Fellowship at the Department of Statistics, Seoul National University, she joined Sookmyung Women's University as an Assistant Professor of Statistics (2010–2014) before moving to Samsung Medical Center, where she has served in progressively senior academic roles since 2014, and was appointed to her current position as Professor and Director of the Biomedical Statistics Center in 2024.

Prof. Kim has been taking a number of professional roles, including Secretary General and Auditor General of the Korean Society of Health Information and Statistics (2015–present), and Statistical Editor of Annals of Laboratory Medicine (2013–present). She also serves as a standing member of the Institutional Review Board (IRB), Panel B, at Samsung Medical Center (2014–present).

Research Interests

- Clinical Research Design, Biomedical Statistics, Big Data and Real-World Data Analytics
- Clinical Predictive Modeling, Digital Healthcare
- Evaluation Methodology in AI- and LLM-based Clinical Decision Support Systems

Representative Publications

1. The Association between Breastfeeding and Non-Alcoholic Fatty Liver Disease in Parous Women: a Nationwide Cohort Study (2021) *Hepatology*, 74(6):2988-2997.
2. Effect of Microvascular Invasion Risk on Early Recurrence of Hepatocellular Carcinoma after Surgery and Radiofrequency Ablation. *Annals of Surgery*, 273(3):564-571.
3. Trends in Survival Rates of Non-Small Cell Lung Cancer with Use of Molecular Testing and Targeted Therapy in Korea, 2010-2020 (2023) *JAMA Network Open*, 6(3):e232002.
4. Recurrence-free Survival After Liver Transplantation Versus Surgical Resection for Hepatocellular Carcinoma: Role of High-risk MRI Features. *Transplantation*, 108(1):215-224.
5. Biomarker-integrated Prognostic Stagings for Alzheimer's Disease (2026) *Nature Communications*, 17:2235.

Target Trial Emulation in Hepatology Research: A Practical Guide from Real-World Evidence to Causal Inference

Kyunga Kim

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Background

Randomized controlled trials (RCTs) remain the gold standard for establishing causal evidence in clinical medicine. However, in hepatology, RCTs are frequently impractical or ethically untenable: rare diseases (PBC, PSC, AIH) preclude adequate power; conditions such as hepatocellular carcinoma (HCC) and cirrhosis require decades of follow-up; and the established efficacy of antiviral therapies for hepatitis B and C renders placebo controls ethically unacceptable. Conventional observational cohort designs have filled this evidential gap but are highly susceptible to immortal time bias, time-zero misalignment, and confounding by indication — all of which can yield spurious treatment effect estimates. Target trial emulation (TTE), first described by Hernán and Robins in 2016,¹ offers a principled framework to address these limitations by explicitly specifying a hypothetical RCT protocol (the “target trial”) and systematically replicating it using real-world data sources such as electronic health records (EHR), national health insurance claims, and disease registries.

How TTE Differs from Conventional Observational Studies

The fundamental distinction lies in the mandatory prespecification of a seven-component protocol before data access: (1) eligibility criteria, (2) treatment strategies defined as sustained rather than point interventions, (3) assignment procedures emulated through propensity score methods or G-estimation, (4) follow-up period, (5) outcome specification, (6) causal contrast (intention-to-treat or per-protocol), and (7) a pre-specified analysis plan.^{1,2} This structure prevents the post-hoc analytical flexibility that inflates false-positive rates in conventional cohort studies. Of particular importance is the three-way alignment principle²: eligibility assessment, treatment assignment, and follow-up must all coincide at a single, explicitly defined time-zero. This principle has direct clinical relevance: the widely cited claim that statin use reduces cancer risk was substantially attenuated when the same data were reanalyzed under the TTE framework with correct time-zero alignment³ — illustrating how methodological design alone can alter clinical conclusions drawn from identical datasets.

Applications in Hepatology: Evidence from Real-World Studies

In chronic hepatitis B (CHB), no randomized controlled trials have compared the chemopreventive

effects of statin therapy on HCC development. This was addressed by emulating a target trial using the Korean National Health Insurance Service database (n=over 1.37 million), comparing new statin initiators with propensity score–matched non-users among CHB patients. Using sequential trial emulation with explicit three-way alignment at time-zero, the study demonstrated a statistically significant reduction in HCC incidence in statin users compared to non-users (adjusted HR 0.56, 95% CI 0.39–0.80), as well as reduced liver cancer–related mortality (HR 0.59, 95% CI 0.35–0.99)⁴ — findings not reliably estimable from conventional observational analyses.

In chronic hepatitis C, no head-to-head RCTs have directly compared individual direct-acting antiviral (DAA) regimens against one another, as each was approved against placebo or historical controls. This evidence gap was addressed by emulating a randomized trial using real-world observational data from British Columbia, Canada, to compare the comparative effectiveness of sofosbuvir/ledipasvir versus other DAA regimens for genotype 1 HCV in terms of sustained virological response.⁵ This study illustrates how TTE enables rigorous head-to-head treatment comparisons that are infeasible within the conventional RCT framework, providing actionable comparative efficacy evidence to inform drug pricing and prescribing policy.

In NAFLD, TTE enables rigorous comparison of emerging pharmacological interventions (e.g., GLP-1 receptor agonists versus SGLT-2 inhibitors) for endpoints including advanced fibrosis or liver-related mortality where no direct-comparison RCTs exist. A target trial was emulated using a nationwide Taiwanese cohort and demonstrated that GLP-1 receptor agonist therapy was associated with significantly reduced risks of cirrhosis and HCC compared to long-acting insulins (cirrhosis: subdistribution HR 0.59, 95% CI 0.43–0.81; HCC: sHR 0.47, 95% CI 0.24–0.93),⁶ underscoring the clinical yield of TTE when RCTs are infeasible.

Beyond these domains, TTE has been applied to several other areas of hepatology. In cirrhosis management, sequential trial emulation using national registry data has been used to compare beta-blocker regimens for portal hypertension prevention and to evaluate antibiotic prophylaxis strategies for spontaneous bacterial peritonitis, with explicit handling of liver transplantation as a competing event. In liver transplantation, TTE frameworks applied to UNOS/OPTN and national registry data have addressed immunosuppression regimen selection, bridging therapy for HCC patients on the waitlist, and MELD threshold effects on post-listing mortality. TTE has also been applied to supportive care decisions in HCC: a target trial was emulated using the clone–censor–weight approach to estimate the causal effect of palliative care consultation on survival time in HCC patients, finding no survival harm and significant reductions in unnecessary life-sustaining interventions and hospital costs.⁷

A Practical Guide: When and How to Apply TTE

TTE is appropriate when three conditions are met: the research question is causal; a well-designed RCT is ethically or practically impossible; and a real-world dataset with sufficient sample size, longitudinal

follow-up, and covariate richness is available. Implementation follows eight sequential steps: (1) define the full target trial protocol before data access; (2) identify an appropriate data source; (3) operationalize eligibility and treatment variables; (4) align time-zero across all three dimensions; (5) address confounding using propensity score matching, inverse probability of treatment weighting (IPTW), or G-methods; (6) handle competing risks and treatment switching; (7) conduct both intention-to-treat and per-protocol analyses; and (8) report transparently according to the TARGET reporting guideline (2025, JAMA),⁸ which mandates a structured target trial protocol table, directed acyclic graph (DAG), propensity score diagnostics, and quantitative sensitivity analyses including E-values.

Conclusion

TTE does not replace RCTs; it answers causal questions that RCTs cannot. In hepatology, where barriers to randomization are unusually formidable, TTE offers a principled and increasingly accepted complement to experimental evidence. Its adoption has been acknowledged in regulatory contexts by the FDA and EMA. As hepatologists increasingly engage with large-scale real-world datasets, fluency in TTE methodology will be an essential competency in evidence-based clinical research.

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Sun Jae Jung
Yonsei University

Self Introduction

Sun Jae Jung, MD, PhD, is an Associate Professor in the Department of Preventive Medicine at the Yonsei University College of Medicine, Korea, where she teaches epidemiological methods and causal inference.

Dr. Jung is a leading epidemiologist whose research program applies advanced epidemiological and causal inference methods to elucidate the dynamic, bidirectional relationships between mental and physical health. She has developed a substantial body of work investigating how major mental health conditions—including post-traumatic stress disorder (PTSD) and major depressive disorder—interact with cardiovascular, endocrine, and reproductive health across the life course.

As Principal Investigator of Korea’s first nationwide child and adolescent self-harm and suicide cohort, she has played a pioneering role in establishing population-level evidence on youth suicide and self-harm. She also serves as the PI for a transdisciplinary hospital-based cohort built in collaboration between clinical disciplines and preventive medicine, grounded in transplant surgery and designed to bridge biological, behavioral, and clinical epidemiology. Across these platforms, she leads multiple studies integrating national big data—including electronic health records, registries, and claims databases—to investigate the interplay between PTSD, trauma exposure, and physical health outcomes.

Her research further examines how biological and social determinants jointly shape suicidal behaviors, psychological resilience, and long-term mental health trajectories. Dr. Jung has served as Principal Investigator or Co-Principal Investigator on major national projects supported by more than \$20 million from the Korean Ministry of Health and Welfare and other national funding agencies.

Her excellence has been recognized with several prestigious awards, including the Young Investigator Award at the International Symposium on Resilience Research (2019), the Young Epidemiologist Award from the Korean Society of Epidemiology (2021), and the Hanmi Young Medical Scientist Award from the Korean Medical Women’s Association (2024). Dr. Jung completed her MD at Yonsei University College of Medicine, received her board certification in Preventive Medicine from Seoul National University College of Medicine, earned her PhD in Epidemiology from Seoul National University, and completed postdoctoral training as a Yerby Fellow at the Harvard T.H. Chan School of Public Health.

Research Interests

Her research aims to identify preventable causes of mental health outcomes at the population level. Trained in epidemiology with a background in cancer epidemiology, She approaches mental health not as discrete clinical events but as dynamic trajectories shaped by time, space, and system-level conditions. Her work focuses on distinguishing individual-based and system-based risks, examining how social environments, service structures, and policy contexts influence the emergence, detection, and progression of mental health problems. By integrating large-scale administrative data, longitudinal cohort studies, and life-course perspectives, Her research seeks to inform precision public mental health strategies that move beyond treatment-centered models toward prevention-oriented population interventions.

Representative Publications

1. Kang S, Yang JS, Yun BH, Gelaye B, An SK, Jung SJ*. (2025) Antipsychotic continuation during pregnancy and risk of postpartum relapse in women with schizophrenia: nationwide register-based study. Br J Psychiatry. 2025 Sep;227(3):614-621. doi: 10.1192/bjp.2024.247. Epub 2025 Jan 10. PMID: 39789797; PMCID: PMC12425161.

2. Kang S, Kim J, Yang JS, Jeon YJ, Lee HH, Suglia SF, Tsai AC, Kang JI, Jung SJ*. (2024) Use of renin-angiotensin system blockers and posttraumatic stress disorder risk in the UK Biobank: a retrospective cohort study. BMC Med. 2024 Oct 23;22(1):489. doi: 10.1186/s12916-024-03704-5. PMID: 39443947; PMCID: PMC11515478.

Application of Directed Acyclic Graphs (DAGs) in Liver Research

Sun Jae Jung Yonsei University

Estimating causal effects is a fundamental goal in epidemiology and clinical research. Although randomized controlled trials (RCTs) provide the most robust framework for causal inference, they are often limited by ethical and practical constraints. As a result, observational studies are widely used in liver research, but they are inherently susceptible to biases such as confounding, selection bias, and information bias. In this context, Directed Acyclic Graphs (DAGs) offer a structured approach to explicitly represent causal assumptions and guide appropriate analytical decisions.

This study aims to provide a concise overview of (1) the basic principles of DAGs, (2) the concept of colliders and associated bias, (3) examples of DAGs used in our research, and (4) the current use and limitations of DAGs in liver research.

1. Basic Concepts of DAGs

A Directed Acyclic Graph is a graphical representation of the assumed data-generating process, where variables are depicted as nodes and causal relationships as directed edges. DAGs do not quantify relationships but clarify causal structure, ensuring that no variable causes itself (acyclicity).

A key strength of DAGs is that they require researchers to define the causal estimand before analysis. Within this framework, variables are classified based on their roles:

- Confounders: common causes of exposure and outcome (should be adjusted for)
- Mediators: variables on the causal pathway
- Colliders: common effects of two variables (should not be adjusted for)

This classification is critical for determining valid adjustment strategies.

2. Confounding and Adjustment

In observational research, statistical adjustment is often used to estimate independent associations. However, without a clear causal framework, such adjustment may introduce bias. DAGs enable identification of backdoor (confounding) paths, which must be blocked to obtain unbiased causal estimates.

A sufficient adjustment set is defined as the minimal set of variables that blocks all confounding paths while preserving causal pathways. Importantly, DAGs demonstrate that indiscriminate adjustment can lead to overadjustment or bias, challenging the assumption that more covariates improve validity.

3. Collider Bias

A central concept in DAG-based reasoning is the collider. Unlike confounders, colliders naturally block paths and should not be conditioned on. However, when a collider (or its descendant) is adjusted for, it opens a non-causal path, introducing collider bias.

This issue is particularly relevant in clinical research, where variables influenced by multiple causes (e.g., biomarkers or intermediate clinical conditions) may inadvertently be treated as covariates. Additionally, adjusting for mediators under certain conditions can also induce collider bias, especially when unmeasured confounders are present.

4. Application in Liver Research

In our research, DAGs were used to represent hypothesized relationships among exposures (e.g., viral infection, alcohol use), intermediate variables, and liver-related outcomes. These models helped identify confounders, clarify causal pathways, and avoid inappropriate adjustment.

A review of recent liver studies shows increasing use of DAGs in contexts such as surgical outcomes, Mendelian randomization, and metabolic liver disease. DAGs are commonly used to define confounders and illustrate causal assumptions, although their depth of application varies across studies.

5. Limitations

Despite their usefulness, DAGs have several limitations:

- They rely heavily on untestable assumptions about causal structure
- There is no standardized approach to DAG construction
- Complex biological processes may be oversimplified
- Unobserved variables are difficult to fully account for
- In practice, DAGs are sometimes used superficially without influencing analysis

6. Conclusion

DAGs provide a powerful framework for improving causal inference in observational studies by clarifying assumptions and guiding adjustment strategies. They are particularly valuable for avoiding confounding and collider bias, two major threats to validity.

However, their effectiveness depends on careful construction and thoughtful integration into the research process. In liver research, while the use of DAGs is growing, more rigorous and consistent application is needed.

Ultimately, this work highlights that appropriate causal reasoning—supported by DAGs—is essential for valid interpretation of observational data.



Ji Won Han
The Catholic University of Korea

Self Introduction

Prof. Ji Won Han is an Assistant Professor in the Department of Gastroenterology and Hepatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea. She is a hepatologist and clinician-scientist whose work focuses on hepatocellular carcinoma (HCC), liver immunology, liver transplantation, and chronic viral hepatitis.

Prof. Han received his M.D. from the College of Medicine, The Catholic University of Korea, in 2011, and completed his internship and residency in Internal Medicine at the Catholic Medical Center, where she obtained the Korean Board of Internal Medicine in 2016. She earned his Ph.D. in Medical Science and Engineering from the Korea Advanced Institute of Science and Technology (KAIST) in 2020, with research focused on T-cell immunity in chronic viral hepatitis and liver transplantation, and subsequently completed his clinical fellowship in Gastroenterology and Hepatology at Seoul St. Mary's Hospital in 2022.

Prof. Han currently serves as a member of the Research and Academic Committees of the Korean Association for the Study of the Liver (KASL), an Editorial Board member of Clinical and Molecular Hepatology, and a member of the Academic and Planning Committees of the Korean Liver Cancer Association (KLCA). He has been recognized with numerous honors, including the 14th LG Chem Future Medical Scientist Award (2022), the KLCA Young Investigator Award in Basic and Translational Research (2025), the Yu Sun-hee Theresa Cancer Research Award (2025), and the SIDDS Young Investigator Award (2026).

Research Interests

- Hepatocellular Carcinoma: Immunotherapy Biomarkers and Treatment Selection
- AI/Machine-Learning Applications in Hepatology (Prediction Models, Large Language Models)
- T-cell Immunology in Liver Disease

Representative Publications

1. Yang K, Lee J, Jang JW, Sung PS, Han JW (Corresponding author). "Evaluating the Clinical Utility of Large Language Models for Hepatocellular Carcinoma Treatment Recommendations: A Nationwide Retrospective Registry Study" PLOS Medicine. 2026.
2. Lee J, Yang H, Bae SH, Cho HS, Sung PS, Jang JW, et al., Han JW (Corresponding author). "Liver Stiffness Measured by Vibration-controlled Transient Elastography Predicts Hepatic Decompensation in Patients with Hepatocellular Carcinoma Receiving Systemic Treatments" Liver Cancer. 2026 .
3. Kim HU, Han JW (Corresponding author), Sung PS, Jang JW, Yoon SK, Choi HJ, You YK. "Machine Learning Based Selection of Resection versus Transplant Improves Survival in Hepatocellular Carcinoma" JAMA Network Open. 2025.
4. Han JW, Lee SK, Kwon JH, Nam SW, Yang H, Bae SH, et al., Jang JW. "A Machine Learning Algorithm Facilitates Prognosis Prediction and Treatment Selection for Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma" Clinical Cancer Research. 2024.
5. Han JW, Kang MW, Lee SK, Yang H, Kim JH, Yoo JS, Cho HS, Jang EJ, Seo DH, Kwon JH, Nam SW, Bae SH, Jang JW, Choi JY, Yoon SK, Sung PS. "Dynamic peripheral T-cell analysis identifies on-treatment prognostic biomarkers of atezolizumab plus bevacizumab in hepatocellular carcinoma" Liver Cancer. 2024

Application of Vibe Coding in Liver Disease Research

Ji Won Han *The Catholic University of Korea*

Background

The emergence of large language models has opened an unexpected avenue for clinician-scientists: the ability to build functional research software through natural language alone. Termed vibe coding by Andrej Karpathy in 2025, this approach repositions the investigator not as a programmer but as a domain expert who communicates intent to an AI that handles the implementation. For hepatologists managing heterogeneous data—laboratory trends, cross-sectional imaging, histopathology, and long-term outcomes—the practical implication is significant. Technical implementation has historically been a rate-limiting step; vibe coding moves that bottleneck upstream, to the clarity of the research question itself.

Tools and Methods

Clinicians approaching vibe coding encounter a range of tools that differ in depth of AI integration. Conversational interfaces such as Claude or ChatGPT generate code through iterative dialogue in a browser with no local setup required; direct API access allows investigator-built scripts to query AI programmatically for repetitive tasks such as extracting structured data from large volumes of free-text reports; Claude Code is a development-focused terminal agent that reads, writes, and executes code within a local project directory—suited to building and iterating on analysis pipelines; and Cowork is a desktop automation tool that directs AI to operate the computer itself, opening applications, managing files, and running scheduled tasks, making it well-suited to recurring non-coding workflows. Across all of these modalities, a useful prompt specifies what data are available, what the output should look like, and any constraints on format or tooling. When errors arise, pasting the error message back verbatim is usually the most efficient path to a fix. What AI cannot supply is the clinical judgment that structures the work: the question, the analytic approach, and a critical eye on whether the result makes sense.

Proof-of-Concept Applications in Liver Disease Research

The following examples reflect actual use of these tools in ongoing hepatology research. A literature management application was developed to organize relevant articles with AI-generated summaries and personal annotations into a searchable local database, supporting systematic reading, research

planning, and manuscript preparation. Connected to Cowork, it delivers a weekly briefing of newly indexed articles without manual input. A machine learning pipeline for predicting hepatic decompensation in patients with advanced HCC receiving systemic therapy—presented at TLW 2025—was developed with assistance for code generation and web calculator implementation, while the study design, methodology, and clinical interpretation remained investigator-driven throughout. A radiomics application built on PyRadiomics was assembled to automate CT feature extraction for an ongoing therapeutic response prediction study in patients with HCC—a workflow that would previously have required dedicated informatics support. An interactive cost-effectiveness tool comparing prophylactic antiviral strategies for hepatitis B reactivation was prototyped and is now undergoing validation and data/manuscript preparation. A matching-adjusted indirect comparison of first-line immunotherapy regimens in HCC (TLW 2026, oral poster presentation) illustrates a broader dimension of vibe coding: AI informed not only the statistical code but the methodological design—including covariate selection, the choice of indirect comparison framework, and the tools (WebPlotDigitizer) used for data extraction from published survival curves.

Conclusions

Vibe coding does not make clinical research easier—it makes a different set of skills decisive. Knowing how to frame a meaningful clinical question, select an appropriate methodology, and critically evaluate the output matters more than knowing how to write code. For hepatologists with training in clinical reasoning and study design, the tools are already accessible. The more pressing challenge may be one of perception: the barrier to computational work is substantially lower than most clinicians assume, and iterative dialogue with AI can yield analytic infrastructure that would otherwise take weeks to build.

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4. From technology adopters to creators: leveraging AI-assisted vibe coding to transform clinical teaching and learning. Med Teach. 2025. Taylor & Francis Online
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Hyesung Lee
Kangwon National University

Self Introduction

Prof. Hyesung Lee is a Associate Professor of the Department of Medical Informatics, Kangwon National University College of Medicine. Prof. Lee received his B.A. in Statistics (2015), M.S. in Pharmaceutical Industrial Science (2017) and Ph.D. in Pharmacoepidemiology (2020) from Sungkyunkwan University.

His professional career spans academia, the pharmaceutical industry, and the public sector. Prior to pursuing his doctoral studies, he gained industry experience as an Assistant at CJ Healthcare and public sector experience as an Assistant Manager at the Korea Institute of Drug Safety & Risk Management (KIDS).

He currently serves as a Member of the Training and Education Committee of the Korean Society of Epidemiology (2023-2026) and as Associate Editor of the Korean Society of Pharmacoepidemiology and Risk Management (2025-).

Research Interests

- Pharmacoepidemiology - Parental and Offspring Health, Drug & Vaccine Safety and Effectiveness
- Environmental Epidemiology

Representative Publications

1. Lee H, Choi EY, Pasternak B, Cesta CE. Sedatives in pregnancy and psychiatric outcomes in offspring. BMJ. 2026 Apr 29;393:s705. doi: 10.1136/bmj.s705. PMID: 42055575. (First & Corresponding Author)
2. Hong B, Lee H, Jung K, Rhee SY, Yon DK, Shin JY. Sodium-glucose cotransporter-2 inhibitors and risk of autoimmune rheumatic diseases: population based cohort study. BMJ. 2025 Oct 15;391:e085196. doi: 10.1136/bmj-2025-085196. PMID: 41093607; PMCID: PMC12522398. (Co-first Author)
3. Lee H, Yoon D, Kim JH, Noh Y, Joo EJ, Han JY, Choe YJ, Shin JY. Association of Influenza Vaccination During Pregnancy with Health Outcomes in Mothers and Children: A Population-Based Cohort Study. Clin Pharmacol Ther. 2025 May;117(5):1381-1392. doi: 10.1002/cpt.3565. Epub 2025 Jan 23. PMID: 39854110. (Co-first Author)
4. Choi A, Lee H, Jeong HE, Lee SY, Kwon JS, Han JY, Choe YJ, Shin JY. Association between exposure to antibiotics during pregnancy or early infancy and risk of autism spectrum disorder, intellectual disorder, language disorder, and epilepsy in children: population based cohort study. BMJ. 2024 May 22;385:e076885. doi: 10.1136/bmj-2023-076885. PMID: 38777351; PMCID: PMC11109903. (Co-first Author)
5. Lee H, Baek YH, Kim JH, Liao TC, Lau WCY, Man KKC, Qin X, Wood S, Ilomäki J, Bell JS, Lai EC, Leung MTY, Chan AYL, Chui CSL, Wong ICK, Shin JY. Trends of polypharmacy among older people in Asia, Australia and the United Kingdom: a multinational population-based study. Age Ageing. 2023 Feb 1;52(2):afad014. doi: 10.1093/ageing/afad014. PMID: 36821644. (First Author)

Sensitivity Analysis Methodologies in Epidemiologic Research

Hyesung Lee Kangwon National University

Sensitivity analysis is a core component of epidemiologic research using real-world healthcare data. Because findings from observational database studies often depend on operational definitions, design choices, measurement assumptions, and analytic decisions, sensitivity analyses are essential for evaluating the robustness and credibility of study results.

This lecture will provide a concise, practice-oriented overview of sensitivity analysis in pharmacoepidemiologic and clinical epidemiologic research. Rather than presenting sensitivity analysis as a separate statistical procedure, the lecture will explain it as a structured approach to examining whether study findings remain consistent under alternative but plausible assumptions. Key components will include exposure definition, outcome definition, comparator selection, cohort inclusion and exclusion criteria, washout and look-back periods, censoring rules, covariate assessment, propensity score methods, and approaches to residual confounding.

For each component, the lecture will briefly introduce the methodological rationale and then illustrate how it can be applied in real-world epidemiologic studies. Practical examples will be used to show how different analytic choices may address specific sources of uncertainty or bias, and how the results of sensitivity analyses should be interpreted in relation to the primary analysis. Particular attention will be given to distinguishing sensitivity analyses that strengthen causal interpretation from those that merely repeat the primary analysis with minor variations.

The lecture will also incorporate practical lessons from manuscript revision. Based on actual revision experiences, it will discuss how sensitivity analyses are requested by reviewers, how additional analyses can be justified scientifically, and how their results can be reported in the Methods, Results, Tables, Figures, and Discussion sections. The lecture will emphasize how to communicate robustness clearly while avoiding overstatement of causal conclusions.

Through this lecture, participants will learn how to design, conduct, interpret, and report sensitivity analyses as an integrated part of epidemiologic research. The ultimate goal is to help researchers use sensitivity analysis not as a checklist item, but as a transparent and scientifically meaningful tool for strengthening the validity and interpretability of observational studies.

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2. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology. 2009.

3. Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. Springer; 2009.

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5.. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies Conducted using Observational Routinely-collect-ed health Data statement. PLoS Medicine. 2015.

6.. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to improve reproducibility and facilitate validity assessment for healthcare database studies. Pharmacoepidemiology and Drug Safety. 2017.

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TRANSLATIONAL HEPATOLOGY

Integrative Approaches to Liver
Diseases: Biomarkers, Microbiome, and
Mendelian Randomization

Chairs
Jaeseok Hwang (Keimyung Univ.)
Neung Hwa Park (Univ. of Ulsan)





Chien-Jen Chen
Academia Sinica, Taiwan

Self Introduction

Professor Chien-Jen Chen received his Sc.D. majored in epidemiology and human genetics from the Johns Hopkins University. He was the founding director of Graduate Institute of Epidemiology and Preventive Medicine, and the Dean of College of Public Health of National Taiwan University. He is now a distinguished professor and president-elect of Academia Sinica in Taiwan. He is internationally well-known for his longitudinal REVEAL-HBV/HCV study, which pioneered the paradigm of viral load as well as molecular and genomic biomarkers in the long-term risk prediction and clinical management of end-stage liver diseases of patients with chronic viral hepatitis. He has been elected as an academician and council member of Academia Sinica, a member of World Academy of Sciences, an international member of US National Academy of Sciences, and an academician and council member of Pontifical Academy of Sciences.

Research Interests

- Chronic Viral Hepatitis and Liver Cancer
- Molecular and Genomic Biomarkers
- Risk Calculators, Precision Preventive Medicine

Representative Publications

1. Tseng TC, Huang SC, Pan MH, Liu CJ, Chen CJ, Yang WT, Tai CH, Su TH, Yang HC, Liu CH, Chen PJ, Yang HI*, Kao JH*. Hepatitis B surface antigen levels identifies patients with inactive chronic hepatitis B from Asia with HCC risk below surveillance threshold. Gut 2025; 74(11):1896-1904.
2. Kim GA, Lim YS*, Han S, Choi GH, Choi WM, Choi J, Sinn DH, Paik YH, Lee JH, Lee YB, Cho JY, Neo NY, Yuen MF, Wong VW, Chan SL, Yang HI, Chen CJ. Viral load-based prediction of hepatocellular carcinoma risk in non-cirrhotic chronic hepatitis B patients: a multinational study for the development and external validation of a new prognostic model. Ann Intern Med 2024; 177(10):1308-1318.
3. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, Ahn SH, Chen CJ*, Wong VW, Seto WK. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12:568-574.
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Promotion of Precision Health Using Molecular and Genomic Biomarkers in Liver Diseases

Chien-Jen Chen *Academia Sinica, Taiwan*

The pathogenesis of liver diseases is a complicated multistage process driven by the interaction of multiple host and environmental risk factors.¹ Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), chemical toxins, lifestyle characteristics, nutritional intake, metabolic dysfunction, and genetic susceptibility interplay with each other in the progression from inflammation, fibrosis, cirrhosis to cancer. Molecular biomarkers of chronic HBV and HCV infection have been successfully used for the precision prediction, prevention, early detection, and treatment of liver diseases.²⁻⁶ There was a dose-response relation between HCC risk and serum level of aflatoxin B₁ (AFB1)-albumin adducts in patients with chronic HBV/HCV infection and habitual alcohol drinkers.⁷⁻⁸ The HCC risk associated with aflatoxin exposure was observed only in chronic HBV carriers with null genotypes of glutathione S-transferase (GST) M1 or T1,⁹ suggesting a striking carcinogen-susceptibility genes interaction. There was a reverse dose-response relation between HCC risk and serum level of retinol and selenium in chronic HBV carriers,¹⁰⁻¹¹ and the inverse association between selenium and HCC was most striking among cigarette smokers and among those with low plasma levels of retinol or various carotenoids.¹²

Elevated serum androgen level was found to be associated with an increased risk of HCC in chronic HBV carriers.¹³ Fewer CAG repeats of androgen receptor gene, A1 allele of CYP17, V allele of SRD5A2 V89L were significantly associated with an increased HCC risk.¹⁴⁻¹⁵ Genetic polymorphisms of human leucocyte antigens, xenobiotic metabolism enzymes, DNA repair enzymes, hormone-related enzymes and receptors, oncogenes, and tumor suppressor genes have been documented to be associated with HCC risk in chronic HBV/HCV carriers and non-carriers.^{1, 16-17}

While the elimination of HBV and HCV through mass screening and anti-viral therapy may minimize liver disease risk in chronic HBV/HCV carriers; the prevention, early detection and prompt treatment of metabolic abnormality may reduce the risk of MALSD and its related end-stage liver diseases. In the era of precision health, we may promote liver health using molecular and genomic biomarkers to predict, prevent, detect, and treat liver diseases at stages as early as possible.

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3. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA-J Am Med Assoc 2006;295:65-73.
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Ki-Tae Suk
Hallym University

Self Introduction

1993.02-1999 Medical Degree, Yonsei University, Wonju College of Medicine, Korea
2003.02-2015 Master of Medicine, Graduate School, Yonsei University, Seoul, Korea
2010.08-2012 Doctor of Medicine, Graduate School, Yonsei University, Seoul, Korea
2014.09-2016 Post-Doctor Research Scholar, Medicine, Columbia University, New York, USA
2016-09 Professor, Hallym University, Chuncheon, Korea

Research Interests

Liver Disease: Cirrhosis and Hepatocellular Carcinoma
Microbiota: Metabolites of Microbiome, Post-Bioitcs, Multi-omics Associated Mechanism
Pharmabiotics: Therapeutics and Diagnostic Marker

Representative Publications

1. Eom JA, Park IG, Hyun JY, Lee NY, Kwon GH, Yoon SJ, Won SM, Ham YL, Lee KJ, Han SH, Yang DH, Kim DJ, Suk KT. Pharmabiotics, *Phocaeicola dorei*, ameliorates cholestatic liver fibrosis by alleviating macrophage efferocytosis of neutrophils. *Nat Commun*. 2026 May 17.
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Microbiome-Metabolite Cross-Talk in Liver Diseases

Ki-Tae Suk *Hallym University*

The gut-liver axis influences hepatic physiology and homeostasis through bidirectional interactions, and high-fat diets and environmental factors can disrupt gut-liver axis. Gut barrier dysfunction and imbalances in the gut microbiome play a significant role in the pathogenesis of liver disease through metabolic changes, increased gut permeability, and the influx of microbial metabolites. Imbalances in TMAO, short-chain fatty acids, endogenous ethanol, and tryptophan metabolites introduced due to gut barrier disruption disrupt immune metabolism. This leads to a loss of immune surveillance capabilities in hepatic immune cells. This review examines the disturbances and causes of gut-liver axis components in liver disease and explores the immune metabolic signals occurring in the disease state. Finally, it presents potential therapeutic strategies for liver disease based on the gut-liver axis.



Sung Won Chung
University of Ulsan

Self Introduction

Prof. Sung Won Chung is an Assistant Professor of the Department of Internal Medicine, Ulsan University College of Medicine.

Prof. Chung graduated from Seoul National University College of Medicine with his medical degree in 2014 and completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital.

Research Interests

Prof. Sung Won Chung is Interested in MASLD and HCC

Representative Publications

1. SW Chung, JS Kim, W-M Choi, J Choi, D Lee, JH Shim, Y-S Lim, HC Lee and KM Kim, Synergistic Effects of Transarterial Chemoembolization and Lenvatinib on HIF-1a Ubiquitination and Prognosis Improvement in Hepatocellular Carcinoma. Clinical Cancer Research.2025; accepted.
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Genetic Causal Inference in Liver Diseases Using Mendelian Randomization

Sung Won Chung University of Ulsan

The field of hepatology is undergoing a major transition, driven by the reclassification of non-alcoholic fatty liver disease into the broader framework of steatotic liver disease, including metabolic dysfunction-associated steatotic liver disease (MASLD) and MetALD.¹ In parallel, large-scale genome-wide association studies and biobank resources have enabled the application of Mendelian randomization (MR) as a genetic causal inference framework in liver disease research. MR uses germline genetic variants as instrumental variables to estimate the causal effects of modifiable exposures on clinical outcomes, thereby reducing bias from confounding and reverse causation that commonly affect conventional observational studies.^{2,3}

This review will summarize the principles, assumptions, and practical interpretation of MR in hepatology. Particular attention will be given to instrument strength, horizontal pleiotropy, sample overlap, population stratification, collider bias, and phenotype heterogeneity, which are especially relevant when studying complex liver diseases.^{3,4} Recent MR applications will then be discussed across major domains of hepatology. In MASLD/MASH, MR studies using imaging-derived liver phenotypes and genetically proxied NAFLD have refined the causal architecture linking liver fat, obesity, type 2 diabetes, and steatohepatitis.^{5,6} In lifestyle epidemiology, MR has challenged several observational narratives, including the proposed benefit of moderate alcohol consumption and the protective effect of habitual coffee intake.^{7,8,9} In hepatocellular carcinoma, MR studies of lipid traits and liver fat illustrate how genetic evidence can clarify—but also complicate—the interpretation of the “lipid paradox” and variant-specific effects of hepatic steatosis.^{10,11}

Finally, this review will discuss the expanding role of drug-target and multi-omics MR for therapeutic prioritization, including genetic evidence related to HSD17B13, GLP-1/GIP receptor pathways, SGLT2 inhibition, and the gut–liver axis.¹²⁻¹⁵ Overall, MR should not be interpreted as a substitute for randomized trials; rather, it serves as a complementary tool for prioritizing causal risk factors, testing biological plausibility, and selecting therapeutic targets in liver disease research.

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KLTS SYMPOSIUM 1

Liver Transplantation for HCC with Portal Vein Tumor Thrombosis: Redefining the Impossible

Chairs

Young Kyoung You (The Catholic Univ. of Korea)

Hae Won Lee (Seoul National Univ.)





Jae Geun Lee
Yonsei University

Self Introduction

Prof. Jae Geun Lee is a Professor of the Department of Surgery, Yonsei University College of Medicine graduated from Yonsei University College of Medicine with his medical degree in 2009 and completed his internship and residency at the Department of Surgery at Severance Hospital, receiving his diploma in General Surgery in 2014.

- Member of Academic Committee in Korean Liver Cancer Association
- Member of Academic Committee in Korean Association of HBP Surgery
- Member of Academic Committee in Korean Transplantation Society
- Member of International Collaboration Committee in Korean Liver Transplantation Society
- Member of Academic Committee in International Living Donor Liver Transplantation Society
- Member of Academic Committee in International Society of Liver Surgeons

Research Interests

- Liver Transplantation
- HCC
- Immunosuppressant
- Infection

Representative Publications

1. Entecavir versus tenofovir on the recurrence of hepatitis B–related HCC after liver transplantation: A multicenter observational study. *Liver Transpl.* 2023 Dec 1;29(12):1272-1281.
2. Risk factors for late-onset *Pneumocystis jirovecii* pneumonia in liver transplant recipients. *Int J Infect Dis.* 2023 Jun;131:166-172. Epub 2023 Apr 11.
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Who, When, and Why: Selection Criteria and Timing for Liver Transplantation in HCC with Portal Vein Tumor Thrombosis

Jae Geun Lee Yonsei University

1. Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. Among the most challenging presentations of advanced HCC is the development of portal vein tumor thrombosis (PVTT), which occurs in approximately 10% to 40% of patients at the time of diagnosis. Historically, the presence of macrovascular invasion, particularly PVTT, has been considered an absolute contraindication for liver transplantation (LT). This exclusion was primarily due to dismal post-transplant survival rates and near-universal recurrence, driven by systemic micrometastases and aggressive tumor biology.

However, the therapeutic landscape for HCC has evolved dramatically over the last decade. The advent of highly effective locoregional therapies (LRT), refined surgical reconstruction techniques, and powerful systemic immunotherapy/tyrosine kinase inhibitor (TKI) combinations has prompted a paradigm shift. Today, clinicians are transitioning from rigid, morphology-based exclusion criteria (such as the Milan Criteria) toward a biology-driven, personalized approach.

This review explores the critical dimensions of **Who** should be considered, **When** transplantation should occur, and **Why** this aggressive surgical strategy is justified for selected HCC patients presenting with PVTT.

2. The “Why”: Rationale for Challenging the Status Quo

The primary justification for expanding liver transplantation to include patients with PVTT lies in the poor prognosis associated with non-surgical standards of care.

Limitations of Non-Transplant Therapies

For patients with HCC and PVTT, conservative treatments—including systemic therapies (such as atezolizumab plus bevacizumab or sorafenib) and locoregional interventions (TACE, TARE)—offer only palliative benefits. Without intervention, the median survival of these patients ranges from 2 to 4 months. Even with modern systemic regimens, median survival rarely exceeds 12 to 18 months. Death in these patients is frequently driven not only by oncological progression but also by liver failure, portal

hypertension, variceal bleeding, and intractable ascites caused by the obstructed portal vein.

The Curative Potential of Liver Transplantation

Liver transplantation addresses two pathologies simultaneously: it removes the entire oncological burden (including intrahepatic metastases and the vascular thrombus) and cures the underlying cirrhotic liver disease. Emerging clinical trials and retrospective cohorts from pioneering centers in Asia and Europe demonstrate that when patients with PVTT are carefully selected and successfully downstaged, they can achieve a 5-year survival rate exceeding 50%50\%50%. While this is lower than the 70–80%70\text{--}80\%70–80% 5-year survival observed in patients meeting the Milan Criteria, it represents an extraordinary survival benefit compared to palliative care.

3. The “Who”: Selection Criteria for Candidates

Expanding liver transplantation to PVTT patients carries a risk of “utility vs. equity” in organ allocation. Because donor organs are scarce, candidates with PVTT must be meticulously screened to identify those who possess favorable tumor biology and a low risk of systemic recurrence.

Selection criteria are broadly classified into anatomical, biological, and functional response parameters:

A. Anatomical Extent of PVTT (The Vp Classification)

The extent of portal vein invasion is a dominant prognostic factor. The Japanese VP classification is widely utilized to stratify these patients:

- **Vp1:** Tumor thrombus in peripheral portal vein branches.
- **Vp2:** Thrombus in segmental branches.
- **Vp3:** Thrombus in lobar/sectorial branches (left or right main branch).
- **Vp4:** Thrombus in the main portal vein trunk or contralateral branch.

Selection Rule: Generally, patients with **Vp1, Vp2, and select Vp3** thrombosis are considered potential candidates for downstaging and subsequent transplantation. True **Vp4** involvement remains a relative or absolute contraindication in most centers due to the extremely high risk of systemic hematogenous spread and technical difficulties in securing a tumor-free vascular margin during hepatectomy.

B. Tumor Biology and Biomarkers

Morphology alone does not dictate outcomes; tumor biology is paramount. The primary biomarkers used to assess biological aggressiveness include:

- **Alpha-Fetoprotein (AFP):** A highly elevated pre-treatment AFP level is a surrogate marker for microvascular invasion and poor differentiation. Candidates must exhibit low baseline AFP or, more importantly, a significant decrease in AFP levels in response to neoadjuvant therapy.
- **Des-gamma-carboxy prothrombin (DCP):** Used in conjunction with AFP to monitor biological ac-

tivity and treatment response.

- **Neutrophil-to-Lymphocyte Ratio (NLR):** Elevated NLR serves as an index of systemic inflammatory response, which correlates with early recurrence.

C. Response to Neoadjuvant Downstaging

The ultimate “Who” is defined by the patient’s response to downstaging. A patient should only be considered for transplantation if their tumor demonstrates a sustained response to neoadjuvant therapy, classified by modified RECIST (mRECIST) criteria as a complete response (CR) or partial response (PR) in both the primary tumor and the thrombus.

4. The “When”: Strategic Timing and the “Test of Time”

Determining the timing of liver transplantation in patients with PVTT requires balancing two opposing risks: the risk of tumor progression during the waiting period versus the risk of transplanting a biologically aggressive tumor too early.

The Concept of the “Test of Time”

The “test of time” is an observational period of **3 to 6 months** following successful downstaging therapy. This delay is mandatory for several reasons:

1. **Filtering Aggressive Phenotypes:** Patients with occult extrahepatic micrometastases or highly aggressive clones will progress rapidly during this window, sparing them from futile transplantation.
2. **Assessing Thrombus Viability:** Radiographic evaluation (via dynamic MRI or CT) during this window confirms whether the portal vein thrombus has become completely necrotic (non-viable) and fibrotic.
3. **Normalizing Tumor Markers:** It allows time for serum AFP levels to drop to acceptable thresholds (typically <100–400 ng/mL).

Downstaging Protocols

To bridge patients to transplantation and achieve the necessary response, aggressive multimodal downstaging protocols are employed:

- **Transarterial Radioembolization (TARE) with Yttrium-90** (TARE is highly effective for PVTT because it delivers high-dose radiation directly to the thrombus via the hepatic artery without causing portal vein ischemia.
- **Stereotactic Body Radiation Therapy (SBRT):** Highly precise external beam radiation can target and shrink the portal vein thrombus, facilitating recanalization.
- **Systemic Therapies:** Emerging protocols combine TKIs or immune checkpoint inhibitors (anti-PD-1/PD-L1) with locoregional therapies to synergistically clear circulating tumor cells and downsize the thrombus.

5. Surgical and Technical Considerations

Even when a candidate is biologically eligible, technical feasibility must be evaluated. Transplanting a patient with PVTT often requires complex vascular reconstruction.

During the recipient hepatectomy, the surgeon must obtain a **pathologically clear margin** on the portal vein. If the thrombus has resolved or retracted, standard anastomosis may be possible. However, if the portal vein wall is damaged or fibrotic, advanced surgical techniques are required:

- **Thrombectomy/Eversion Endarterectomy:** Stripping the organized thrombus from the portal vein wall.
- **Vascular Interposition Grafts:** Utilizing donor iliac vein grafts to bypass the diseased portal vein segment, anastomosing directly to the superior mesenteric vein (SMV) or splenic vein.

Confirming the absence of viable tumor cells at the surgical margin via intraoperative frozen section is critical to prevent immediate recurrence at the vascular anastomosis.

6. Conclusion and Future Outlook

The paradigm of liver transplantation for HCC with portal vein tumor thrombosis has shifted from absolute exclusion to selective inclusion.

To achieve optimal post-transplant outcomes, transplant programs must adhere to a strict **“Who, When, and Why”** framework:

- **Why:** Because traditional palliative pathways offer dismal survival, while liver transplantation offers a potential cure for both the cancer and the underlying liver disease.
- **Who:** Highly selected patients with segmental or lobar PVTT (Vp1-Vp3) who exhibit favorable tumor biology (low AFP) and complete or partial response to neoadjuvant therapy.
- **When:** Only after a mandatory **3-to-6-month** “test of time” window to prove tumor stability and biological dormancy.

As systemic immunotherapies and targeted radiation therapies continue to advance, the success of downstaging protocols will improve. This will likely allow more patients with PVTT to safely access liver transplantation, redefining the boundaries of transplant oncology.



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Prashant Bhangui
Medanta Institute, India

Self Introduction

Educational Background:

- * Master in Hepatobiliary and Pancreatic Surgery, Henri Bismuth Hepatobiliary Institute, Villejuif, France (October 2009).
- * European Inter University Diploma in Hepato-Biliary-Pancreatic Cancers: Oncosurgical Strategies, Universite Paris XI, Republique Francaise, France (July 2009).
- * Master Of Surgery (M.S), Goa Medical College, Goa University (November 2004). Goa University Gold Medal
- * Bachelor Of Medicine and Bachelor Of Surgery (M.B.B.S), Goa Medical College, Goa University (November 1999).

Currently the Director of Liver Transplantation and Hepatobiliary Surgery at Medanta-The Medicity Hospital in Delhi NCR, India; a Center with one of the largest experiences in LDLT worldwide (close to 5000 LDLT's).

Research Interests

Dr. Bhangui's key areas of clinical expertise and research include the multidisciplinary management of patients with hepatobiliary cancers like hepatocellular carcinoma and colorectal liver tumours, advancing the field of Transplant Oncology, as well as advances and innovations in living donor liver transplantation.

For his academic and clinical excellence in management of patients with HCC, he was awarded the prestigious K.N. Udupa Memorial Oration 2016 by the Indian Society Of Organ Transplantation (ISOT), the Vanguard Award 2016 by the International Liver Transplant Society (ILTS), and the REAL Award by ILTS in 2023.

Representative Publications

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Downstaging to Transplant: Converting the Unresectable to the Transplantable

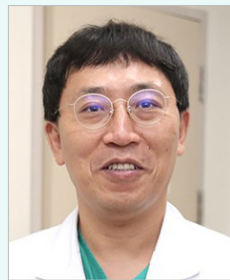
Prashant Bhangui *Medanta Institute, India*

Patients with advanced HCC that are not amenable for surgery (resection) are typically those who have either extensive bilobar disease or those with portal vein tumour thrombosis (PVTT).

There is enough evidence to show the feasibility and success of downstaging modalities, and also the efficacy of the downstaging modalities like TACE, SBRT, TARE to convert non resectable / non transplantable patients with locally advanced HCC to transplantable patients post DS. The advent of efficacious immunotherapy as a downstaging modality has further made this conversion to LT possible.

In patients with PVTT, it is generally thought that LT may not be suitable or possible upfront. However, downstaging these patients to within expanded institutional transplant criteria (beyond conventional number/size criteria, but with complete treatment of the PVTT and no extrahepatic disease), could offer an option of a curative LT after an adequate waiting period. Tumour biology based on biomarker response, radiological response, as well as evidence of response on PET scan may help in determining the best candidates for LT post DS.

Further, it is true that LT is by far the more “oncologically correct” option in patients with advanced HCC post successful DS as opposed to resection or other ablative/systemic therapies. When accepting these patients for transplant, “transplant benefit” should always be considered and one needs to respect the “triple equipoise” concept. The feasibility and success of LT in a select group of patients with PVTT has been demonstrated, and over the years, we have become wiser to understand in which group of patients LT could be a good option.



Deok-Bog Moon
University of Ulsan

Self Introduction

Deok-Bog Moon, MD is the Professor, Hepato-Biliary Surgery and Liver Transplantation, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

He completed resident courses of General Surgery in 1997. Since 2001, he has been specialized in Hepato-Biliary Surgery and Liver Transplantation at Asan Medical Center.

He is am Hepato-Biliary and Liver Transplantation surgeon, working as a team-member of at Hepato-Biliary Surgery and Liver Transplantation unit with Professor Sung-Gyu Lee, at Asan Medical Center, Seoul, Korea.

His main works include Liver transplantation, Hepatectomy, and Biliary-pancreas surgery with vascular reconstruction for all kinds of Hepatobiliary-pancrease malignancy.

In liver transplantation, His major is recipient surgery including hepatectomy & implantation & hepatic artery anastomosis under microscope. The technique learned from liver transplantation is also very useful to perform hepatobiliary-pancreas surgery. Therefore, his main interest is to perform the challenging operation in the field of hepatobiliary-pancreas surgery which was inoperable before introduction of techniques used for liver transplantation.

Research Interests

Hepatic Resection, Hepatocellular Carcinoma, Klatskin's Tumor, Liver Transplantation, Biliary and Pancreatic Surgery

Representative Publications

1. Massive subcapsular hematoma of liver graft after living donor liver transplantation: A Case Report. Transplantation Proceedings, 2003;35: 1469-1472.
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Operative Strategy and Technical Pitfalls in Liver Transplantation for HCC with Portal Vein Tumor Thrombosis

Deok-Bog Moon University of Ulsan

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy; portal vein tumor thrombosis (PVTT) is detected in up to 40% cases of HCC at diagnosis, resulting in a poor prognosis with a median survival of 2.7–4.0 months without treatment. Consequently, liver transplantation (LT) is generally considered a contraindication for patients with HCC with PVTT, and palliative treatment is primarily recommended in most clinical guidelines.

However, recent advancements in downstaging (DS) strategies have introduced a paradigm shift in the selection criteria for LT candidates. These advancements include the development of novel locoregional approaches such as Yttrium-90 (Y-90) transarterial radioembolization (TARE) and stereotactic body therapy (SBRT) and the emergence of immunotherapeutic agents that are increasingly being incorporated into DS protocols. Particularly, a good response to DS strategies utilizing single or combined locoregional and/or systemic treatments has been investigated as a potential selection criterion for LT. Recent studies have reported promising outcomes in patients undergoing LT following successful DS of HCC with PVTT.

Downstaging treatment might result in anatomical changes in the hepatic hilum and perihepatic structures related to fibrosis, sclerosis, and ongoing inflammation. As a result, Living donor liver transplantation (LDLT) for downstaged HCC-PVTT pateints is surgically complicated operations, and we have to prepare all things related to the operation preoperatively, intraoperatively, and also postoperatively for successful surgery.

Our surgical strategy focused on minimizing tumor manipulation before inflow and outflow were occluded. To this end, we developed and adopted a “no-touch total hepatectomy” technique that emphasizes early inflow division. Within this framework, two variants were implemented over time: a no-touch en bloc total hepatectomy with hepatic inferior vena cava (IVC) removal followed by IVC replacement (since July 15, 2010) and a no-touch left-sided approach for right-sided HCC (since October 10, 2012). Prior to the adoption of these techniques (2010–2012), we pursued a no-touch intent by performing early hilar dissection with division of the hepatic artery and portal vein, thereby interrupting the inflow supply to HCC and securing inflow control before liver mobilization, which reduced forceful manipulation and the risk of intravascular tumor propagation. The details of these ques have been described

previously [20,21]. Even in cases where PVTT appeared nonviable on preoperative imaging studies after DS treatment, we proceeded with combined PV resection to include areas suspected of microscopic invasion. Intraoperative biopsy of PVTT and PV wall was performed to confirm negative resection margins of the remnant PV. When necessary, PV flow was re-established using a jump graft, including an iliac vein from a deceased donor or a synthetic vascular graft after combined main PV resection.

We retrospectively reviewed records of 3098 consecutive patients with HCC and macroscopic PVTT who underwent LDLT at our institution between October 1997 and December 2022; 137 recipients diagnosed with macroscopic PVTT on pretransplant imaging examination were included (downstaging-responder group, 83; nonresponder group, 54). Main oncological outcomes were OS, DFS, and impact of downstaging response on post-transplant outcomes. The median post- LDLT follow-up period was 38.3 (0.5–261.7) months. Vp1, 2, 3, and 4 portal-vein tumor thromboses were present in 51 (37.2%), 36 (26.3%), 36 (26.3%), and 14 (10.2%) patients, respectively. DFS and OS per the PVTT classification were not different ($P = 0.299$ and 0.188 , respectively). In multivariate analysis, poor downstaging response ($HR = 2.59$, $P = 0.001$), PET hypermetabolism ($HR = 1.81$, $P = 0.038$), and larger tumor size ($HR = 1.11$, $P = 0.0161$) were independent recurrence and OS predictors; tumor number ($HR = 1.09$, $P = 0.0102$) and Edmonson–Steiner grade IV ($HR = 0.83$, $P = 0.0236$) additionally predicted recurrence. Downstaging responders had better outcomes than nonresponders: 1-, 3-, and 5-year DFS, 74%, 68%, and 65% vs 41%, 22%, and 20%, respectively; OS, 96%, 71%, and 67% vs 70%, 40%, and 35%, respectively ($P < 0.0001$).

In regards to technical aspects in LDLT for downstaged HCC PVTT, I will present at the congress venue.

As a take home message, in carefully selected patients with HCC and PVTT who achieved successful downstaging, even including Vp4 cases, LDLT may confer oncologically acceptable survival. However, LDLT for downstaged HCC PVTT patients are complicated operation and first of all, we have to prepare for it to achieve excellent short-term outcomes.

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Kwang-Woong Lee
Seoul National University

Self Introduction

Professor Lee graduated from Seoul National University. He has been with Samsung Medical Center and National Cancer Center, Korea as a hepatic and transplant surgeon. He has also been in Johns Hopkins University Hospital as a LDLT consultant. He is a professor of department of surgery, Seoul National University, Korea. He performed the first successful hepatocyte transplantation in Korea when he was in Samsung Medical Center. He developed several innovative techniques to reduce biliary complications after liver transplantation such as high hilar dissection (HHD) and Tailored Telescopic Reconstruction (TTR) of bile duct. He also played an important role to change deceased donor allocation system in Korea (split liver transplantation regulation and Deceased donor allocation system based on MELD) by publishing several important papers analyzing Korean database. He has performed more than 150 cases of LDLT in Kazakhstan, Georgia, Indonesia, Mongolia and Myanmar since 2013. He performed most of living donors by laparoscopically since Dec. 2015 and performed the world first minimal invasive recipient surgery using Robot and/or laparoscopic approach. He is the past president of Korean Liver Transplantation Society and a secretary general of iLDLTG (international living donor liver transplantation group).

Research Interests

His research topics are related to the unmet needs in liver transplantation such as diagnostic or aggressive marker of HCC in liquid biopsy, hepatocyte or liver tumor organoids, microbiome research in liver transplantation, gene delivery into the graft, cancer stem cell, best immunosuppressant for HCC, GWAS so on.

Representative Publications

1. Total robot-assisted recipient's surgery in living donor liver transplantation: First step towards the future. Lee KW, Choi Y, Lee S, Hong SY, Suh S, Han ES, Hong SK, Yang SM, Yi NJ, Suh KS J Hepatobiliary Pancreat Sci. 2023 Mar 3. doi: 10.1002/jhbp.1327.

2. Laparoscopic donor and recipient hepatectomy followed by robot-assisted liver graft implantation in living donor liver transplantation. Lee KW, Choi Y, Hong SK, Lee S, Hong SY, Suh S, Han ES, Yi NJ, Suh KS. Am J Transplant. 2022 Apr;22(4):1230-1235. doi: 10.1111/ajt.16943. Epub 2022 Jan 11. PMID: 34971490

3. Shorter operation time and improved surgical outcomes in laparoscopic donor right hepatectomy compared with open donor right hepatectomy. Han ES, Lee KW, Suh KS, Yi NJ, Choi Y, Hong SK, Lee JM, Hong KP, Hong SY, Suh S. Surgery. 2021 Dec;170(6):1822-1829. doi: 10.1016/j.surg.2021.06.005. Epub 2021 Jul 10. PMID: 34256932

4. Donor wound satisfaction after living-donor liver transplantation in the era of pure laparoscopic donor hepatectomy. Lee JM, Shehta A, Lee KW, Hong SK, Cho JH, Yi NJ, Suh KS. Surg Endosc. 2021 May;35(5):2265-2272. doi: 10.1007/s00464-020-07640-2. Epub 2020 May 19. PMID: 32430524

5. Pure Laparoscopic Living Donor Hepatectomy for Donors With Right Portal Vein Anatomical Variations. Shehta A, Lee JM, Lee KW, Hong SK, Cho JH, Yi NJ, Suh KS. Liver Transpl. 2019 Sep;25(9):1445-1454. doi: 10.1002/lt.25582. Epub 2019 Jul 8. PMID: 31169982

Post-Transplant Care and Recurrence Management:
Adjuvant and Salvage Strategies

Kwang-Woong Lee Seoul National University

The management of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) has historically represented one of the most formidable challenges in clinical oncology. Traditionally, macrovascular invasion was considered an absolute contraindication for liver transplantation (LT) due to the aggressive biological nature of such tumors and the nearly universal risk of systemic recurrence. However, the evolution of surgical techniques, the refinement of locoregional therapies (LRT), and the emergence of potent systemic agents have collectively pushed the boundaries of what is considered “transplantable”.

Liver transplantation for HCC with PVTT is no longer considered impossible, but it remains a high-stakes oncological procedure that demands a rigorous, specialized post-transplant care protocol. The management of these patients must be proactive, aggressive, and grounded in the latest evidence regarding tumor biology and immunosuppression.

- 1. Immunosuppression Pivot:** Transitioning to an mTOR inhibitor-based regimen (everolimus or sirolimus) should be the standard of care for PVTT recipients. This switch, typically occurring 1-3 months post-transplant, leverages the anti-proliferative and anti-angiogenic properties of these agents to suppress micrometastatic disease.
- 2. Intensive Surveillance:** A high-frequency monitoring schedule is mandatory. This includes AFP and PIVKA-II every 2-3 months, dynamic liver MRI or CT every 2-3 months, and chest CT every 3-6 months for at least the first two post-operative years.
- 3. Adjuvant Implementation:** In high-risk PVTT cases, the use of adjuvant lenvatinib or adoptive immunotherapy with CIK cells should be considered to reduce the risk of early recurrence.
- 4. Aggressive Salvage:** If recurrence occurs, aggressive intervention is essential. Surgical resection of localized intra- or extrahepatic lesions offers the best chance for prolonged survival. Locoregional therapies and systemic TKIs should be utilized as part of a comprehensive multidisciplinary strategy.
- 5. Cautious Immunotherapy:** Immune checkpoint inhibitors should be reserved for refractory cases as a last resort. Treatment must be preceded by an evaluation of graft PD-L1 expression and a detailed risk-benefit analysis regarding the potential for severe allograft rejection.

By integrating these strategies, clinicians can optimize the long-term outcomes for patients with advanced HCC, successfully redefining the boundaries of liver transplantation in the modern era.

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KLTS SYMPOSIUM 2

Body Composition and Fluid Dynamics in Liver Transplantation

Chairs

Dong-Sik Kim (Korea Univ.)

Bong-Wan Kim (Ajou Univ.)





Suk-Won Suh
Chung-Ang University

Self Introduction

Prof. Suk-Won Suh is a professor of the department of Surgery, Chung-Ang University College of Medicine and is currently holding a position of Chief of Chung-Ang University Hospital Transplant Center.

Prof. Suh graduated from Chung-Ang University College of Medicine with his medical degree in 2007 and completed his internship and residency at the Department of Surgery at Chung-Ang University Hospital, receiving his diploma in General Surgery in 2012.

Since 2024, Prof. Suh has been taking a number of roles, including auditor of the Korean society of Transplantation (2025-), planning board officer of the Korean Association of Hepato-Biliary-Pancreatic Surgery (2024-) and external cooperation officer of the Korean Surgical Society (2024-).

Research Interests

Hepatocellular Carcinoma, Circulating Tumor Cell, Hepatic Resection, Liver Transplantation

Representative Publications

- 1. Suh SW, Park HJ, Choi YS. Preoperative volume assessment using bioelectrical impedance analysis for minimizing blood loss during hepatic resection. HPB (Oxford). 2022;24(4):568-574.
- 2. Suh SW. Bioelectrical Impedance Analysis for Preoperative Volemia Assessment in Living Donor Hepatectomy. J Pers Med. 2022;12(11):1755.

Beyond Body Mass Index (BMI): Clinical Utility of InBody and Bioimpedance in Liver Transplant Evaluation

Suk-Won Suh *Chung-Ang University*

As the demand for liver transplantation (LT) is increasing, living donor LT (LDLT) has emerged as a valuable alternative option to deceased donor LT (DDLT). Currently, LDLT is performed at a greater frequency than that of DDLT due to the limited availability of deceased donor organs, especially in Asian populations. LDLT is a preferred treatment for selected hepatocellular carcinoma (HCC) patients because it can treat both the tumor and underlying liver diseases including hepatitis B viral infection, which increases the risk of tumor recurrence after hepatic resection. In LDLT, donor safety remains a major concern because living donors are typically healthy adults who do not derive any medical benefit from the procedure. It is important to make consistent efforts to minimize the potential risks to the living donors to justify such an operation.

Excessive blood loss during hepatic resection has been reported to be significantly associated with postoperative morbidity and mortality. Bleeding from the hepatic vein, which drains directly into the inferior vena cava (IVC), can be severe and cannot be controlled by portal triad clamping. A low central venous pressure (CVP) during hepatic resection has been a widely used approach to reduce surgical blood loss and improve clinical outcomes. Hepatic blood congestion, induced by elevated CVP, leads to an incremental increase in the transmural pressure and the distension of the hepatic vein, which is consequently torn easily, promoting blood loss at the time of parenchymal transection. Preoperative fluid restriction is a widely used method for lowering the CVP; however, it is sometimes not sufficient, which makes hepatic resection difficult. Bioelectrical impedance analysis (BIA) is a practical method for volemia assessment, which has the advantages of noninvasiveness, rapid processing, easy handling, and it is relatively inexpensive. This method evaluates the human body composition, and the ratio of extracellular water to total body water (ECW/TBW) can be calculated as an index of volemia status. A previous study showed that ECW/TBW and CVP were significantly correlated, which can be used preoperatively to significantly reduce the intraoperative bleeding during hepatic resection.

We introduced BIA for maintaining a low CVP during hepatic resection, to improve operative outcomes that I would introduce two studies of BIA.

We investigated 192 patients who underwent hepatic resection from January 2017 to December 2020. The ratio of extracellular water:total body water (ECW/TBW), as an index of volume status, was mea-

sured using InBody S10 (Biospace, Seoul, Korea). The correlation between the ECW/TBW and CVP was determined, and their influences on operative outcomes were analyzed. ECW/TBW and CVP showed a significant correlation; an ECW/TBW <0.378 correlated with a CVP <5 mmHg (R2 =0.839, p <0.001). Estimated blood loss (EBL) was significantly increased in patients with an ECW/TBW ≥0.378 compared to those with a ratio <0.378 (508 ± 321 vs. 324 ± 193, mL, p <0.001). Identified predictors for an EBL ≥500 mL were operative time (odds ratio [OR], 1.008; 95% confidence interval [CI], 1.001–1.015; p =0.021) and an ECW/TBW <0.378 (OR, 0.263; 95% CI, 0.121–0.572; p =0.001).

We analyzed 51 living donors who underwent right hemihepatectomy between July 2015 and May 2022. The ratio of extracellular water:total body water (ECW/TBW;an index of volemic status) was measured. ECT/TBW <0.378 was correlated to central venous pressure (CVP) <5 mm Hg in a previous study and we used this value for personalized preoperative management. In the BIA group (n =21), donors with ECW/TBW ≥0.378 (n =12) required whole-day nothing by mouth (NPO), whereas those with ECW/TBW < 0.378 (n =9) required midnight NPO, similar to the control group (n =30). In comparison with the control group, the BIA group had a significantly lower central venous pressure (p <0.001) from the start of surgery to the end of surgery, leading to a better surgical field grade (p = 0.045) and decreased operative duration (240.5 ± 45.6 vs. 276.5 ± 54.0 min, p =0.016). A cleaner surgical field (surgical field grade 1) was significantly associated with decreased operative duration (p =0.001) and estimated blood loss (p <0.001). Preoperative BIA was the only significant predictor of a cleaner surgical field (odds ratio, 6.914; 95% confidence interval, 1.6985–28.191, p =0.007).

Preoperative volemia assessment using BIA can improve operative outcomes by creating a favorable surgical environment in liver resection and living donor hepatectomy.

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Toshimi Kaido

St. Luke's International Hospital, Japan

Self Introduction

Education and Degree

- 1987 M.D., Graduated from Kyoto University
- 1996 Ph.D., Graduated from Graduate School of Medicine, Kyoto University

Career

- 1999-2001 Assistant Professor, First Department of Surgery, Kyoto University
- 2007-2009 Assistant Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University
- 2009-2019 Associate Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University
- 2019- Professor and Head of Gastroenterological and General Surgery, St. Luke's International University and Hospital

He has published more than 300 peer reviewed English papers in high impact factor journals including New Engl J Med, Hepatology, Am J Transplant, and Ann Surg.

Research Interests

Liver Transplantation, Hepato-Biliary-Pancreas Cancer, Perioperative Management, ERAS, Surgical Nutrition (Especially Sarcopenia), Education

Representative Publications

1. Kaido T, Miyachi Y, Mitsuoka K, et al. Successful introduction of ERAS in pancreaticoduodenectomy: what is real minimally invasive surgery? Ann Clin Nutr Metab 2025;17(2):156-61.
2. Kaido T. Recent evolution of living donor liver transplantation at Kyoto University: How to achieve a one-year overall survival rate of 99%? Hepatobiliary Pancreat Dis Int 2020;19(4):328-33.
3. Miyachi Y, Kaido T, Hirata M, et al. The combination of male donor's high muscle mass and quality is an independent protective factor for graft loss after living donor liver transplantation. Am J Transplant 2020;20(12):3401-12.
4. Hamaguchi Y, Kaido T, Okumura S, et al. Proposal for new selection criteria considering pre-transplant muscularity and visceral adiposity in living donor liver transplantation. J Cachexia Sarcopenia Muscle 2018;9(2):246-54.
5. Kaido T, Ogawa K, Fujimoto Y, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 2013;13(6):1549-56.

Prognostic Significance of Sarcopenia and Visceral Fat in Liver Transplant Recipients

Toshimi Kaido

St. Luke's International Hospital, Japan

Patients undergoing liver transplantation (LT) are often associated with sarcopenia. In this lecture, we would like to introduce the significance of sarcopenia and body compositions including visceral fat in patients undergoing LT, perioperative exercise/nutritional therapy, and our new criteria for LT considering pre-transplant body compositions.

First, we prospectively measured skeletal muscle mass (SMM) and handgrip strength (HGS) in 72 adult patients who underwent living donor LT (LDLT). Sarcopenia was defined as low SMM and low HGS1). The overall survival (OS) rates were significantly lower in patients with sarcopenia than those without sarcopenia (p < 0.001). Perioperative nutritional therapy significantly increased OS rates in patients with low SMM. Moreover, patients who received preoperative exercise/nutritional therapy had significant increase in muscle strength and physical activity.

Next, we focused on body compositions. We evaluated pre-transplant skeletal muscle mass, muscle quality, and visceral adiposity by measuring skeletal muscle mass index (SMI), intramuscular adipose tissue content (IMAC), and visceral-to-subcutaneous adipose tissue area ratio (VSR) respectively for 277 consecutive patients who underwent adult LDLT between January 2008 and July 20162). OS rates of patients with low SMI, high IMAC, and high VSR (abnormal factors) were significantly lower than those with high SMI, low IMAC, and low VSR, respectively. On multivariate analysis, these factors were identified as independent risk factors for mortality after LDLT. One-year OS rate of patients with no abnormal factor, each one factor, two factors, three factors were 98%, 78%, 60%, and 41%, respectively. Interestingly, the more the number of abnormal factors, the higher incidence of posttransplant bacteremia3). Moreover, patients with sarcopenic obesity showed worse survival after LDLT compared with non-sarcopenic/non-obesity patients4).

Based on these findings, we have established new selection criteria for LDLT: 1) to exclude patients with three abnormal factors (recommend deceased donor LT), 2) to perform perioperative exercise/nutritional therapy. As a result, one-year OS rate after LDLT has dramatically increased to 99%5).

In conclusion, pretransplant sarcopenia and abnormal body compositions including visceral fat were closely related to poor prognosis after LDLT. New selection criteria for LDLT considering pre-transplant body compositions with perioperative exercise/nutritional therapy achieved excellent outcomes.

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3. Kamo N, Kaido T, Miyachi Y, et al. Preoperative abnormal body composition is closely related to bacteremia after living donor liver transplantation. Nutrition 2020;77:110798.

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Minseob Kim
Seoul National University

Self Introduction

Prof. Minseob Kim is a Clinical Assistant Professor in Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Seoul National University Hospital.

Prof. Kim graduated from Seoul National University College of Medicine in 2015 and completed his internship and residency in General Surgery at Seoul National University Hospital. He completed fellowship training in Hepato-Biliary-Pancreatic Surgery and Liver Transplantation, as well as in Critical Care Medicine at Seoul National University Hospital.

He has clinical experience in the management of critically ill surgical patients, including those in the intensive care unit, and currently practices in the field of liver transplantation and hepato-biliary-pancreatic surgery. He is an active member of several academic societies, including the Korean Association of Hepato-Biliary-Pancreatic Surgery, the Korean Society for Transplantation, and the Korean Society of Critical Care Medicine.

Research Interests

Hepatocellular Carcinoma, Liver Transplantation, Liver Cirrhosis

Representative Publications

1. Kim M, Woo HY, Kang C, Lim L, Lee H, Ryu HG, Oh SY, Phase angle as a potential predictor for unplanned ICU readmission risk in critically ill surgical patients: a retrospective cohort study. Phase angle as a potential predictor for unplanned ICU readmission risk in critically ill surgical patients: a retrospective cohort study. International Journal of Surgery (Lond, Engl). 2025 Nov 20;109(10):101097. doi: 10.1097/JS9.00000000000003827. PMID: 39351570; PMCID: PMC11438817.
2. Kim M, Han KD, Ko SH, Woo Y, Han JH. Effect of smoking on the risk of gastrointestinal cancer after cholecystectomy: A national population-based cohort study. World J Gastrointest Surg. 2024 Sep 27;16(9):2796-2807. doi: 10.4240/wjgs.v16.i9.2796. PMID: 39351570; PMCID: PMC11438817.
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5. Kim MS, Min SK, Ahn S, Kim HG, Choi C, Mo H, Han A, Ha J. Modified Brachio-basilic/brachial Arteriovenous Fistula Creation with Short-segment Elevation Preserving the Axilla. Ann Vasc Surg. 2020 Aug;67:448.e1-448.e10. doi: 10.1016/j.avsg.2020.02.037. Epub 2020 Mar 21. PMID: 32209414.

Extracellular Water Imbalance and Fluid Overload:
Impact on Early Graft Function and Complications

Minseob Kim Seoul National University

End-stage liver disease (ESLD) is characterized by a profound disturbance of body fluid homeostasis. Splanchnic vasodilation, portal hypertension, and neurohormonal activation drive effective arterial underfilling and sodium retention, expanding the extracellular water (ECW) compartment as ascites and peripheral edema. The hyperdynamic circulatory state and cirrhotic cardiomyopathy further compromise volume handling. As fibrosis advances, the ECW to total body water ratio (ECW/TBW) — the edema index — rises in parallel with sarcopenia and malnutrition, and signals worsening pre-transplant prognosis.

Liver transplantation (LT) imposes acute insults onto this background. Massive volume shifts during the anhepatic and reperfusion phases, transfusion, and post-reperfusion vasoplegia amplify interstitial fluid accumulation, producing visceral and graft edema that may impair hepatic microcirculation. Clinically, this manifests as early allograft dysfunction (EAD), acute kidney injury (AKI), pulmonary complications, and prolonged mechanical ventilation.

Multiple studies have established postoperative fluid balance as a modifiable determinant of LT outcomes. Cumulative positive fluid balance over the first four postoperative days has been independently associated with AKI and renal replacement therapy. Chloride-liberal fluid administration on the first postoperative day independently predicts AKI, and a systematic review has confirmed that restrictive intraoperative strategies reduce pulmonary complications and shorten ventilation. Importantly, a large retrospective cohort of 1,833 LDLT recipients demonstrated that early postoperative weight gain $\geq 3\%$ — a clinical surrogate of fluid overload — was independently associated with EAD, graft failure, and overall mortality, with systemic inflammation as a plausible mediator. Yet the COLT randomized trial — the first to test stroke-volume-guided goal-directed fluid therapy after LT — found that GDFT was feasible but did not improve early pulmonary or renal function. The persistent hyperdynamic circulation of cirrhosis appears to defeat conventional preload-based algorithms, suggesting that fluid distribution and tissue hydration, rather than circulating volume alone, must be optimized.

This framing motivates a body-composition-based approach. BIA-derived parameters — particularly ECW/TBW and phase angle — are non-invasive surrogates that integrate the chronic dysregulation of ESLD with acute perioperative shifts. The use of BIA in LT has roots dating back nearly three decades,

and recent work has shown that pre-transplant ECW/TBW elevation tracks with fibrosis severity, sarcopenia, and reduced survival, while phase angle independently predicts mortality in cirrhotic patients. Personalized perioperative volume management guided by BIA has been demonstrated feasible in living donor hepatectomy. Parallel evidence from kidney and heart transplantation, where bioimpedance-defined overhydration predicts delayed graft function and post-transplant mortality, supports the generalizability of the principle. What remains unmet is the prospective integration of compartment-level body composition assessment into LT perioperative care: while crude surrogates such as weight gain capture the clinical signal, BIA-derived markers may distinguish intravascular from interstitial expansion and identify patients in whom ECW imbalance drives early graft dysfunction.

Taken together, these data position extracellular water imbalance as a clinically actionable target across the perioperative continuum — from preoperative risk stratification to intraoperative goal-directed therapy informed by tissue-level hydration, to ICU management aimed at restoring physiologic compartment balance. Identifying patients in whom ECW expansion drives early graft dysfunction may open a path toward personalized perioperative optimization in liver transplantation.

Keywords: Liver transplantation, Extracellular water, Fluid overload, Edema index, Bioimpedance analysis, Early allograft dysfunction

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Seung-Young Oh
Seoul National University

Self Introduction

Current Position

2022.03-Present Clinical Associate Professor
Department of Critical Care Medicine, Seoul National University Hospital
Department of Surgery, Seoul National University College of Medicine

Education

2001.03-2007.02 M.D., Seoul National University College of Medicine, Seoul, Korea
2012.03-2014.02 M.S., Seoul National University College of Medicine, Seoul, Korea
2014.09-2026.08 Ph.D., Seoul National University College of Medicine, Seoul, Korea

Postdoctoral Career

2007.03-2008.02 Intern, Department of Surgery, SNUH
2008.03-2012.02 Resident, Department of Surgery, SNUH
2012.03-2014.02 Fellow, Department of Surgery, SNUH
2014.03-2018.02 Clinical Instructor, Department of Surgery, SNUH
2018.03-2022.02 Clinical Assistant Professor, Department of Critical Care Medicine, SNUH

Academic Membership

2012- Korean Surgical Society Member
2012- Korean Gastric Cancer Association Member
2014- Korean Society of Critical Care Medicine Member
2015- Korean Society of Traumatology Member
2017- Korean Society of Acute Care Surgery Member
2017- Korean Society of Surgical Metabolism and Nutrition Member

Body Composition after Liver Transplantation: Clinical Prediction, Risk Stratification, and Therapeutic Intervention

Seung-Young Oh Seoul National University

Liver transplantation substantially extends survival, but the trajectory of the recipient’s body composition in the years that follow—and the complications that trajectory quietly predicts—receives far less clinical attention than it warrants. This lecture examines the post-transplant evolution of skeletal muscle mass, visceral adiposity, and intramuscular fat infiltration, and demonstrates how serial measurement of these parameters can shift clinical management from a reactive to an anticipatory model.

Post-transplant body composition changes in three distinct, sequential phases. In the first twelve weeks, ongoing muscle catabolism—driven by high-dose corticosteroids, surgical stress, and enforced immobility—continues despite restored hepatic function, often erasing the muscle reserve the recipient had preserved before the operation. Months three through twelve represent the true anabolic window, when steroid reduction, improved oral intake, and physical rehabilitation converge to enable meaningful recovery—provided that opportunity is not lost to inadequate nutrition or inactivity. Beyond year one, visceral adipose tissue expands disproportionately, post-transplant obesity develops in 40–60% of recipients within three years, and body mass index alone cannot identify the sarcopenic obesity phenotype that carries the worst long-term prognosis.

The clinical utility of these findings extends well beyond risk prediction at a single time point. Serial CT-derived skeletal muscle index and visceral adipose tissue measurements function as a metabolic surveillance system with a measurable lead time over conventional laboratory monitoring: rising visceral fat at the six-month postoperative scan precedes new-onset diabetes after transplantation by three to nine months, and persistent low muscle attenuation at twelve months independently predicts histological NAFLD recurrence and five-year mortality. Pre-operative muscle data also identify patients at heightened risk for post-transplant infectious complications, acute kidney injury, and prolonged intensive care stays—with direct implications for surgical planning and immunosuppression management.

Built on a synthesis of findings accumulated to date on body composition changes in liver transplant recipients, this session aims to provide a practical guide for how body composition assessment can be translated into real-world clinical care going forward.

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KLTS SYMPOSIUM 3

Liver Transplantation in the Era of MASLD

Chairs

Kwang-Woong Lee (Seoul National Univ.)

Prashant Bhangui (Medanta Institute, India)





Bo-Hyun Jung
Inje University

Self Introduction

Education

2001-2007	Inje University College of Medicine, Bachelor of Medicine
2010-2013	University of Ulsan College of Medicine, Master's Degree in Medicine
2014-2017	University of Ulsan College of Medicine, PhD in Medicine

Experience

2007-2008	Intern, Asan Medical Center
2008-2012	Resident in Surgery, Asan Medical Center
2012.3-2015.2	Clinical Fellowship, Liver Transplantation and Hepatobiliary Surgery, Asan Medical Center
2015-2021	Assistant Professor, Department of Surgery, Inje University Haeundae Paik Hospital
Currently	Associate Professor, Division of Liver Transplantation and HBP Surgery, Department of Surgery, Inje University Haeundae Paik Hospital
Currently	Chief, Division of Liver Transplantation and HBP Surgery, Department of Surgery, Inje University Haeundae Paik Hospital

Representative Publications

1. Development and validation of a digital PCR assay targeting plasma FAR1 methylation for early detection of hepatocellular carcinoma. Sun Jae Park, Yun Young Lee, Yong-kyu Chung, Bo-Hyun Jung, Joon An, Jinil Han, Youngho Moon, Hee-Jung Wang. Epigenetics. 2026 Dec;21(1):2653956. doi: 10.1080/15592294.2026/2653956. Epub 2026 Apr 20.
2. Synergistic effect of combined hyperthermia and radiotherapy mediated by AQP5 reduction in pancreatic cancer. Jaewan Jeon, Hyosun Jang, Geumju Park, Hyeon Jeong Hwang, Mi Hwa Lee, Minji Kang, Seung Bum Lee, Wonyi Jang, Wanyeon Kim, Hye Young Kim. Bo-Hyun Jung, Yong-kyu Chung, Junghwan Lee, Hyesook Youn, Sunmi Jo, BuHyun Youn. Int J Hyperthermia. 2026 Dec;43(1):264451. doi: 10.1080/02656736.2026.2644451. Epub 2026 Mar 23.
3. A Case of Primary Hepatic Leiomyoma Incidentally Found in a Middle-aged Woman without Underlying Diseases. The Korean Journal of Gastroenterology, 2024-01-25 | Journal article. DOI: 10.4166/kjg.2023.143. Contributors: Yong-Kyu Chung; Bo-Hyun Jung; Yoo Na Lee; Su-Bin Song; Hee-jung Wang
4. Pediatric liver transplantation for Wilson disease. Jeong-Ik Park1 , Bo Hyun Jung2. Ann Liver Transplant 2023; 3(2): 80-85 <https://doi.org/10.52604/alt.23.0019>
5. Liver transplantation for hepatic epithelioid hemangioendothelioma: A review of European and Korean experience. Jeong-Ik Park1 , Bo Hyun Jung. Ann Liver Transplant 2023; 3(1): 6-10 <https://doi.org/10.52604/alt.23.0003>.
6. Future-directed studies on immunosuppressive treatments and xenografts for organ transplantationJeong-Ik Park1 , Bo Hyun Jung. Ann Liver Transplant 2022; 2(1): 1-7 <https://doi.org/10.52604/alt.22.0003>.

The MASLD Era and Its Impact on the Liver Donor Pool

Bo-Hyun Jung Inje University

The global rise of metabolic dysfunction-associated steatotic liver disease (MASLD) has markedly reduced the living donor liver transplantation (LDLT) donor pool. In many centers, 17–25% of prospective donors are excluded due to hepatic steatosis. In the MASLD era, steatotic donors should no longer be viewed as absolute contraindications but as a modifiable resource through preoperative optimization, while maintaining donor safety as the top priority.

Macrovesicular steatosis above 30% increases risks of primary non-function (PNF), early allograft dysfunction (EAD), biliary complications, and poorer short-term graft survival due to heightened ischemia-reperfusion injury. For donors, it is associated with impaired regeneration and higher postoperative morbidity. In the long term, remnant liver steatosis recurrence shows a cumulative incidence of 12.1% at 5 years, 22.1% at 10 years, and 27.7% at 15 years. Independent risk factors include male sex, donation to pediatric recipients, and BMI >25 kg/m² at donation (Goto et al., 2023).

Steatosis is largely reversible. The cornerstone is lifestyle modification aiming for ≥5–10% body weight loss (ideally ≥10% for right lobe donation) via calorie-restricted (1,200–1,600 kcal/day), high-protein Mediterranean-style diet and daily 45–60 min aerobic plus resistance exercise. Multimodal evaluation using MRI-PDFF, Fibroscan, CT volumetry, and selective biopsy is essential. The ILTS-iLDLT 2025 Consensus recommends individualized assessment beyond BMI, focusing on remnant volume, GRWR, and cardiometabolic health. Most motivated donors achieve <20–30% steatosis within 4–12 weeks.

One study demonstrates that donors achieving ≥10% weight loss have comparable donor complications, hospital stay, and recipient outcomes to non-steatotic grafts. In treated moderate steatosis cases, postoperative LFT, ICU stay, and complication rates are similar to controls, with no PNF observed and comparable graft/patient survival when recipient cardiometabolic risks are controlled. These approaches can safely expand the donor pool by 15–25%.

In the MASLD era, proactive preoperative optimization safely transforms steatotic donors into a valuable resource for LDLT. Protocolized multimodal evaluation, tailored interventions, and rigorous long-term metabolic follow-up are critical. High-volume centers should adopt standardized protocols to sustainably address organ shortage while upholding donor safety.

Keywords: MASLD, Living donor liver transplantation, Hepatic steatosis, Donor optimization, Donor pool expansion



Fengqiang Gao
Zhejiang University, China

Self Introduction

He received both his Master’s and Ph.D. training at Zhejiang University School of Medicine under the supervision of Professor Xiao Xu. He has published more than 10 papers as first author or co-first author. During this period, he participated in dozens of liver transplantation surgeries and porcine large-animal experiments. In 2025, he joined the MRC Cambridge Stem Cell Institute, University of Cambridge School of Clinical Medicine, as a visiting Ph.D. student for joint training. During his doctoral studies, he was awarded the National Scholarship and was selected for an oral presentation at ATW 2023.

Research Interests

His Research Interests Focus on Liver Graft Injury Repair and Regeneration, as well as Transplant Oncology.

Representative Publications

- 1. Gao F, Dong L, Xu X*. Sorafenib restores pentose phosphate pathway-related redox homeostasis via the c-Raf/HSP90/G6PD axis in hepatic ischemia-reperfusion injury. MedComm. 2026.
- 2. Gao F, Dong L, Xu X*. Impact of donor-recipient sex-matching patterns on liver transplantation outcomes: a cohort study based on United Network of Organ Sharing data. Hepatobiliary Surg Nutr. 2025.
- 3. Gao F, Zhuang L, Xu X*. Stratification for efficacy of adjuvant FOLFOX plus lenvatinib after liver transplantation for hepatocellular carcinoma in recurrence prevention. Hepatobiliary Pancreat Dis Int. 2025.
- 4. Gao F, Qiu X, Xu X*. Targeting the Hepatic Microenvironment to Improve Ischemia/Reperfusion Injury: New Insights into the Immune and Metabolic Compartments. Aging Dis. 2022.
- 5. Wang K, Gao F, Xu X*. Clinical Practice Guidelines on Liver Transplantation for Extended Criteria Donor Grafts in China (2025 Edition). Chin Med J (Engl). 2026.

From Selection Criteria to Classification System:
A Novel Framework of Liver Transplantation for
Hepatocellular Carcinoma

Fengqiang Gao Zhejiang University, China

Background

Liver transplantation (LT) is one of the most effective curative treatments for hepatocellular carcinoma (HCC), yet post-transplant tumor recurrence remains the major obstacle to long-term survival. Precise recipient selection is therefore central to transplant oncology. Over the past three decades, many HCC LT selection criteria have been proposed worldwide, moving from morphology-based thresholds to systems that incorporate tumor biology and molecular markers. However, most criteria have been evaluated using a single study endpoint, such as post-LT survival or recurrence. In clinical practice, whether a criterion is scientifically sound and practically reasonable should be assessed across multiple dimensions, including oncologic safety, net survival benefit, eligible population, and fairness under organ scarcity. At the same time, donor organ shortage is a global challenge, driving increasing clinical use of expanded criteria donor grafts, particularly steatotic grafts. However, the impact of steatotic grafts on the prognosis of HCC recipients remains unclear. This lecture will connect these two issues within an integrated Tumor-Donor-Recipient framework.

Precision Selection of Liver Transplant Recipients with HCC

The first part will review the evolution of HCC LT selection from the Milan criteria to expanded and biology-informed systems such as the Hangzhou criteria, AFP models, Metroticket 2.0, and HALT-HCC et al. Depending on data from the China Liver Transplant Registry (CLTR) and UNOS, the lecture will summarize a head-to-head comparison of 13 established criteria in LT recipients with HCC. Rather than judging criteria by a single endpoint, the proposed Risk-Benefit Benchmarking framework integrates three dimensions: 5-year overall survival, survival benefit compared with predicted non-LT survival, and the number of eligible beneficiaries. This multidimensional approach shows that biological criteria can expand access while maintaining acceptable oncologic outcomes.

Steatotic Grafts in Liver Transplantation for HCC

Expanded criteria donor livers are increasingly using globally, and steatotic grafts represent a particularly relevant opportunity and challenge for HCC LT. Our UNOS-based study showed that steatotic grafts can be safely used in selected HCC liver transplant recipients. The risk associated with steatotic grafts

was mainly amplified by cold ischemia time ≥ 6 hours, donor BMI ≥ 40 kg/m², and recipient NAFLD. By integrating these factors, the Hazard Associated with Macrosteatotic Liver (HAML) score can help minimize the risk of steatotic grafts in liver transplantation for HCC patients.

Keywords

Atezolizumab, Bevacizumab, Durvalumab, Tremelimumab, Hepatocellular carcinoma

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Young-In Yoon
University of Ulsan

Self Introduction

Prof. Young-In Yoon is an Associate Professor in the Division of Liver Transplantation and Hepato-Biliary Surgery, Department of Surgery, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea.

Prof. Yoon graduated from Yonsei University School of Medicine, Wonju, Korea in 2008, and completed her internship and residency in the Department of Surgery at Asan Medical Center, receiving board certification in General Surgery in 2013. She subsequently obtained her Master’s degree (2013) and PhD (2016) from Ulsan University College of Medicine.

After completing a Clinical Fellowship at Asan Medical Center (2013–2016), she served as Clinical Assistant Professor at Korea University Anam Hospital (2016–2018) before returning to Asan Medical Center as Clinical Assistant Professor (2018–2023), and was promoted to her current position of Associate Professor in March 2023.

Her research focuses on living donor liver transplantation, laparoscopic hepatic resection, and outcomes in hepatocellular carcinoma, with over 25 SCI/SCIE publications as first or corresponding author in leading journals including Annals of Surgery, Journal of Hepatology, American Journal of Transplant, and International Journal of Surgery. Her research focuses on living donor liver transplantation, laparoscopic hepatic resection, and outcomes in hepatocellular carcinoma, with over 25 SCI/SCIE publications as first or corresponding author in leading journals including Annals of Surgery, Journal of Hepatology, American Journal of Transplant, and International Journal of Surgery.

Research Interests

Living Donor Liver Transplantation (LDLT), Laparoscopic and Minimally Invasive Liver Resection, Hepatocellular Carcinoma (HCC) Surgery and Outcomes, Hepatobiliary Surgery Complications, ABO-Incompatible Transplantation, Portal Vein Reconstruction Techniques

Representative Publications

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2. Yoon YI, Moon DB, Lee SG, et al. Living-donor liver transplantation in hepatocellular carcinoma with portal-vein tumor thrombosis. Int J Surg. 2025 Nov. doi: 10.1097/JS9.0000000000004077.
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1. Yoon YI, Lee SG, Hwang S, et al. Safety of right liver donation after improving steatosis through weight loss in living donors: a retrospective study. Hepatol Int. 2024 Mar. doi: 10.1007/s12072-024-10641-1. (SCIE/IF 5.9)
2. Yoon YI, Song GW, Lee SG, et al. Safe use of right lobe living donor livers with moderate steatosis in adult-to-adult living donor liver transplantation: a retrospective study. Transpl Int. 2021 Mar. doi: 10.1111/tri.13859. (SCIE/IF 3.8)

Recurrent Steatosis in Living Donors after Pre-Donation Weight Reduction and Subsequent Weight Regain

Young-In Yoon University of Ulsan

The rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) in the general population has inevitably expanded into the living donor pool, with an increasing proportion of potential donors presenting with hepatic steatosis at initial evaluation. As steatosis remains a leading cause of donor disqualification, pre-donation weight reduction has emerged as a widely adopted strategy to achieve acceptable graft quality and ensure donor safety. While short-term outcomes following donation in this population appear comparable to standard donors, the long-term hepatic fate of these donors after procurement has received far less attention.

Weight regain following donation is not uncommon, and when it occurs in donors who reduced weight specifically to meet donation criteria, the liver is particularly vulnerable to recurrent steatosis. Unlike donors who were never steatotic, this subgroup carries an underlying metabolic predisposition that was temporarily suppressed rather than fundamentally corrected. Serial liver function tests and imaging studies in long-term follow-up reveal that a significant proportion of these donors develop recurrent hepatic fat accumulation, accompanied by progressive elevation of aminotransferases, mirroring the trajectory seen in the general MASLD population.

These findings carry important clinical implications. Sustainable weight management — extending well beyond the pre-donation period — is essential for this growing donor subgroup. Emerging pharmacological strategies, including GLP-1 receptor agonists, may offer new opportunities for long-term metabolic control, though evidence specific to the living donor population remains limited. Dedicated post-donation surveillance protocols, incorporating both biochemical and imaging follow-up, are needed to detect and manage recurrent steatosis early, ultimately safeguarding the long-term health of donors who gave a part of themselves for others.



Tae-Seok Kim
Keimyung University

Self Introduction

- 1996.3-2003.2 M.D., Chung-Ang University, School of Medicine
- 2007.3-2013.2 M.S., Sungkyunkwan University, School of Medicine
- 2003.3-2004.2 Intern, Chung-Ang University Medical Center, Seoul
- 2004.3-2008.2 Resident, Department of Surgery Samsung Medical Center
- 2008.5-2011.4 Public Health Doctor for Military Service
- 2011.5-2013.2 Fellowship, Division of Transplantation, Department of Surgery, Samsung Medical Center
- 2013.3-2014.2 Fellowship, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Catholic University of Korea, Uijeongbu St. Mary's Hospital
- 2014.3-Present Assistant Professor/Associate Professor, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Keimyung University School of Medicine
- 2021.9-Present Director of Organ Transplantation Center

Research Interests

Hepatocellular Carcinoma, Cholangiocarcinoma, Liver Transplantation, Organ Preservation

Representative Publications

1. Surgical outcome and risk scoring to predict survival after hepatic resection for hepatocellular carcinoma with portal vein tumor thrombosis. Kim TS, Yang K, Choi GH, Yang HY, Kim DS, Jo HS, Choi GS, Kim KW, Yoon YC, Han J, Kim DJ, Hwang S, Kang KJ Ann Hepatobiliary Pancreat Surg. 2024 May 31;28(2):134-143
2. Effect of anatomical liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. Shin SW, Kim TS, Ahn KS, Kim YH, Kang KJ. Int J Surg. 2023 Sep 1;109(9):2784-2793
3. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. Shin SW, Ahn KS, Kim SW, Kim TS, Kim YH, Kang KJ. Ann Surg. 2021 Apr 1;273(4):656-666.
4. Small graft size and hepatocellular carcinoma outcomes in living donor liver transplantation: a retrospective multicentric cohort study. Kim DG, Hwang S, Lee KW, Kim JM, You YK, Choi D, Ryu JH, Kim BW, Kim DS, Cho JY, Nah YW, Ju MK, Kim TS, Lee JG, Kim MS, Parente A, Kim KH, Schlegel A, Choi SJN, Joo DJ; Korean Organ Transplantation Registry Study Group. Int J Surg. 2024 Aug 1;110(8):4859-4866.

Recurrent and de novo MASLD after Liver Transplantation

Tae-Seok Kim Keimyung University

Background

With the global shift in liver disease epidemiology, Metabolic dysfunction–associated steatotic liver disease has emerged as a leading indication for liver transplantation. Post-transplant, both recurrent MASLD (in patients transplanted for steatotic liver disease) and de novo MASLD (in those transplanted for other etiologies) are increasingly recognized. These entities are driven by persistent or newly acquired metabolic risk factors, including obesity, insulin resistance, dyslipidemia, and the diabetogenic effects of immunosuppressive agents. Despite their growing prevalence, the clinical impact and optimal management strategies remain incompletely defined.

Methods

This symposium reviews current evidence on the incidence, risk factors, natural history, and clinical outcomes of recurrent and de novo MASLD following liver transplantation. Data are derived from observational cohort studies, registry analyses, and recent consensus statements. Particular emphasis is placed on mechanistic pathways, including metabolic dysregulation, genetic susceptibility (e.g., PNPLA3 variants), and the role of immunosuppressive regimens.

Results

Recurrent steatosis occurs in up to 70–90% of recipients transplanted for MASLD within 5 years, with a subset progressing to steatohepatitis and fibrosis. De novo MASLD develops in approximately 20–40% of recipients transplanted for non-MASLD indications. While simple steatosis is often considered benign, emerging data suggest that progressive fibrosis may occur in a clinically relevant proportion, potentially impacting long-term graft and patient survival. Risk factors consistently associated with post-transplant MASLD include post-transplant weight gain, poorly controlled diabetes, and calcineurin inhibitor–based immunosuppression. However, the progression to advanced fibrosis or graft dysfunction remains heterogeneous and incompletely predictable.

Conclusions

Recurrent and de novo MASLD represent significant and underappreciated challenges in the long-term

care of liver transplant recipients. Early identification of high-risk patients, optimization of metabolic comorbidities, and individualized immunosuppressive strategies are critical. Future directions include the development of non-invasive biomarkers for fibrosis progression, targeted pharmacologic therapies, and prospective studies to clarify the impact of MASLD on graft survival and overall outcomes. This symposium aims to provide a comprehensive, evidence-based framework for clinicians managing this evolving post-transplant condition.

Key words: Liver transplantation; MASLD; Recurrent vs De Novo; Metabolic syndrome; Steatohepatitis

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KASL BRANCH EARLY MORNING WORKSHOP 2

[Daejeon-Sejong-Chungcheong]

Chair
Seok Hyun Kim (Chungnam National Univ.)



**Hyuk Soo Eun***Chungnam National University*

Self Introduction

Prof. Hyuk Soo Eun is an Associate Professor of the Department of Internal Medicine, Chungnam National University College of Medicine.

Prof. Eun graduated from Chungnam National University College of Medicine with his medical degree and completed his internship and residency at the Department of Internal Medicine at Chungnam National University Hospital.

Hyuk Soo Eun earned his Ph.D. in Medical Science from KAIST (Korea Advanced Institute of Science and Technology). He subsequently completed a fellowship in Gastroenterology at Chungnam National University Hospital, where he later served as a Clinical Assistant Professor and then now serve as an Associate Professor.

Since 2020, Hyuk Soo Eun has been serving as a member of the Research Committee (연구위원회) of the Korean Association for the Study of the Liver (KASL) and as an editorial board member (간행위원회) of the Korean Liver Cancer Association (KLCA).

Representative Publications

1. Lee H, Kim SY, Kim SH, Jeong S, Kim KH, Kim CG, Koh JY, Kim HD, Han JW, Yu H, Lee W, Min S, Park SH, Eun HS, Shin EC. TCR signaling via NFATc1 constrains IL-15-induced bystander activation of human memory CD8+ T cells. *Immunity*. 2025 Dec 9;58(12):2957-2971.e8. doi: 10.1016/j.immuni.2025.10.002 (Co-Corresponding author)
2. Moon GY, Park HS, Kim HN, Choi HG, Han Y, Eun HS, Lee TH, Bu J. Cell-Free DNA Versus Circulating Tumor Cells: A Pilot Study of Alpha-Fetoprotein Analysis for Diagnosis and Treatment Monitoring in Hepatocellular Carcinoma. *Biosensors (Basel)*. 2025 Sep 4;15(9):579. doi: 10.3390/bios15090579. (Co-Corresponding author)
3. Baek EB, Eun HS, Song JY, Hong EJ, Park SH, Kumbukgahadeniya P, Park SM, Kim SH, Kim SO, Kim HN, Cho YE, Won YS, Kwon HJ. Vitamin D supplementation ameliorates ductular reaction, liver inflammation and fibrosis in mice by upregulating TXNIP in ductular cells. *Nat Commun*. 2025 May 13;16(1):4420. doi: 10.1038/s41467-025-59724-z. (Co-First author)
4. Rou WS, Jeon HJ, Eun HS, Lee HS, Park JH, Joo JS, Kim JS, Lee ES, Kim SH, Lee JE, Shin KS, Kim SH, Yeo MK, Lee JM, Kwon IS, Lee BS. Association of Survival with Radiologic-Pathologic Discordance in Patients with Hepatocellular Carcinoma: A Nationwide Cohort Study Based on the Primary Liver Cancer Registry in Korea. *Gut Liver*. 2025 Apr 1. doi: 10.5009/gnl240393. (Co-Corresponding author)
5. Jong-Min Jeong, Sung Eun Choi, Young-Ri Shim, Hee-Hoon Kim, Young-Sun Lee, Keungmo Yang, Kyurae Kim, Min Jeong Kim, Katherine Po Sin Chung, Seok-Hwan Kim, Jin-Seok Byun, Hyuk Soo Eun, Won-Il Jeong. CX3CR1+ macrophages interact with hepatic stellate cells to promote hepatocellular carcinoma through CD8+ T cell suppression *Hepatology*. 2024 Jul 19. doi: 10.1097/HEP (Co-Corresponding author)

Management of Hepatic Hydrothorax in Patients with Hepatorenal Syndrome: A Hemodynamic-Centered Approach

Hyuk Soo Eun*Chungnam National University*

1. Introduction and Clinical Significance

Hepatic hydrothorax is a significant complication of decompensated cirrhosis, occurring in approximately 5% to 10% of patients. It is defined as a transudative pleural effusion, typically exceeding 500 mL, arising from the migration of ascitic fluid through diaphragmatic defects. Recent propensity score-matched studies have demonstrated that hepatic hydrothorax is an independent predictor of mortality, with mortality risk often exceeding that of patients with refractory ascites alone. The clinical management becomes profoundly complex when hepatic hydrothorax coexists with hepatorenal syndrome, as the standard treatments for hepatic hydrothorax can further destabilize renal hemodynamics.

2. Diagnostic Work-Up: Confirming the Dual Challenge

Diagnosis requires a systematic approach to both the pleural space and renal function.

- **Pleural Fluid Analysis:** Diagnostic thoracentesis is mandatory to confirm a transudative profile (Serum-Pleural Albumin Gradient [SPAG] > 1.1 g/dL) and to exclude spontaneous bacterial empyema. Spontaneous bacterial empyema is diagnosed when the polymorpho-nuclear cell count exceeds 250 cells/mm³ with a positive culture, or > 500 cells/mm³ if the culture is negative.
- **Renal Assessment:** Renal impairment must be identified using the International Club of Ascites (ICA) criteria, where an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours is diagnostic of Acute Kidney Injury (AKI). HRS-AKI is specifically diagnosed when there is no response to 2 days of diuretic withdrawal and plasma volume expansion with albumin.

3. Therapeutic Strategy: Prioritizing Renal Protection

The core message for patients with declining renal function is that management must shift from fluid removal to hemodynamic stabilization.

A. Immediate Cessation of Diuretics

Aggressive diuresis with spironolactone or furosemide is the first-line therapy for uncomplicated hepatic hydrothorax. However, in the setting of rising serum creatinine or HRS-AKI, diuretics must be reduced

or completely discontinued. Continued diuresis in these patients exacerbates effective arterial underfilling, further driving renal vasoconstriction.

B. Hemodynamic Support with Vasoconstrictors and Albumin

For patients with hepatic hydrothorax and HRS-AKI, the standard of care is the combination of vasoconstrictors (e.g., Terlipressin) and intravenous albumin.

- Terlipressin: Counteracts splanchnic vasodilation, thereby improving renal perfusion.
- Albumin: Acts as a volume expander and possesses anti-inflammatory properties. This approach stabilizes systemic hemodynamics, which may indirectly improve hepatic hydrothorax by reducing the neurohumoral drive for sodium retention.

C. Cautious Drainage and Contraindications

- Thoracentesis: Should be reserved for symptomatic relief of dyspnea and limited to 1.5–2 liters to avoid re-expansion pulmonary edema and further circulatory insult.
- Chest Tube Avoidance: Chest tube insertion is strictly contraindicated in patients with hepatic hydrothorax. It leads to massive protein depletion, electrolyte imbalance, and a high risk of renal failure and infection.

D. The Role of TIPS as a Bridge

Transjugular intrahepatic portosystemic shunt is highly effective for refractory hepatic hydrothorax as it directly lowers portal pressure. However, in patients with existing renal failure, transjugular intrahepatic portosystemic shunt should be used selectively as a bridge to transplantation, as it carries risks of worsening hepatic encephalopathy and cardiac failure in severely decompensated patients.

4. Definitive Path: Liver Transplantation

Liver transplantation remains the only curative treatment for both hepatic hydrothorax and hepatorenal syndrome. Given that hepatic hydrothorax is associated with high waitlist mortality, these patients should be prioritized for transplant evaluation. Liver transplantation resolves the underlying portal hypertension and restores normal renal function in most hepatorenal syndrome cases.

5. Conclusion

In cirrhotic patients where hepatic hydrothorax and hepatorenal syndrome coexist, the kidneys must be protected at all costs. The management strategy must transition from aggressive diuresis to hemodynamic stabilization using terlipressin and albumin. Symptomatic hepatic hydrothorax should be managed with cautious, infrequent thoracentesis while definitively bridging the patient to liver transplantation.

Keywords: Hepatic hydrothorax, Hepatorenal syndrome, AKI, Terlipressin, Albumin, Liver transplantation

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2. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol, 2018. 69(2): p. 406-460.

3. Biggins, S.W., et al., Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology, 2021. 74(2): p. 1014-1048.

4. Ma, B., et al., The impact and role of hepatic hydrothorax in the prognosis of patients with decompensated cirrhosis: A retrospective propensity score-matched study. Frontiers in Medicine, 2022. Volume 9 - 2022.

5. Rössle, M. and A.L. Gerbes, TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut, 2010. 59(7): p. 988-1000.

6. Singh, V., et al., Asia-Pacific association for study of liver guidelines on management of ascites in liver disease. Hepatol Int, 2023. 17(4): p. 792-826.

7. Vidyani, A., et al., Diagnosis and Management of Hepatic Hydrothorax. Korean J Gastroenterol, 2024. 83(2): p. 45-53.

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HEALTH INSURANCE & POLICY FORUM

Chairs

In Hee Kim (Jeonbuk National Univ.)

Hyun Woong Lee (Yonsei Univ.)





Hyungmin Lee

Korea Disease Control and Prevention Agency

Self Introduction

2013.2	Master's Degree, College of Medicine, Graduated School of Hanyang University, Seoul
2008.3-2011.2	Residency, Department of Preventive Medicine, College of Medicine, Hanyang University, Seoul
2003.2	College of Medicine, Hanyang University, Seoul
2022.5-Present	Director, Korea Disease Control and Prevention Agency
2020-2022	Assistant Secretary, Office of the President the Republic of Korea
2017-2020	Director, Division of Healthcare Associated Infection Control, Korea Centers for Disease Control and Prevention
2012-2016	Deputy Director, Korea Centers for Disease Control and Prevention

Research Interests

General Concerns of Infectious Disease Epidemiology and Control Policy

National Viral Hepatitis Elimination Strategy

Hyungmin Lee

Korea Disease Control and Prevention Agency

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Ae Ran Kwak

Health Insurance Review and Assessment Service

Reimbursement Principles and History of Viral Hepatitis Treatment

Ae Ran Kwak

Health Insurance Review and Assessment Service



Soon Sun Kim
Ajou University

Self Introduction

Soon Sun Kim is a Professor at the Department of Gastroenterology, Ajou University School of Medicine, a position she has held since March 2025. Previously, she served at the same institution as Associate Professor (2020–2025), Assistant Professor (2016–2020), Clinical Assistant Professor (2012–2016), and Clinical Fellow (2010–2012).

She completed her residency and internship in Internal Medicine at Ajou University Hospital. Prof. Kim earned her Ph.D. in Medicine from Ajou University School of Medicine in 2013 and also received her Master’s degree and Doctor of Medicine from the same institution.

In addition, she has served as the Insurance Director of the KLCA since 2024 and as the Insurance Director of the KASL since 2026.

Research Interests

- Hepatocellular Carcinoma
- Biomarkers
- Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
- Microbiome

Representative Publications

1. Kim SS, et al. Bacteroides eggerthii ameliorates MASLD through host–microbe signaling and highlights 2-hydroxyisocaproate as a potential effector. Clin Mol Hepatol. 2026;32(1):239-257.
2. Kim SS, Lee J, Ahn SB, et al. Clinical Course and Prognosis of Long-Term Survivors of Hepatocellular Carcinoma. Aliment Pharmacol Ther. 2025;61(8):1333-1342.
3. Son JA, Weon JH, Baek GO, Ahn HR, Choi JY, Yoon MG, et al. Circulating small extracellular vesicle-derived splicing factor 3b subunit 4 as a non-invasive diagnostic biomarker of early hepatocellular carcinoma. J Exp Clin Cancer Res. 2023;42:288.
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Unmet Need of Clinical Practice in Chronic Viral Hepatitis

Soon Sun Kim Ajou University

Introduction

Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) remain the major causes of liver cirrhosis and hepatocellular carcinoma (HCC) in Korea, imposing a substantial disease burden and liver-related mortality. Despite recent advances in antiviral therapy and the accumulation of robust clinical evidence, gaps still exist between evidence-based clinical practice and the current healthcare and reimbursement systems, highlighting the need for continued discussion and policy development. This lecture aims to review the major unmet needs and future directions in the management of chronic viral hepatitis, focusing on the recent revisions of the clinical practice guidelines by the Korean Association for the Study of the Liver (KASL)

1. CHB

The 2026 KASL Clinical practice guidelines for management of CHB introduced a novel HBV DNA-based classification system for the natural history of CHB, moving beyond the conventional immunologic phase classification. Limitations of the traditional concepts of immune tolerance and the “gray zone” have been increasingly recognized, particularly regarding their inability to adequately reflect actual clinical outcomes and HCC risk. Based on accumulating evidence, a simplified treatment strategy centered on viremia has been proposed. Recent large-scale cohort studies and meta-analyses from Korea and other countries have demonstrated that patients with moderate viremia have an increased risk of HCC, even among those with normal or minimally elevated ALT levels. Significant histologic liver injury and elevated HCC risk have also been reported in these patient populations. In addition, growing clinical and cost-effectiveness evidence suggests that earlier antiviral treatment may reduce liver-related complications and mortality, leading to increasing interest in expanding treatment eligibility. Although the current reimbursement criteria of the National Health Insurance system are based on the existing clinical environment and prior evidence, some discrepancies remain between the current reimbursement policy and the newly revised guideline recommendations. Under the current reimbursement criteria, certain patients with moderate viremia and normal or minimally elevated ALT levels may not qualify for treatment coverage despite having a substantial risk of HCC, potentially limiting timely treatment initiation. Therefore, further discussion integrating emerging clinical evidence and the Korean healthcare

environment will be necessary in the future.

2. CHC

CHC has become a largely curable disease with direct-acting antiviral agents (DAAs), allowing effective prevention of liver cirrhosis and HCC through early diagnosis and prompt treatment linkage. Since 2025, anti-HCV testing has been incorporated into the National Health Screening Program for 56-year-old adults in Korea, providing an important opportunity for early detection of asymptomatic infections. However, in real-world clinical practice, patient loss still occurs during confirmatory testing, linkage to care, and treatment initiation. Therefore, systematic management strategies and enhanced patient education are needed to improve the continuum of care.

The 2025 revised KASL clinical practice guidelines for CHC emphasize a simplified care model to improve treatment accessibility.¹ With the widespread use and high efficacy of pangenotypic DAAs, the revised guideline suggests: 1) the use of pangenotypic DAAs without genotype testing in treatment-naïve patients; 2) simplified treatment strategies for patients without cirrhosis or with compensated cirrhosis, and; and 3) selective genotype testing only in specific situations such as treatment failure or risk of reinfection.

The current reimbursement system was originally established based on earlier treatment paradigms, and further discussion may be warranted in light of the evolving treatment landscape centered on pangenotypic DAAs. As the use of pangenotypic DAAs expands, simplified pretreatment evaluation strategies may become feasible in selected patient populations. Accordingly, future consideration may be given to the selective application of genotype testing based on clinical judgment.

Conclusion

The treatment landscape for chronic hepatitis B and C is rapidly evolving with advances in antiviral therapy, and recent clinical practice guidelines increasingly emphasize earlier treatment initiation and simplified care pathways. Accordingly, it is important to continuously share and discuss the unmet needs encountered in real-world clinical practice while balancing emerging evidence with the realities of the Korean healthcare system. Close collaboration among clinicians, academic societies, and healthcare policy stakeholders will be essential to further improve treatment accessibility and patient management systems. Such efforts are expected to play a key role in achieving the WHO goal of viral hepatitis elimination while reducing the burden of liver disease and improving public health outcomes in Korea.

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KASL BRANCH EARLY MORNING WORKSHOP 3

[Daegu-Gyeongbuk]

Chair

Won Young Tak (Kyungpook National Univ.)





Byoung Kuk Jang
Keimyung University

Self Introduction

Prof. Byoung Kuk Jang is a Professor of the Department of Internal medicine, Keimyung University College of Medicine. Prof. Jang graduated from Keimyung University College of Medicine with his medical degree in 1995 and completed his internship and residency at the Department of Internal medicine at Keimyung University Dongsan Hospital, receiving his diploma in Internal medicine in 2000. Professor Jang has held various positions, including Chairman of the Fatty Liver Disease Research Group at the Korean Association for the Study of the Liver (2024–2025).

Research Interests

MASLD, Liver Fibrosis, HCC

Representative Publications

- 1. KASL clinical practice guidelines for the management of metabolic dysfunction-associated steatotic liver disease 2025. Clin Mol Hepatol. 2025 Feb;31(Suppl):S1-S31.
- 2. A Real-World Retrospective Cohort Study on the Clinical Effect of Silymarin (Legalon) on Liver Damage and Diseases Using a Domestic Multicenter Common Data Model. Gut Liver. 2025 Jul 25. doi: 10.5009/gnl240575.
- 3. Clusterin deficiency exacerbates cholestatic liver disease through ER stress and NLRP3 inflammasome activation. Cell Biosci. 2025 Mar 15;15(1):36.
- 4. Clusterin inhibits lipopolysaccharide induced liver injury. Sci Rep. 2025 Feb 18;15(1):5975.
- 5. Lobeglitazone inhibits LPS-induced NLRP3 inflammasome activation and inflammation in the liver. PLoS One. 2023 Aug 24;18(8):e0290532.

Clinical Application of Non-Invasive Modalities for Fibrosis Assessment in MASLD

Byoung Kuk Jang Keimyung University

Accurate and non-invasive assessment of liver fibrosis is critical in the management of metabolic dysfunction-associated steatohepatitis (MASH), as the degree of fibrosis is the principal determinant of long-term outcomes. Although the Fibrosis-4 (FIB-4) index and vibration-controlled transient elastography (VCTE) are widely recommended in current clinical guidelines, their real-world diagnostic accuracy — particularly for the detection of significant fibrosis ($\geq F2$) — and the practical utility of the guideline-endorsed sequential strategy of FIB-4 followed by VCTE in intermediate- and high-risk patients have not been rigorously validated in Korean tertiary care settings. This study evaluated the diagnostic accuracy of non-invasive tests (NITs), including FIB-4 and Vibration-Controlled Transient Elastography (VCTE), in patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH) diagnosed via liver biopsy at four tertiary university hospitals in Daegu. We further investigated the clinical utility of the sequential screening strategy recommended by current guidelines: performing VCTE for patients classified as intermediate or high risk by FIB-4.

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KASL BRANCH EARLY MORNING WORKSHOP 4

[Gwangju - Jeonnam]

Chair
Sung Bum Cho (Chonnam National Univ.)



**Min-Ho Shin***Chonnam National University*

Self Introduction

Professor Min-Ho Shin has been serving as a Professor in the Department of Preventive Medicine at Chonnam National University Medical School since 2006. He graduated from Chonnam National University Medical School in 1998 and obtained his board certification in Preventive Medicine in 2002. Since 2022, he has also been serving as the Director of the Gwangju-Jeonnam Regional Cancer Center at Chonnam National University Hwasun Hospital.

Regionally Led Project for HCV Micro-Elimination: Jindo-gun

Min-Ho Shin*Chonnam National University*

Hepatitis C virus (HCV) infection remains a global concern, with an estimated worldwide prevalence of approximately 1.6%.[1] In South Korea the seroprevalence is around 0.7% in both sexes, yet many infected individuals are unaware of their status, sustaining silent transmission and progression to cirrhosis and hepatocellular carcinoma. Although no vaccine exists, direct-acting antivirals (DAAs) achieve sustained virologic response in 95–99% of treated patients. Treatment uptake nonetheless remains low: 2019 National Health Insurance Service data indicated that of an estimated 380,000 people with HCV in Korea, only 47,546 received antiviral therapy — roughly one in five. Closing this gap requires expanded screening, earlier diagnosis, and active linkage to care.

The World Health Organization's 2030 elimination targets are typically pursued through national strategies,[2] but country- or province-wide programs alone cannot reach populations whose infection risk is geographically and demographically concentrated. Microelimination — scaling down elimination efforts to defined subpopulations or small geographic units such as counties, townships, or even villages — has emerged as a complementary approach allowing tailored case-finding, efficient resource allocation, and measurable progress within a realistic time frame.[3] In Korea, where HCV burden is sharply clustered in rural counties with aged populations and limited healthcare access, layered programs operating simultaneously at national, provincial, county, and sub-county levels are likely more effective than top-down efforts alone.

Since HCV became a Class 3 notifiable infectious disease in 2016, surveillance has revealed pronounced geographic clustering. Cumulative incidence between 2017 and 2022 was highest in Jeollanam-do, Busan, Gyeongsangnam-do, Incheon, and Jeju, with leading county-level rates in Jindo-gun and Shinan-gun (Jeollanam-do), Sunchang-gun (Jeollabuk-do), Namhae-gun (Gyeongsangnam-do), and Seogu (Busan). Liver cancer incidence between 2014 and 2018 followed a strikingly similar pattern, concentrated in Shinan-gun, Jindo-gun, Ulleung-gun, Namhae-gun, and Sunchang-gun.[4] This overlap reinforces the well-established link between chronic HCV infection and hepatocellular carcinoma in these communities,[5] and underscores why elimination efforts targeting these specific geographies are warranted.

To address this disparity, Jeollanam-do launched a community-based HCV elimination initiative built

around an integrated pathway of case-finding, laboratory confirmation, and timely treatment. The pilot began in February 2023 across six high-burden counties — Jangheung, Gangjin, Haenam, Wando, Jindo, and Shinan. Activities were delivered through local public health centers and included community outreach, point-of-care anti-HCV antibody testing using rapid kits, an awareness questionnaire for seropositive participants, reflex HCV RNA testing, genotyping of viremic cases, linkage to antiviral therapy, and post-treatment follow-up. In this first phase, 2,455 residents were screened, yielding 26 antibody-positive and 13 RNA-positive cases, all receiving treatment support. In 2024 coverage expanded to seven counties with Goheung-gun, screening 7,814 residents and identifying 68 antibody-positive and 25 viremic cases. The program continued in 2025 with 9,540 participants; 194 were antibody-positive, 153 underwent confirmatory RNA testing, 46 were viremic, and 37 received treatment support.

Jindo-gun showed the highest HCV incidence throughout — reaching 251.6 per 100,000 in 2025, more than ten times the provincial average — alongside an exceptionally aged demographic that compounds undiagnosed long-standing infection. Accordingly, Jindo-gun has transitioned the effort into a regionally led, self-financed five-year program (2026–2030) targeting the entire county population not previously covered, approximately 19,261 adults aged ≥20 years. The total budget of KRW 459 million is funded entirely from county resources. The program advances beyond case-finding by establishing a full life-cycle management system connecting early detection, prompt treatment, sustained follow-up of untreated cases reported since 2017, and registration of antibody-positive individuals into the national liver cancer screening program. Implementation proceeds sequentially through the townships (myeon) with the highest incidence — Jisan-myeon in 2026, then Gunnae-myeon, Uisin-myeon, Jindo-eup, and Jodo-myeon by 2030 — with activities delivered down to the village level, bringing microelimination to its most granular operational scale. The goal is a 90% reduction in HCV incidence by 2030, with operational targets of ≥70% antibody screening coverage, 90% treatment linkage among RNA-positive cases, 90% engagement of previously untreated patients, and 70% adherence to liver cancer surveillance.

As of early April 2026, first-year activities in Jisan-myeon screened 1,571 of 2,167 actual residents (72.4%), identifying 119 antibody-positive individuals (7.6%). Antibody positivity varied markedly across the 37 villages within this single township, ranging from 0% in eight villages to 25.0% in the highest-prevalence village, with several villages exceeding 15%. This more than tenfold within-township heterogeneity — observed at a spatial scale finer than any administrative unit currently used for HCV surveillance in Korea — provides direct empirical support for extending microelimination below the county and even township level. Reflex RNA testing and treatment linkage are scheduled through May and June 2026. In parallel, an untreated-patient registry compiled from notifications since 2017 enrolled 57 of 64 traceable cases (89%), of whom 53 remained antibody-positive and are being prioritized for re-engagement.

Eliminating HCV-attributable liver cancer disparities in Korea will require not a single nationwide campaign but a layered architecture of elimination programs operating at multiple administrative scales

— national strategy setting the framework, provincial programs covering high-burden regions, and county- or village-level microelimination reaching residents that broader efforts inevitably miss. The Jindo-gun program illustrates how this finest layer can be operationalized in a high-burden rural jurisdiction, and offers a transferable model for other Korean regions facing similar HCV-associated cancer risk.

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KASL SYMPOSIUM 5

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Alcohol-Related Liver Disease (MetALD)

Chairs

Stefano Romeo (Karolinska Institutet, Sweden)

Yong Kyun Cho (Sungkyunkwan Univ.)





Stefano Romeo
Karolinska Institutet, Sweden

Self Introduction

Stefano Romeo is a Professor of Clinical Diabetology at Karolinska Institutet (Department of Medicine, Huddinge) and leads the Human Translational Genetics research group. His work focuses on how human genetic variation drives metabolic disease, with a main emphasis on metabolic dysfunction-associated steatotic liver disease (MASLD), and links to diabetes and cardiovascular disease.

He earned his medical degree in 2001 (Campus Bio-Medico University of Rome), became a specialist in Endocrinology and Metabolic Diseases in 2006, and completed a PhD in 2009 from Sapienza University of Rome that was carried out at UT Southwestern in Dallas, TX, USA. He later held a Clinical lectureship in Endocrinology at the University of Cambridge (2009 to 2011) and he became a Professor at the University of Gothenburg in 201, and was appointed professor at Karolinska Institute in September 2024.

Research Interests

Human and Molecular Genetics of Steatotic Liver Disease

Representative Publications

1. Mureddu M, Pelusi S, Jamialahmadi O, Vujkovic M, Miano L, Eidgah Torghabehei H, Ronzoni L, Malvestiti F, Saracino M, Periti G, Moretti V, Teerlink CC, Lynch JA, Tsao PS, Johnson JP, La Mura V, Dilella R, Alqahtani SA, Cherubini A, Russo FP, D'Ambrosio R, Fraquelli M, Petta S, Miele L, Vespasiani-Gentilucci U, Bugianesi E, Mancina RM, Parini P, Prati D, Chang KM, Schneider CV, Romeo S*, Valenti LV.* Carriage of rare APOB variants predisposes to severe steatotic liver disease and hepatocellular carcinoma. J Clin Invest. 2026 Feb 10:e201762. doi: 10.1172/JCI201762. Online ahead of print. PMID: 41665936 *Corresponding IF: 13.6;

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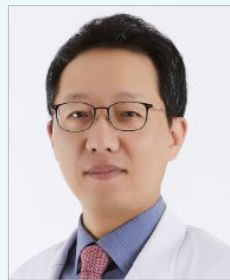
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Outcomes and Prognosis in MASLD: Genetic Determinants from Single-Nucleotide Polymorphisms to Beyond

Stefano Romeo *Karolinska Institutet, Sweden*

The lecture will present steatotic liver disease as a genetically heterogeneous disorder that sits at the intersection of hepatic lipid handling, insulin resistance and systemic cardiometabolic disease. The central message will be that human genetics has moved the field beyond simple fat accumulation. Common and rare germline variants in genes such as PNPLA3, TM6SF2, MBOAT7, GCKR, GPAM, MARC1, HSD17B13, CIDEA and ATG7 identify pathways controlling triglyceride synthesis, lipid droplet remodeling, inflammation, fibrosis and cancer risk. These variants do not merely predict liver fat; they help explain why some people develop progressive liver disease while others mainly show systemic metabolic complications. The lecture will highlight a key conceptual advance: the separation of MASLD into at least two biological trajectories, one embedded in cardiometabolic syndrome and another predominantly liver-driven. This distinction supports a precision-medicine approach, using genetic risk, polygenic scores and multi-omics to stratify people for surveillance and treatment.

**Sang Gyune Kim**

Soonchunhyang University

Self Introduction

Dr. Sang Gyune Kim is a Professor of Internal Medicine and hepatologist at Soonchunhyang University College of Medicine in the Republic of Korea. He graduated from Soonchunhyang university college of medicine and completed his internship and residency at the department of Internal medicine at Soonchunhyang university hospital, receiving his diploma in Soonchunhyang university bucheon hospital.

He serves as a director of health insurance affairs at Korean liver cancer association, secretary general at KASL steatotic liver disease study group, director of academic affairs at KASL liver cirrhosis study group, Executive director of academic affairs and director of planning affairs at Korean association of clinical ultrasound.

Research Interests

His clinical and academic work focuses on metabolic dysfunction-associated steatotic liver disease (MASLD), liver cirrhosis and portal hypertension, and non-invasive assessment of liver fibrosis.

Representative Publications

1. Kim SG, et al. Lower incidence of hepatocellular carcinoma with tenofovir alafenamide in chronic hepatitis B: Evidence from a large-scale cohort. *JHEP Reports*. 2025;7:101268.
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MASLD vs. MetALD: Interactions between Alcohol Intake and Metabolic Risk Factors

Sang Gyune Kim

Soonchunhyang University

1. Definition and Diagnostic Classification: The Spectrum of Metabolic- and Alcohol-Related Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is strictly defined as the presence of hepatic steatosis accompanied by at least one of five cardiometabolic risk factors (CMRFs), in the absence of harmful levels of alcohol consumption or other identifiable causes of liver injury. To further stratify the pathophysiological spectrum of steatotic liver disease according to alcohol intake beyond the category of pure MASLD, a newly introduced entity termed metabolic dysfunction and alcohol-associated liver disease (MetALD) has emerged.

MetALD refers to patients who fulfill the diagnostic criteria for MASLD while simultaneously consuming moderate amounts of alcohol. Importantly, MetALD should not be regarded merely as a mixture of two etiologies, but rather as a distinct clinical entity with unique biological and prognostic characteristics.

1) Diagnostic Thresholds for Cardiometabolic Risk Factors and Alcohol Consumption

The five cardiometabolic risk factors required for the diagnosis of MASLD and MetALD represent key indicators of systemic metabolic dysfunction. According to current diagnostic algorithms, metabolic risk factors should be assessed in all adult patients with radiologic or histologic evidence of hepatic steatosis, regardless of serum aminotransferase levels.

The cardiometabolic risk factors include:

- Overweight or obesity (BMI ≥ 25 kg/m², or ≥ 23 kg/m² in Asians) or increased waist circumference according to ethnicity-specific cutoffs
- Dysglycemia, including fasting glucose ≥ 100 mg/dL, HbA1c $\geq 5.7\%$, or established type 2 diabetes mellitus
- Elevated blood pressure ($\geq 130/85$ mmHg) or use of antihypertensive medication
- Hypertriglyceridemia (≥ 150 mg/dL) or lipid-lowering treatment
- Reduced HDL cholesterol (< 40 mg/dL in men, < 50 mg/dL in women)

Among individuals meeting at least one metabolic risk criterion, cumulative weekly alcohol consump-

tion serves as the pivotal discriminator between MASLD, MetALD, and alcohol-associated liver disease (ALD).

MASLD is defined by mild alcohol intake (≤ 140 g/week in women and ≤ 210 g/week in men), whereas MetALD encompasses moderate alcohol consumption (140–350 g/week in women and 210–420 g/week in men). Alcohol intake exceeding these thresholds is classified as ALD regardless of metabolic status.

Unlike the previous nonalcoholic fatty liver disease (NAFLD) framework, which relied heavily on the exclusion of significant alcohol intake, the newly adopted nomenclature emphasizes an affirmative diagnosis centered on metabolic dysfunction. This conceptual transition represents a major paradigm shift in hepatology.

2) Challenges in Real-World Clinical Diagnosis and the Role of Biomarkers

Although more than 95% of patients previously diagnosed with NAFLD fulfill the criteria for MASLD, alcohol intake assessment based solely on self-reporting frequently underestimates actual consumption because of intentional underreporting.

Accordingly, phosphatidylethanol (PEth), a direct whole-blood biomarker of alcohol intake, has gained increasing clinical importance. PEth remains detectable for approximately 2–4 weeks following alcohol exposure and enables more accurate identification of patients who may otherwise be misclassified as having pure MASLD instead of MetALD or ALD.

2. Global Epidemiology and Demographic Characteristics

Globally, MASLD has become the dominant chronic liver disease, affecting approximately 30–38% of the adult population. However, the burden and prognosis of MetALD and ALD vary substantially depending on the coexistence of metabolic risk factors such as obesity and diabetes mellitus.

1) Large-Scale Population-Based Cohort Studies and Korean Epidemiologic Data

Population-based studies from the United States and Europe indicate that approximately 3–5% of adults meet the diagnostic criteria for MetALD, with prevalence rates rising to 8–10% in countries where obesity and hazardous alcohol consumption coexist extensively. Moreover, detailed analyses of patients previously categorized as MASLD reveal that approximately 15–30% are reclassified as MetALD because of moderate or greater alcohol intake.

A nationwide Japanese cohort including 184,463 individuals between 2004 and 2022 demonstrated an overall steatotic liver disease prevalence of 26.9%, consisting of MASLD (22.7%), MetALD (2.1%), and ALD (1.1%). Longitudinal analyses showed continuous increases in both MASLD and MetALD regardless of body composition, whereas ALD increased most sharply among lean individuals, suggesting that alcohol-related hepatotoxicity may be particularly severe even in individuals with normal BMI.

Large-scale Korean cohort studies have demonstrated findings consistent with these global trends while also highlighting unique risk profiles among Korean populations. A nationwide Korean National Health Insurance Service (KNHIS) cohort study involving approximately 1.3 million adults aged 40–79 years with more than 9 years of follow-up reported prevalence rates of 33.11% for MASLD, 3.93% for MetALD, and 1.00% for ALD accompanied by metabolic dysfunction.

Furthermore, in the Korean Ansung–Ansan cohort including approximately 9,500 participants with a median follow-up of 17.5 years, individuals with MetALD, which accounted for 4.5% of the cohort, demonstrated a 1.75-fold significantly increased risk of progression to advanced liver fibrosis compared with those with pure MASLD.

Similarly, a Korean primary care cohort study involving 2,535 patients showed that liver fibrosis burden assessed by magnetic resonance elastography (MRE) was substantially greater in MetALD than in either pure MASLD or ALD, strongly supporting the concept that the combination of metabolic dysfunction and alcohol consumption accelerates liver disease progression in Korean patients.

2) Sex-Specific Epidemiologic Heterogeneity and Female Vulnerability

Epidemiologic data consistently demonstrate that MASLD prevalence is generally higher in men than in women, likely because of the hepatoprotective effects of estrogen and differences in visceral fat distribution.

However, in the setting of MetALD, women appear substantially more vulnerable to alcohol-related hepatotoxicity than men. Women exhibit lower gastric alcohol dehydrogenase activity and a higher body fat-to-water ratio, resulting in greater blood alcohol concentrations following equivalent alcohol intake. Moreover, estrogen sensitizes hepatic Kupffer cells, thereby amplifying inflammatory responses to alcohol-induced injury.

Consequently, women may develop more severe liver injury with lower cumulative alcohol exposure, experience more rapid progression to cirrhosis, and exhibit poorer post-transplant outcomes than men. These findings suggest that female patients with MetALD may follow a particularly aggressive clinical trajectory even under comparable metabolic and alcohol-related conditions.

3. Pathophysiologic Interactions: The Synergistic Cascade between Alcohol and Metabolic Risk Factors

The central pathophysiologic feature of MetALD lies in the synergistic rather than merely additive interaction between metabolic dysfunction and alcohol toxicity. Although pure ALD and MASLD share susceptibility genes and histologic characteristics, their coexistence dramatically accelerates fibrosis progression and hepatocarcinogenesis.

1) Interaction between Obesity and Alcohol: Disruption of Lipid Metabolism

Obesity, particularly abdominal obesity, is a major determinant of liver disease development. Excess vis-

ceral adiposity promotes adipose tissue lipolysis and increases the flux of free fatty acids into the liver. Concurrent alcohol intake acts as a critical second hit by inhibiting mitochondrial β -oxidation through reversal of the NADH/NAD⁺ ratio during ethanol metabolism.

As a result, excessive fatty acid influx combined with impaired lipid degradation induces massive hepatocellular lipid accumulation. Furthermore, alcohol itself may contribute to weight gain, thereby perpetuating a vicious cycle between obesity and hepatic steatosis.

2) Synergistic Pathophysiology between Insulin Resistance and Type 2 Diabetes Mellitus

Chronic heavy alcohol consumption independently promotes systemic insulin resistance and increases the risk of type 2 diabetes mellitus (T2DM). When alcohol-induced injury converges with severe insulin resistance, inflammatory signaling pathways become markedly amplified.

In patients with severe insulin-resistant diabetes (SIRD), excessive alcohol consumption exacerbates oxidative stress through CYP2E1 induction and generates abundant reactive oxygen species (ROS), leading to lipid peroxidation and exaggerated inflammatory cytokine release. Together, alcohol and metabolic overload create a highly pro-inflammatory and profibrogenic hepatic microenvironment.

3) Genetic Susceptibility and the Triple Collision of Alcohol and Metabolic Dysfunction

Genetic polymorphisms substantially influence the magnitude of synergistic liver injury. The PNPLA3 I148M variant, one of the best-characterized lipid metabolism-related genetic variants, promotes both metabolic steatosis and alcohol-induced liver injury.

Particularly in ALD patients, the coexistence of insulin resistance and PNPLA3 mutations acts as an independent driver of hepatic inflammatory activity and represents one of the strongest promoters of fibrogenesis.

4) Disruption of the Gut-Liver Axis

Both metabolic dysfunction and alcohol synergistically disrupt intestinal homeostasis. These factors induce gut dysbiosis and impair intestinal epithelial barrier integrity, thereby facilitating translocation of endotoxins and bacterial DNA into the portal circulation.

The influx of these microbial products activates hepatic Kupffer cells and triggers profound innate immune activation, further exacerbating hepatic inflammation and fibrosis.

4. Long-Term Clinical Outcomes and Mortality: Exponential Increases in Liver-Related Events and Carcinogenesis

The clinical impact of concurrent metabolic dysfunction and alcohol consumption is multiplicative rather than additive. Longitudinal cohort studies consistently demonstrate substantial differences in rates of advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) among patients with MASLD, MetALD, and ALD.

1) Multiplicative Interaction between Alcohol and Metabolic Risk Factors

A large population-based cohort study involving more than 6,700 individuals followed over 12 years clearly demonstrated the synergistic effects of alcohol and metabolic risk factors, particularly T2DM.

Compared with individuals without diabetes or hazardous alcohol consumption:

- Patients with diabetes alone exhibited a 2.5-fold increase in liver-related events
- Patients with hazardous alcohol use alone demonstrated a 3.5-fold increase
- Patients with both diabetes and hazardous alcohol consumption showed an approximately 20-fold increase in liver-related events

Similarly, alcohol consumption exceeding 15 drinks per week increased liver-related mortality across all BMI categories, with substantially greater mortality risk among obese individuals. These findings strongly suggest that patients with MetALD or alcohol misuse accompanied by metabolic dysfunction represent a particularly high-risk subgroup for cirrhosis progression.

2) Risk Stratification of Major Adverse Liver Outcomes (MALO)

Recent analyses from JAMA Internal Medicine and the UK Biobank demonstrated clear risk stratification according to steatotic liver disease subtype.

Compared with pure MASLD, MetALD was associated with a 1.23–1.56-fold higher risk of major adverse liver outcomes (MALO), including cirrhosis, hepatic decompensation, and HCC. In contrast, ALD was associated with a 2.33–2.95-fold higher MALO risk than MASLD.

Among all prognostic indicators, baseline fibrosis severity, particularly as assessed using the FIB-4 index, emerged as the strongest independent predictor of adverse liver outcomes.

3) Synergistic Amplification of Hepatocellular Carcinoma Risk

The synergistic interaction between obesity, diabetes mellitus, and alcohol intake is also evident in hepatocarcinogenesis.

In a Japanese nationwide cohort involving approximately 10 million individuals, the risk of primary HCC increased by 3.55-fold to as high as 5.39-fold among patients with MASLD, MetALD, and ALD compared with healthy controls.

Beyond HCC, the coexistence of metabolic dysfunction and alcohol consumption dose-dependently increased the risk of multiple gastrointestinal malignancies, including esophageal, gastric, and colorectal cancers.

Patients harboring the combined triad of PNPLA3 risk variants, metabolic syndrome, and substantial alcohol intake represent an exceptionally high-risk population for both cirrhosis and HCC development.

5. Diagnostic Risk Stratification and Non-Invasive Test Strategies

Accurate assessment of fibrosis severity remains fundamental in the management of steatotic liver disease. Current EASL–EASD–EASO integrated guidelines recommend a sequential two-step non-invasive risk stratification strategy using serum-based and imaging-based modalities.

The first step involves FIB-4 calculation to exclude advanced fibrosis in low-risk individuals. Patients classified as intermediate or high risk subsequently undergo vibration-controlled transient elastography (VCTE) to identify advanced fibrosis and cirrhosis.

However, interpretation of non-invasive tests in MetALD requires caution because acute alcohol-related inflammation and severe obesity may artificially elevate biomarkers such as the enhanced liver fibrosis (ELF) score or interfere with ultrasound-based elastography measurements.

Accordingly, fibrosis assessment in MetALD should incorporate recent alcohol consumption patterns, potentially aided by PEth measurements, while accounting for concomitant acute hepatic inflammation.

6. Multidisciplinary Treatment Strategies and Future Classification Systems

Effective management of MetALD requires simultaneous targeting of both metabolic dysfunction and alcohol consumption. Because these pathogenic factors mutually amplify disease progression, addressing only one component is unlikely to achieve meaningful therapeutic benefit.

1) Simultaneous Approaches to Complete Abstinence and Weight Reduction

The most effective strategy for preventing disease progression differs according to disease etiology. Complete alcohol abstinence remains the cornerstone of ALD management, whereas sustained weight reduction represents the most effective intervention for MASLD.

Therefore, patients with MetALD require not merely alcohol reduction but permanent abstinence combined with aggressive metabolic correction, including at least 5–10% body weight reduction.

Because each additional component of metabolic syndrome—including hypertension, dyslipidemia, and T2DM—incrementally increases the risk of cirrhosis and HCC, secondary prevention strategies are critically important.

2) Integration of Emerging Pharmacologic Therapies

For patients inadequately controlled by lifestyle modification alone, pharmacologic therapies targeting systemic metabolic dysfunction should be considered.

GLP-1 receptor agonists such as semaglutide and dual GIP/GLP-1 agonists such as tirzepatide improve hepatic steatosis and inflammation through substantial weight reduction and metabolic improvement.

In patients with fibrotic metabolic steatohepatitis, the recently approved thyroid hormone receptor- β agonist resmetirom may represent an important therapeutic option. Furthermore, bariatric metabolic surgery may provide significant survival benefits in selected patients with severe obesity.

3) The Next Evolution in Nomenclature: Emergence of the ALD-Met Concept

Patients with severe alcohol consumption exceeding current MetALD thresholds who simultaneously harbor significant metabolic dysfunction, such as severe obesity or T2DM, are currently classified within the broad ALD category.

However, these individuals exhibit dramatically higher cirrhosis-related mortality than patients with isolated alcohol misuse. Consequently, expert groups have proposed a new category termed “ALD with metabolic dysfunction (ALD-Met)” for patients fulfilling criteria for severe alcohol intake while also possessing multiple major metabolic risk factors.

Further refinement of steatotic liver disease nomenclature may facilitate identification of the highest-risk populations and promote implementation of multidisciplinary surveillance and personalized treatment strategies.

Conclusion

Alcohol consumption and metabolic dysfunction interact synergistically to amplify hepatic injury and worsen clinical outcomes. Clinicians should no longer regard alcohol use disorder, insulin resistance, and obesity as separate disease processes but rather as components of a unified pathophysiologic threat requiring comprehensive and proactive therapeutic intervention.



Young Nyun Park
Yonsei University

Self Introduction

Young Nyun Park is a world-renowned authority in liver pathology and a Professor at Yonsei University College of Medicine. She currently chairs the Medical Science Division of the Korean Academy of Science and Technology (KAST). After earning her MD and PhD from Yonsei University, she completed specialized fellowship training in liver pathology at Mount Sinai Medical Center in the United States.

Her research focuses on the mechanisms of hepatocarcinogenesis, cancer stem cells, and the tumor microenvironment. A prolific scholar with an H-index of 88, she has published over 300 peer-reviewed papers in premier journals, including J Hepatol and Hepatology. Her expertise has been instrumental in shaping global diagnostic standards as a key contributor to the WHO Classification of Tumours (4th, 5th, and 6th editions) and as an author of the definitive textbook, Practical Hepatic Pathology. She currently serves as an Associate Editor for the journal Liver Cancer.

Professor Park is a distinguished member of the International Liver Pathologists Study Group (the “Gnomes”), an elite, invitation-only global collective. Her extensive leadership career includes serving as Vice Dean of Yonsei University College of Medicine (2018–2024), President of the Korean Liver Cancer Association (2020–2021), and Hosting Chair for the 2023 Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE).

Research Interests

Hepatocellular Carcinoma, Cholangiocarcinoma, Hepatocarcinogenesis, Tumor Microenvironment, MASLD

Representative Publications

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Standardizing Histological Grading and Staging in Metabolic Dysfunction-Associated Steatohepatitis (MASH) Clinical Trials: Consensus Position Statements from the International Pathology Group

Young Nyun Park Yonsei University

As the landscape of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Steatohepatitis (MASH) rapidly evolves, liver biopsy remains the regulatory “gold standard” for evaluating drug efficacy in clinical trials. However, significant inter-observer variability and a lack of standardized diagnostic definitions have historically introduced statistical “noise” into clinical data, often complicating the path to regulatory approval.

This session aims to introduce the core recommendations of the 2025 the International MASLD Pathology Group (IPMG) Consensus Position Statement, which was developed through a rigorous Delphi process involving 25 global liver pathology experts who achieved over 80% agreement on 162 critical recommendations. These standards encompass the technical optimization of biopsy tissue processing—including minimum sample requirements and staining protocols—and provide refined, consensus-based morphological definitions for key features such as hepatocyte ballooning, lobular inflammation, and steatosis to minimize diagnostic ambiguity. Furthermore, the guidelines advocate for a unified application of advanced grading and staging systems to better reflect therapeutic response and meet the stringent requirements of primary clinical endpoints.

The implementation of these standards represents a fundamental shift in drug development strategy; by reducing inter-observer variability and minimizing statistical variance, they allow for a clearer interpretation of a drug’s true therapeutic effect. This alignment is crucial for meeting the rigorous expectations of the FDA and EMA for accelerated approval pathways. Moreover, these guidelines future-proof clinical trials by providing the standardized “Ground Truth” necessary for integrating AI-based histological analysis. Ultimately, the IMPG Consensus Position Statement serves as a vital roadmap, and its adoption is essential for ensuring that the next generation of MASH therapies is evaluated with the highest level of scientific and clinical integrity.



Dae Won Jun
Hanyang University

Self Introduction

Prof. Dae Won Jun is a Professor in the Division of Hepatology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea. He also holds appointments in the Department of Clinical Medicine at the Hanyang University Graduate School of Biomedical Science and Engineering, and in the Department of Digital Convergence Medicine at the Hanyang University College of Engineering.

Prof. Jun currently serves as Chair of the Fatty Liver Research Group of the Korean Association for the Study of the Liver (KASL), a member of the Transfusion Adverse Reaction Subcommittee of the Korea Disease Control and Prevention Agency, and a member of the Korea Medical Dispute Mediation and Arbitration Agency. He has previously served as Director of Research Planning of the Korean Society of Gastroenterology (2022–2023), Director of Education (2016–2017) and Director of Research Planning (2020–2021) of KASL, as well as Director of Publication (2016–2017) and Director of Research (2015–2016) of the Korean Liver Cancer Association.

Research Interests

Metabolic dysfunction-associated steatotic liver disease (MASLD / MASH), Non-invasive tests for liver fibrosis, Hepatic lipid metabolism and lipid droplet biology, Lifestyle and pharmacological interventions for fatty liver disease, Chronic hepatitis B and hepatocellular carcinoma

Representative Publications

	Title	Journal	Year	Role	IF
1	Efficacy and safety of time-restricted eating in metabolic dysfunction-associated steatotic liver disease	Journal of Hepatology	2025	Corresponding	IF: 33.0
2	Diagnostic Performance of Noninvasive Tests in Patients with MetALD in a Health Check-up Cohort	Journal of Hepatology	2024	Corresponding	IF: 33.0
3	LDI, a Lipid Droplet Inhibitor, Disrupts Lipid Accumulation and Modulates Hepatic Lipid Profiles in Fatty Liver	Advanced Materials	2025	Corresponding	IF: 26.8
4	Diagnostic accuracy of the Fibrosis-4 index for advanced liver fibrosis in metabolic dysfunction-associated steatotic liver disease with type 2 diabetes: A systematic review and meta-analysis	Clinical and Molecular Hepatology	2024	Corresponding	IF: 16.9
5	Prevalence, distribution and hepatic fibrosis burden of the different subtypes of steatotic liver disease in primary care settings	Hepatology	2024	Corresponding	IF: 15.8

Future of MASH Treatment: GLP-1/GIP Agonists, Resmetirom, and Beyond

Dae Won Jun Hanyang University

Background and Aims

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), have emerged as leading causes of cirrhosis, hepatocellular carcinoma, and cardiovascular morbidity. The therapeutic landscape has undergone a paradigm shift since the U.S. Food and Drug Administration (FDA) granted accelerated approval of resmetirom in March 2024 as the first agent for noncirrhotic MASH with moderate-to-advanced fibrosis, followed by the approval of semaglutide 2.4 mg for MASH in August 2025. This review summarizes the rapidly expanding pipeline of MASH therapeutics, with particular emphasis on emerging targets beyond the established incretin and thyroid hormone receptor axes.

Approved Therapies

In the pivotal MAESTRO-NASH phase 3 trial (N=966), resmetirom 80 mg and 100 mg achieved MASH resolution without worsening of fibrosis in 25.9% and 29.9% of patients, respectively, compared with 9.7% for placebo, and fibrosis improvement of at least one stage in 24.2% and 25.9% versus 14.2% for placebo. A recent prespecified subgroup analysis of MAESTRO-NASH demonstrated that resmetirom retained comparable efficacy in patients receiving background GLP-1 receptor agonist or SGLT2 inhibitor therapy, and that weight loss of ≥5% was associated with enhanced histologic response, providing rationale for combination strategies. The ongoing MAESTRO-NASH OUTCOMES trial (N=845) will assess progression to hepatic decompensation in patients with compensated MASH cirrhosis, with results expected in late 2026. In the ESSENCE phase 3 trial, semaglutide 2.4 mg produced significant histologic improvement in MASH, and mediation analysis revealed that its effects on steatohepatitis and non-invasive markers of fibrosis were only partially mediated by body weight reduction, indicating substantial weight-independent hepatic benefit. The cardiorenal benefits of semaglutide demonstrated in the SELECT and FLOW trials further support an integrated metabolic approach to MASH.

Novel Incretin-Based Multi-Agonists

In the phase 2 SYNERGY-NASH trial (N=190), tirzepatide, a dual GLP-1/GIP receptor agonist, produced MASH resolution without worsening of fibrosis in 44%, 56%, and 62% of patients at the 5-, 10-, and 15-

mg doses, respectively, compared with 10% for placebo. Survodutide, a glucagon/GLP-1 dual agonist with an 8:1 ratio, demonstrated MASH improvement in 47%, 62%, and 43% of patients receiving 2.4, 4.8, and 6.0 mg, respectively, versus 14% for placebo, and a reduction in liver fat content of at least 30% in 63%, 67%, and 57% versus 14% for placebo in its phase 2 trial (N=293), which led to FDA Breakthrough Therapy designation and initiation of the phase 3 LIVERAGE program enrolling approximately 3,390 patients. In the IMPACT phase 2b trial (N=212) of pemvidutide, a balanced 1:1 glucagon/GLP-1 dual agonist, MASH resolution without worsening of fibrosis occurred in 58% of patients receiving 1.2 mg and 52% receiving 1.8 mg, compared with 20% for placebo (p<0.0001). Retatrutide, a triple GLP-1/GIP/glucagon agonist, achieved up to 86% reduction in hepatic fat fraction at 48 weeks in its phase 2a trial, with 93% of participants in the 12-mg arm attaining liver fat content below 5%. Maridebart cafraglutide (MariTide), a long-acting peptide-antibody conjugate combining GLP-1 receptor agonism with GIP receptor antagonism, produced weight reductions of 12.3% to 16.2% in participants with obesity and 8.4% to 12.3% in those with obesity and type 2 diabetes over 52 weeks, with a 21-day half-life permitting monthly or less frequent dosing; the apparent efficacy of both GIP receptor agonism (tirzepatide) and antagonism (MariTide) in producing weight loss reflects the context-dependent duality of GIP signaling and has stimulated renewed interest in GIP biology for MASH.

FGF21 Analogues

FGF21 analogues have emerged as highly effective agents for fibrosis regression. In a recent network meta-analysis of 29 randomized controlled trials encompassing 9,324 patients, pegozafermin ranked first for both fibrosis regression (SUCRA 79.92) and MASH resolution (SUCRA 91.75), followed by survodutide and tirzepatide for MASH resolution. Efruxifermin, although failing its phase 2b primary endpoint at 36 weeks, showed sustained fibrosis improvement at 96 weeks. Efimosfermin alfa (BOS-580), a long-acting FGF21 analogue, achieved MASH resolution in 68% of patients compared with 29% for placebo (p=0.002) and fibrosis improvement in 45% versus 21% (p=0.038) in a 24-week phase 2 trial, supporting once-monthly dosing convenience.

Targeting Genetic Risk Variants

The PNPLA3 I148M variant, the strongest genetic determinant of MASLD heritability, has become a target for RNA-based precision therapeutics. AZD2693, a GalNAc-conjugated antisense oligonucleotide developed by AstraZeneca, reduced hepatic PNPLA3 mRNA by 89%, decreased liver fat content by 7.6% at the 25-mg dose and 12.2% at the 50-mg dose (placebo-corrected), and reduced serum hsCRP and interleukin-6 levels in homozygous 148M risk allele carriers in its phase 1 program; the phase IIb FORTUNA trial is ongoing. JNJ-75220795/ARO-PNPLA3, a GalNAc-siRNA developed by Janssen and Arrowhead, reduced liver fat content by up to 46% in homozygous carriers at the highest dose but produced no effect in heterozygous carriers, exemplifying genotype-dependent precision medicine. Additional PNPLA3-targeted agents (LY3849891, ALN-PNP) are in early-phase development. GSK4532990/ARO-HSD, a

siRNA targeting HSD17B13, mimics the protective loss-of-function variant and is undergoing evaluation in the phase 2b HORIZON trial in patients with stage 3 fibrosis.

De Novo Lipogenesis (DNL) Inhibition

Direct pharmacologic blockade of hepatic DNL has emerged as an orally bioavailable therapeutic strategy complementary to incretin- and FGF21-based approaches. Denifanstat, a selective oral fatty acid synthase (FASN) inhibitor, achieved significant histologic improvement in the phase 2b FASCINATE-2 trial (N=168), with MASH resolution without worsening of fibrosis in 36% of denifanstat-treated patients versus 13% with placebo (p=0.0044) and a ≥ 2 -point reduction in NAS without worsening of fibrosis in 52% versus 20% (p=0.0003). Secondary analyses using AI-based digital pathology showed that in the qFibrosis stage 4 subgroup, denifanstat produced at least one-stage regression in 85% (11/13) of patients compared with 33% (1/3) with placebo. Denifanstat received FDA Breakthrough Therapy designation, and a phase 2 proof-of-concept trial of denifanstat in combination with resmetirom in F4 MASH is planned to initiate in the second half of 2026, predicated on preclinical evidence of synergy (80% NAS improvement with combination versus 33% and 25% with monotherapies). Ketohexokinase (KHK) inhibitors constitute another emerging class targeting fructose-driven lipogenesis: LY3522348, a selective dual inhibitor of KHK-C and KHK-A isoforms, demonstrated acceptable safety and pharmacokinetics in its first-in-human phase 1 study, while BI-9787 (Boehringer Ingelheim), a zwitterionic KHK inhibitor with improved oral bioavailability, and PF-06835919 (Pfizer) are advancing through early clinical evaluation. Upstream lipogenic targets including ATP-citrate lyase (ACLY) and monoacylglycerol acyltransferase-2 (MGAT2) have demonstrated preclinical efficacy and are progressing toward clinical development.

Mitochondrial Targets

Modulation of mitochondrial bioenergetics represents a conceptually distinct strategy. Mitochondrial uncouplers increase fatty acid oxidation and reduce the reductive force required for DNL; HU6 (Rivus Pharmaceuticals), a controlled-release derivative, is in phase 2 evaluation, and next-generation compounds including DNP-methyl ether and controlled-release mitochondrial protonophore are designed to mitigate the toxicity associated with historical 2,4-dinitrophenol. MSDC-0602K, a mitochondrial pyruvate carrier modulator, improved glucose, insulin, liver enzymes, and NAS in biopsy-confirmed MASH with F1–F3 fibrosis and is now in phase 3 evaluation of glycemic and cardiovascular outcomes.

Amylin Pathway and Next-Generation Multi-Hormonal Agents

Cagrilintide, a long-acting amylin analogue, combined with semaglutide (CagriSema) produced significant weight loss and HbA1c improvement in phase 2 trials and is now being evaluated in multiple phase 3 studies, including a head-to-head comparison with tirzepatide; this combination may provide a tolerability-favorable alternative for patients unable to tolerate GLP-1 monotherapy. Dual amylin/calcitonin receptor agonists are in early clinical development. NA 941 (Biomed Industries), an oral non-pep-

tide quadruple receptor agonist modulating IGF-1, GLP-1, GIP, and glucagon signaling, demonstrated an acceptable phase 1b safety profile and has entered a phase 2 MASH trial enrolling approximately 180 participants; its sister compound NA 931 achieved up to 13.8% weight loss over 13 weeks while reportedly preserving lean mass, addressing a key limitation of current GLP-1–based therapies. Efinopegdutide (MK-6024), a GLP-1/glucagon dual agonist with 2:1 potency ratio, produced a 72.7% relative reduction in liver fat at week 24, compared with 42.3% with semaglutide, in a head-to-head phase 2a trial.

Gut–Liver Axis

Recent mechanistic work has identified the vasoactive intestinal peptide (VIP)–VIPR2 axis as a suppressor of hepatoprotective IL-22 secretion by intestinal type 3 innate lymphoid cells, with genetic or pharmacologic VIPR2 blockade reducing hepatic steatosis in preclinical models, highlighting a novel neuroimmune therapeutic target. Parallel strategies targeting bile acid receptors (non–bile acid FXR agonists, TGR5 agonists), FGF19 analogues, and gut microbiome modulation (probiotics, fecal microbiota transplantation, phage-based therapies) are being explored as adjunctive approaches addressing the intestinal contribution to MASH pathogenesis.

Conclusions

The MASH therapeutic landscape has transitioned from a single-approved-agent era to a diversified pipeline encompassing metabolic, hepatic, genetic, and gut-liver axis targets. The rational selection of therapy is increasingly guided by fibrosis stage, comorbid metabolic disease, genetic background, and tolerability, with combination regimens poised to become the standard of care for advanced disease. Long-term outcome data from MAESTRO-NASH OUTCOMES, LIVERAGE, ESSENCE part 2, IMPACT phase 3, and the denifanstat–resmetirom combination trial will be pivotal in translating surrogate histologic improvements into durable reductions in liver-related and cardiovascular events.

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STATE-OF-THE-ART LECTURE

Chair
Young-Suk Lim (Univ. of Ulsan)





David A. Brenner
Sanford Burnham Prebys, USA

Self Introduction

He received extensive training in clinical medicine and biomedical research at Yale, NIH, and UCSD, resulting in Board certification in Internal Medicine and Gastroenterology. He is a physician scientist, dedicated to using state-of-the-art technology to translate biomedical research into improving health. He has taken leadership positions as Chief of Gastroenterology at UNC, Chapel Hill, Chairman of Medicine at Columbia University, Vice Chancellor of Health Sciences and Dean of the Medical School at UCSD, and now President and CEO of Sanford Burnham Prebys Medical Discovery Institute. He has more than 200 peer reviewed publications, two patents, and recognition among Highly Cited Researchers by Web of Science and Clarivate Analytics.

Research Interests

He directs a laboratory Studying Chronic Liver Disease, Hepatocellular Cancer, Pancreatic Cancer, and Aging.

Representative Publications

1. Kim HY, Mizrahi O, Lee W, Rosenthal SB, Han C, Yee BA, Blue SM, Diaz J, Jonnalagadda J, Hokutan K, Jang H, Ma CT, Bobkov A, Sergienko E, Jackson MR, Stefanovic B, Kisseleva T, Yeo GW, Brenner DA. LARP6 regulates the mRNA translation of fibrogenic genes in liver fibrosis. *bioRxiv*. 2025 Jan 18; PubMed Central PMCID: PMC11761402.
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Developing Drugs for Liver Fibrosis

David A. Brenner *Sanford Burnham Prebys, USA*

Background & Aims

The extent of liver fibrosis correlates closely with morbidity and mortality in patients. Excessive alcohol consumption and/or the metabolic syndrome result in a synergistic development of liver fibrosis (Met-ALD), which is characterized by increased Collagen Type I deposition, produced by activated Hepatic Stellate Cells (HSCs). However, there are no therapies that target liver fibrosis. Targeting collagen production in activated HSCs is an important strategy to halt liver fibrosis.

Methods

Gene expression profiles of human HSCs were analyzed using single nucleus (sn)RNA-seq of NORMAL, MASL, MASH, and MetALD livers. The mRNA of La-related protein 6 (LARP6), an RNA-binding protein which binds to the 5' stem-loop region of collagen mRNAs, was highly induced in activated HSCs from MetALD patients. To determine the role of LARP6 in HSC activation, isolated primary human HSCs were transfected with LARP6-specific (or control) dsRNA and used to generate human liver spheroids. Human liver spheroids were composed of human liver cells in physiological ratios: 57% hepatocytes, 28% NPCs, and 15% dsRNA-transfected HSCs. Upon formation of spheroids at day 7, human liver spheroids were cultured in MASH- or MetALD-cocktails for an additional 7 days. The MASH-cocktail contained palmitate, oleate, fructose, glucose, LPS, and human TGF- β 1, while MetALD cocktail was prepared by adding 100 mM ethanol to the MASH-cocktail. To identify a LARP6 inhibitor, we developed a high throughput assay using FRET that fluorometrically distinguished between LARP6 binding to the 5'UTR SL and unbound RNA.

Results

snRNA-sequencing identified LARP6 as one of the most highly induced genes in activated human HSCs from MASH and MetALD livers (vs NORMAL or MASL HSCs). The binding of LARP6 to collagen mRNA was validated using an enhanced CLIP (eCLIP) assay, with eCLIP peaks enriched at the 5'UTR regions of *COL1A1*, *COL1A2*, and *COL3A1*, demonstrating the specific binding of LARP6 to Collagen Type I/III mRNAs. Ribosome profiling revealed a significant reduction in the translation of *COL1A1*, *COL1A2*, and

COL3A1 in LARP6-knockdown human HSCs. Knockdown of LARP6 suppressed TGF β 1-induced expression of fibrogenic genes in human HSCs. The development of liver fibrosis was examined in human liver spheroids which contained LARP6-knocked down human HSCs. Knockdown of LARP6 markedly reduced Collagen Type I/III deposition in MASH-or MetALD-induced human liver spheroids. The HTP screening identified hundreds of potential LARP6 inhibitors. A counter-screen eliminated artifactual fluorescence and a secondary screen identified four compounds with high binding affinity.

Conclusions

LARP6 regulates the activation of human HSCs from MASH or MetALD livers through specific binding to Collagen Type I/III mRNAs. Our results suggest that targeting LARP6 in human HSCs may provide new strategies for anti-fibrotic therapy.

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2026 KASL CLINICAL PRACTICE GUIDELINES: CHRONIC HEPATITIS B

Chairs
Young-Suk Lim (Univ. of Ulsan)
Tatsuya Kanto (Japan Institute for Health Security, Japan)





In Hee Kim
Jeonbuk National University

Self Introduction

Prof. In Hee Kim is a Professor of the Department of Internal Medicine, Jeonbuk National University College of Medicine and is currently holding a position of Chief of the Department of Gastroenterology and Hepatology, Jeonbuk National University Hospital simultaneously.

Prof. Kim graduated from Jeonbuk National University College of Medicine with his medical degree in 1995 and completed his internship and residency at the Department of Internal Medicine at Jeonbuk National University Hospital, receiving his diploma in Internal Medicine in 2001.

Prof. Kim has been taking a number of roles, including Chairman of the Jeonbuk Branch of Korean Association for the Study of the Liver (2019-2022), Director of the Committee of Healthcare Policy (2024-2025) of the Korean Association for the Study of the Liver, and Chairman of the Committee for 2026 KASL clinical practice guidelines for management of chronic hepatitis B.

Research Interests

- Viral Hepatitis, Hepatitis B, Hepatitis C, Hepatitis E
- Cirrhosis, Portal Hypertension, Alcoholic Liver Disease, Non-Alcoholic Fatty Liver Disease
- Hepatocellular Carcinoma
- Healthcare Policy

Representative Publications

1. Core indicators related to the elimination of hepatitis B and C virus infection in South Korea: A nationwide study. Clin Mol Hepatol 2023;29:779-793.
2. Efficacy and safety of sofosbuvir-velpatasvir and sofosbuvir-velpatasvir-voxilaprevir for hepatitis C in Korea: a Phase 3b study. Korean J Intern Med 2023;38:504-513.
3. Etiology and clinical characteristics of acute viral hepatitis in South Korea during 2020–2021: a prospective multicenter study. Scientific Reports 2023;13:14271
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5. Direct-Acting Antiviral Therapy and Risk of Hepatocellular Carcinoma Recurrence in Patients with Chronic Hepatitis C. Gut Liver. 2021 May 15;15(3):327-328.

Management of Chronic Hepatitis B: 2026 KASL Update

In Hee Kim *Jeonbuk National University*

Despite a decline in overall prevalence to below 3% in South Korea, chronic hepatitis B (CHB) remains a significant public health burden, affecting approximately 1.2 million individuals, particularly in the 40–60 age group. Chronic hepatitis B (CHB) is a major risk factor for the occurrence of liver cirrhosis and hepatocellular carcinoma (HCC) in Korea and a liver-related mortality rate of 18.9 per 100,000—far exceeding the WHO target of 4.0. Although safe and effective oral antiviral therapies for CHB are available and have been shown to prevent HCC and reduce mortality with long-term treatment, the treatment rate among all hepatitis B patients in Korea remains low at 22.2%.

The existing hepatitis B guidelines limit the treatment target to the immunoactive phase with elevated ALT based on the immunological natural history classification. Recently, international guidelines from organizations such as the WHO, EASL, and AASLD been updated to expand the treatment criteria for chronic hepatitis B. However, there are still limitations as the guidelines continue to base treatment decisions on ALT levels or maintain unclear criteria.

The Korean Association for the Study of the Liver (KASL) conducted a comprehensive revision of the 2022 clinical practice guidelines. KASL guideline moves beyond an ALT-centered framework for assessing liver injury in the treatment of CHB and introduces a new classification system based on HBV DNA levels. This update incorporates the latest evidence regarding the natural history of CHB, the risk of HCC in the ‘grey zone’ (indeterminate phase), and the long-term efficacy of antiviral therapies. The revised guidelines redefine the natural history classification of CHB by prioritizing viral load over conventional immunological stages, which often fail to reflect the full clinical spectrum of disease progression. Key updates include:

1. Natural History of CHB Based on Viral Load

KASL guideline classifies the natural history into four phases based on HBV DNA levels: 1) high viremic phase (>8 log₁₀ IU/mL), 2) HBeAg-positive moderate viremic phase (2,000 IU/mL–8 log₁₀ IU/mL), 3) low viremic phase (<2,000 IU/mL), and 4) HBeAg-negative moderate viremic phase (2000 IU/mL–8 log₁₀ IU/mL). Risk of HCC is the highest in the moderate viremic phase.

2. Simplified Treatment Strategy for CHB

KASL guideline integrates the new natural history classification with treatment initiation criteria to streamline clinical decision-making. In patients with high viremia (serum HBV DNA >8 log₁₀ IU/mL), antiviral therapy should be considered in those older than 30 years, those with elevated liver enzymes, or those with significant liver fibrosis. In the absence of these risk factors for disease progression or HCC, close monitoring is recommended. In patients with moderate viremia (serum HBV DNA ≥2,000 IU/mL and ≤8 log₁₀ IU/mL), antiviral therapy is recommended, as they are at high risk for liver disease progression and HCC. In patients with low viremia (serum HBV DNA <2,000 IU/mL), cirrhosis should be assessed, and if absent, patients should be monitored without antiviral therapy while alternative causes of liver disease are evaluated in the presence of ALT elevation.

The KASL guideline provide updated, evidence-based recommendations designed to simplify treatment pathways and expand clinical indications. By widening the scope of antiviral therapy to include patients in the indeterminate phase who remain at risk for HCC and liver cirrhosis, it aims to reduce CHB-related mortality and HCC incidence. Furthermore, this will serve as a crucial strategy for achieving the goal of eliminating hepatitis B.

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KASL SYMPOSIUM 7

Liver Cirrhosis, Portal Hypertension, and
Acute-on-Chronic Liver Failure (ACLF):
Advancing the Continuum of Care from
Organ Failure to Recovery

Chair
Jae Young Jang (Soonchunhyang Univ.)





Jung Hee Kim
Hallym University

Self Introduction

Jung Hee Kim is an Associate Professor in the Department of Internal Medicine at Hallym University College of Medicine. She currently serves as a key faculty member in the Division of Gastroenterology and Hepatology at Hallym University Dongtan Sacred Heart Hospital.

Prof. Kim earned her Medical Degree (Master of Medicine) from the Kyung Hee University Graduate School of Medicine in 2009. She subsequently completed her internship and residency in Internal Medicine at Samsung Medical Center, Sungkyunkwan University School of Medicine, where she received her board certification. Recognizing her commitment to academic excellence, she was recently awarded her Ph.D. in Medicine from Sungkyunkwan University in 2024.

Prof. Kim is deeply involved in the academic community and maintains active memberships in several prestigious organizations. She is a Full Member of the Korean Association for the Study of the Liver (KASL) and the Korean Liver Cancer Association (KLCA). Additionally, she contributes to the advancement of diagnostic standards through her active participation in the Korean Society of Clinical Ultrasound (KSCU).

Representative Publications

1. Kim Jung Hee, Rethinking ACLF Prognosis: Can Machine Learning Outperform Conventional Scores? Editorial on: Predictive Machine Learning model in ICU Patients with Acute-on-Chronic Liver Failure and Two or More Organ Failures. Clin Mol Hepatol. 2025 Sep 23.
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ACLF across Definitions: Harmonizing Diagnostic Criteria and Organ Failure Assessment

Jung Hee Kim Hallym University

Background

Acute-on-chronic liver failure (ACLF) is a rapidly evolving and potentially reversible syndrome occurring in patients with chronic liver disease, characterized by acute hepatic decompensation, organ failure, and high short-term mortality. Although increasingly recognized as a distinct clinical entity, ACLF remains heterogeneously defined across different geographic regions and scientific societies.

Divergent definitions proposed by APASL, EASL-CLIF, NACSELD, and other regional consortia reflect fundamental differences in conceptual frameworks, including the nature of precipitating events (hepatic vs. extrahepatic), the stage of underlying liver disease, and the role of extrahepatic organ failure. These discrepancies lead to variations in patient selection, clinical phenotypes, and prognostic assessment, ultimately limiting comparability across studies and hindering therapeutic development.

Importantly, the epidemiological burden of ACLF varies significantly depending on the definition applied, with broader organ failure-based criteria such as *EASL-CLIF* identifying substantially more patients compared to more restrictive definitions like NACSELD or APASL. This highlights that current definitions may capture fundamentally different patient populations rather than a single uniform syndrome.

Conceptual Differences across Definitions

The *APASL definition* emphasizes acute hepatic insult as the central driver of ACLF, requiring the presence of jaundice and coagulopathy followed by the development of ascites and/or hepatic encephalopathy within four weeks. This approach focuses on early-stage disease and predominantly hepatic dysfunction. In contrast, the *EASL-CLIF definition* conceptualizes ACLF as a syndrome of acute decompensation associated with organ failure(s), identified using the CLIF-SOFA scoring system across six organ systems, including liver, kidney, brain, coagulation, circulation, and respiration. This definition allows for both hepatic and extrahepatic precipitants and stratifies disease severity based on the number and type of organ failures. The *NACSELD definition* further shifts the focus toward extrahepatic organ failure, particularly in the context of infection. ACLF is defined by the presence of two or more extrahepatic organ failures, such as circulatory shock, need for mechanical ventilation, renal replacement therapy, or

severe hepatic encephalopathy.

Central Role of Organ Failure and Disease Dynamics

Organ failure is the most important determinant of prognosis in ACLF, with mortality increasing exponentially as the number of failing organs rises. Importantly, ACLF is a highly dynamic syndrome, and early reassessment of organ failure provides superior prognostic value compared to baseline evaluation alone.

The use of standardized tools such as the CLIF-SOFA scoring system has improved risk stratification; however, differences in organ failure definitions across consortia remain a major barrier to harmonization. In addition, several prognostic models have been developed, including the AARC score, NACSELD organ failure score, and CLIF-C ACLF score. While these models are clinically useful, none are ideal, as they are limited by subjectivity (e.g., assessment of hepatic encephalopathy), ceiling effects in laboratory parameters, and the lack of continuous objective variables. These limitations underscore the need for more precise and dynamic prognostic systems.

Pathophysiological Insights and Implications

Emerging evidence indicates that ACLF is driven by an intense systemic inflammatory response mediated by pathogen-associated and damage-associated molecular patterns. This inflammatory cascade leads to immune dysregulation, tissue hypoperfusion, mitochondrial dysfunction, and ultimately multi-organ failure.

These findings suggest that ACLF is not merely a progression of liver disease but a systemic disorder involving complex interactions between the liver, immune system, and other organ systems. Understanding these mechanisms provides a critical foundation for redefining ACLF beyond static diagnostic criteria and supports the development of mechanism-based therapeutic strategies.

Future Directions

Future research and clinical strategies should focus on: Dynamic and integrated diagnostic models incorporating both hepatic and extrahepatic factors; Biomarker-driven approaches reflecting systemic inflammation and immune dysfunction; Standardization of organ failure assessment across ICU and non-ICU settings; Mechanism-based therapies targeting inflammation, immune dysregulation, and mitochondrial injury; Early identification and prevention strategies, including control of alcohol misuse, viral hepatitis, and metabolic risk factors; Optimization of transplant timing and expansion of non-transplant therapeutic options; Ultimately, harmonization of ACLF definitions should align with pathophysiological understanding and clinical decision-making to improve patient outcomes.

Conclusions

ACLF is a complex, dynamic, and potentially reversible syndrome at the intersection of liver failure and

systemic inflammation. While multiple definitions have contributed to advancing our understanding, their heterogeneity remains a major limitation.

A harmonized approach—integrating unified diagnostic criteria, phenotypic classification, and pathophysiological insights—will be essential to advance research, optimize management, and improve survival in patients with ACLF.

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Rakhi Maiwall
Institute of Liver and Biliary Sciences, India

Self Introduction

Dr Rakhi Maiwall is currently working as Professor of Hepatology and Incharge liver intensive care at the Institute of Liver and Biliary Sciences.

Research Interests

She has special interest in critical care hepatology and renal dysfunction in patients with cirrhosis and liver failure. She has published original articles in indexed journals and has more than 200 publications and contributed 12 book chapters.

Representative Publications

1. Maiwall R, Kulkarni AV, Arab JP, Piano S. Acute liver failure. Lancet. 2024 Aug 24;404(10454):789-802.
2. Maiwall R, Bajpai M, Singh A et al. Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial. Clin Gastroenterol Hepatol. 2022 Apr;20(4):e831-e854.
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Management of Acute Kidney Injury in ACLF: Current Evidence and Unmet Needs

Rakhi Maiwall *Institute of Liver and Biliary Sciences, India*

Definition and Pathophysiology of AKI and HRS-AKI in ACLF

The definition of acute kidney injury (AKI) has evolved to explicitly incorporate urine output criteria. AKI is now diagnosed by any of the following: an increase in serum creatinine by at least 0.3 mg/dl (26.5 μ mol/L) within 48 hours; or an increase in serum creatinine by at least 50% from baseline, known or presumed to have occurred within the prior 7 days; and/or urine output of 0.5 ml/kg or less for a duration of at least 6 hours. Hepatorenal syndrome with acute kidney injury (HRS-AKI) has seen substantial changes in its diagnostic criteria and conceptual framework. The latest guidelines now recognise that HRS may be present even in the context of tubular injury, proteinuria, or pre-existing chronic kidney disease (CKD). According to these new criteria, HRS-AKI is diagnosed in patients with cirrhosis and ascites who fulfil the updated AKI definition (including urine output criteria) and do not show improvement in serum creatinine and/or urine output within 24 hours following adequate volume resuscitation—administered only when clinically indicated—and in the absence of strong evidence for an alternative cause of AKI. Notably, the previous requirement for a 48-hour course of albumin administration for diagnosis has been eliminated. Additionally, the nomenclature for HRS subtypes has been revised. Biomarkers have been acknowledged for their potential role in detecting acute glomerular and severe tubular injury, although specific thresholds are yet to be established. In the context of acute on chronic liver failure (ACLF), HRS portends a poorer prognosis, mainly due to a diminished response to vasoconstrictor therapy. This necessitates early and continuous initiation of terlipressin and a tailored management approach.

AKI in ACLF: Clinical Course, Pathogenesis, and Management Strategies

AKI is the most commonly affected extrahepatic organ system in patients with ACLF and typically progresses rapidly. The underlying pathophysiology is primarily driven by liver failure, which precipitates AKI in these patients. Importantly, AKI in ACLF is frequently characterised by a higher incidence of structural kidney injury, which calls for alternative therapeutic strategies. Due to the predominance of structural kidney damage, the use of biomarkers indicating tubular injury may aid in differentiating between structural and functional renal impairment, as well as in the early identification of patients unlikely to

respond to terlipressin. Cholemic nephropathy—a form of structural AKI requiring renal histology for definitive diagnosis—is more prevalent in ACLF patients. However, there is a pressing need for reliable noninvasive diagnostic tools. Differentiating specific phenotypes of structural AKI, such as cholemic nephropathy versus acute tubular necrosis (ATN), can be crucial in guiding management strategies. Prevention of AKI in ACLF may be approached through the use of intravenous albumin, antioxidants, and interventions aimed at reducing systemic inflammation. In terms of management, early initiation of continuous renal replacement therapy (CRRT), guided by renal biomarkers, is advocated. Monitoring of volume status with point-of-care ultrasound (POCUS) and dynamic, urine output-based surveillance of renal function are also recommended for optimising outcomes. Despite advancements, several gaps remain in the management of AKI in ACLF. These include the need for a validated definition of HRS-AKI specific to this population, an individualised approach to albumin dosing, determination of optimal mean arterial pressure (MAP) targets, and the integration of extracorporeal therapies.

Deciding when and how to start dialysis in ACLF patients is challenging, especially with progressive AKI. Early initiation of renal replacement therapy (RRT), guided by biomarkers and clinical assessment—particularly in HRS-non-responders or septic shock—is recommended to improve outcomes. Continuous RRT is preferred over intermittent dialysis modes, as it helps reduce cytokine-driven inflammation and organ failure. Urine output remains important for starting and stopping RRT, and sub-stratifying stage 3 AKI by oliguria may help determine post-transplant outcomes. Stage 3 AKI in ACLF does not preclude liver transplantation, but more research is needed to assess outcomes based on oliguria and RRT duration. Future studies should examine mitochondrial dysfunction, immune function, cytokine response, and the effects of CRRT and extracorporeal therapies in ACLF-AKI, including combinations like CRRT plus plasma exchange. The effectiveness of different extracorporeal modalities (e.g., DIALIVE, cytosorb, hemoperfusion) versus plasma exchange, and differences in post-transplant outcomes between cholemic nephropathy and ATN phenotypes, also require investigation. Hemoperfusion may offer promise for cholemic nephropathy due to its link to bile acids.

The other exciting area is the assessment of kidney health and outcomes of AKI after recovery in ACLF patients. Currently, there are limited studies evaluating the prevalence of acute or chronic kidney disease in ACLF patients and its impact on clinical outcomes. Following recovery or liver transplantation, what proportion of patients develop acute or chronic kidney disease and the pathogenetic mechanisms need to be investigated. The other paradigm change is expected in the way the syndrome of ACLF would be redefined by global experts and harmoniozation of the current definitions of ACLF. Interestingly, most of the proposed definitions incorporate renal dysfunction signifying the prognostic impact and how kidney outcomes correlate closely with outcomes of ACLF patients.

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Yu Jun Wong
Duke-NUS Medical School, Singapore

Self Introduction

Dr. Wong is a Senior Consultant Gastroenterologist at the Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore, and Clinical Associate Professor at Duke-NUS Medical School. He graduated from the National University of Malaysia and completed hepatology fellowship training at the University of Alberta, Edmonton, Canada.

His clinical and research interests focus on chronic liver disease, particularly the development of non-invasive risk stratification of portal hypertension and risk stratification in cirrhosis. He also conducts research in viral hepatitis C and metabolic dysfunction-associated steatotic liver disease. Dr. Wong has authored more than 100 peer-reviewed publications and regularly speaks at regional and international scientific meetings.

Dr. Wong's research contributions have been recognized with several awards, including the AASLD Early Career Investigator Award in Clinical/Translational Science (2022) and the AASLD Foundation Healthcare Disparities Research Award (2024). He is also a recipient of the Nurturing Clinician Scientist Scheme (NCSS) from SingHealth and has received multiple Best Oral Presentation Awards at GIHEP (2018, 2021, 2023). He currently serves as an editorial board member of Hepatology and is a member of the AASLD Portal Hypertension Special Interest Group. His contributions to peer review were recognized with the Outstanding Reviewer Award from Hepatology in 2024 and 2025.

In addition to research, Dr. Wong leads industry-sponsored clinical trials and was awarded the Clinical Trialist Award in 2025. He is actively involved in mentoring medical students and trainees, receiving the Outstanding Mentor Award from the Singapore Medical Association in 2023 and 2025. Dr. Wong also contributes to regional professional societies and currently serves as a member of the APAGE Emerging Leaders Committee and an Executive Committee member of the Chapter of Gastroenterology, Academy of Medicine, Singapore.

Research Interests

Cirrhosis & Portal Hypertension, Viral hepatitis, Autoimmune Liver Disease & Steatotic Liver Disease

Representative Publications

1. Wong YJ, Lam L, Soret PA, et al. Prognostic value of liver stiffness measurement vs. biochemical response in primary biliary cholangitis. *J Hepatol.* 2026;84(2):275-283. doi:10.1016/j.jhep.2025.09.024.
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Achieving Recompensation in Cirrhosis: Evidence and Future Directions

Yu Jun Wong *Duke-NUS Medical School, Singapore*

Progression of liver cirrhosis is no longer uni-directional when effective etiological cure is now available. A new concept of “recompensation” represents a paradigm shift in the management of cirrhosis—moving from irreversible decline to potential recovery. This lecture synthesises emerging evidence on the drivers of recompensation, including disease aetiology control, portal pressure reduction, and dynamic changes in non-invasive markers such as liver stiffness. We will examine how concepts from Baveno criteria and longitudinal cohorts inform clinical decision-making, and where current definitions fall short. The talk also explores future directions, including digital biomarkers and personalised monitoring, to identify patients most likely to achieve sustained clinical stability and improved survival.

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Self Introduction

Dong-Sik Kim, M.D., Ph.D. graduated from Korea University College of Medicine and had residency training at Korea University Medical Center. He finished fellowship training at the Asan Medical Center (HBP surgery and liver transplantation) and the University of Cincinnati (Abdominal Transplantation) and started an academic appointment as an assistant professor at the University of Cincinnati. Currently, he is working at Korea University Medical Center Anam hospital as a professor and chairman of department of surgery and the director of the Organ Transplantation Center. He is serving as the chairman of the scientific committee(Liver) and board member of the Korea society of transplantation, the Korea liver transplantation society and the Korean association of liver surgery.

Research Interests

Small-for-Size Syndrome, Ischemia-Reperfusion Injury, Liver Cancer, Immunosuppressives, Translational Research

Representative Publications

1. H. S. Jo, Y. I. Yoon, K. H. Kim, P. Tabrizian, R. Marino, P. Marin-Castro, W. Andraus, J. Kim, G. S. Choi, D. G. Kim, D. J. Joo, C. Florez-Zorrilla, D. Balci, H. Petrowsky, K. J. Halazun and D. S. Kim*. Predicting futile outcomes following deceased donor liver transplantation in non-HCC patients with MELD-Na score above 30: a retrospective international multicenter cohort study. *Int J Surg* 2025; 111(5):3148-3158.

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ACLF: Transplant before It's Too Late

Dong-Sik Kim Korea University

Acute-on-chronic liver failure (ACLF) represents one of the most time-critical scenarios in hepatology, characterized by acute decompensation of cirrhosis with organ failure(s) and a profoundly high short-term mortality. Without liver transplantation (LT), 28-day mortality exceeds 70% in ACLF grade 3, and patients with three or more organ failures demonstrate greater 14-day waitlist mortality than Status 1A (acute liver failure) candidates—underscoring an urgent need for expedited transplant decision-making.

Despite this, only a small fraction of ACLF-2 and ACLF-3 patients ultimately receive LT. This gap reflects not a lack of benefit, but a failure to act within the narrow therapeutic window. Data from both the APASL ACLF Research Consortium (AARC) and EASL-CLIF studies establish the first week after ACLF onset as the “golden window”—the period during which transplantation confers maximum survival benefit, before progression to refractory sepsis or irreversible multiorgan failure forecloses the option entirely.

Clinical decision-making differs substantially between deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) settings. In DDLT-dominant systems, the principal challenge is that MELD-based allocation inadequately reflects ACLF severity, underrepresenting true waitlist mortality risk. ACLF-specific prioritization programs have demonstrated improved survival through systematic early listing. For ACLF-3 patients with a CLIF-C ACLF score ≤ 64 , prompt listing and access to good-quality grafts (donor risk index ≤ 1.6) is recommended; those exceeding this threshold require daily reassessment.

In contrast, LDLT—predominant across Asia due to limited deceased donation—offers the structural advantage of bypassing waitlist delays. Implementation of an urgent LDLT program in Korea demonstrated that critically ill ACLF patients, including those previously excluded by conventional CLIF-C thresholds, can achieve acceptable outcomes when appropriately. Preoperative respiratory failure (PaO₂/FiO₂ <200), use of older donors, and uncontrolled sepsis are the primary predictors of poor post-transplant survival following LDLT, collectively defining the boundary between salvageable and futile transplantation.

The 35-expert international consensus on transplant futility identifies persistent fever, refractory hemodynamic instability, severe frailty, and sustained hyperlactatemia (>9 mmol/L) as markers of likely futility. Crucially, these should never be applied rigidly; dynamic daily reassessment by a multidisciplinary team

is essential, given ACLF's inherently fluctuating trajectory.

ACLF-2 and ACLF-3 demand immediate transplant evaluation—not deferral. Whether through expedited DDLT allocation or an organized urgent LDLT program, transplantation before the window closes is the only intervention proven to alter the natural course of ACLF. Delay is not a neutral act; it is a missed opportunity to save a life.

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KASL-AASLD BREAKFAST WORKSHOP

The Evolving Landscape of Liver Transplantation: From Policy to Practice

Chairs

Jung-Hwan Yoon (Seoul National Univ.)

W. Ray Kim (Mayo Clinic, USA)





Parissa Tabrizian

Icahn School of Medicine at Mount Sinai, USA

Self Introduction

Parissa Tabrizian, MD, MSc, FACS is a board-certified surgeon, professor of surgery who specializes in hepatobiliary and liver transplantation at the Recanati/Miller Transplantation Institute. Dr. Tabrizian earned her medical degree at the University of Vienna medical school and completed her general surgery residency at the Mount Sinai Medical Center in New York. She completed fellowships in surgical oncology and multiorgan transplant surgery at Mount Sinai Hospital. In 2015, Dr. Tabrizian obtained a master’s degree in clinical research from the Icahn School of Medicine, New York. Dr. Tabrizian performs a wide range of both open and advanced laparoscopic procedures. Her research interests include hepatocellular carcinoma, cholangiocarcinoma, and liver transplantation.

She has participated in large-scale projects, and collaborated with fellow researchers in this field, to produce numerous peer-reviewed publications. She is an active member of the American and European Societies for Organ Transplantation. She was privileged to receive invitations to both national and international conferences to present her work, including a Presidential Plenary Session.

Research Interests

- Hepatocellular Carcinoma, Cholangiocarcinoma, and Liver Transplantation
- Resection, Immunotherapy

Expanding the Donor Pool: Donation after Circulatory Death, Donation after Brain Death, and Ex-vivo Graft Management Strategies

Parissa Tabrizian

Icahn School of Medicine at Mount Sinai, USA

The lecture provided a comprehensive overview of the evolution of modern transplantation and the strategies that have transformed the field in the face of persistent organ scarcity. The discussion focused on how innovation, policy reform, and advances in surgical and preservation technologies have collectively expanded the donor pool and increased access to life-saving transplantation for more patients.

Key topics included the growing role of donation after circulatory death (DCD) and donation after brain death (DBD) in addressing the shortage of donor organs. The lecture highlighted how careful donor selection, improved procurement techniques, and evolving allocation policies have enabled successful utilization of organs that were previously considered marginal or unusable. Particular emphasis was placed on the importance of expanding acceptance criteria while maintaining excellent post-transplant outcomes.

The presentation also explored advances in ex-vivo graft management strategies, including machine perfusion technologies and organ preservation techniques that allow for improved assessment, optimization, and recovery of donor grafts prior to transplantation. These innovations have significantly enhanced graft viability, reduced ischemic injury, and facilitated the safe use of extended-criteria donor organs.



Willscott Naugler
Oregon Health & Science University, USA

Self Introduction

Dr. Naugler finished an Internal Medicine residency at Oregon Health & Science University (OHSU), followed by a year as a Chief Resident in the program. Following this he completed a Gastroenterology & Hepatology Fellowship at the University of California, San Diego, where he studied liver regeneration and hepatocarcinogenesis in the laboratory of Michael Karin. After fellowship, Dr. Naugler took a faculty position at OHSU, and in 2011 began leading both the liver transplant and multidisciplinary liver tumor programs. He has been continually involved in liver transplant administration through the US Orgon Procurement & Transplantation Network (OPTN), participating in the crafting of the current OPTN policies regarding allocation, including equity between patients with liver tumors as compared to liver failure.

Research Interests

Liver Regeneration, Liver Transplantation, Outcomes in Hepatocellular Carcinoma Management

Representative Publications

1. Lhewa D, Green EW, Naugler WE. Multidisciplinary Team Management of Hepatocellular Carcinoma Is Standard of Care. Clin Liver Dis 2020;24:771-787.

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Optimizing Allocation and Policy Models: Balancing Equity and Efficiency in Opt-in vs. Opt-out Systems

Willscott Naugler *Oregon Health & Science University, USA*

1. Objectives

- a. Overview of factors involved in a national organ procurement and allocation system
- b. Need for organ donation is rising (South Korea, Spain, US)
- c. Describe Opt-in and Opt-out systems for deceased donors
- d. Comparison of 3 nations’ procurement and allocation systems: South Korea, Spain, United States
- e. What it takes to successfully implement an Opt-out national policy
- f. Pitfalls of implementing a national Opt-out organ donation system

2. Overview

- a. Transplant side
 - i. Demand for organ transplant (need)
 - ii. Integrated and experience transplant teams including high level of pre-transplant care
 - iii. National resources (insurance, etc) to pay for expensive transplants
- b. Organ donation and procurement
 - i. National system that is activated when a brain-dead patient is identified
 - ii. Buy in from public that they can trust the national system is treating their loved ones with care, respect, and doing it in a way that benefits all citizens

3. Significant Organ Shortage in Most Countries, Thus Need for More Organ Donation

- a. Living donation (possible for lung, liver, kidney)
 - i. South Korea leads the world in living donation, but demand still far exceeds live donation rates
- b. Deceased donor
 - i. Donation after brain death
 - ii. Donation after cardiac death
 - iii. Impact of new technologies: pumps

4. Definition of Opt-in Versus Opt-out National Organ Donation Systems

5. Comparison of Three Countries: South Korea, United States, Spain

- a. Consent (opt-in versus opt-out)
- b. Family role
- c. Deceased donor donation rates

6. Factors Needed to Support an Opt-out National Donation Policy

- a. Robust national registry (who has opted-out)
- b. Public support
 - i. Trust in the government (usually supported by state-wide education campaigns)
 - ii. Clear accessible ways for people to Opt-out (refuse to donate)
- c. Highly structured system for identifying potential donors and aggressively promoting donation
 - i. Training physicians to identify potential donors early
 - ii. Easy access to transplant coordinators

7. Pitfalls of Implementing a National Opt-out Organ Donation System

- a. Ethical concerns—is silence really consent?
 - i. Patients may fear that doctors won’t try as hard to save their lives if they are a potential organ donor
 - ii. Patients may fear that organs are only being used for the wealthy, connected, etc. (eg, not in a fair way)
- b. Case studies of implementing Opt-out systems and what can go wrong
 - i. Spain
 - ii. United Kingdom
 - iii. Chile
 - iv. Brazil

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10.1016/j.xkme.2024.100812. PMID: 38665993; PMCID: PMC11044131.

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Suk Kyun Hong
Seoul National University

Self Introduction

Prof. Suk Kyun Hong is a Clinical Associate Professor in the Division of HBP Surgery and Transplant Center at Seoul National University Hospital, Seoul National University College of Medicine. He specializes in hepatobiliary surgery, liver transplantation, and surgical management of hepatocellular carcinoma, with major contributions in living donor liver transplantation, donor hepatectomy, transplant oncology, and peri-transplant outcomes research.

He completed his medical education and all surgical training at Seoul National University and Seoul National University Hospital, including internship, residency, and fellowship, and obtained both an M.S. and Ph.D. from the Graduate School of Seoul National University. His academic roles include Clinical Assistant Professor and, since March 2022, Clinical Associate Professor, as well as a Visiting Scholar position at Stanford University in the Division of Abdominal Transplantation. He is board-certified in general surgery and HBP surgery, is a Fellow of the American College of Surgeons (FACS), and has received multiple national and international awards, including ILTS Rising Star and Vanguard Awards and the Doosan Yonkang Award in Hepato-Biliary-Pancreatic Surgery.

Research Interests

- Living Donor Liver Transplantation and Donor Safety
- Hepatocellular Carcinoma, Transplant Oncology, and Recurrence Biology
- Pure Laparoscopic Donor Hepatectomy and Minimally Invasive Hepatobiliary Surgery
- Perioperative Outcomes, Biliary Complications, and Immunosuppression after Liver Transplantation
- Biomarkers, Liquid Biopsy, and Precision Approaches in Liver Transplantation and HCC

Representative Publications

1. Kim DW, Park JH, Hong SK, Jung MH, Pyeon JO, Lee JY, Suh KS, Yi NJ, Choi Y, Lee KW, Kim YJ. Exploring methylation signatures for high de novo recurrence risk in hepatocellular carcinoma. Clin Mol Hepatol. 2025 Apr;31(2):563-576. doi: 10.3350/cmh.2024.0899. Epub 2025 Jan 13. PMID: 40241383; PMCID: PMC12016632.

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3. Hong SK, Hong SY, Lee JM, Choi Y, Yi NJ, Lee KW, Suh KS. Criteria for selecting living liver donors to optimize recipient outcomes in pure laparoscopic donor right hepatectomy: a cohort study. Int J Surg. 2024 Jun 1;110(6):3203-3211. doi: 10.1097/JS9.0000000000001317. PMID: 38477118; PMCID: PMC11175737.

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Expanding Recipient Criteria for HCC: Lessons from Living Donor Liver Transplantation and Regional Experiences

Suk Kyun Hong *Seoul National University*

Liver transplantation (LT) is the most comprehensive curative treatment for hepatocellular carcinoma (HCC) because it removes both the tumor and the underlying cirrhotic liver. However, the conventional Milan criteria do not fully reflect the current clinical reality, especially in living donor liver transplantation (LDLT), where decisions are made in a different context from deceased donor allocation systems. As shown in the uploaded lecture materials, Milan criteria are still widely used for allocation policy, insurance coverage, and downstaging targets in several regions, but they are often too restrictive in LDLT and do not adequately capture tumor biology.

Because of these limitations, recipient selection for HCC has gradually moved beyond simple morphologic criteria. Earlier attempts to expand candidacy mainly focused on tumor size and number, including the UCSF criteria and the up-to-seven rule. More recently, biologic markers such as alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (PIVKA-II), positron emission tomography findings, and treatment response have been incorporated into selection frameworks in order to identify patients with favorable tumor biology among those beyond Milan criteria. This change is also reflected in the 2022 BCLC update, which accepts that transplant candidacy should be interpreted in a broader and more biologically informed way in selected patients, rather than by size and number alone.

LDLT experience in Asia has played an important role in this change. In Asian countries, LDLT has allowed greater flexibility in applying transplant oncology principles, and several centers have reported acceptable outcomes even beyond Milan criteria when expansion was combined with biologic selection. The Kyoto criteria are one representative example, showing that expanded indication can be justified when tumor burden remains controlled and PIVKA-II suggests less aggressive disease. In this setting, the main issue is not whether criteria should be expanded indiscriminately, but how favorable tumors can be selected more precisely.

Regional experience from Korea provides an important practical perspective. As described in the uploaded materials, Korea remains one of the most active LDLT regions in the world, and HCC accounts for a large proportion of adult LDLT cases in real practice. This clinical environment has made it necessary

to reconsider LT not only as a rescue option for patients with poor liver function, but also as one of the important treatment options for selected patients with preserved liver function who have a substantial risk of non-transplantable recurrence after resection. The same materials also emphasize that, even in Child-Pugh A patients, detailed assessment of cirrhosis severity, portal hypertension, tumor multiplicity, and biologic aggressiveness is important when deciding between resection, salvage transplantation, and primary transplantation.

Another lesson from LDLT is that biologic selection performs better than morphology alone. The uploaded lecture materials highlight the MoRAL concept based on AFP and PIVKA-II, showing that recurrence risk can be stratified across conventional morphologic boundaries. This is clinically important because some patients within Milan criteria still show aggressive behavior, whereas some beyond Milan criteria may have acceptable post-transplant outcomes if biology is favorable. In the same context, dynamic markers such as response to downstaging and decreasing biomarker levels may be more informative than a single pretransplant imaging snapshot.

Looking forward, the field is likely to move further toward precision selection. The lecture materials describe ongoing interest in liquid biopsy, circulating tumor DNA, and other omics-based approaches for pretransplant risk assessment, response monitoring, and post-transplant surveillance. Although these tools are not yet fully established in routine practice, they fit well with the current direction of transplant oncology, which is to select patients on the basis of recurrence biology rather than tumor morphology alone. In this respect, lessons from LDLT and Asian regional experience suggest that expansion of recipient criteria is reasonable only when it is disciplined, biology-oriented, and balanced against donor safety.

In conclusion, expanding recipient criteria for HCC should not be understood simply as moving beyond Milan numerically. Rather, it should be understood as refining selection through integration of tumor burden, biologic markers, treatment response, liver function, and regional transplant context. LDLT experience, particularly from Asia, suggests that carefully selected patients beyond conventional criteria can achieve acceptable outcomes. However, the key to successful expansion is not wider indication itself, but better identification of tumors with favorable biology.

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KASL SYMPOSIUM 6

Transformative Strategies for Functional Cure of Chronic Hepatitis B: Novel Insights and Future Perspectives

Chairs

Han Chu Lee (Univ. of Ulsan)

Man-Fung Yuen (The Univ. of Hong Kong, Hong Kong)



**Man-Fung Yuen***The University of Hong Kong, Hong Kong*

Self Introduction

Professor Yuen currently serves as Chair Professor at The University of Hong Kong and holds the Li Shu Fan Medical Foundation Professorship in Medicine. He is also Chief of the Division of Gastroenterology and Hepatology at Queen Mary Hospital, Hong Kong. After earning his MBBS in 1992, Professor Yuen pursued further academic distinction, obtaining three doctoral degrees: Doctor of Medicine (awarded the Sir Patrick Manson Gold Medal, 2001), Doctor of Philosophy (2005), and Doctor of Science (2017).

Professor Yuen is internationally recognised for his work on chronic hepatitis B and hepatocellular carcinoma. His research spans disease prevention, natural history, virology, serology, and therapeutic development. Professor Yuen has published over 650 research articles in many medical journals, including the most prestigious ones e.g., New England Journal of Medicine, Lancet and its specialty journals, Nature Medicine, Nature Review Disease Primers, Nature Review Gastroenterology and Hepatology and top Gastroenterology and Hepatology Journals. Of all these publications, he has served as the lead author on 10 seminal and original articles published in New England Journal of Medicine, Lancet Gastroenterology and Hepatology, Lancet Infectious Diseases and Nature Medicine. He has been invited to deliver more than 370 lectures worldwide.

Currently, Professor Yuen leads numerous international clinical trials investigating new antiviral and immunomodulatory therapies for chronic hepatitis B. He is also serving as a consultant and scientific advisor for many international pharmaceutical and biotech companies for developing novel agents for hepatitis B disease. In addition, he is at the forefront of research into novel biomarkers for overt and occult hepatitis B infection. His expertise is sought by several international coalitions, including the International Coalition to Eliminate HBV (ICE-HEP) and the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP). He is a member of the Asia Pacific Liver Disease Alliance and serves on the Advisory Council of The Hepatitis Fund, a Swiss-based foundation.

In recognition of his outstanding contributions, Professor Yuen was awarded the “Bruce Witte Distinguished Scholar” in November 2025 from the Hepatitis B Foundation – Baruch S. Blumberg Institute, a world-renowned institute dedicated to Dr. Blumberg, the Nobel laureate for the discovery of hepatitis B virus.

Research Interests

Natural History, Virology, Serology, Prevention and Treatment of Chronic Hepatitis B Infection

Representative Publications

1. Yuen MF, Asselah T, Jacobson IM, et al. Efficacy and safety of the siRNA JNJ-73763989 and/or the capsid assembly modulator JNJ-56136379 (Bersacapavir) with nucleos(t)ide analogues for the treatment of chronic hepatitis B virus infection: results from the phase 2b randomised REEF-1 study. *Lancet Gastroenterol Hepatol* 2023;8(9):790-802.
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3. Yuen MF, Lim SG, Plesniak R, et al. Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection. *N Engl J Med* 2022;387(21):1957-1968.
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Antisense Oligonucleotides vs. siRNA: Which Represents the Better Option for HBV Treatment?

Man-Fung Yuen*The University of Hong Kong, Hong Kong*

Existing treatment for chronic hepatitis B virus (HBV) infection includes nucleos(t)ide analogues and pegylated interferon (Peg-IFN). However, a functional cure—defined as undetectable HBV DNA and sustained loss of HBsAg for at least 24 weeks after treatment cessation—is rarely achieved with these agents. Consequently, there has been significant interest in developing novel direct-acting antivirals and immunomodulators, many of which are currently being actively investigated in clinical trials.

RNA interference has emerged as a promising strategy for achieving a functional cure. The principal approaches include small interfering RNAs (siRNA) and antisense oligonucleotides (ASO). Structurally, siRNAs are double-stranded RNA molecules with two overhanging nucleosides at the 3' end, whereas ASOs are single-stranded DNA molecules incorporating modified RNA-like segments, commonly arranged in a Gapmer structure. For cellular uptake, siRNAs require conjugation with N-Acetylgalactosamine (GalNAc) to facilitate hepatocyte entry, while ASOs can be taken up without such conjugation. Both modalities target and suppress viral antigen mRNAs and pre-genomic RNA, but their intracellular mechanisms differ. siRNAs mediate degradation of viral mRNAs and pre-genomic RNAs via the RNA-induced silencing complex (RISC), predominantly in the cytoplasm of infected hepatocytes. In contrast, ASOs utilise RNase H to deplete viral RNAs in both the cytoplasm and nucleus. Treatment with these agents has resulted in profound and sustained suppression of HBsAg, HBeAg, HBcrAg, HBV DNA, and HBV RNA levels in patients.

In the phase II B Clear study, HBsAg seroclearance was achieved in 9–10% of patients receiving ASOs. Further data on functional cure rates are anticipated from the phase III B-Well study to be presented at EASL in May 2026. Earlier clinical trials of siRNAs demonstrated a mean HBsAg reduction of approximately 1.5 to 2 log from baseline, with absolute HBsAg levels dropping below 100 IU/mL in about 60–80% of patients. This response generally persisted for up to one year after treatment cessation, and a cohort study reported sustained HBsAg control for up to four to five years of follow-up. More recent evidence indicates that some patients have achieved HBsAg seroclearance during treatment with newer siRNA agents.

In summary, ASOs have demonstrated efficacy in achieving HBsAg seroclearance in a proportion of patients, while siRNAs show great promise for substantial and long-lasting reductions in HBsAg, with

effects sustained over several years.

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Edward Gane
University of Auckland, New Zealand

Self Introduction

Dr. Gane trained in hepatology and liver transplantation at the King’s College Institute of Liver Studies, London where he completed his doctoral thesis on pathogenesis of hepatitis C. In 1998, Dr Gane returned to New Zealand to set up the first national liver transplant unit. In 2007, Dr. Gane opened a dedicated Phase I research centre (Auckland Clinical Studies, now New Zealand Clinical Research) which helped develop the first oral cures for hepatitis C and is now focused on developing a finite cure for hepatitis B.

Dr. Gane is also the Government lead advisor for the New Zealand HBV and HCV elimination strategies. He is also assisting Pacific Island Governments with their HBV strategies

Research Interests

- Finite Cure for Hepatitis B
- New Therapies for HCC and NASH
- In vivo Gene Therapies for Inherited and Acquired Liver Diseases

Representative Publications

1. Lim SG, Baumert TF, Boni C, Gane E, Levrero M, et al. Scientific Basis of Combination Therapy for functional cure in Chronic Hepatitis B (CHB)” (reference number: NRGH-21-085V1B), Nature Reviews GH 2023; 20: 238-53.
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Rationale and Selection of Gene Therapies in Chronic Hepatitis B

Edward Gane *University of Auckland, New Zealand*

Current HBV Cure strategies target the high viral and antigen burden and inadequate host immune responses which characterise chronic HBV infection. The success to date with combinations of novel antivirals (entry inhibitors, capsid assembly modulators, siRNAs, PPAD-5/7 inhibitors, monoclonal anti-HBs antibodies) and immunomodulators (pegylated Interferon-alpha, toll-like receptor agonists, therapeutic vaccines, checkpoint inhibitors), has been limited, with rates of HbsAg loss <5% in the subset of patients with low baseline HbsAg level (<100 IU/mL).

Any effective functional cure strategy will require therapies that can directly target the HBV reservoirs of HBV cccDNA and HBV integrants within the host genome. Earlier studies suggest that half-life of cccDNA is long, years or decades, and elimination of cccDNA relies on turnover of infected hepatocytes. This could be expedited through therapies that silence cccDNA transcriptional activity, through mutagenesis, or degradation. Depending on efficiency of delivery and editing, these approaches could potentially provide function cure for all HbsAg positive patients after a single treatment, so-called “one and done”.

Gene therapies modify genes to treat or cure disease including inherited diseases, cancers and infectious diseases and provide new hope for achieving functional cure through three mechanisms:

1. Eliminate or silence HBV DNA (cccDNA) in infected hepatocytes.
2. Prevent viral replication and antigen production.
3. Restore or boost immune control over HBV

In vitro cell and animal models of HBV infection confirm the gene editing with gene therapy can attain very high efficiency of both episomal and integrated HBV directly degrades cccDNA.

In vivo gene therapy for HBV consists of a single strand guide RNA to target the specific HBV DNA sequence in cccDNA and integrated HBV DNA plus the gene editing or effector mRNA. They are bundled into lipid nanoparticle that is administered as an intravenous infusion. The LNPs are taken up through the LDL receptors on hepatocytes, thereby limiting extrahepatic exposure. Once released from the endosomes into the cytoplasm, the effector mRNA is translated to form the editing enzyme– either Cas9 or ARCUS nuclease that cuts the DNA or TEMPO methylase that silences the DNA. This complexes with the guide RNA to transit into the nucleus to bind precisely to target HBV genes and edit them, stopping

production of all HBV proteins, pgRNA and DNA – the core elements of Functional Cure.

In vivo gene editing carries both short- and long-term safety concerns. Short-term risks include infusion-related reactions (IRRs) and ALT elevations. Mild IRRs with flushing, back pain, fever and hypotension are observed in most patients during or after the infusion. More severe IRRs with hypoxaemia and circulatory collapse, are rare but may require intensive care. The mechanism for these IRRs is not well understood but may result from complement activation-related pseudoallergy (Type III hypersensitivity to antibodies to Peg or other components of the LNP) or innate immune activation (TLR activation by lipid or RNA components of the LNP, or from the indels resulting from editing). There is no evidence of Type I hypersensitivity or cytokine release syndrome. Strategies employed to mitigate IRRs include premedication prior to the infusion with high-dose corticosteroids, antihistamines, paracetamol and NSAIDs, followed by intravenous fluids during the infusion. It is hoped newer generations of proprietary LNP platforms will reduce the severity and frequency of infusion-related reactions.

Drug induced liver injury (DILI) has also been observed following in vivo gene editing, usually transient Grade 1-2 aminotransferase elevations during the first weeks post-dose which resolve spontaneously within 14 days. However, recently the Intellia Transthyretin gene editing programme for amyloid cardiomyopathy and peripheral neuropathy (nex-z, NTLA-2001) was put on hold because of 4 Grade 4 ALT elevations including one patient who fulfilled Hy's Law and died from complications of acute liver failure. The cause of this hepatocellular injury remains unknown but does not seem to be exacerbated by repeat doses.

Late risks are the life-long risks from unwanted effects of host DNA editing - on- and -off target and germline editing. Off-target editing (where the guide RNA will have complementary sequence within the host genome other than the target gene) can result in unwanted and unpredictable effects if the matches sit within coding regions of genes. This risk can be largely mitigated by comprehensive in silico computational analysis of the whole human genome and by extensive preclinical cellular assays. Any identifiable matches will necessitate further refinement of the guide RNA.

On-target editing with CRISPR-Cas9 will always cause double stranded breaks (DSB) of host DNA, which can result in chromosomal translocation and lifetime risk of carcinogenesis.

Finally, germline editing, where the therapy edits genomic DNA within ova and spermatozoa and hence create editing of the next generation, is prevented by the LNP delivery which limits uptake to cells that express LDL receptors.

These long-term risks have led to the regulatory authorities mandating 15-year follow-up after administration of in vivo editing therapies.

New gene therapy approaches should reduce the risk of chromosomal translocation. The ARCUS CRISPR approach by Precision Biosciences, which employs a novel endonuclease, derived from algae rather than bacterium, produces overhanging DSBs, thereby preventing translocation. This has entered Phase

I in CHB patients. Base editing and prime editing platforms are also safer and are currently under development for inherited diseases such as hypercholesterolemia, alpha-1-antitrypsin deficiency and Wilson's Disease.

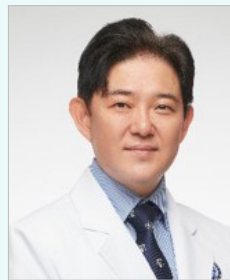
The safest approach is epigenetic silencing which does not cut the DNA. It silences both cccDNA and integrant transcriptional activity through methylation and compaction of the target HBV genes and the associated histones. Three epigenetic silencing editing programs have already entered clinical trials in CHB patients, and the first clinical results will be presented at EASL this May.

Preliminary results from the ARCUS nuclease (Precision) and epigenetic silencing (Tune) are encouraging. However more studies are required to determine the optimal biological dose. Reproducing the high efficacy achieved in preclinical models in patients will be challenging. Firstly, the efficiency of editing of cccDNA needs to approach 100%, otherwise relapse will occur. Secondly, therapies that simply cut the cccDNA may fail if double stranded breaks are rejoined by normal cellular DNA repair machinery, thereby restoring HBV transcriptional activity. Possible strategies to increase success will include repeated doses (not the "one and done" approach of CRISPR therapies in human inherited diseases. The optimal intervals between doses have yet to be determined.

Other strategies to optimise the antiviral efficacy of gene editing therapies include combining with novel therapies which reduce the cccDNA pool, including (1) capsid assembly modulators which block of cccDNA replenishment preventing capsid disassembly; (2) entry inhibitors such as surface monoclonal antibodies and bulivertide, which block hepatocyte reinfection; (3) interferon- α which enhances cccDNA degradation; and (4) bispecific TCR antibodies which induce cytolytic clearance of infected hepatocytes.

Also, although Functional Cure or Sterilising Cure has been the goal (undetectable HBsAg and HBV DNA off all treatment), Partial Cure could become an alternative endpoint (undetectable pgRNA, core, e, and core-related antigens, despite persistent low level HBsAg produced from integrants) if the therapy achieves superior editing of cccDNA compared to HBV integrants. Durable loss of pgRNA is expected to prevent viral replication off-treatment, raising the possibility that a finite treatment duration could result in permanent NUC cessation.

In conclusion, gene editing has the potential to cure every individual living with HBV infection. To-date host-targeting in vivo gene editing has been largely confined to lethal inherited diseases, where the short and long-term risks of this approach are justified. When considering gene editing for HBV infection, any benefits of reducing life-time risks of HCC will need to outweigh short-term and long-term risks of gene editing. Even if gene editing can achieve high rates of functional cure, the contribution to country and global HBV elimination will ultimately be determined by safety, accessibility in the community and cost.



Sang Hoon Ahn
Yonsei University

Self Introduction

Sang Hoon Ahn, M.D., Ph.D., is a Professor of Internal Medicine at Yonsei University College of Medicine, and currently serves as Chief of the Department of Gastroenterology and Hepatology and Director of the Yonsei Gastroenterology Center at Severance Hospital, Seoul, Korea.

He completed his postdoctoral fellowship at the Liver Research Center, Brown Medical School, USA (2001–2003), and further expanded his global academic experiences as a Visiting Professor at the WHO Collaborating Centre for Virus Reference and Research, Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne, Australia (2008–2009).

Prof. Ahn is an active leader in numerous academic societies. He currently serves on the Executive Council of the APASL, and as a Trustee of the JGH Foundation. He was Secretary-General of the KASL (2022–2024), and is now a Director of the Korean Academy of Medical Sciences.

He also holds significant roles as a government advisor in Korea. He has served as an expert consultant to the Ministry of Health and Welfare, the Ministry of Food and Drug Safety (MFDS), the Korea Centers for Disease Control and Prevention (KCDC), and the National Evidence-based Healthcare Collaborating Agency (NECA). Since 2025, he has been appointed as a non-standing member of the Central Administrative Appeals Commission under the Anti-Corruption and Civil Rights Commission.

Prof. Ahn has played key editorial roles in leading journals. He is currently Deputy Editor of the Journal of Gastroenterology and Hepatology, Associate Editor of Gut and Liver, Hepatology International, and Clinical and Molecular Hepatology. He has also served on editorial boards for Hepatology, Journal of Hepatology, Liver International.

Research Interests

Prof. Ahn's major research interests focus on viral hepatitis B and C, MASLD and liver fibrosis. His expertise spans from molecular virology to clinical trials for new drug development and formulation of practice guidelines. He has led over 80 clinical trials as a principal investigator and has published more than 600 peer-reviewed SCI(E) papers. He has been invited to lecture internationally more than 140 times.

Representative Publications

1. HCV self-testing: Bridging screening gaps and ensuring cost-effectiveness for both high-risk and universal populations: Correspondence to editorial on "Self-testing strategy to eliminate hepatitis C as per World Health Organization's goal: Analysis of disease burden and cost-effectiveness" Clin Mol Hepatol 2025 Apr;31(2):e163-e165.
2. Aspirin Use and Risk of HCC and Gastrointestinal Bleeding in Patients With HBV-Related Cirrhosis: A Landmark Analysis J Gastroenterol Hepatol 2025 Nov;40(11):2750-2757.
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Do Capsid Inhibitors Have a Role in Achieving HBV Cure?

Sang Hoon Ahn Yonsei University

Current nucleos(t)ide analogues (NAs) effectively suppress HBV but rarely achieve a functional cure (<10% HBsAg loss for 10 years) due to persistent viral reservoirs that drive continuous immune exhaustion. To address this significant efficacy gap, Capsid Assembly Modulators (CAMs) have emerged as a leading frontier in the global therapeutic pipeline.

This presentation evaluates the mechanistic evolution, early clinical hurdles, and the future role of CAMs in achieving a functional cure. Mechanisms and Early Clinical Hurdles: CAMs provide a biological complement to NAs by targeting the HBV core protein (HBc) to prevent pregenomic RNA (pgRNA) encapsidation and block the replenishment of the cccDNA reservoir. They function through two distinct pathways: Class I (inducing aberrant nucleocapsids) and Class II (accelerating perfectly formed but empty nucleocapsids). Despite profound early promise, first-generation CAMs encountered a significant clinical paradox. While combining early CAMs with NAs drove significantly deeper declines in HBV DNA and RNA, they failed to achieve meaningful HBsAg seroclearance. This mechanistic failure stems from a biological blind spot: pure viral suppression hides nucleic acids from host immune sensors, and CAMs cannot stop HBsAg production originating from integrated HBV DNA, leading to inevitable post-treatment relapse.

To overcome monotherapy efficacy ceilings, clinical development has strategically pivoted toward next-generation compounds designed to drive deep cccDNA suppression and immune activation. Class A CAMs, such as GLS4, act as "Immune Awakeners". By inducing aberrant capsid formation, they force cytoplasmic pgRNA exposure, directly activating RIG-I sensors to break immune tolerance and induce a potent innate immune response. Phase 2b data indicates that GLS4 combined with entecavir drives steep virological collapse while reversing cellular exhaustion. Simultaneously, next-generation Class E CAMs, such as ALG-000184 (Pevifoscorvir), operate as "Viral Starvers" via a dual-action blockade. By preventing both pgRNA encapsidation downstream and capsid disassembly upstream, these agents effectively choke off the source of HBV antigens, resulting in unprecedented multi-log reductions across HBV DNA, RNA, HBsAg, HBeAg, and HBcrAg.

Capsid inhibitors possess a definitive clinical role in achieving HBV functional cure, but exclusively within rational combination therapies rather than as standalone agents. Next-generation CAMs are the indispensable backbone of future sterilization strategies. Transitioning to a finite functional cure will rely on multi-mechanistic regimens that simultaneously combine deep replication blockade (NAs + CAMs), targeted antigen reduction (siRNAs/ASOs), and host immune reconstitution.



Seng-Gee Lim

National University of Singapore, Singapore

Self Introduction

Professor Seng-Gee Lim is Director of Hepatology at the National University Health System and Professor of Medicine at the National University of Singapore. A leading hepatologist in Asia, his clinical and research interests focus on viral hepatitis, liver cirrhosis, hepatocellular carcinoma, liver failure, and liver transplantation. He has published over 250 peer-reviewed papers, secured more than SGD 48 million in research funding, and serves on the editorial boards of several leading hepatology journals. Professor Lim has held numerous international leadership roles, including Chairman of the Singapore Hepatitis Conference and former Congress Chairman of APASL Liver Week. He is internationally recognized for his contributions to HBV research and the development of curative strategies for chronic hepatitis B.

Endpoints of Chronic Hepatitis B Therapy: Partial, Functional, and Sterilizing Cure

Seng-Gee Lim

National University of Singapore, Singapore

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ADVANCES IN EXPERIMENTAL HEPATOLOGY

Chairs

Yoon Mee Yang (Sungkyunkwan Univ.)

Hyun Young Kim (Dankook Univ.)





Michael Karin
Sanford Burnham Prebys, USA

Self Introduction

Education

- 1975 B.Sc. Biology, Tel Aviv University, Tel Aviv, Israel
- 1979 Ph.D. Molecular Biology, University of California, Los Angeles, CA
- 1980 Postdoc, Molecular Biology, Fox Chase Cancer Research, Philadelphia, PA
- 1981 Postdoc, Biochemistry and Molecular Biology, University of California, San Francisco, CA

Professional Experience

- 1975-1979 Graduate Student: Molecular Biology Institute, UC Los Angeles
- 1979-1980 Postdoctoral Fellow: Fox Chase Institute for Cancer Research, Philadelphia, PA
- 1980-1981 Postdoctoral Fellow: Department of Medicine and Biochemistry, UC San Francisco
- 1981-1982 Assistant Research Biochemist: Metabolic Research Unit, UC San Francisco
- 1982-1985 Assistant Professor of Microbiology: School of Medicine, University of Southern California
- 1986-1987 Associate Professor: Department of Medicine, UC San Diego
- 1987-1989 Associate Professor: Department of Pharmacology, UC San Diego
- 1989-2015 Professor, Department of Pharmacology, UC San Diego
- 1993-2005 Founder and Consultant: Celgene Pharmaceuticals (formerly "Signal Pharmaceuticals"), San Diego, CA
- 2010-2017 Professor, Department of Pathology, UC San Diego
- 2015-2025 Distinguished Professor, Departments of Pharmacology and Pathology, UC San Diego
- 2025-Present Director, Center for Metabolic and Liver Diseases, Sanford Burnham Prebys Medical Discovery Institute

Research Interests

Michael Karin received a PhD in Molecular Biology from UCLA in 1979 and conducted postdoctoral research with Prof. Beatrice Mintz at Fox Chase Cancer Center from 1979 to 1980 and with Prof. John Baxter at UCSF from 1980 to 1983. He served as an Assistant Professor in the Department of Microbiology at USC School of Medicine from 1983 to 1985 and, in 1986, joined the Department of Pharmacology at UCSD School of Medicine, where he rose through the ranks to become a Distinguished Professor until his retirement in 2024. That same year, Karin joined the Sanford Burnham Prebys Medical Research Institute as the Director of the Center for Metabolic and Liver Diseases.

Throughout his academic career, Karin investigated stress and inflammation signaling, employing a full range of experimental approaches from biochemistry and molecular cell biology to animal pathophysiology. By discovering how infection, inflammation, radiation, or environmental stressors activate AP-1, NF- κ B, and other transcription factors, he explored how these processes contribute to the pathogenesis of cancer, as well as degenerative and metabolic diseases.

Karin group elucidated fundamental mechanisms by which inflammation and obesity promote tumor development and contribute to type II diabetes and insulin resistance and was among the first to highlight the role of inflammation in metabolic disease. Karin's group established how members of the IL-6 cytokine family control the development of colorectal (CRC) and liver (HCC) cancers through activation of STAT3 and YAP and identified cell type-specific mechanisms by which NF- κ B activation via I κ B kinases (IKK)—which his group was the first to discover—affects the pathogenesis of various cancers. His research also demonstrated that not only innate immune cells, such as macrophages, but also adaptive immune cells, including T regulatory cells and B lymphocytes, contribute to tumorigenesis. This body of work helped to establish the field of Inflammation and Cancer.

At the Frontline of Metabolic Liver Disease: Stress and Inflammation

Michael Karin Sanford Burnham Prebys, USA

The incidence of non-alcoholic (MASLD/MASH) and alcoholic (ALD/ASH) fatty liver diseases has grown dramatically in the past 20 years, and their current annual health care costs exceed 150 billion US dollars. Much of the mechanistic investigation of MASLD and ALD pathogenesis had focused on hepatocyte intrinsic metabolic aberrations. However, it has become increasingly clear that the gut-liver axis also plays a critical pathogenic and protective role by serving as a conduit through intestinal microbes and their metabolites, such as endotoxin (lipopolysaccharide, LPS) reach the liver and as a source of anti-microbial peptides (AMP). Starting with RNA-seq analysis of transcriptomic changes that accompany MASLD and MASH development in response to high fructose diet (HFrD) we found pronounced upregulation of Toll-like receptors (TLRs) and their downstream signaling effectors in the diseased liver, suggesting HFrD-induced translocation of intestinal microbes and/or endotoxin.

Consistent with the existence of diet induced endotoxemia, we observed signs of barrier disruption and aberrant IL-22 signaling, a cytokine that contributes to several key aspects of the intestinal epithelial barrier, including AMP induction. Consistent with these findings, administration of recombinant IL-22Fc fusion protein to re-ignite IL-22 signaling resulted in the complete resolution of all MASLD/MASH signs in mice fed HFrD or Western diet (WD). Surprisingly, however, the therapeutic effect was blocked by ablation of IL-22Ra in intestinal epithelial cells (IEC), but was unaffected by its ablation in hepatocytes, indicating that IL-22 acted in the intestine rather than the liver. Further investigation indicated that IL-22Fc treatment inhibited the diet-induced expansion of absorptive enterocytes, thereby minimizing the absorption of dietary fats and sugars. IL-22 signaling was also found to protect the liver from ALD, whose pathogenesis is strongly dependent on gut-to-liver bacterial translocation. Together with our collaborations Drs. Cristina Llorente and Bernd Schnable at UCSD we found that extensive alcohol consumption in mice and humans results in the downregulation of muscarinic acetylcholine receptor 4 (M4), which is specifically expressed in intestinal goblet cells.

Accordingly, M4 induction and activation provided complete protection from both ALD and MASLD through the stimulation of IL-22 dependent anti-microbial immunity. Collectively, these studies indicate that the intestinal epithelial barrier and the mucosal neuroimmune network play instrumental roles in the pathogenesis, as well as resolution, of non-alcoholic and alcoholic fatty liver diseases.



Won-Il Jeong
KAIST

Self Introduction

Prof. Won-Il Jeong received his Doctor of Veterinary Medicine (D.V.M., 1999) and Ph.D. (2004) from Kyungpook National University, followed by postdoctoral training at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), NIH, USA. He joined KAIST as an assistant professor in 2008, was subsequently promoted to associate professor, tenured full professor, and is currently serving as a KAIST Endowed Chair Professor.

He is currently the Director of the Center for Hepatic Glutamate and Its Function at KAIST and will assume the role of Associate Editor of Hepatology beginning in 2027. He also served as Deputy Editor of Clinical and Molecular Hepatology (CMH) and as a member of the editorial board of Hepatology.

His research team investigates the pathogenesis of diverse liver diseases, including steatosis, inflammation, fibrosis, and hepatocellular carcinoma (HCC). Their work has been published in leading journals such as Cell Metabolism, Nature Biomedical Engineering, Hepatology, Journal of Hepatology, Gastroenterology, and Nature Communications.

Research Interests

Alcohol-Associated Liver Disease (ALD), Steatotic Liver Disease (SLD), Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Liver Fibrosis, Hepatocellular Carcinoma, Liver Immunology, Liver Neurology

Representative Publications

1. Lee K, Lee J, Byun J, Lee E, Kim P, Kim W, Jeong WI. Alcohol-induced oxidative stress triggers mitochondrial Ca2+ release through the permeability transition pore. Clin Mol Hepatol. 2026 Apr;32(2):e205-e210. doi: 10.3350/cmh.2026.0005

2. Yang K*, Kim K*, Ryu T, Shim YR,... , Jeong WI. VGLUT3-mediated glutamate secretion by binge drinking triggers hepatic inflammation by activating mGluR5/NOX2 in Kupffer cells. Nature Communications, 2025 July 1;16:5546.

3. Jeong JM*, Choi SE*, Shim YR, ..., Eun HS, Jeong WI. CX3CR1+ macrophages interact with hepatic stellate cells to promote hepatocellular carcinoma through CD8+ T cell suppression. Hepatology, 2025 Sep 1;82(3):655-668. doi: 10.1097

4. Agno KC*, Yang K*, Byun SH, Oh S, Lee S, Kim H, Kim K, Choi S, Jeong WI* and Jeong JW*. Body Temperature-Responsive, Stiffness-Varying and Non-Reusable Intravenous Needle with On-Site Temperature Sensing for Improved Patient Care. Nature Biomedical Engineering 2023 Oct 30. doi: 10.1038/s41551-023-01116-z. (*Co-corresponding)

5. Kim HH*, Shi YR*, Kim HN, Yang K, Ryu T, Kim K, Choi SE, Kim MJ, Woo C, Chung KPS, Hong SH, Jung Y, Hwang GS, Kim W, Kim SH, Eun HS, Seong JK, Jeong WI. xCT-mediated glutamate excretion in white adipocytes stimulates interferon-γ production by natural killer cells in obesity. Cell Reports 2023, 42, 112636

Unveiling the Impact: Hepatic Glutamate and Its Receptor in Liver Disease

Won-Il Jeong KAIST

In our recent studies, we identified an intrinsic glutamatergic signaling pathway between hepatocytes and non-parenchymal cells that is closely associated with liver disease. Here, we briefly outline the respective roles and mechanisms of glutamate in steatosis, steatohepatitis, and fibrosis.

Steatosis

Chronic alcohol intake induces cysteine deficiency and glutathione depletion, impairing the liver’s anti-oxidant defense. To compensate, hepatocytes activate the xCT transporter, which imports cystine while exporting glutamate. The released glutamate stimulates metabotropic glutamate receptor 5 (mGluR5) in hepatic stellate cells (HSCs), driving the production of 2-arachidonoylglycerol (2-AG). This lipid mediator then activates cannabinoid receptor 1 (CB1R) in hepatocytes, promoting de novo lipogenesis and fat accumulation. Thus, glutamate functions as a signaling molecule linking oxidative stress to lipid synthesis, and inhibition of mGluR5 or CB1R can attenuate hepatic steatosis.

Steatohepatitis

In alcoholic steatohepatitis (ASH), glutamate plays a pro-inflammatory role. Chronic alcohol consumption causes glutamate to accumulate in hepatocytes via VGLUT3, and binge drinking triggers its release through mitochondrial calcium-mediated SNARE complex activation, driven by ROS-induced transient opening of the mitochondrial permeability transition pore (mPTP). The secreted glutamate activates mGluR5 in Kupffer cells, leading to NADPH oxidase 2 (NOX2)-dependent ROS production and hepatic inflammation. Alcohol-induced hepatocyte ballooning further facilitates pseudosynapse formation between hepatocytes and Kupffer cells, reinforcing this pathological interaction. Clinical evidence confirms that elevated plasma glutamate and VGLUT3 expression correlate with ASH severity. Therefore, glutamate serves as a key mediator of hepatocyte-immune cell communication that drives inflammation in steatohepatitis.

Fibrosis

In liver fibrosis, glutamate exerts dual effects. On one hand, mGluR5 activation in NK cells enhances their cytotoxicity and IFN-γ production, enabling them to eliminate activated HSCs and suppress fibrosis. On

the other hand, in advanced fibrosis, HSCs increase glutamate uptake, reducing extracellular glutamate and thereby limiting NK cell stimulation. This allows HSCs to evade immune surveillance and promotes fibrosis progression. Thus, glutamate can both support antifibrotic immune responses and facilitate fi- brogenesis, depending on disease stage.

Conclusion

Glutamate is not merely a metabolic byproduct but a critical signaling molecule in liver disease progres- sion. In steatosis, it drives lipid accumulation via the xCT–mGluR5–2AG–CB1R axis. In steatohepatitis, it promotes inflammation through hepatocyte–Kupffer cell pseudosynapses and ROS generation. In fibrosis, it modulates NK cell cytotoxicity, with protective effects in early disease but immune evasion in advanced stages. Collectively, these findings highlight the glutamatergic signaling pathway as a central mechanism and a promising therapeutic target in alcoholic and metabolic liver diseases.

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2. Choi WM*, Ryu T*, Lee JH, Shim YR, Kim MH, Kim HH, Kim YE, Yang K, Kim K, Choi SE, Kim W, Kim SH, Eun HS, Jeong WI. Metabotropic glutamate receptor 5 in natural killer cells attenuates liver fibrosis by exerting cytotoxicity to activated stellate cells. Hepatology, 2021, 74(4), 2170-2185.

3. Kim HH*, Shi YR*, Kim HN, Yang K, Ryu T, Kim K, Choi SE, Kim MJ, Woo C, Chung KPS, Hong SH, Jung Y, Hwang GS, Kim W, Kim SH, Eun HS, Seong JK, Jeong WI. xCT-mediated glutamate excretion in white adipocytes stimulates interferon-γ production by natural killer cells in obesity. Cell Reports 2023, 42, 112636

4. Yang K*, Kim K*, Ryu T, Shim YR, Kim HH, Choi SE, Kim MJ, Chung PSK, Lee E, Lee KW, Jeon J, Kim P. Kim YS, Ku T, Jeong H, Nam KT, Lim G, Choi DW, Kim SH, Eun HS, Kim W, Jeong WI. VGLUT3-mediated glutamate secretion by binge drinking triggers hepatic inflammation by activating mGluR5/NOX2 in Kupffer cells. Nature Communications, 2025 July 1;16:5546.

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Michael Karin
Sanford Burnham Prebys, USA

Self Introduction

Education

- 1975 B.Sc. Biology, Tel Aviv University, Tel Aviv, Israel
- 1979 Ph.D. Molecular Biology, University of California, Los Angeles, CA
- 1980 Postdoc, Molecular Biology, Fox Chase Cancer Research, Philadelphia, PA
- 1981 Postdoc, Biochemistry and Molecular Biology, University of California, San Francisco, CA

Professional Experience

- 1975-1979 Graduate Student: Molecular Biology Institute, UC Los Angeles
- 1979-1980 Postdoctoral Fellow: Fox Chase Institute for Cancer Research, Philadelphia, PA
- 1980-1981 Postdoctoral Fellow: Department of Medicine and Biochemistry, UC San Francisco
- 1981-1982 Assistant Research Biochemist: Metabolic Research Unit, UC San Francisco
- 1982-1985 Assistant Professor of Microbiology: School of Medicine, University of Southern California
- 1986-1987 Associate Professor: Department of Medicine, UC San Diego
- 1987-1989 Associate Professor: Department of Pharmacology, UC San Diego
- 1989-2015 Professor, Department of Pharmacology, UC San Diego
- 1993-2005 Founder and Consultant: Celgene Pharmaceuticals (formerly "Signal Pharmaceuticals"), San Diego, CA
- 2010-2017 Professor, Department of Pathology, UC San Diego
- 2015-2025 Distinguished Professor, Departments of Pharmacology and Pathology, UC San Diego
- 2025-Present Director, Center for Metabolic and Liver Diseases, Sanford Burnham Prebys Medical Discovery Institute

Research Interests

Michael Karin received a PhD in Molecular Biology from UCLA in 1979 and conducted postdoctoral research with Prof. Beatrice Mintz at Fox Chase Cancer Center from 1979 to 1980 and with Prof. John Baxter at UCSF from 1980 to 1983. He served as an Assistant Professor in the Department of Microbiology at USC School of Medicine from 1983 to 1985 and, in 1986, joined the Department of Pharmacology at UCSD School of Medicine, where he rose through the ranks to become a Distinguished Professor until his retirement in 2024. That same year, Karin joined the Sanford Burnham Prebys Medical Research Institute as the Director of the Center for Metabolic and Liver Diseases.

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Senescent Hepatocytes as Tumor Seedbeds in MASH: Lessons from Single-Cell Maps

Michael Karin Sanford Burnham Prebys, USA

Hepatocellular carcinoma (HCC) originates from differentiated hepatocytes undergoing compensatory proliferation in livers damaged by viruses or metabolic dysfunction-associated steatohepatitis (MASH). While increasing HCC risk, MASH is associated with p53-dependent hepatocyte senescence, which we found to be triggered by hypernutrition-induced DNA breaks. How this presumably tumorsuppressive response is bypassed to license oncogenic mutagenesis and enable HCC evolution was previously unknown. Our studies identified the gluconeogenic enzyme fructose-1,6-bisphosphatase 1 (FBP1) as a p53 target that is elevated in senescentlike MASH hepatocytes but suppressed through promoter hypermethylation and proteasomal degradation in most human HCCs. FBP1 first declines in metabolically stressed premalignant disease-associated hepatocytes (daHep) and HCC progenitor cells (HcPC), paralleling the protumorigenic activation of AKT and NRF2. By accelerating FBP1 and p53 degradation, AKT and NRF2 enhance the proliferation and metabolic activity of previously senescent HCC progenitors. The senescence-reversing and proliferation-supportive NRF2–FBP1–AKT–p53 metabolic switch, operative in mice and humans, also enhances the accumulation of DNA-damage-induced somatic mutations needed for MASH-to-HCC progression. New insights to HCC-related mutagenic mechanisms will also be discussed.

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*Turning Evidence into New Standards in Liver Disease Care
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2026 KLCA PRACTICE GUIDANCES

Stereotactic Body Radiation Therapy

Chair
Sang Hoon Park (Hallym Univ.)





Sang Min Yoon
University of Ulsan

Self Introduction

Doctor Sang Min Yoon is currently a professor in the Department of Radiation Oncology at Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. He held the position of associate professor from 2014 to 2020, assistant professor from 2009 to 2014, and clinical instructor from 2007 to 2009 at Asan Medical Center, University of Ulsan College of Medicine.

Throughout his career, Dr. Yoon has established a robust academic profile, particularly in the field of radiation oncology for hepatocellular carcinoma. According to Google Scholar, he has amassed a total of 5,544 citations and an h-index of 40. His research has shown remarkable growth in recent years, achieving an h-index of 26 and an i10-index of 56 since 2021 alone. Beyond his research, Dr. Yoon currently serves as the Chair of the Research Committee in the Korean Liver Cancer Association (KLCA) and the Chair of the Public Relations Committee in the Korean Society for Radiation Oncology (KOSRO).

He graduated from Kyungpook National University College of Medicine in 1998 and completed his residency at Asan Medical Center from 2000 to 2004. Dr. Yoon underwent clinical fellowships at Asan Medical Center, Samsung Medical Center, and National Cancer Center Korea from 2004 to 2007. Additionally, he was a visiting scholar at the University of California San Diego in the USA from August 2013 to July 2014. He earned his master's degree in 2003 and a doctorate in 2009 at the University of Ulsan College of Medicine.

Research Interests

His research interest is "Radiation therapy for hepatocellular carcinoma". He has published about 100 international scientific peer review papers in addition to 30 domestic scientific journals.

Representative Publications

1. Lee HI, Son J, Cho B, Goh Y, Jung J, Park JH, Chie EK, Kim KS, Kim YH, Kang HC, Yoon SM. Development and validation of a prediction model for cardiac events in patients with hepatocellular carcinoma undergoing stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2025;122(5):1272-1281. (Corresponding author)
2. Shin YS, Yun JK, Jung J, Park JH, Song SY, Choi EK, Choi S, Kim HR, Kim YH, Kim DK, Lee GD, Yoon SM. Comparison of metastasectomy and stereotactic body radiation therapy for pulmonary oligometastasis from hepatocellular carcinoma: a propensity score-weighted analysis. *Int J Radiat Oncol Biol Phys* 2025;121(2):432-441. (Corresponding author)
3. Jung J, Joo JH, Kim SY, Kim JH, Choi J, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Park J, Yoon SM. Radiologic response as a prognostic factor in advanced hepatocellular carcinoma with macroscopic vascular invasion after transarterial chemoembolization and radiotherapy. *Liver Cancer* 2022;11(2):152-161. (Corresponding author)
4. Yoon SM, Kim SY, Lim YS, Kim KM, Shim JH, Lee D, An J, Jung J, Kim JH, Lee HC. Stereotactic body radiation therapy for small (≤ 5 cm) hepatocellular carcinoma not amenable to curative treatment: Results of a single-arm, phase II clinical trial. *Clin Mol Hepatol* 2020;26:506-515. (First author)
5. Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, Lee HC, Lim YS. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized trial. *JAMA Oncol* 2018;4(5):661-669. (First author)

Stereotactic Body Radiation Therapy: KLCA Expert Consensus-Based Practical Recommendations

Sang Min Yoon *University of Ulsan*

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KLCA SYMPOSIUM 3

Therapeutic Update and Emerging Therapy in HCC

Chairs

Hee Chul Park (Sungkyunkwan Univ.)

Do Young Kim (Yonsei Univ.)





Kei Shibuya
Gunma University, Japan

Self Introduction

Education

2003 M.D., Faculty of Medicine, Gunma University
2012 Ph.D., Graduate School of Medicine, Gunma University

Professional Experience

2018-Present Lecturer, Dept. of Radiation Oncology, Diagnostic and Interventional Radiology, Gunma University Hospital
2011-2018 Assistant Professor, Dept. of Radiation Oncology, Diagnostic and Interventional Radiology, Gunma University Hospital

Board Certified Radiologist and Japan Radiological Society, Board Certified Physician
The Japanese Society of Interventional Radiology, Certified Vascular Specialist and Japanese College of Angiology

Research Interests

Carbon-Ion Radiotherapy for Liver Tumors, Interventional Radiology, Multimodal Treatment Strategies, Portal Vein and Hepatic Vein Embolization, Cost-Effectiveness Analysis

Representative Publications

1. Hatanaka T, Shibuya K, Kakizaki S, et al. Carbon-ion radiotherapy achieves outcomes equivalent to surgical resection for hepatocellular carcinoma. *Hepatology Communications* 9(9): e0801, 2025.
2. Tomizawa K, Shibuya K, et al. Repeated Carbon-Ion Radiation Therapy for Intrahepatic Recurrent Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys* 116(5): 1100-1109, 2023.
3. Shibuya K, et al. Efficacy and Safety of 4 Fractions of Carbon-Ion Radiation Therapy for Hepatocellular Carcinoma: A Prospective Study. *Liver Cancer* 11(1): 61-74, 2022.
4. Shibuya K, et al. A feasibility study of high-dose hypofractionated carbon-ion radiation therapy using four fractions for localized hepatocellular carcinoma measuring 3 cm or larger. *Radiother Oncol* 132: 230-235, 2019.
5. Shibuya K, et al. Short-course carbon-ion radiotherapy for hepatocellular carcinoma: A multi-institutional retrospective study. *Liver Int* 38(12): 2239-2247, 2018.

Carbon Ion Therapy: The Next Step in Precision Radiotherapy

Kei Shibuya Gunma University, Japan

Hepatocellular carcinoma (HCC) is increasingly managed through multidisciplinary pathways in which hepatologists, surgeons, interventional radiologists, medical oncologists, and radiation oncologists repeatedly reassess treatment intent based on tumor status and hepatic reserve. In this setting, the central challenge is not simply achieving local tumor control, but doing so without depleting liver function or limiting future treatment options. Carbon ion radiotherapy (CIRT) has emerged as a promising modality in this context, offering highly conformal dose delivery with greater biological effectiveness than conventional photon-based radiotherapy, and has attracted growing interest as a local treatment option for patients in whom standard resection or ablation is not feasible.

The clinical appeal of CIRT in HCC lies in its ability to combine potent local tumor control with preservation of uninvolved liver parenchyma. This is particularly relevant for lesions that are large, adjacent to major vessels, inaccessible to thermal ablation, or associated with reduced hepatic reserve. Contemporary studies have reported excellent local control rates and acceptable toxicity with hypofractionated CIRT schedules, and encouraging outcomes have also been observed in patients with major vascular invasion, recurrent intrahepatic disease, and impaired liver function. Furthermore, recent comparative analyses suggest that CIRT may outperform transarterial chemoembolization (TACE) in selected patients with solitary tumors, and may achieve survival outcomes comparable to surgical resection in carefully selected potentially resectable cases. These findings indicate that CIRT has moved beyond proof of concept and is becoming a clinically relevant option for physicians involved in the longitudinal management of HCC.

CIRT should not be viewed as a competitor to surgery or systemic therapy, but rather as a complementary modality that fills therapeutic gaps and enables more individualized sequencing of local and systemic interventions. It may be particularly valuable when curative local control is desired but conventional therapies are contraindicated, technically incomplete, or likely to compromise hepatic reserve, and may also serve as a repeatable treatment option for patients with recurrent intrahepatic disease in the context of chronic liver disease. Although current clinical results are encouraging, CIRT remains a developing technology, and continued progress in treatment planning, radiobiological modeling, and multicenter validation is expected to refine patient selection and broaden its institutional applicability.

The next major step for CIRT will likely be its incorporation into combination treatment strategies. As immunotherapy-based regimens assume a central role in intermediate- and advanced-stage HCC, the value of effective yet liver-sparing local therapy is being reconsidered. CIRT is well positioned for this transition, delivering strong local control with short-treatment period and minimal impact on residual liver function and thereby helping to preserve eligibility for ongoing systemic treatment. The radio-biological properties of CIRT have also raised interest in potential synergy with immune checkpoint inhibitors, positioning it as a plausible partner in future multimodal protocols, with possible roles in consolidation after systemic response, salvage after incomplete locoregional therapy, and tumor conversion in selected advanced cases. Current evidence already supports the role of CIRT as the next step in precision radiotherapy for HCC, and continued clinical investigation will be essential to fully define its place within the evolving multidisciplinary liver cancer care.

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Gyoung Min Kim
Yonsei University

Self Introduction

Education

- 1997.03-2005.02 M.D., College of Medicine, Seoul National University
- 2008.02-2010.02 M.D., College of Medicine, Seoul National University
- 2010.03-2016.02 Ph.D., College of Medicine, Seoul National University

Professional Experience

- 2012.03-2014.02 Clinical Instructor, Department of Radiology, Korea University Anam Hospital
- 2014.03-2024.02 Assistant Professor, Department of Radiology, Yonsei University Severance Hospital
- 2024.03- Associate Professor, Department of Radiology, Yonsei University Severance Hospital
- 2018.07-2020.06 Scientific Committee, Korean Liver Cancer Association
- 2021.01-2022.12 Chair of Scientific Committee, Korean Society of Interventional Radiology
- 2021.07-2022.06 Scientific Committee, Korean Liver Cancer Association
- 2022.07-2023.06 Research Committee, Korean Liver Cancer Association
- 2025.01-2026.12 Director of International Liaison, Korean Society of Interventional Radiology

Reviewer of Journal of Vascular and Interventional Radiology, Cardiovascular and Interventional Radiology, and Korean Journal of Radiology

Representative Publications

1. Clinical course of patients with hepatocellular carcinoma who experienced radiologic complete response after radioembolization. Moon S, Kim GM, Won JY, Kwon JH, Park J, Han K, Kim MD, Kim HC, Kim DK, Choi JY. Front Oncol. 2024 Jan 30;14:1349632. doi: 10.3389/fonc.2024.1349632.
2. Cryoablation of Hepatocellular Carcinoma with High-Risk for Percutaneous Ablation: Safety and Efficacy. Kim GM, Won JY, Kim MD, Park SI, Lee do Y, Shin W, Shin M, Han KH, Kim do Y, Kim SU. Cardiovasc Intervent Radiol. 2016 Oct;39(10):1447-54.
3. Transarterial Chemoembolization Using Sorafenib in a Rabbit VX2 Liver Tumor Model: Pharmacokinetics and Antitumor Effect. Kim GM, Kim MD, Kim do Y, Kim SH, Won JY, Park SI, Lee do Y, Shin W, Shin M. J Vasc Interv Radiol. 2016 Jul;27(7):1086-92.
4. Safety and Efficacy of Transarterial Radioembolization Combined with Chemoembolization for Bilobar Hepatocellular Carcinoma: A Single-Center Retrospective Study. Kwon JH, Kim GM, Han K, Won JY, Kim MD, Lee DY, Lee J, Choi W, Kim YS, Kim DY, Han KH. Cardiovasc Intervent Radiol. 2018 Mar;41(3):459-465.
5. Thoracic Duct Embolization for Treatment of Chyle Leakage After Thyroidectomy and Neck Dissection. Moon S, Park J, Kim GM, Han K, Kwon JH, Kim MD, Won JY, Kim HC. Korean J Radiol. 2024 Jan;25(1):55-61. doi: 10.3348/kjr.2023.0658.

Advances in Interventional Oncology: From TACE to TARE and Beyond

Gyoung Min Kim Yonsei University

Interventional oncology encompasses a broad spectrum of minimally invasive therapies, including transarterial treatments such as chemoembolization and radioembolization, as well as local ablative modalities such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and irreversible electroporation (IRE).

In the management of hepatocellular carcinoma (HCC), iodized oil-based transarterial chemoembolization (TACE) has reached a high level of technical refinement, largely driven by advances in low-profile microcatheters and cone-beam CT imaging. Current research efforts are increasingly focused on combination strategies with immune-oncology therapies. In contrast, the use of drug-eluting bead TACE has gradually declined, owing to its limitations—particularly reduced efficacy in small tumors—as well as the rapid advancement of radioembolization.

Transarterial radioembolization (TARE) has evolved significantly over the past decade. Landmark studies, including LEGACY, DOSISPHERE-01, and RASER, have demonstrated its favorable therapeutic efficacy, leading to its incorporation into major clinical guidelines as a standard treatment option. Notable progress has also been made in the field of dosimetry, where personalized dosimetry has enabled optimization of tumor-absorbed dose, translating into improved clinical outcomes. Furthermore, technique-specific strategies such as radiation segmentectomy, radiation lobectomy, and radiation major hepatectomy have been developed to tailor treatment according to tumor burden and therapeutic intent (curative, bridging, or downstaging), with promising clinical results supported by prospective studies. Nevertheless, dosimetric challenges remain, particularly in segmentation and image registration, as well as in defining safe dose thresholds for preserving normal liver parenchyma, highlighting the need for further investigation.

From a biological perspective, radioembolization is also expected to exert synergistic effects when combined with immune-mediated therapies, and this area is currently under active exploration.

Among local ablative therapies, RFA has long been established as the standard of care. However, MWA is increasingly being adopted due to its ability to achieve larger ablation volumes in shorter procedural times. Cryoablation and IRE, while offering advantages in treating tumors adjacent to major vessels or critical structures with relative safety, remain less widely utilized due to procedural complexity, longer treatment times, and, in the case of IRE, the requirement for general anesthesia.

In summary, interventional oncology for HCC continues to evolve rapidly, driven by technological innovation, improved dosimetric strategies, and integration with systemic therapies, paving the way for more personalized and effective treatment paradigms.



Stephen Lam Chan

The Chinese University of Hong Kong, Hong Kong

Self Introduction

MBBS, MD (CUHK), FRCP (Edin., Lond.), FHKCP, FHKAM (Medicine)

Stephen Lam CHAN is a Clinical Professor in the Department of Clinical Oncology at the Chinese University of Hong Kong (CUHK). He is renowned for his clinical and translational research on hepatobiliary and pancreatic cancers. Prof. Chan has authored over 270 papers published in peer-reviewed journals. Internationally, he has served on the scientific committees of ASCO and ESMO conferences, and is currently the President of the International Liver Cancer Association (ILCA). Prof. Chan is an associate editor for journals such as the Journal of Hepatology. Locally, he is a board director of the CUHK Medical Centre and the Assistant Dean (Health Systems) of the Faculty of Medicine at CUHK. He also established the Hand in Hand Cancer Foundation, a charity dedicated to serving patients in need.

Research Interests

Primary: Hepatocellular Carcinoma (HCC), Translational Studies, Therapeutics

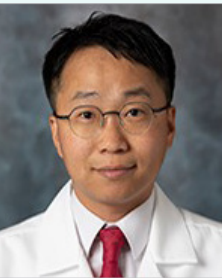
Secondary: Biliary Tract Cancer (BTC), Therapeutics

Representative Publications

1. Chan, S.L., Ryoo, B.Y., Mo, F., Chan, L.L., Cheon, J., Li, L., Wong, K.H., Yim, N., Kim, H., Yoo, C. Multicentre phase II trial of cabozantinib in patients with hepatocellular carcinoma after immune checkpoint inhibitor treatment. *J Hepatol.* 2024 Aug;81(2):258-264. doi: 10.1016/j.jhep.2024.03.033.
2. Lau, G., Abou-Alfa, G.K., Cheng, A.L., Sukeepaisarnjaroen, W., Dao, T.V., Kang, Y.K., Thungappa, S.C., Kudo, M., Sangro, B., Kelley, R.K., Furuse, J., Park, J.W., Sunpaweravong, P., Fasolo, A., Yau, T., Kawaoka, T., Azevedo, S., Reig, M., Assenat, E., Yarchoan, M., He, A.R., Makowsky, M., Gupta, C., Negro, A., Chan, S.L. Outcomes in the Asian subgroup of the phase III randomised HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *J Hepatol.* 2025 Feb;82(2):258-267. doi: 10.1016/j.jhep.2024.07.017; PMID: 39089633.
3. Kwong, T.T., Xiong, Z., Zhang, Y., Wu, H., Cao, J., Wong, P.P.C., Liu, X., Wang, J., Wong, C.H., Tse, G.M.K., Sung, J.J.Y., Zhou, J., Cheng, A.S.L., Chan, S.L. Overcoming immunotherapy resistance in hepatocellular carcinoma by targeting myeloid IL-8/CXCR2 signaling. *Mol Ther.* 2025 Apr 2;33(4):1659-1673. doi: 10.1016/j.jymthe.2025.02.002. PMID: 39916327
4. Rimassa, L*, Chan, S.L*, Sangro, B., Lau, G., Kudo, M., Reig, M., Breder, V., Ryu, M.H., Ostapenko, Y., Sukeepaisarnjaroen, W., Varela, M., Tougeron, D., Crysler, O.V., Bouattour, M., Van Dao, T., Tam, V.C., Faccio, A., Furuse, J., Jeng, L.B., Kang, Y.K., Kelley, R.K., Paskow, M.J., Ran, D., Xynos, I., Kurland, J.F., Negro, A., Abou-Alfa, G.K. Five-year overall survival update from the HIMALAYA study of tremelimumab plus durvalumab in unresectable HCC. *J Hepatol.* 2025 Apr 11:S0168-8278(25)00226-0. doi: 10.1016/j.jhep.2025.03.033. PMID: 40222621. (*Co-first author)
5. Chan, L.L., Chan, A.W.H., Yip, T.C.F., Wong, G.L.H., Ngai, A.K.H., Mo, F., Chok, S.H., Kung, J.W.C., Chu, C.M., Mok, K., Li, M.S.C., Wong, V.W.S., Chan, S.L. Attenuation of the second peak of bimodal recurrence of HBV-related HCC after curative treatment in the antiviral era. *J Hepatol.* 2025 Jun 9:S0168-8278(25)02266-4. doi: 10.1016/j.jhep.2025.05.028. PMID: 40499818.

Novel Molecular and Cellular Therapies in HCC: The Next Wave

Stephen Lam Chan *The Chinese University of Hong Kong, Hong Kong*



Ju Dong Yang

Cedars-Sinai Medical Center, USA

Self Introduction

- 1999.03-2005.02 Medical School - Sungkyunkwan University School of Medicine, Seoul, Korea
- 2009.03-2011.05 Research Fellowship - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2009.09-2011.05 Master's Degree in Clinical and Translational Research - Clinical and Translational Science Activities, Mayo Graduate School
- 2011.06-2014.05 Residency - Internal Medicine, University of Arkansas for Medical Science, Little Rock, AR
- 2014.07-2017.12 Gastroenterology Fellowship, T32 Grant - Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN
- 2018.01-2018.12 Transplant Hepatology Fellowship - Transplant Hepatology, Mayo Clinic, Rochester, MN
- 2023.01-Present Associate Professor of Medicine, Department of Medicine, Cedars-Sinai

Research Interests

The Yang Lab is dedicated to advancing the early detection and risk stratification of hepatocellular carcinoma (HCC) through the discovery and validation of circulating biomarkers, including circulating tumor cells and extracellular vesicles. By integrating these insights with predictive modeling and molecular profiling, the lab develops precision therapies tailored to individual patients and optimizes treatment responses. Leveraging population-based data, the Yang Lab also addresses global disparities in liver cancer care, guiding more equitable and effective clinical strategies.

Representative Publications

1. Antibiotic Use Linked to Worse Outcomes in Patients With Gastrointestinal and Liver Cancer on Immune Checkpoint Inhibitors: A Meta-Analysis. Rezaee-Zavareh MS, Karimi-Sari H, Parhizkar Roudsari P, Khattab O, Attia AM, Danpanichkul P, Hwang SY, Liu JS, Yalda T, Chen PJ, Gong J, Ferrone CR, Rich NE, Parikh ND, Pinato DJ, Singal AG, Yang JD. Am J Gastroenterol. 2026 Feb 12. doi: 10.14309/ajg.0000000000003956. Online ahead of print. PMID: 41677135.
2. Gastrointestinal cancer statistics in 2022 and projection to 2050: GLOBOCAN estimates across 185 countries. Danpanichkul P, Pang Y, Tothananunroj P, Dejvajara D, Kim D, Saokhieo P, Suparan K, Muthiah MD, Duangsonk K, Bernal DO, Lui RN, Wijarnpreecha K, Abou-Alfa GK, Wallace MB, Roberts LR, Singal AG, Yang JD. Cancer. 2026 Jan 1;132(1):e70245. doi: 10.1002/cncr.70245.
3. Impact of pre-transplant immune checkpoint inhibitor use on post-transplant outcomes in HCC: A systematic review and individual patient data meta-analysis. Rezaee-Zavareh MS, Yeo YH, Wang T, Guo Z, Tabrizian P, Ward SC, Barakat F, Hassanein TI, Dave S, Ajmera V, Bhoori S, Mazzaferro V, Chascsa DMH, Liu MC, Aby ES, Lake JR, Sogbe M, Sangro B, Abdelrahim M, Esmail A, Schmderer A, Chouik Y, Rudolph M, Sohal D, Giudicelli H, Allaire M, Akce M, Guadagno J, Tow CY, Massoumi H, De Simone P, Kang E, Gartrell RD, Martinez M, Paz-Fumagalli R, Toskich BB, Tran NH, Solino GA, Poltronieri Pacheco DM, Kalman RS, Agopian VG, Mehta N, Parikh ND, Singal AG, Yang JD. J Hepatol. 2025 Jan;82(1):107.

Multidisciplinary Horizons: From Immune Checkpoint Blockade to Liver Transplantation

Ju Dong Yang

Cedars-Sinai Medical Center, USA

Liver transplantation remains a definitive therapy for patients at high risk of liver-related mortality, including those with hepatocellular carcinoma, as it addresses both the malignancy and the underlying liver disease while improving long-term and recurrence-free outcomes. Because donor organs are scarce and recurrence risk rises with more advanced tumors, transplantation is typically limited to early-stage disease. For patients beyond conventional transplant criteria such as the Milan criteria, locoregional therapies can be used to reduce tumor burden and achieve eligibility, with variable success; outcomes are more favorable in patients with lower tumor burden, whereas larger or more advanced tumors are less likely to be successfully downstaged, underscoring the need for improved strategies. In this context, immune checkpoint inhibitors have emerged as an important therapeutic option, demonstrating efficacy in advanced disease and generating interest in their application at earlier stages. Combinations such as atezolizumab with bevacizumab and durvalumab with tremelimumab have shown meaningful activity, and ongoing investigations continue to expand their potential role. Emerging data also suggest that combining systemic immunotherapy with locoregional approaches may enhance treatment response and facilitate downstaging, as reflected in recent late-phase trials evaluating multimodal regimens. Established locoregional treatments, including transarterial chemoembolization, radioembolization, and ablation, remain central to disease control and transplant bridging, helping to limit progression and reduce waitlist dropout. The integration of immunotherapy into this framework offers a promising avenue to further expand transplant candidacy. However, its use in the pre-transplant setting raises important concerns, particularly the risk of allograft rejection due to immune activation. Early reports indicate that rejection rates may be comparable to those seen without immunotherapy, but the evidence remains limited, and multiple variables—including treatment timing, duration, and immunosuppression strategies—likely influence outcomes. As a result, carefully designed prospective studies are needed to better define the safety and efficacy of these approaches and to guide optimal patient selection, with the ultimate goal of safely broadening access to curative transplantation for patients with more advanced disease.

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MINI SPECIAL INTEREST GROUP 2

The KASL Abdominal Ultrasound Study Group

Chair
Moon Young Kim (Yonsei Univ. Wonju)





Jeong-Ju Yoo
Soonchunhyang University

Self Introduction

Prof. Jeong-Ju Yoo, currently an Associate Professor in the Department of Hepatology, Internal Medicine, at Soonchunhyang University College of Medicine, Soonchunhyang University Bucheon Hospital, Korea.

She completed her medical education at Seoul National University College of Medicine, earning her M.D. degree in 2009, followed by a Master's (2015) and Ph.D. (2019) in Internal Medicine from the same institution.

Her professional career includes medical internship (2009-2010) and residency in Internal Medicine (2010-2014) at Seoul National University Hospital. She was also a Research Fellow at the Department of Internal Medicine and Liver Research Institute at Seoul National University College of Medicine (2014-2015). In 2016, She joined Soonchunhyang University Bucheon Hospital as an Assistant Professor, and She has been serving as an Associate Professor since 2024.

Her clinical and research interests primarily focus on hepatology, particularly viral hepatitis, liver cirrhosis, hepatocellular carcinoma, liver fibrosis, and metabolic liver diseases. She has published numerous peer-reviewed articles and have received multiple awards for excellence in research and presentations, including Best Presentation Awards at major academic conferences.

Currently, she actively participate in several academic societies, serving on various committees, including the Korean Association for the Study of the Liver, Korean Liver Cancer Association, and Korean Society of Gastroenterology.

Research Interests

- Hepatocellular Carcinoma (HCC): Pathogenesis, Therapeutic Strategies, and Prognostic Factors
- Metabolic Liver Diseases: Non-Alcoholic Fatty Liver Disease (NAFLD) and Metabolic-Associated Fatty Liver Disease (MAFLD)
- Liver Fibrosis and Portal Hypertension: Non-Invasive Diagnostic Methods and Clinical Management
- Clinical Applications of Ultrasound and Elastography in Liver Disease
- Prognostic Modeling and Biomarkers for Chronic Liver Diseases
- Viral Hepatitis Management and Antiviral Therapies

Representative Publications

1. Jeong-Ju Yoo et al. "Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex." Journal of Hepatology, 2019;70:847-854.
2. Jeong-Ju Yoo et al. "Validation of the Texas Hepatocellular Carcinoma Risk Index Predictive Model for Hepatocellular Carcinoma in Asian Cohort." Clinical Gastroenterology and Hepatology, 2024 Mar 13; S1542-3565(24)00255-6.
3. Jeong-Ju Yoo et al. "Risk of dyslipidemia in chronic hepatitis B patients taking tenofovir alafenamide: a systematic review and meta-analysis." Hepatology International, 2023 Apr 26.
4. Jeong-Ju Yoo et al. "Efficacy of antiviral prophylaxis in HBsAg-negative, anti-HBc positive patients undergoing hematopoietic stem cell transplantation." Liver International, 2015 Dec;35(12):2530-2536.
5. Jeong-Ju Yoo et al. "Long-term prognosis and the need for histologic assessment of chronic hepatitis B in the serological immune-tolerant phase." Clinical and Molecular Hepatology, 2023 Apr;29(2):482-495.

Ultrasound Assessment of Liver Fibrosis: Comparison with 2D Shear Wave Elastography and FibroScan

Jeong-Ju Yoo Soonchunhyang University

The non-invasive assessment of liver fibrosis has become a cornerstone in the management of chronic liver diseases, shifting the clinical paradigm from invasive biopsy to imaging-based diagnostics. Among the various modalities available, Vibration-Controlled Transient Elastography (VCTE, FibroScan) and 2D Shear Wave Elastography (2D-SWE) are the most widely utilized in clinical practice. FibroScan, as the first widely validated tool, offers a robust body of evidence across diverse etiologies including viral hepatitis and metabolic dysfunction-associated steatotic liver disease (MASLD). However, its primary limitation lies in the lack of real-time B-mode imaging, which can lead to technical challenges in patients with obesity, ascites, or narrow intercostal spaces.

In contrast, 2D-SWE is integrated into conventional ultrasound systems, allowing for anatomical visualization and the precise placement of a Region of Interest (ROI) within the liver parenchyma. This real-time guidance enables clinicians to avoid large vessels, gallbladder, or focal lesions, significantly improving technical success rates and reliability. Recent comparative studies and meta-analyses suggest that 2D-SWE provides diagnostic accuracy for significant fibrosis and cirrhosis that is at least comparable to, if not slightly superior to, VCTE. Specifically, 2D-SWE tends to exhibit better performance in discriminating early-stage fibrosis and offers higher feasibility in difficult-to-scan patients.

Despite these advantages, VCTE remains a highly standardized and rapid screening tool with well-established cut-off values for longitudinal follow-up. The choice between these two modalities should be guided by the patient's clinical context, the availability of equipment, and the need for a comprehensive morphological assessment of the liver. This lecture provides a detailed comparison of the technical principles, diagnostic performance, and practical considerations for both 2D-SWE and FibroScan in the modern hepatology landscape.

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ARTIFICIAL INTELLIGENCE (AI) IN HEPATOLOGY

Chair

Chang Hyeong Lee (Daegu Catholic Univ.)

Kang Mo Kim (Univ. of Ulsan)





Junil Kim
Soongsil University

Self Introduction

Prof. Junil Kim is a Professor of the Department of Bioinformatics, Soongsil University College of Natural Science and is currently holding a position of Director of the Institute for Biological Systems.

Prof. Kim graduated from Interdisciplinary Graduate Program in Bioinformatics at Seoul National University with his master's degree in 2008 and received his Ph.D. degree in systems biology from Korea Advanced Institute of Science and Technology (KAIST) in 2014.

Since 2022, Prof. Kim has been taking a number of roles, including committee member of the Korean Society of Bioinformatics (2022-Present), the Korean Society of Molecular and Cellular Biology (2022-Present), Korea Genome Organization (2023-Present), and the Korean Society for Biochemistry and Molecular Biology (2024-Present).

Research Interests

- Piecing Together Jigsaw Puzzle and Single Cell Dynamics in Time-Space Continuum Using AI
- Evolutionary Design Principle of Biomolecular Regulatory Networks
- Predicting Phenotypes of the Bio-Organisms from Genomic Information and Their Interactions

Representative Publications

1. Sooyeon Yoo*, Kwanghoon Lee*, Junseo Seo*, Hwisoo Choi, Seong-Ik Kim, Junyoung Chang, Yu-Mi Shim, Junil Kim**, Jae-Kyung Won**, Sung-Hye Park**, "Spatiotemporal resolved single-nucleus transcriptomics reveals cellular and regional vulnerability in the midbrain in Parkinson's disease", Accepted for publication in Signal Transduction and Targeted Therapy (IF: 52.7), May 2026
2. Hye Jeong Yun*, Chan Ho Park*, Dahye Yun*, Hye-Ri Shin*, Jeong Dong Lee, Changhee Park, Kiyeon Kim, Heejun Shim, Hyejin Sim, Se Min Kim, Min Jung Kim, Ji Won Park, Seung-Bum Ryoo, Yoojoo Lim, Seung-Yong Jeong, Kyu Joo Park, Tae-You Kim, Junil Kim**, Jae-Kyung Won**, and Sae-Won Han**, "CEBPB expression in tumor cells drives immune evasion in colorectal cancer via CTLA4 upregulation in T cells Cancer Communications", Cancer Communications (IF: 24.9), Vol. 46, 0013, 24 Feb 2026
3. Chae Won Kim*, Heewon Park*, Dohyeon Kim, Yuchang Seong, Minhae Kwon**, and Junil Kim**, "CluVar: Clustering of Variants using autoencoder for inferring cancer subclones from single cell RNA sequencing data", Briefings in Bioinformatics, Vol. 26, Issue 6, bbaf603, 15 Nov 2025
4. Junil Kim, Michaela Mrugala Rothová, Esha Madan, Siyeon Rhee, Guangzheng Weng, António Palma, Linbu Liao, Eyal David, Ido Amit, Morteza Chalabi Hajkarim, Vignesh Vudatha, Andrés Gutiérrez-García, Eduardo Moreno, Robert Winn, Jose Trevino, Paul B. Fisher, Joshua M. Brickman, Rajan Gogna, Kyoung Jae Won, "Neighbor-specific gene expression revealed from physically interacting cells during mouse embryonic development", PNAS (IF: 12.777), Vol. 120, Issue 2, e22053711120, 3 Jan. 2023
5. Dongha Kim*, Junil Kim*, Young Suk Yu, Yong Ryoul Kim, Sung-hee Baek, Kyoung-Jae Won, "Systemic approaches using single cell transcriptome reveal that C/EBP γ regulates autophagy under amino acid starved condition", Nucleic Acids Research (IF: 19.160), Vol. 50, Issue 13, 7298-7309, 22 July 2022 (*Co-first authors, **Corresponding authors)

Decoding Tumor Microenvironment Heterogeneity and Therapeutic Response via Advanced Transformer Modeling of Spatial Transcriptomics

Junil Kim Soongsil University

Spatial transcriptomics (ST) has revolutionized our understanding of tissue architecture by profiling gene expression within its native context. However, capturing complex spatial dependencies and directly linking these architectural features to functional drug responses remain critical challenges. In this presentation, I introduce two complementary, transformer-based frameworks designed to scale from foundational spatial modeling to interpretable therapeutic prediction within the tumor microenvironment (TME).

First, I introduce NicheLLM, a transformer-based foundation model specifically engineered for ST data. Leveraging high-resolution Xenium data across multiple cancer types (lung, breast, pancreatic, and ovarian), NicheLLM learns spatially informed representations by predicting local neighborhood structures and spatial density. Without relying on explicit coordinates, it effectively captures niche-driven transcriptional variability and uncovers cell-cell communication signatures associated with tumor heterogeneity.

Second, to translate these spatial architectures into clinical insights, I introduce DrugGTN, an interpretable graph transformer framework. DrugGTN bridges the gap between ST data and external drug-perturbation priors (LINCS/CMAP) by converting tissue slides into segment graphs. A graph transformer encoder learns contextualized tissue-state representations, mapping them to drug-induced program shifts to calculate a sample-level 'ResponseScore' that integrates immune activation, suppressive burden, and spatial accessibility. Validated across retrospective HCC, RCC, and Visium cohorts, StructRx demonstrates that spatial accessibility acts as a critical, context-dependent modifier of drug efficacy, especially in immune-exclusion settings.

Together, these frameworks provide a robust, scalable paradigm for leveraging spatial transcriptomics—moving from foundational decoding of TME landscapes to the precise, interpretable prediction of microenvironmental drug responses.



Sung Hak Lee

The Catholic University of Korea

Self Introduction

Prof. Sung Hak Lee currently works as a professor at the department of hospital pathology at Seoul St. Mary's hospital (2022-Present)

Prof. Lee received his Doctor of Medicine from The Catholic University of Korea in 2002. He received his Ph.D. from The Catholic University of Korea in 2013. Dr. Lee completed his residency in pathology at the Catholic Medical Center.

After the program, he was an assistant professor, department of hospital pathology at Seoul St. Mary's hospital (2014-2018). Then he was an associate professor in the same institute (2018-2021). Prior to his professorship, he worked as a visiting scholar at Center for biomedical informatics and biostatistics (CB2), University of Arizona and Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic (2017-2018).

Research Interests

- GI and Hepatobiliary Tract Pathology
- Artificial Intelligence in Computational Pathology
- Bioinformatics Analysis in Molecular Pathology

Representative Publications

1. Spatial dissection of tumour microenvironments in gastric cancers reveals the immunosuppressive crosstalk between CCL2+ fibroblasts and STAT3-activated macrophages. *Gut*. 2025 Apr 7;74(5):714-727.
2. Artificial Intelligence Applications in Image-Based Diagnosis of Early Esophageal and Gastric Neoplasms. *Gastroenterology*. 2025 Aug;169(3):396-415.e2.
3. Adaptive compression framework for giga-pixel whole slide images. *Nat Commun*. 2025 Dec 3;17(1):207.
4. Deep learning-based prediction of molecular cancer biomarkers from tissue slides: A new tool for precision oncology. *Clin Mol Hepatol*. 2022 Oct;28(4):754-772.
5. Deep Gaussian process with uncertainty estimation for microsatellite instability and immunotherapy response prediction from histology. *NPJ Digit Med*. 2025 May 19;8(1):294.

Deep Learning and Digital Pathology in HCC: From Diagnosis to Prognosis

Sung Hak Lee

The Catholic University of Korea

Pathology is central to the diagnosis, classification, prognostication, and treatment planning of hepatocellular carcinoma (HCC). With the implementation of digital pathology, conventional glass slides can now be converted into whole-slide images (WSIs), enabling deep learning-based computational analysis of routine hematoxylin and eosin-stained tissue sections. These technologies have the potential to enhance the role of pathologists by providing reproducible diagnostic support, quantitative image analysis, biomarker prediction, and prognostic stratification.

The field is now shifting from task-specific CNN models toward pathology foundation models and multimodal artificial intelligence. Unlike conventional CNNs, foundation models learn generalizable tissue representations from large-scale histopathology datasets and can be adapted to multiple downstream tasks, including tumor classification, biomarker prediction, prognosis estimation, and slide retrieval. In the future, multimodal models integrating pathology with radiology, clinical data, genomics, transcriptomics, and treatment information may provide a more comprehensive understanding of HCC biology and support precision oncology.

In conclusion, deep learning and digital pathology are reshaping HCC pathology from diagnosis to prognosis. Robust, interpretable, and multimodal AI systems may ultimately support more accurate diagnosis, refined prognostic stratification, and personalized treatment decisions in HCC.



Seng Chan You
Yonsei University

Self Introduction

Dr. Seng Chan You attained his Ph.D. from Ajou University's Department of Biomedical Informatics. He immersed himself in the Observational Health Data Sciences and Informatics (OHDSI) community, earning recognition through the "Best Community Contribution Award for Clinical Evidence Generation" at the 2017 OHDSI symposium.

Post-Ph.D., Dr. You launched his career at Yonsei University College of Medicine, acquiring M.D. and M.S. degrees in Internal Medicine. Transitioning through the Department of Preventive Medicine and Public Health, he's now an associate professor in Biomedical System Informatics. His exceptional research was acknowledged with the 2021 Young Scientist Award from the Wunsch Medical Award, notably for his international study comparing ticagrelor and clopidogrel across the OHDSI network. In 2024, Dr. You was appointed as an Associate Editor for The Journal of the American College of Cardiology (JACC).

Dr. You's interests span medical big data, A.I., and digital therapeutics. His commitment to both OHDSI and developing the Common Data Model (CDM) in the Korean medical society remains unwavering.

Research Interests

Medical Big Data, A.I., and Digital Therapeutics

Representative Publications

1. Song JW, Park J, ..., You SC. Large Language Model Assistant for Emergency Department Discharge Documentation. JAMA Network Open vol 8(10) e253842, 2025 Oct.
2. Cho S, Eom S, ..., You SC, Hee Tae Yu, Boyoung Joung, Artificial intelligence–derived electrocardiographic aging and risk of atrial fibrillation: a multi-national study, European Heart Journal Vol 46(9), Pages 839–852, 1 2025 March 1.
3. You SC, Seo SI et al. Ranitidine Use and Incident Cancer in a Multinational Cohort. JAMA Netw Open 6(9):e2333495, 2023 Sep 5.
4. You SC et al. Comprehensive Comparative Effectiveness and Safety of First-Line β -Blocker Monotherapy in Hypertensive Patients: A Large-Scale Multicenter Observational Study. HYPERTENSION Vol 77(5) 1528-1538. 2021 May.
5. You SC et al. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. JAMA. 324(16):1640-1650, 2020 Oct 27.

Multimodal AI and Large Language Models for Cancer Research

Seng Chan You

Yonsei University

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SPECIAL INTEREST GROUP 2

The KASL Alcohol-Related Problem Study Group

Chairs

Jae Young Jang (Soonchunhyang Univ.)

Wonhyo Seo (Ewha Womans Univ.)





Heechul Nam
The Catholic University of Korea

Self Introduction

Prof. Heechul Nam is an Associate Professor of Internal Medicine at The Catholic University of Korea, where he also received his medical degree and completed his residency. Currently, he serves on the Guideline and External Affairs Committees of KASL, and is an editorial board member for the Journal of Liver Cancer.

Research Interests

HCC, HBV, ALD

Representative Publications

1. Nam H, Kim DY, Kim DY, Kim JH, Kim CW, et al. Development and validation of a risk prediction model for patients with hepatocellular carcinoma receiving atezolizumab-bevacizumab. *Hepatology*. 2026 May 1;83(5):1098-1110.
2. Nam H, Sung PS, Lee SW, Song DS, Kwon JH, Jang JW, et al. Incorporating ALBI Grade with Geriatric Nutritional Risk Index Enhances Hepatocellular Carcinoma Risk Stratification. *Liver Cancer* 2024;1-18.
3. Nam H, Lee J, Han JW, Lee SK, Yang H, Lee HL, et al. Analysis of Immune-Related Adverse Events of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicentre Cohort Study. *Liver Cancer* 2024;13:413-425.
4. Nam H, Lee SW, Kwon JH, Lee HL, Yoo SH, Kim HY, et al. Prediction of Hepatocellular Carcinoma by On-Therapy Response of Noninvasive Fibrosis Markers in Chronic Hepatitis B. *Am J Gastroenterol* 2021;116:1657-1666.
5. Nam H, Lim JH, Kim TW, Kim EN, Oum SJ, Bae SH, et al. Extracellular Superoxide Dismutase Attenuates Hepatic Oxidative Stress in Nonalcoholic Fatty Liver Disease through the Adenosine Monophosphate-Activated Protein Kinase Activation. *Antioxidants (Basel)* 2023;12.

Update on Clinical Trial Design and Endpoints in Alcohol-Associated Liver Disease

Heechul Nam *The Catholic University of Korea*

Introduction

Alcohol-associated liver disease (ALD) remains one of the leading causes of liver-related morbidity and mortality worldwide. The recent transition in steatotic liver disease nomenclature reflects a critical paradigm shift in hepatology, moving away from stigmatizing terms toward a more accurate pathophysiological classification. As detailed in the publication Designing clinical trials to address alcohol use and alcohol-associated liver disease: an expert panel consensus statement, the newly introduced category of metabolic dysfunction and alcohol-associated liver disease (MetALD) addresses the substantial overlap between cardiometabolic risk factors and alcohol consumption. The diagnostic criteria for MetALD specifically include individuals with metabolic dysfunction who consume 140 to 350 grams of alcohol per week for women, and 210 to 420 grams per week for men.¹ The recognition of MetALD is vital for clinical trial design, as the “dual-hit” synergy of metabolic dysfunction and alcohol toxicity significantly accelerates liver fibrosis progression compared to either factor alone.²

Overcoming the Limitations of Traditional Endpoints

Historically, clinical trials for severe alcohol-associated hepatitis (sAH) have relied heavily on short-term outcomes, such as 28-day or 90-day mortality, as their primary endpoints.^{3,4} However, the exclusive reliance on mortality fails to capture the comprehensive clinical burden of the disease.

To address this critical unmet need, researchers in the landmark study Natural history and development of a novel composite endpoint in patients with alcohol-associated hepatitis: Data from a prospective multicenter study evaluated a large cohort of AH patients to establish a multidimensional metric. They introduced the AlcHepNet composite endpoint, which captures major adverse liver outcomes (MALOs) over a 180-day period. This 6-part composite index incorporates all-cause mortality, liver transplantation, the new onset or worsening of hepatic decompensation (such as ascites or encephalopathy), liver-related hospital admissions, an increase in the Model for End-Stage Liver Disease (MELD) score of $\geq$ 5 points, and early return to drinking.⁵ Notably, formally including “return to drinking” elevates alcohol relapse from a mere covariate to a definitive indicator of therapeutic failure, underscoring the necessity of treating the underlying alcohol use disorder (AUD) concurrently with the liver injury.

Integration of Objective Biomarkers and Non-Invasive Tests

The subjective nature of self-reported alcohol consumption has historically compromised the integrity of ALD clinical trials due to severe recall bias and underreporting. In the comprehensive review Clinical trial design, biomarkers and end points in metabolic and alcohol-related liver disease, the integration of objective biomarkers is strongly emphasized to enhance diagnostic accuracy and trial reliability. Phosphatidylethanol (PEth), a direct alcohol metabolite, has emerged as the preferred objective monitor, accurately reflecting alcohol consumption over the preceding 2 to 4 weeks.²

Furthermore, while non-invasive tests (NITs) such as Liver Stiffness Measurement (LSM) by vibration-controlled transient elastography (VCTE) are increasingly utilized to stage fibrosis, their application in ALD trials requires careful interpretation. Acute inflammation and short-term alcohol abstinence can induce a rapid decline in liver stiffness within days to weeks. This dynamic change acts as a significant confounding variable, making it difficult to distinguish true anti-fibrotic drug efficacy from the spontaneous resolution of inflammation. Therefore, multimodal assessments combining imaging and serum-based biomarkers are recommended to properly evaluate therapeutic responses.^{2,6}

Emerging Therapeutic Pipelines

The therapeutic pipeline for ALD is expanding toward targeted mechanisms such as the gut-liver axis and epigenetic modulation. Fecal microbiota transplantation (FMT) has emerged as a promising strategy to correct alcohol-induced dysbiosis, showing higher short-term survival (at 1 and 3 months) in sAH patients ineligible for steroids.³ Another breakthrough candidate is larsucosterol (DUR-928), a first-in-class endogenous sulfated oxysterol that functions as an epigenetic modulator by inhibiting DNA methyltransferases, thereby reducing lipotoxicity, inflammation, and cell death.⁷ The Phase 2b AHFIRM trial demonstrated clinically meaningful trends; specifically, subgroup analysis of the U.S. cohort showed a dramatic 57% to 58% reduction in 90-day mortality compared to placebo.

Perhaps the most revolutionary advancement in the management of MetALD and AUD involves the utilization of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). GLP-1 RAs correct metabolic dysfunction and also act on central reward pathways to reduce alcohol craving and consumption. A recent landmark cohort study of over 600,000 U.S. veterans with type 2 diabetes demonstrated that the initiation of GLP-1 RAs is associated with a significantly reduced risk of incident AUD (HR 0.82) when compared to SGLT-2 inhibitors.⁸ Similarly, a randomized clinical trial showed that low-dose semaglutide significantly reduced alcohol consumption and craving in patients with AUD.⁹ Consequently, GLP-1 RAs offer a promising “dual-target” therapeutic strategy for the complex pathophysiology of MetALD.

Conclusion

The modernization of clinical trials in ALD and MetALD depends on the precise stratification of patients utilizing updated nomenclature, the adoption of the multidimensional AlcHepNet composite endpoint,

and the rigorous application of objective biomarkers like PEth. As the therapeutic landscape expands to include epigenetic modulators and GLP-1 RAs, successful drug development will fundamentally require an integrated, multidisciplinary framework combining hepatology and addiction medicine

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4. Rady ED, Anouti A, Mitchell MC, Cotter TG. Current Clinical Trials for Alcohol-Associated Hepatitis. *Am J Pathol* 2026;196:182-191.
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6. Lee BP, Witkiewitz K, Mellinger J, Anania FA, Bataller R, Cotter TG, et al. Designing clinical trials to address alcohol use and alcohol-associated liver disease: an expert panel Consensus Statement. *Nat Rev Gastroenterol Hepatol* 2024;21:626-645.
7. Shiffman M, Da B, Goel A, Kwong A, Stein L, Moreno C, et al. Larsucosterol for the Treatment of Alcohol-Associated Hepatitis. *NEJM Evid* 2025;4:EVIDoa2400243.
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9. Hendershot CS, Bremmer MP, Paladino MB, Kostantinis G, Gilmore TA, Sullivan NR, et al. Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 2025;82:395-405.



Wonhyo Seo
Ewha Womans University

Self Introduction

Wonhyo Seo is a professor in the College of Pharmacy at Ewha Womans University. He received his D.V.M. degree from Kyungpook National University in 2008 and earned his Ph.D. in science from KAIST in 2016. He subsequently conducted postdoctoral research at the National Institutes of Health. Since 2021, he has been serving as a faculty member at Ewha Womans University's College of Pharmacy.

Research Interests

Liver Fibrosis, Alcoholic Liver Disease, Animal Model Development, LLM-Based Gene Prediction System

Representative Publications

1. Seol Hee Park, Seo Bhin Park, Jisoo Kang, Ga-Young Kim, Yunseo Bong, Minkyung Gu, Sumin Shin, Young-Sun Lee, Wonhyo Seo, Gao Bin. Multiomics Characterization of an Alcohol-induced Hepatocellular Carcinoma Mouse Model. *Lab Animal* (2026) doi: 10.1038/s41684-026-01724-7
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3. Michaela Jeong, Sumin Shin, Gyeongseok Lee, Yeji Lee, Seo Bhin Park, Jisoo Kang, Young-Sun Lee, Wonhyo Seo, Hyukjin Lee. Therapeutic gene silencing of GTSE1 with engineered lipid nanoparticles enables the treatment of liver fibrosis. *Journal of Controlled Release* (2024) doi: 10.1016/j.jconrel.2024.08.012.
4. Seojeong Park, Seohui Hwang, Jingyang Sun, Naeun Sheen, Sumin Shin, Tae Hyun Kim, Wonhyo Seo, Jae-Sang Ryu, and Youngjoo Kwon. A novel A2a adenosine receptor inhibitor effectively mitigates hepatic fibrosis in a metabolic dysfunction-associated steatohepatitis mouse model. *International Journal of Biological Sciences* (2024) doi: 10.7150/ijbs.92371

Immune Dysfunction in Alcohol-Associated Liver Disease

Wonhyo Seo *Ewha Womans University*

Alcohol-associated liver disease (ALD) is not merely a consequence of the direct hepatotoxic effects of ethanol and its metabolite acetaldehyde, but rather a progressive immune-disruptive disorder driven by aberrant crosstalk among hepatocytes, Kupffer cells, neutrophils, lymphocytes, gut-derived signals, as well as systemic inflammatory mediators. Despite Toll-like receptor 4 signaling and inflammasome activation are well-established contributors to alcohol-induced liver injury, these pathways alone are insufficient to fully explain the complexity of cell death mechanisms and the pathological hallmarks of ALD. Emerging evidence indicates that chronic alcohol exposure induces sterile inflammation through damage-associated molecular patterns, mitochondrial stress, extracellular vesicle-mediated signaling, and inter-organ communication along the gut-liver axis. These processes activate hepatic immune cells, particularly neutrophils and resident macrophages (Kupffer cells), while simultaneously modulat-ing their survival and functional states, thereby reshaping the hepatic microenvironment. Mechanisti-cally, hepatocyte-derived exosomal mitochondrial double-stranded RNA has been shown to activate Toll-like receptor 3 signaling in Kupffer cells, promoting IL-17A-driven inflammatory responses and link-ing hepatocyte injury to innate immune activation. At the level of innate immune sensing, alcohol co-operates with interferon signaling to trigger Z-DNA-binding protein 1 (ZBP1)-dependent inflammatory cell death, including pyroptosis, apoptosis, and necroptosis, via ADAR1 suppression, JNK activation, and Z-RNA formation. In parallel, alcohol-induced catecholamine signaling enhances growth differentiation factor 15 expression, which promotes Kupffer cell apoptosis and may serve as a compensatory mecha-nism to limit excessive inflammation. Recent studies further demonstrate that binge alcohol exposure induces vesicular glutamate transporter 3 (VGLUT3)-dependent glutamate secretion from perivenous hepatocytes, activating mGluR5/NOX2 signaling in Kupffer cells and amplifying hepatic inflammation.

Collectively, these findings indicate that immune dysfunction in ALD is characterized by the coexistence of excessive inflammatory activation and impaired immune regulation. This dual imbalance contributes to hepatocellular injury, fibrosis progression, increased susceptibility to infection, and ultimately hepa-tocarcinogenesis. A deeper understanding of these immune networks provides a mechanistic founda-tion for the development of targeted immunomodulatory therapies in ALD.



Ki-Tae Suk
Hallym University

Self Introduction

1993.02-1999 Medical Degree, Yonsei University, Wonju College of Medicine, Korea
2003.02-2015 Master of Medicine, Graduate School, Yonsei University, Seoul, Korea
2010.08-2012 Doctor of Medicine, Graduate School, Yonsei University, Seoul, Korea
2014.09-2016 Post-Doctor Research Scholar, Medicine, Columbia University, New York, USA
2016-09 Professor, Hallym University, Chuncheon, Korea

Research Interests

Liver Disease: Cirrhosis and Hepatocellular Carcinoma
Microbiota: Metabolites of Microbiome, Post-Bioitics, Multi-omics Associated Mechanism
Pharmabiotics: Therapeutics and Diagnostic Marker

Representative Publications

1. Eom JA, Park IG, Hyun JY, Lee NY, Kwon GH, Yoon SJ, Won SM, Ham YL, Lee KJ, Han SH, Yang DH, Kim DJ, Suk KT. Pharmabiotics, *Phocaeicola dorei*, ameliorates cholestatic liver fibrosis by alleviating macrophage efferocytosis of neutrophils. *Nat Commun.* 2026 May 17.
2. Vázquez-Castellanos JF, Yoon SJ, Won SM, Raes J, Kwon HC, Si J, Suk KT. Stage-dependent gut microbiome and functional signatures across the liver disease spectrum: an integrative multicohort study. *Gut.* 2026 Mar 23;gutjnl-2025-337436.
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4. Kang EJ, Cha MG, Kwon GH, Han SH, Yoon SJ, Lee SK, Ahn ME, Won SM, Ahn EH, Suk KT. *Akkermansia muciniphila* improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis. *Microbiome.* 2024 Sep 28;12(1):181.
5. Sharma SP, Gupta H, Kwon GH, Lee SY, Song SH, Kim JS, Park JH, Kim MJ, Yang DH, Park H, Won SM, Jeong JJ, Oh KK, Eom JA, Lee KJ, Yoon SJ, Ham YL, Baik GH, Kim DJ, Suk KT. Gut microbiome and metabolome signatures in liver cirrhosis-related complications. *Clin Mol Hepatol.* 2024 Oct;30(4):845-862.

Gut–Liver Axis in Alcohol-Associated Liver Disease:
Mechanistic Insights and Translational Implications

Ki-Tae Suk Hallym University

The growing recognition of the role of the gut microbiome’s impact on alcohol-related diseases, especially in alcohol-associated liver disease, emphasizes the need to understand molecular mechanisms involved in governing organ-organ communication in order to identify novel avenues to combat alcohol-related diseases. The gut-liver axis refers to the bidirectional communication and interaction between gut and liver. Intestinal microbiota play a pivotal role in maintaining homeostasis within the gut-liver axis and this axis plays a significant role in alcohol-associated liver disease. The intricate communication between intestine and liver involves communication between multiple cellular components in each organ that enable them to carry out their physiological functions. In this presentation, we focus on novel approaches to understanding how chronic alcohol exposure impacts the microbiome, and individual cells within the liver and intestine, as well as the impact of ethanol on the molecular machinery required for intra- and inter-organ communication.

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SPECIAL INTEREST GROUP 3

The KASL Steatotic Liver Disease Study Group

Novel Technologies in Steatotic Liver Disease (SLD) Research

Chairs

Yong Kyun Cho (Sungkyunkwan Univ.)

Jin-Woo Lee (Inha Univ.)





Murim Choi
Seoul National University

Self Introduction

Murim Choi is a Professor at the Department of Biomedical Sciences, Seoul National University College of Medicine. He graduated from Seoul National University (SNU), Seoul, Korea, majoring in Molecular Biology (BS and MS). During the Ph.D. course at Duke University, he studied cardiovascular system development in mice. In his postdoctoral training at Yale University, he studied human genetics, setting up a whole exome sequencing pipeline and applying it to various human diseases to identify causal genes. He received a K99/R00 grant for the postdoctoral work and was a recipient of the SNU Invitation Program for Distinguished Scholar grant. Since establishing his independent lab at SNU, he has been studying the genetic mechanisms of rare disease and complex trait initiation, progression, and phenotypic variability. In 2018, he was selected as a member of the Young Korean Academy of Science and Technology and is currently a Samsung Research Fellow. He is a Senior Editor for eLife and serves editor roles for Experimental Molecular Medicine and Molecules and Cells.

Research Interests

Murim Choi’s main scientific question is to elucidate the genetic mechanisms of human diseases. To address this, his expertise lies in the functional interpretation of human genetic variants using genomic and bioinformatic methodologies. His current approach combines developmental biology and genetics, shaped by the fact that most pediatric rare disease patients experience congenital problems. More recently, his group has undertaken common disease research. His group recently established a bioinformatic pipeline that allows screening of eQTL signals only functioning in the metabolic dysfunction-associated steatotic liver disease (MASLD) status and validated its utility. His lab has recently established protocols for advanced functional genomics approaches, including single-cell sequencing, saturation mutagenesis, modifier screening, perturbation screening, and cell tracing techniques, to understand the genetic mechanisms underlying disease progression. He has a strong interest in clinical and translational research, especially in elucidating genotype-phenotype relationships that may lead to human diseases.

Representative Publications

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MASH Pathogenesis through Single-Cell Analysis

Murim Choi *Seoul National University*

Genome-wide association study (GWAS) enabled us with novel genes and variants that are associated with common complex diseases. However, understanding true causal relationship of these variants with disease traits remain to be further clarified. Therefore, we propose to use expression quantitative trait loci (eQTL) approach in understanding common complex diseases, which we have improved to be used to identify disease- and individual-specific variants that are causal to the diseases. Using fatty liver as a model, I will present our recent findings on how genetic variants shape inter-individual heterogeneity in complex traits.



Yohan Kim
Sungkyunkwan University

Self Introduction

Prof. Yohan Kim is an Assistant Professor in the Department of Metabiohealth, School of Medicine, Sungkyunkwan University, where he leads the STAR (STem cell for Advanced Regeneration) Laboratory. His research focuses on human liver organoids and assembloids, regenerative medicine, liver biology, and disease modeling, with particular emphasis on human primary hepatocyte organoids and liver tissue engineering.

Prof. Hong graduated from Seoul National University College of Medicine with his medical degree in 1984 and completed his internship and residency at the Department of Surgery at Seoul National University Hospital, receiving his diploma in General Surgery in 1989.

Since joining Sungkyunkwan University in 2024, Prof. Kim has been actively involved in international collaborations and academic activities in the field of stem cells and organoid research. He currently serves as an academic committee member of the Korean Society for Stem Cell Research and contributes to several international scientific programs and workshops related to organoids, regenerative medicine, and advanced in vitro modeling systems.

Research Interests

Prof. Yohan Kim’s research interests focus on human organoid and assembloid technologies, regenerative medicine, stem cell biology, and advanced in vitro disease modeling systems. His laboratory is particularly interested in developing human primary hepatocyte organoids and multi-cellular liver assembloids that recapitulate human liver physiology and pathology.

His current research includes liver disease modeling, metabolic liver diseases, cholestatic liver diseases, liver fibrosis, and liver cancer using human organoid platforms. In addition, his group is actively developing vascularized and multi-organ assembloid systems for studying tissue-tissue interactions, aging, and regenerative mechanisms.

Representative Publications

- 1. Human assembloids recapitulate periportal liver tissue in vitro. *Nature*. 2026. 650 (8101), 438-449.
- 2. Liver organoids: Current advances and future applications for hepatology. *Clin Mol Hepatol*. 2024 Dec 31(Suppl):S327-S348.
- 3. Human chemically-derived hepatic progenitors (hCdHs) as a source of liver organoid generation: Application in regenerative medicine, disease modeling, and toxicology testing. *Biomaterials*. 2023 Oct:122360.
- 4. Adenine base editing and prime editing of chemically-derived hepatic progenitors rescues genetic liver disease. *Cell Stem Cell*. 2021 Sep 2;28(9):1614-1624.e5.
- 5. Small molecule-mediated reprogramming of human hepatocytes into bipotent progenitor cells. *J Hepatol*. 2019 Jan;70(1):97-107.

Human Periportal Liver Assembloids for in vitro Tissue Modeling

Yohan Kim *Sungkyunkwan University*

Recent advances in human organoid technology have transformed the field of biomedical research by enabling the generation of physiologically relevant in vitro tissue models. Compared with conventional two-dimensional culture systems and animal models, organoids provide improved structural organization, multicellular interactions, and human-specific functional properties. In particular, liver organoid technology has emerged as a promising platform for studying liver development, regeneration, disease progression, drug toxicity, and regenerative medicine. Nevertheless, current liver organoid systems still face substantial limitations in faithfully reproducing the complex multicellular architecture and zoned microenvironment of native human liver tissue.

The liver is composed of highly specialized epithelial and non-parenchymal cell populations that interact dynamically to regulate tissue homeostasis and regeneration. Among these microenvironments, the periportal region plays essential roles in bile transport, metabolic regulation, immune signaling, and tissue remodeling. Importantly, many cholangiopathies and fibrotic liver diseases initiate within or strongly affect the periportal niche. However, recreating this specialized multicellular architecture in vitro has remained challenging due to the limited availability and expandability of primary human hepatocytes and the difficulty of integrating multiple liver cell populations into a stable and functional tissue model.

Although recent studies have reported hepatocyte-like cells derived from pluripotent stem cells or expandable liver progenitors, these systems often exhibit immature phenotypes and fail to fully recapitulate adult hepatocyte functionality. Moreover, direct long-term expansion of primary adult human hepatocytes obtained from patient tissues has historically been difficult because hepatocytes rapidly lose their proliferative potential and mature hepatic characteristics under conventional in vitro culture conditions.

In this study, we established human hepatocyte organoids (h-HepOrgs) from patient-derived liver tissues and demonstrated their long-term expansion while preserving key functional and transcriptional characteristics of primary human hepatocytes. Using optimized culture conditions, the generated organoids maintained hepatocyte identity, donor-specific transcriptional signatures, bile canaliculi organization, and hepatic metabolic functions over prolonged culture periods. Importantly, these organoids retained clinically relevant hepatic features that are typically lost in conventional hepatocyte cultures.

Comprehensive molecular and functional analyses revealed that h-HepOrgs exhibit robust expression of mature hepatocyte markers, including ALB, HNF4A, ASGR1, and multiple cytochrome P450 enzymes. In addition, polarized bile canaliculi-like structures were maintained within the organoids, suggesting preservation of hepatocyte polarity and transport functions. Transcriptomic analyses further demonstrated that the expanded organoids closely resemble native liver tissue and maintain patient-specific molecular signatures, highlighting their potential utility for personalized medicine applications.

To further reconstruct the periportal liver niche, we integrated h-HepOrgs with cholangiocyte organoids and portal mesenchymal cells to generate multicellular periportal liver assembloids. These assembloids reproduced key structural and transcriptional features of the periportal liver region, including spatial cellular organization and epithelial-mesenchymal interactions. Notably, cholangiocytes and mesenchymal cells became incorporated into the hepatocyte parenchyma, enabling formation of a more physiologically relevant tissue architecture compared with conventional monocellular organoid systems.

The resulting periportal liver assembloids enabled investigation of multicellular signaling pathways involved in liver homeostasis and disease progression. Furthermore, this platform successfully modeled biliary fibrotic processes and ductular reaction-like phenotypes, which are difficult to reproduce using existing in vitro systems. Under fibrotic conditions, the assembloids exhibited expansion of cholangiocyte populations and activation of mesenchymal components, recapitulating pathological features observed in human cholestatic and fibrotic liver diseases.

Collectively, our study establishes a human periportal liver assembloid platform that recapitulates essential aspects of human liver tissue organization, cellular interactions, and pathological remodeling. This system provides a powerful human in vitro platform for studying liver biology, modeling complex liver diseases, evaluating therapeutic responses, and advancing regenerative medicine approaches. Furthermore, the development of physiologically relevant human liver assembloids may contribute to reducing reliance on animal models and accelerating the implementation of next-generation non-animal biomedical research platforms.

Key words: Organoids, Assembloids, Liver Assembloids

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3. Ramli MNB, et al. Human pluripotent stem cell-derived organoids as models of liver disease. *Gastroenterology*. 2020;159:1471–1486.
4. Takebe T, Wells JM. Organoids by design. *Science*. 2019;364:956–959.
5. Lei Y, et al. Human assembloids recapitulate periportal liver tissue in vitro. *Nature*. 2026 Feb;650(8101):438-449.

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Chulhong Kim
POSTECH

Self Introduction

Educational Background

2006.08-2009-05 Ph.D., Department of Biomedical Engineering, Washington University
1997.03-2004.02 B.Sc., Department of Electrical, Electronic and Computer Engineering, Kyungpook National University, Daegu, Republic of Korea

Professional Experience

2024.09-Present Head of School of Convergence Science and Technology
2023.06-Present Vice-Director of POSTECH-CATHOLIC BioMed Engineering
2023.06-Present Namgo Chair Professorship
2013.02-Present Professor of Department of Electrical Engineering, Convergence IT Engineering, and Mechanical Engineering, Pohang University of Science and Technology (POSTECH)
2010.08-2013.01 Assistant Professor of Department of Biomedical Engineering, University at Buffalo, The State University of New York
2009.05-2010.08 Postdoctoral Training, Department of Biomedical Engineering Washington University ()

Research Interests

- Multimodal Imaging: Photoacoustic, Ultrasound, Optical/AFM/RF, Magnetic
- High Performance Computing (CPU/GPU/DSP), Processing, and Artificial Intelligent in Healthcare
- Digital Healthcare
- Medical Device Commercialization

Representative Publications

1. D.Lee,..., D. Oh*, Y. Ahn*, and C. Kim*, "3D multiparametric ultrasound imaging of steatotic liver disease in a study with male rats", Nature Communications, Vol. 16, pp. 10226 (2025) IF: 15.7
2. J. Kim,..., [C. Liu*, C. Kim*, and Y. Ahn*], "Non-invasive Photoacoustic Cerebrovascular Monitoring of Early-stage Ischemic Strokes In Vivo", Advanced Science, Vol. 12, 2409361 (2025) IF: 14.3
3. E. Park,..., [J. Jang*, and C. Kim*], "Label-free mid-infrared dichroism-sensitive photoacoustic microscopy for histostructural analysis of engineered heart tissues", Light: Science and Applications, Vol. 15, pp. 49 (2026) IF: 23.4
4. C. Yoon,..., [C. Jung*, and C. Kim*], "Deep learning-based virtual staining, segmentation, and classification in label-free photoacoustic histology of human specimens", Light: Science and Applications, Vol. 13, 226 (2024) IF: 20.6
5. S. Cho, ..., C. Kim*, "An ultrasensitive and broadband transparent ultrasound transducer for ultrasound and photoacoustic imaging in-vivo", Nature Communications, Vol. 15, pp. 1444 (2024) IF: 16.6

Advances in SLD Diagnosis Using 3D Multiparametric Imaging

Chulhong Kim POSTECH

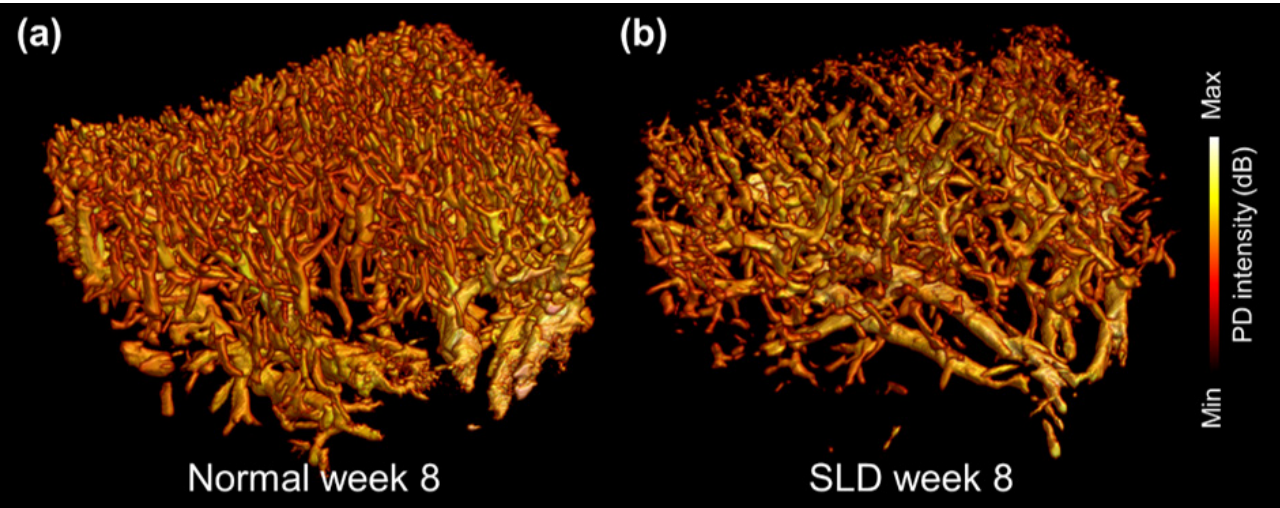
Ultrasound imaging (USI) is commonly used for diagnosing steatotic liver disease (SLD), the most prevalent chronic liver disease, but its utility is limited by variability and insufficient diagnostic performance. Given the hemodynamic disturbances induced by SLD, ultrafast Doppler imaging (UFD) can offer additional utility by revealing hepatic vascular changes. Here, we integrated UFD with attenuation imaging (ATI) and acoustic structure quantification (ASQ), both quantitative USI, to develop a 3D multiparametric hepatic USI system capable of in vivo scanning in rats, enabling longitudinal SLD monitoring.¹

Statement of Contribution/Methods

Using an 18 MHz, 128-element linear array transducer, 11-angle planewave transmissions were triggered by automated respiratory gating based on ultrasound (US), acquiring 600 US frames at a frame rate of 1000 HZ. This imaging procedure was repeated with mechanical probe translation to enable volumetric imaging. For UFD, 150 stable frames were processed into 2D power Doppler (PD) images via UFD processing. Subsequently, 3D PD and vessel skeleton images were reconstructed via vascular modeling of successive 2D PD slices, enabling quantification of hemodynamic and vascular-morphologic indices. For ATI, center frequency shifts across depth windows were extracted to evaluate the degree of attenuation. ASQ was performed by analyzing US signal amplitude distribution to assess deviations from the Rayleigh distribution. 8-week 3D USI monitoring was conducted in normal (n = 4), SLD progression (n = 4), and SLD recovery (n = 4) groups, with a single-time-point imaging in the SLD validation group (n = 25).

Results/Discussion

UFD visualized the 3D hepatic vascular network in rats with a resolution of 113 μm. This study is the first to longitudinally characterize overall vascular alterations under SLD conditions (Fig. 1a,b). 3D UFD revealed progressive vascular rarefaction and torsion during SLD progression, with a clear trend of restoration observed during SLD recovery. UFD indices were strongly associated with SLD progression. The all-around US score, integrating all US indices, exhibited excellent diagnostic performance, demonstrating that UFD can be harmonized with existing quantitative USI. The developed system can offer practical utility for SLD diagnosis/monitoring, and be applicable to a broad range of liver diseases.



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1. Lee, D., Heo, J., Mun, H. et al. 3D multiparametric ultrasound imaging of steatotic liver disease in a study with male rats. Nat Commun 16, 10226 (2025).

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KAHBPS SYMPOSIUM 1

Expanding Indications for Hepatic
Resection in HCC: Challenging the
Boundaries

Chairs
Hee Chul Yu (Jeonbuk National Univ.)
Jaehong Jeong (Soonchunhyang Univ.)





Young Chul Yoon
The Catholic University of Korea

Self Introduction

Biography

Professor Young Chul Yoon is a board certified hepato-biliary-pancreas surgeon and surgical oncologist. Dr. Yoon received his medical degree (2001) at Catholic University College of Medicine, Seoul, Korea. Presently, Dr. Yoon is director of hepato-biliary-pancreas surgery division and liver transplantation, Department of Surgery at the Incheon St. Mary's Hospital and the chief of Transplantation Center.

Dr. Yoon's primary clinical interest is in the treatment of hepato-biliary-pancreas cancers with an emphasis in conducting clinical trials as an active investigator. Dr. Yoon has authored about 20 published articles in international journals.

Professional Experience

- 2023.01-2023.12 Academic Director of the Korean Liver Transplantation Society
- 2020.01-Present Academic Director of Gyeongin Association of The Korean Association of Hepato-Biliary-Pancreatic Surgery
- 2021.03-Present Speciality Examination Director of The Korean Association of Hepato-Biliary-Pancreatic Surgery
- 2021.07-2022.06 Public Relation Director of The Korean Liver Cancer Association
- 2022.07-Present Editor of Korean Journal of Hepato-Biliary-Pancreatic Surgery
- 2025.03-Present Education Committee Chair of the Korean Liver Transplantation Society
- 2025.03-Present Information Committee Chair of Korean Association of Liver Surgery

Research Interests

HBP Surgery and Liver Transplantation

Representative Publications

1. Biliary Internal Stents and Biliary Complications in Adult Liver Transplantation. Young Chul Yoon, Kambiz Etesami, Navpreet Kaur, Juliet Emamaullee, Jim Kim, Shannon Zielsdorf, Aaron Ahearn, Linda Sher, Yuri Genyk, Yong Kyong Kwon. Transpl Proc. 2021 Jan-Feb;53(1):171-176.
2. Ultrasound Guided Intraoperative Liver Radiofrequency Ablation by Surgeons. Yoon YC. J Surg Ultrasound 2018; 5: 39-44.
3. Clinical analysis of recurrent hepatocellular carcinoma after living donor liver transplantation. Yoon YC, Hong TH, You YK, Kim DG. Clin Transplant 2013 Mar-Apr; 27(2).
4. Liver regeneration and factors influencing liver regeneration in donor and recipients of adult living donor liver transplantation using right lobe graft. Yoon YC, Park JH, Hong TH, You YK, Kim DG. J Korean Soc Transplant 2011 Jun;25(2).
5. Hepatic artery protection using a polyglycolic acid sheet during pancreaticoduodenectomy: A multicenter study. Jun Suh Lee, Young Chul Yoon , Tae Ho Hong , Yoo-Seok Yoon , Sung Eun Park. J Hepatobiliary Pancreat Sci. 2023 Oct 4.

Resection Beyond BCLC Guidelines: Surgical Outcomes in BCLC B or C

Young Chul Yoon *The Catholic University of Korea*

The Barcelona Clinic Liver Cancer classification has long served as the dominant framework for treatment allocation in hepatocellular carcinoma. Within this algorithm, surgical resection is generally confined to very early or early-stage disease, whereas intermediate-stage disease is directed toward transarterial chemoembolization and advanced-stage disease toward systemic therapy. Although this population-based model provides a useful prognostic map, its rigid application may underestimate the potential survival benefit of curative-intent surgery in carefully selected patients with BCLC B or C disease.

Intermediate-stage hepatocellular carcinoma is highly heterogeneous. Patients classified as BCLC B may range from those with limited multinodular disease and well-preserved liver function to those with bulky bilobar tumors, impaired hepatic reserve, and poor expected response to locoregional therapy. This heterogeneity explains why a uniform “TACE-only” strategy is increasingly inadequate. Subclassification systems such as the Bolondi criteria, as well as quantitative tools including tumor burden score, help identify a surgical window within BCLC B. Patients with preserved liver function, limited tumor burden, absence of severe portal hypertension, technically resectable anatomy, adequate future liver remnant, and favorable tumor biology may achieve long-term survival after resection. Retrospective studies and meta-analyses have consistently suggested superior overall survival for resection compared with TACE in selected BCLC B patients. However, these data must be interpreted cautiously because surgical cohorts are intrinsically enriched for fitter patients with lower tumor burden and better hepatic reserve. Propensity score matching and inverse probability weighting can reduce measured imbalance but cannot fully eliminate residual confounding. Therefore, the current evidence supports selective resection, not blanket surgical expansion for all BCLC B patients.

The role of surgery in BCLC C disease is most relevant in hepatocellular carcinoma with macrovascular invasion, particularly portal vein tumor thrombosis. While macrovascular invasion has traditionally been regarded as a contraindication to surgery, accumulating Asian data suggest that the extent of vascular invasion is critical. Resection may provide meaningful survival benefit in selected patients with segmental or sectoral portal vein tumor thrombosis, especially Vp1 or Vp2 disease, and in some carefully chosen Vp3 cases when complete anatomical resection is feasible. In contrast, main portal trunk involvement,

superior mesenteric vein extension, uncontrolled extrahepatic spread, or poor hepatic reserve generally remain contraindications to upfront surgery. The practical message is that portal vein tumor thrombosis should not be treated as a single biological entity; the anatomic level of invasion, liver function, tumor burden, and systemic disease status must be integrated.

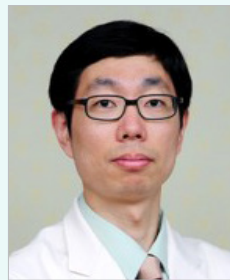
Modern systemic therapy has also changed the concept of resectability. Immune checkpoint inhibitor–based combinations and tyrosine kinase inhibitor–based regimens can induce meaningful tumor response in a subset of initially unresectable patients. In this setting, response to systemic therapy functions as a biological selection test. Patients who demonstrate sustained radiologic response, no new extrahepatic disease, preserved performance status, and adequate liver reserve may become candidates for conversion surgery. This strategy shifts the treatment paradigm from static stage-based allocation toward dynamic biology-based decision-making.

In conclusion, BCLC guidelines should be understood as a map rather than a law. Surgical resection beyond conventional BCLC boundaries is not justified for all intermediate or advanced hepatocellular carcinoma patients, but it should be actively considered in selected cases. The ideal candidates are those with technically complete resectability, preserved liver function, low tumor burden, favorable tumor biology, limited vascular invasion, and acceptable operative risk. Future treatment allocation should move beyond stage labels alone and incorporate anatomy, biology, and physiology. In expert centers, carefully selected resection for BCLC B disease, limited portal vein tumor thrombosis, and post-systemic therapy conversion cases may offer a chance of long-term survival that would otherwise be missed by strict adherence to standard algorithms.

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**Dongho Hyun***Ewha Womans University*

Self Introduction

Prof. Dongho Hyun is a Professor of the Department of Radiology, Sungkyunkwan University College of Medicine.

He graduated from Soonchunhyang University College of Medicine with his medical degree in 2003 and completed his internship and residency at the Department of Radiology at Asan Medical Center in 2011.

Since 2021, he has been taking a number of roles, including treasury secretary of KSIR (2021-2022), secretary of scientific committee of KSIR (2023-2024).

Research Interests

Transarterial Treatment of HCC, Portal Hypertension Intervention, Lymphatic Intervention

Representative Publications

1. Cha DI, Lee MW, Hyun D, Ahn SH, Jeong WK, Rhim H. Combined Transarterial Chemoembolization and Radiofrequency Ablation for Hepatocellular Carcinoma Infeasible for Ultrasound-Guided Percutaneous Radiofrequency Ablation: A Comparative Study with General Ultrasound-Guided Radiofrequency Ablation Outcomes. *Cancers (Basel)*. 2023 Oct 28;15(21):5193. doi: 10.3390/cancers15215193. PMID: 37958370; PMCID: PMC10650828.
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4. Hyun D, Lee HY, Cho JH, Kim HK, Choi YS, Kim J, Zo JI, Shim YM. Pragmatic role of noncontrast magnetic resonance lymphangiography in postoperative chylothorax or cervical chylous leakage as a diagnostic and preprocedural planning tool. *Eur Radiol*. 2022 Apr;32(4):2149-2157. doi: 10.1007/s00330-021-08342-6. Epub 2021 Oct 26. PMID: 34698929.
5. Lee HN, Hyun D, Lee WH, Kim SS, Bae SH, Hwang JA, Ko SE. Ultrasound-Guided Deployment of a Plug-Based Vascular Closure Device in Femoral Arteries with Calcified Plaque or Stenosis. *J Vasc Interv Radiol*. 2021 Jun;32(6):802-806. doi:10.1016/j.jvir.2021.02.017. PMID: 34051988.

Bridging with Locoregional Therapy: Role of TARE, TACE in Downstaging

Dongho Hyun*Ewha Womans University*

Transarterial treatment has been playing a palliative role in the treatment of hepatocellular carcinoma (HCC) according to various guidelines. Currently there are two versions: transarterial chemoembolization (TACE) and transarterial radioembolization (TARE). They have similarities and differences in terms of procedural sequence, mode of action on tumor, impact on liver function and future liver remnant (FLR), and reimbursement. One thing to underline is that TACE causes reversible damage while TARE leads to irreversible injury.

In a context of HCC treatment, there is a difference between the eastern and western countries. In the eastern countries, patients with HCC rarely undergo deceased donor liver transplantation (DDLT). Accordingly, a concept of bridging or downstaging is not commonly applied in a daily practice. However, living donor liver transplantation (LDLT) is popular among HCC patients. TACE is considered as an alternative treatment modality in patients who is beyond liver transplantation (LT) eligibility criteria and do not have a potential liver donor or are reluctant to LDLT. For this purpose, on-demand TACE is performed without a plan for surgery until liver function is allowed.

In the same context, TARE is considered in patients who have HCCs which is large or have vascular invasion with a curative intention. Since the costs for TARE is much higher than that of TACE, both physicians and patients hope excellent outcomes. Recently, TARE is considered in HCCs beyond resection eligibility criteria in terms of tumor burden and remnant liver function. Radiation lobectomy, one of the procedural methods of TARE, can both control tumor and induce FLR hypertrophy.

The current lecture will go through basic concept of TACE and TARE. Articles on the outcomes on downsizing or downstaging with TACE and TARE will be reviewed.

**Jeong-Ju Yoo**

Soonchunhyang University

Self Introduction

Prof. Jeong-Ju Yoo, currently an Associate Professor in the Department of Hepatology, Internal Medicine, at Soonchunhyang University College of Medicine, Soonchunhyang University Bucheon Hospital, Korea.

She completed her medical education at Seoul National University College of Medicine, earning her M.D. degree in 2009, followed by a Master's (2015) and Ph.D. (2019) in Internal Medicine from the same institution.

Her professional career includes medical internship (2009-2010) and residency in Internal Medicine (2010-2014) at Seoul National University Hospital. She was also a Research Fellow at the Department of Internal Medicine and Liver Research Institute at Seoul National University College of Medicine (2014-2015). In 2016, She joined Soonchunhyang University Bucheon Hospital as an Assistant Professor, and She has been serving as an Associate Professor since 2024.

Her clinical and research interests primarily focus on hepatology, particularly viral hepatitis, liver cirrhosis, hepatocellular carcinoma, liver fibrosis, and metabolic liver diseases. She has published numerous peer-reviewed articles and have received multiple awards for excellence in research and presentations, including Best Presentation Awards at major academic conferences.

Currently, she actively participate in several academic societies, serving on various committees, including the Korean Association for the Study of the Liver, Korean Liver Cancer Association, and Korean Society of Gastroenterology.

Research Interests

- Hepatocellular Carcinoma (HCC): Pathogenesis, Therapeutic Strategies, and Prognostic Factors
- Metabolic Liver Diseases: Non-Alcoholic Fatty Liver Disease (NAFLD) and Metabolic-Associated Fatty Liver Disease (MAFLD)
- Liver Fibrosis and Portal Hypertension: Non-Invasive Diagnostic Methods and Clinical Management
- Clinical Applications of Ultrasound and Elastography in Liver Disease
- Prognostic Modeling and Biomarkers for Chronic Liver Diseases
- Viral Hepatitis Management and Antiviral Therapies

Representative Publications

1. Jeong-Ju Yoo et al. "Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex." *Journal of Hepatology*, 2019;70:847-854.
2. Jeong-Ju Yoo et al. "Validation of the Texas Hepatocellular Carcinoma Risk Index Predictive Model for Hepatocellular Carcinoma in Asian Cohort." *Clinical Gastroenterology and Hepatology*, 2024 Mar 13; S1542-3565(24)00255-6.
3. Jeong-Ju Yoo et al. "Risk of dyslipidemia in chronic hepatitis B patients taking tenofovir alafenamide: a systematic review and meta-analysis." *Hepatology International*, 2023 Apr 26.
4. Jeong-Ju Yoo et al. "Efficacy of antiviral prophylaxis in HBsAg-negative, anti-HBc positive patients undergoing hematopoietic stem cell transplantation." *Liver International*, 2015 Dec;35(12):2530-2536.
5. Jeong-Ju Yoo et al. "Long-term prognosis and the need for histologic assessment of chronic hepatitis B in the serological immune-tolerant phase." *Clinical and Molecular Hepatology*, 2023 Apr;29(2):482-495.

From Unresectable to Resectable: How Immunotherapy Is Changing the Surgical Landscape

Jeong-Ju Yoo

Soonchunhyang University

The management of hepatocellular carcinoma (HCC) has historically been divided into two distinct pathways: curative-intent surgical options for early-stage patients and palliative systemic therapies for those with advanced disease. However, the surgical landscape is undergoing a fundamental shift due to the remarkable efficacy of immune checkpoint inhibitors (ICIs). The emergence of potent systemic combinations, most notably atezolizumab plus bevacizumab and tremelimumab plus durvalumab, has introduced the concept of "conversion therapy" for initially unresectable HCC. This strategy aims to downstage tumors that were previously considered inoperable—due to massive size, multinodularity, or portal vein tumor thrombosis (PVTT)—to a point where radical surgical resection or even liver transplantation becomes a viable, curative option.

Unlike traditional cytotoxic chemotherapy, which often yielded poor response rates in HCC, modern immunotherapy-based regimens can achieve deep and durable responses while preserving underlying liver function. This is a critical advantage for HCC patients, as the majority suffer from concomitant cirrhosis. By reducing the tumor burden and inducing a robust anti-tumor immune memory, ICIs not only facilitate R0 resection but also potentially minimize the risk of post-surgical recurrence by eliminating micrometastases. Furthermore, the integration of ICIs with locoregional treatments, such as transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC), has shown synergistic effects, significantly increasing the conversion rate compared to monotherapy. This "bridge to surgery" approach is effectively redefining the boundaries of "resectability" from a purely anatomical assessment to a biology-driven decision-making process.

Despite these clinical advancements, several challenges remain in integrating immunotherapy into the surgical workflow. Determining the optimal timing for surgery after the initiation of immunotherapy is crucial to avoid perioperative complications related to immune-related adverse events (irAEs) or excessive inflammatory adhesions. Moreover, the lack of reliable biomarkers to predict which patients will achieve a successful conversion response necessitates a more personalized approach. Future research must focus on identifying molecular signatures and radiological indicators that can guide the selection of candidates for conversion surgery. In conclusion, immunotherapy is not just a palliative tool but a transformative force that is expanding the surgical horizon, offering a second chance at a cure for patients once deemed terminal in the pre-immunotherapy era.



Kiyoshi Hasegawa
The University of Tokyo, Japan

Self Introduction

Educational Background

- 1993 M.D., University of Tokyo Medical School, Tokyo, Japan
- 1993-1994 Resident in General Surgery, Thoracic Surgery, Pediatric Surgery and Anesthesiology, The University of Tokyo Hospital, Tokyo, Japan
- 2003 Ph.D., University of Tokyo Graduate School of Medicine, Tokyo, Japan

Professional Experiences

- 1994-1996 Active Staff & Surgeon, Fujieda Municipal Hospital, Fujieda, Shizuoka, Japan
- 1999-2000 Active Staff & Surgeon, Kanto Medical Center NTT EC, Tokyo, Japan
- 2003-2007 Assistant Professor in Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine and the University Hospital, The University of Tokyo, Tokyo, Japan
- 2008-2009 Lecturer in Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine and the University Hospital, The University of Tokyo, Tokyo, Japan
- 2009-2017 Associate Professor in Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine and the University Hospital, The University of Tokyo, Tokyo, Japan
- 2017-Present Professor and Chairman in Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine and the University Hospital, The University of Tokyo, Tokyo, Japan
- 2019-Present Professor and Chairman in Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine and the University Hospital, The University of Tokyo, Tokyo, Japan

Research Interests

- Surgical Treatment for Primary and Metastatic Liver Cancer
- Liver Transplantation
- Thick Silk Fibroin Vascular Graft
- Development of a New Pancreatic Fistula Prevention Material
- Colorectal Liver Metastases and Perioperative Chemotherapy

Representative Publications

1. Eguchi S, Umeshita K, Soejima Y, Eguchi H, Egawa H, Fukumoto T, Haga H, Hasegawa K, Kasahara M, Nagano H, Takada Y, Tokushige K, Ueda Y, Mochida S, Matsushima H, Adachi T, Ohdan H; Japanese Liver Transplantation Society. An Analysis of 10,000 Cases of Living Donor Liver Transplantation in Japan: Special Reference to the Graft-Versus-Recipient Weight Ratio and Donor Age. *Ann Surg.* 279(1):94-103. 2024.

2. Li Z, Rammohan A, Gunasekaran V, Hong S, Chen CY, Kim J, Hervera Marquez KA, Hsu SC, Kirimker O, Akamatsu N, Shaked O, Finotti M, Yeow M, Genedy L, Dutkowski P, Nadalin S, Boehnert MU, Polak WG, Bonney GK, Mathur A, Samstein B, Emond JC, Testa G, Olthoff KM, Rosen CB, Heimbach JK, Taner T, Wong TC, Lo CM, Hasegawa K, Balci D, Cattral M, Sapisochin G, Selzner N, Bin Jeng L, Broering D, Joh JW, Chen CL, Suk Suh K, Rela M, Clavien PA. Novel Benchmark for Adult-to-Adult Living-Donor Liver Transplantation. Integrating Eastern and Western Experiences. *Ann Surg.* 278(5):798-806. 2023.

3. Ito D, Kawaguchi Y, Inagaki Y, Ito K, Mihara Y, Kaneko J, Tanaka M, Fukayama M, Kokudo N, Hasegawa K. "Assessment of liver function-related mRNA expression and fluorescence imaging in outflow-obstructed regions in rats." *BMJ Surg Interv Health Technol.* 4(1): e000156. 2022

Surgical Considerations after Neoadjuvant or Conversion Therapy in HCC

Kiyoshi Hasegawa *The University of Tokyo, Japan*

The therapeutic landscape of hepatocellular carcinoma (HCC) has changed dramatically with the introduction of molecular targeted agents and immune checkpoint inhibitor-based combination therapies. Modern first-line regimens have achieved response rates that were rarely observed in the sorafenib era, leading to an increasing number of patients initially deemed unsuitable for curative resection being re-considered for surgery after systemic therapy.

This shift has renewed interest in the concepts of neoadjuvant and conversion therapy in HCC. The BR-HCC Expert Consensus 2023 introduced a framework for oncological resectability classification, defining resectable (R) and borderline resectable disease (BR1 and BR2) based on tumor burden, vascular invasion, and extrahepatic spread. In parallel, conversion surgery has been redefined to encompass both functional conversion, in which insufficient future liver remnant precludes initial resection, and oncological conversion, in which tumor extent or biology initially predicts poor postoperative outcomes. These developments underscore that resectability is no longer a static anatomical judgment but a dynamic condition influenced by systemic therapy.

Radiologic response does not always equate to pathological eradication of viable tumor. Emerging data from neoadjuvant and conversion studies in HCC suggest a clinically relevant discordance between imaging-based response and pathological response, underscoring the need for careful interpretation of treatment effect before surgery.

Systemic therapy may also affect perioperative decision-making. Immune checkpoint inhibitor-based therapy can reshape the tumor microenvironment and may induce inflammatory or fibrotic changes, although its direct impact on surgical difficulty remains insufficiently defined. Anti-VEGF therapy requires particular attention to bleeding and wound-healing risks, making appropriate drug withdrawal and reassessment of liver function essential before major hepatectomy.

Our institutional experience illustrates both the feasibility and the complexity of this evolving strategy. In patients classified as BR1 or BR2 according to the current resectability framework, systemic therapy has enabled surgery in a meaningful proportion of cases. In a prospective multicenter study evaluating lenvatinib in patients with advanced HCC—who would now be entirely classified as BR1 or BR2 according to the current criteria—subsequent surgical resection was achieved in more than half of enrolled

patients, with acceptable perioperative outcomes. Long-term survival was substantially better in resected patients compared with those who did not undergo surgery. Nonetheless, recurrence after surgery remains frequent, even among responders; importantly, many recurrences are still amenable to curative-intent treatment, suggesting that appropriate patient selection and multimodal management can translate into favorable long-term survival.

These observations raise an important question: how should we select candidates for surgery after systemic therapy? While conversion surgery offers the potential for prolonged survival and even cure in selected patients, the key challenge lies in identifying those who derive the greatest benefit. Although multiple factors, including radiologic response patterns, tumor markers, liver function dynamics, and biological behavior, are likely to be relevant, optimal criteria for patient selection have yet to be established and warrant further investigation. In this context, surgery should be considered as an integral component of multimodal treatment strategies aimed at improving long-term outcomes.

In conclusion, systemic therapy has expanded the boundaries of surgical resection in HCC, transforming resectability into a dynamic and potentially reversible state. The challenge moving forward is not simply to increase resection rates, but to identify patients in whom surgery meaningfully alters the natural history of disease. Clarifying surgical considerations after neoadjuvant or conversion therapy will be essential to define the evolving boundary between systemic disease control and curative resection in hepatocellular carcinoma.

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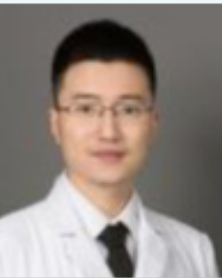
How AI Is Transforming Future Liver Surgery

Chairs

Sung Su Yun (Yeungnam Univ.)

Dongho Choi (Hanyang Univ.)





Xin Wang
Sichuan University, China

Self Introduction

Education

- 2013.9-2016.6 Sichuan University, West China School of Clinical Medicine, Pancreatic Surgery, Doctor of Surgery
- 2010.9-2013.9 Sichuan University, West China School of Clinical Medicine, Hepatobiliary and Pancreatic Surgery, Master of Surgery
- 2005.9-2010.9 China Medical University, Bachelor of Clinical Medicine

Work and Research Experience

- 2016.7-2018.7 Sichuan University West China Hospital, Resident Physician in Training
- 2018.9-2022.6 Sichuan University West China Hospital, Specialist Physician / Lecturer / Attending Physician
- 2022.6-Present Pancreatic Surgery, Associate Professor / Associate Chief Physician

Participation in Academic Organizaions

- Youth Member, Minimally Invasive Pancreatic Surgery Group, Pancreatic Subcommittee, Chinese Research Hospitals Association
- Youth Member, Minimally Invasive Diagnosis and Treatment Group, Pancreatic Cancer Committee, Chinese Anti-Cancer Association
- Vice President, Youth Committee, Pancreatic Disease Branch, Sichuan Provincial Medical Doctor Association
- Secretary, Pancreatic Disease Branch, Sichuan Provincial Medical Doctor Association

Awards

Third Prize, Sichuan Provincial Science and Technology Progress Award

Representative Publications

1. Wang X, Wang M, Zhang H, Peng B. Laparoscopic partial splenectomy is safe and effective in patients with focal benign splenic lesion. Surg Endosc. 2014 Dec; 28(12): 3273-8. doi: 10.1007/s00464-014-3600-0. Epub 2014 Jun 18. PubMed PMID: 24939157.
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3. Wang X, Li Y, Peng B. Laparoscopic spleen-preserving distal pancreatectomy with intraoperative vascular repair. Surg Endosc. 2014 Apr;28(4):1330. doi: 10.1007/s00464-013-3328-2. Epub 2014 Jan 1. PubMed PMID: 24380982.
4. Wang X, Li Y, Zhou J, Wu Z, Peng B. Hand-assisted laparoscopic splenectomy is a better choice for patients with supramassive splenomegaly due to liver cirrhosis. J Laparoendosc Adv Surg Tech A. 2012 Dec;22(10):962-7. doi: 10.1089/lap.2012.0237. Epub 2012 Oct 15. PubMed PMID: 23067068.
5. Wang X, Li Y, Peng B. Hand-assisted laparoscopic technique in the setting of complicated splenectomy: a 9-year experience. World J Surg. 2013 Sep; 37(9):2046-52. doi: 10.1007/s00268-013-2114-6. PubMed PMID: 23756773.

Intraoperative Assessment and AI-Assisted Coaching System in Hepatobiliary Surgery

Xin Wang Sichuan University, China

My research focuses on AI in surgery. This talk will cover intelligent laparoscopic liver surgery technologies: automatic surgical phase recognition, 3D anatomical reconstruction & intelligent registration, and intraoperative bleeding identification, with applications in surgical research, training education and in-tra-op navigation.

**Maki Sugimoto***Teikyo University, Japan*

Self Introduction

Dr. Sugimoto subsequently pursued advanced research training in the United States as a Visiting Fellow at the Department of Veterans Affairs Palo Alto Health Care System in Silicon Valley.

He developed his clinical and surgical expertise through positions within the National Hospital Organization and Tokyo Medical Center. He later served as an Associate Professor at Kobe University and the International University of Health and Welfare.

Dr. Sugimoto is currently a Professor at the Okinaga Research Institute, Teikyo University, and is also affiliated with the Department of Hepato-Biliary-Pancreatic Surgery at Teikyo University Hospital. He serves as Director of the Innovation Lab, where he leads interdisciplinary research integrating medicine, engineering, and digital technologies.

In addition to his academic career, he is the Founder and CEO of Holoeyes Inc., a medical technology company pioneering the use of extended reality (XR) and artificial intelligence for surgical planning, medical imaging visualization, and digital surgical navigation. His work focuses on the transformation of surgical practice through spatial computing, including the automatic conversion of medical imaging data into interactive 3D and XR environments

Augmented Reality for Preoperative Planning and Intraoperative Visualization

Maki Sugimoto*Teikyo University, Japan*

This lecture will discuss the clinical potential of augmented reality (AR) for preoperative planning and intraoperative visualization in hepatobiliary and pancreatic surgery. Patient-specific three-dimensional anatomical models reconstructed from medical imaging data can enhance surgeons' spatial understanding of complex vascular and organ relationships before surgery. By integrating these models into AR and extended reality environments, surgeons can intuitively review surgical anatomy, simulate operative strategies, and share procedural concepts with the surgical team.

The lecture will also address the role of intraoperative AR visualization as a supportive technology for anatomical orientation and surgical decision-making. Particular attention will be given to the visualization of tumors, vessels, bile ducts, pancreatic ducts, and planned resection planes in relation to the operative field. In addition, the presentation will introduce current challenges, including registration accuracy, device usability, workflow integration, and clinical validation.

Recent advances in XR technologies have further expanded their application beyond preoperative simulation to intraoperative video visualization. This lecture will introduce the development of a wireless video transmission system that delivers three-dimensional endoscopic images from robotic laparoscopic surgery to an XR head-mounted display, particularly Apple Vision Pro, using the Network Device Interface (NDI) protocol. This system enables low-latency video streaming with an approximate delay of 30 milliseconds, demonstrating the feasibility of a monitor-free endoscopic surgical environment that does not rely on conventional external monitors. Furthermore, by superimposing patient-specific three-dimensional organ models reconstructed from preoperative CT images onto real-time endoscopic video, this approach may provide image-guided surgical support for intraoperative anatomical orientation, surgical navigation, and recognition of planned transection lines and critical vascular structures.

Through practical examples and ongoing developments, this lecture will highlight how AR-based surgical support and XR-based intraoperative visualization may contribute to safer procedures, improved surgical education, more effective communication within multidisciplinary surgical teams, and the future transformation of endoscopic and robotic surgery.



Daichi Kitaguchi
University of Tsukuba, Japan

Self Introduction

Education

2006-2012 M.D., University of Tsukuba
2019-2023 Ph.D., University of Tsukuba

Professional Experience

2012-2017 Resident, Department of Surgery, University of Tsukuba
2017-2025 Department of Colorectal Surgery, National Cancer Center Hospital East
2025-2026 Research Fellow, IRCAD France
2026-Present Assistant Professor, Department of Surgery, University of Tsukuba

Research Interests

- Colorectal Cancer and Colorectal Surgical Oncology
- Minimally Invasive Colorectal Surgery
- Surgical Data Science and AI-Assisted Surgical Analysis
- Clinical Trials of Novel Surgical Technologies and Medical Devices
- Evidence Synthesis: Systematic Reviews and Meta-Analyses

Representative Publications

1. Kitaguchi D, Forgione A, Innocenzi C, et al. A systematic review and Bayesian network meta-analysis of randomized controlled trials on multiple skin closure techniques following stoma closure. *Colorectal Dis.* 2026 Mar;28(3):e70412.
2. Kitaguchi D, Fuse N, Wakabayashi M, et al. Exploring the impact of an artificial intelligence-based intraoperative image navigation system in laparoscopic surgery on clinical outcomes: A protocol for a multicenter randomized controlled trial. *Eur Surg Res.* 2025 Dec 26:1-14.
3. Kitaguchi D, Kosugi N, Ishikawa Y, et al. A multicentre randomized controlled trial exploring the clinical usefulness of the intraoperative use of an artificial intelligence-based anatomical navigation system. *Br J Surg.* 2025 May 31;112(6):znaf121.
4. Kitaguchi D, Harai Y, Kosugi N, et al. Artificial intelligence for the recognition of key anatomical structures in laparoscopic colorectal surgery. *Br J Surg.* 2023 Sep 6;110(10):1355-1358.
5. Kitaguchi D, Watanabe Y, Madani A, et al; Computer Vision in Surgery International Collaborative. Artificial Intelligence for Computer Vision in Surgery: A Call for Developing Reporting Guidelines. *Ann Surg.* 2022 Apr 1;275(4):e609-e611.

Real-Time AI Navigation in Minimally Invasive Surgery

Daichi Kitaguchi *University of Tsukuba, Japan*

Background

Artificial intelligence (AI) is increasingly being integrated into surgical practice, and several AI-based systems have already been approved as medical device software. AI is widely regarded as a transformative technology, and many surgeons expect it to reshape surgical practice. However, an important question remains unanswered: what does AI actually change in real surgical settings? Despite rapid technological progress, the clinical value of AI in surgery remains unclear. My research therefore focuses on understanding how AI can meaningfully improve surgical outcomes rather than simply advancing technology.

Objective

This research aims to determine whether AI-based systems can provide measurable benefits during colorectal surgery, particularly in anatomical recognition and surgical navigation, and to explore how AI-driven data integration may contribute to improved surgical outcomes.

Methods

We first developed semantic segmentation models capable of automatically identifying critical anatomical landmarks in real time during colorectal surgery, including the ureter and autonomic nerves. These structures must be preserved to prevent injury and serve as key landmarks for identifying the correct dissection plane. However, they can sometimes be difficult to recognize, particularly for less experienced surgeons. To develop these models, we constructed large annotated datasets from surgical videos and trained segmentation algorithms for ureter and autonomic nerve recognition. The resulting models were subsequently validated and published. However, commonly used performance metrics such as the Dice coefficient or Intersection-over-Union (IoU) evaluate algorithmic accuracy rather than real clinical usefulness. We therefore conducted a prospective observational study during live colorectal surgeries to assess the practical performance of the AI models in the operating room. During surgery, the time required to identify the target anatomy was compared between surgeons and the AI system. Following this evaluation, we further investigated the clinical value of AI through a multicenter randomized controlled trial (RCT), comparing AI-assisted colorectal surgery with conventional surgery per-

formed without AI navigation.

Results

In the prospective observational study, 89 comparisons between surgeon detection and AI detection were analyzed. The AI system identified the target anatomy faster than surgeons in 75% of cases. Sub-group analysis showed that AI outperformed trainee surgeons in 84% of comparisons. These findings suggest that AI-based anatomical recognition can match or exceed human performance in real surgical environments, particularly when supporting less experienced surgeons. In the multicenter RCT, 90 patients undergoing colorectal surgery were enrolled and randomly assigned to either the AI-navigation group (n = 43) or the conventional surgery group (n = 43). The AI-navigation group demonstrated a significantly shorter time to detect the target anatomy compared with the control group. However, other clinical outcomes, including total operative time, blood loss, and intraoperative or postoperative complications, did not differ significantly between the groups. These results suggest that while AI can improve intraoperative anatomical recognition, its direct impact on broader surgical outcomes remains uncertain.

Future Perspective

To further investigate the clinical value of AI in surgery, we are currently developing an integrated framework for postoperative outcome prediction and surgical performance analysis. This system integrates preoperative patient characteristics, imaging data such as MRI, and intraoperative surgical video analysis. Through surgical video analysis, we aim to develop models capable of evaluating surgical skill and identifying procedural patterns associated with improved outcomes. By combining intraoperative data with patient-specific preoperative factors, such systems may enable more accurate prediction of postoperative clinical courses. Ultimately, AI could support surgeons not only by identifying anatomical structures but also by providing explainable intraoperative guidance and decision support, thereby improving surgical strategies and patient outcomes.

Conclusion

Although AI technologies are rapidly advancing in surgical fields, their true clinical value must be carefully evaluated. Our studies demonstrate that AI can enhance anatomical recognition during colorectal surgery, particularly for less experienced surgeons. However, improved intraoperative recognition does not necessarily translate into better overall surgical outcomes. Future AI systems should therefore focus on integrating multimodal clinical data to provide meaningful decision support and outcome-oriented surgical guidance.

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navigation system in laparoscopic surgery on clinical outcomes: A protocol for a multicenter randomized controlled trial. Eur Surg Res. 2025 Dec 26:1-14.

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Xin Wang
The Chinese University of Hong Kong, Hong Kong

Self Introduction

Prof. Wang obtained his Ph.D. in Oncology from University of Cambridge, UK, in 2014, and conducted postdoctoral research in the Department of Biomedical Informatics at Harvard Medical School from 2013 to 2015. He is currently an Associate Professor (tenured) in the Department of Surgery at The Chinese University of Hong Kong (CUHK) Faculty of Medicine. He also serves as the Director of the Division of Biomedical Informatics, Principal Investigator at the Li Ka Shing Institute of Health Sciences, and Coordinator of the Translational Genomics Program.

Prof. Wang has published over 100 SCI papers in high-impact journals such as Nature Medicine, Gastroenterology, Gut, Hepatology, and Clinical Cancer Research. Committed to translating research into clinical practice, Prof. Wang holds 15 patents covering AI-assisted diagnosis using medical imaging and histopathology, miRNA liquid biopsies, mRNA-LNP vaccines, and RIBOTAC/PROTAC-based drug development. His team has received several prestigious awards, including the Second Prize of Natural Science Award from the Ministry of Education of China (2025), the Second Prize of Natural Science Award of the Wu Wenjun AI Science and Technology Award (2025), and two gold medals and one silver medal at the Geneva International Exhibition of Inventions (2026).

Research Interests

Prof. Xin Wang’s primary research areas are cancer bioinformatics, AI-powered precision oncology, and innovative diagnostics and therapeutics development. He focuses on mechanistic and translational studies of major human cancers, developing novel methodologies that integrate bioinformatics, systems biology, machine learning, and artificial intelligence. In close collaboration with molecular biologists and experimental oncologists, he is particularly interested in dissecting cancer heterogeneity and elucidating the mechanisms underlying specific cancer subtypes. Working alongside clinicians, his team is dedicated to multi-center studies on molecular biomarkers and medical image-based AI models for early cancer detection, diagnosis, prognosis, and molecular subtyping. Moreover, leveraging new drug targets identified through integrative multi-omics analysis, his lab develops innovative cancer therapeutics, including RIBOTACs, PROTACs, and mRNA vaccines.

Representative Publications

1. Cui H †, Zhu Z †, Xu E †, Qi L †, Cheng Y †, Zhang Y †, Ling Zhang, Matthew Yibo Cheng, Bin Yang, Ruifang Sun, Xiaofei Zhuang, Yanfeng Xi, Ting Yan, Caixia Cheng, Ning Ding, Huijuan Liu, Lu Wang, Min Guo, Dinghe Guo, Haoyu Zhang, Meilan Peng, Zhekun An, Yongjia Weng, Fang Wang, Meng Liu, Ruixin Xiong, Bin Song, Weihua Yin, Zhang W*, Cheng X, Liu Z, Zhan Q*, Wang X*, Cui Y*. The consensus molecular subtypes of esophageal squamous cell carcinoma. *Signal Transduction and Targeted Therapy* 2026, 11(1):65.
2. Qi L †, Liang J-Y †, Li Z-W, Xi S-Y, Lai Y-N, Gao F, Zhang XR, Wang DS, Hu MT, Cao Y, Xu LJ, Chan RCK, Xing BC*, Wang X*, Li Y*. Deep learning-derived spatial organization features on histology images predicts prognosis in colorectal liver metastasis patients after hepatectomy. *iScience* 2023, 26: 107702.
3. Zhu Y †, Huang C †, Zhang C †, Zhou Y †, Zhao E, Zhang Y, Pan X, Huang H*, Liao W*, Wang X*. LncRNA MIR200CHG inhibits EMT in gastric cancer by stabilizing miR-200c from target-directed miRNA degradation. *Nature Communications* 2023, 14: 8141.
4. Chen H †, Gao F †, He M †, Ding XF, Wong AM, Sze SC, Yu AC, Sun T, Chan AWH, Wang X*, Wong N*, Long-read RNA Sequencing identifies Novel Splice Variants in Hepatocellular Carcinoma and Tumor-specific Isoforms, *Hepatology* 2019, 70: 1011–1025.
5. Sonohara F †, Gao F †, Iwata N, Kanda M, Koike M, Takahashi N, Yamada Y, Kodera Y, Wang X*, Goel A*. Genome-wide Discovery of a Novel Gene-expression Signature for the Identification of Lymph Node Metastasis in Esophageal Squamous Cell Carcinoma, *Annals of Surgery* 2019, 269(5):879-886

**AI-Powered Computational Pathology and Radiology:
Reshaping Surgical Decision Making in Primary and
Metastatic Liver Cancer**

Xin Wang *The Chinese University of Hong Kong, Hong Kong*

Primary liver cancer, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), as well as metastatic liver cancers like colorectal liver metastases (CRLM), represents a substantial and growing global health burden. Despite refinements in hepatic surgery, perioperative care, and multidisciplinary treatment, long-term outcomes remain constrained by recurrence rates reaching up to 70% at five years for HCC. A key contributor is marked intra- and inter-tumor biological heterogeneity, which conventional staging and classification frameworks—including TNM staging for primary liver cancers, BCLC staging for HCC, and the Fong Clinical Risk Scoring (CRS) system for CRLM—fail to capture at the individual patient level. There is therefore an urgent unmet need for quantitative, reproducible biomarkers to support core surgical decisions: patient selection, resection extent, and surveillance intensity.

Artificial intelligence (AI) addresses this challenge through two complementary pillars. Radiomics extracts high-throughput quantitative features, such as texture, shape, intensity, and spatial heterogeneity imperceptible to the human eye, from routine CT and MRI that are imperceptible to the human eye, converting imaging into mineable high-dimensional data. Computational pathology leverages deep learning to analyze gigapixel H&E whole-slide images (WSIs), quantifying spatial organization features (SOFs), architectural patterns, and tumor-stroma interactions that constitute a quantitative ‘digital biopsy’. Together, these technologies enable a transition from subjective assessment to objective, data-driven prognostication.

An expanding clinical evidence base now supports the utility of these approaches. In CRLM, deep learning-derived SOFs from routine H&E WSIs outperform the conventional CRS for postoperative risk stratification. In HCC, multicenter models predict post-resection survival with high accuracy, demonstrating that tumor regions associated with poor outcomes are characterized by macrotrabecular architecture, vascular spaces, and reduced immune infiltration. Concurrently, the Recurr-NET framework, integrating multiphasic CT with clinical variables, predicts HCC recurrence with external AUROCs of 0.758–0.798 across 1,231 patients, significantly outperforming histological microvascular invasion (MVI) and clinical risk scores. In ICC, multimodal deep learning of routine histopathology surpasses TNM staging, with interpretable morphological features correlating closely with molecular subtypes.

In parallel, AI-powered radiology is augmenting preoperative planning and postoperative surveillance. Deep learning and radiomics models allow for the non-invasive prediction of occult MVI before surgery in HCC, with deep learning demonstrating superior cross-institutional robustness. AI-driven automated Couinaud segmentation enables precise computation of the future liver remnant, and MRI-based nomograms predict post-hepatectomy liver failure (AUC 0.81). Radiomics and deep learning models further predict early recurrence in both CRLM and HCC, enabling risk-adapted surveillance.

Beyond conventional clinical outcomes, AI is enabling non-invasive prediction of molecular markers and subtypes—“virtual molecular profiling”—from routine data. H&E-based deep learning predicts CTNNB1 and TP53 mutations with clinically meaningful accuracy and reclassifies combined hepatocellular-cholangiocarcinoma into molecularly distinct subgroups. Quantitative contrast-enhanced MRI markers predict PD-L1 expression and CTNNB1 mutation status, while self-supervised DCE-MRI models distinguish proliferative from non-proliferative HCC subtypes—a distinction with potential surgical relevance given the aggressive biological phenotype of proliferative tumors.

The greatest clinical impact arises from multimodal integration: models combining CT, histopathology, and clinical variables achieve accurate prognostic prediction and improve postoperative risk stratification in multicenter ICC cohorts over single-modality approaches. Such convergent systems has the potential to serve as real-time surgical decision-support tools at critical junctures—from preoperative risk stratification to intraoperative margin assessment and postoperative surveillance triage.

Despite these advances, important barriers remain. A recent meta-analysis of deep learning models for MVI prediction in HCC confirmed that model generalizability consistently declines in external validation, underscoring the need for prospective interventional trials. Regulatory frameworks, liability considerations, and seamless integration into surgical workflows must also be addressed. Federated learning enables multi-institutional model development while keeping sensitive patient data behind local firewalls, addressing both data scarcity and privacy concerns. Explainable AI techniques are progressively rendering deep learning models more transparent and clinically interpretable.

In conclusion, AI-powered computational pathology and radiology represent a paradigm shift in liver cancer surgery. By translating complex data into actionable surgical intelligence, these tools amplify—rather than replace—surgical judgment, enabling a transition from population-based strategies to individualized precision care. The integration of AI intelligence into unified surgical dashboards, providing real-time augmented decision support across all phases of care, holds the potential to fundamentally reshape the standard of care and improve survival for patients with primary and metastatic liver cancer.

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KAHBPS SYMPOSIUM 3

How to Approach Benign Liver Tumors

Chairs

Dong-Hwan Jung (Univ. of Ulsan)

Jongman Kim (Sungkyunkwan Univ.)





Dong Ik Cha
Sungkyunkwan University

Self Introduction

Prof. Cha is an Assistant Professor of Abdominal Radiology at Samsung Medical Center, Sungkyunkwan University School of Medicine.

Prof. Cha graduated from CHA University College of Medicine, Korea, with a Bachelor of Medicine degree in 2009. He completed his internship and residency in Radiology at Samsung Medical Center in 2014. Since March 2022, Prof. Cha has been serving as an Assistant Professor of Abdominal Radiology at Samsung Medical Center.

Research Interests

- HCC Diagnosis and Prognosis
- Liver Transplantation
- Liver CT, Liver MRI, Contrast Enhanced Ultrasound

Representative Publications

1. Preoperative skeletal muscle assessment as a predictor of liver regeneration in living donor liver transplantation. Eur Radiol. 2026.
2. Prediction of microsatellite-stable/epithelial-to-mesenchymal transition molecular subtype gastric cancer using CT radiomics and clinicopathologic factors. Eur J Radiol. 2025
3. Preoperative assessment of microvascular invasion risk using gadoxetate-enhanced MRI for predicting outcomes after liver transplantation for single hepatocellular carcinoma within the Milan criteria. Eur Radiol. 2024.
4. Recurrence-free Survival After Liver Transplantation Versus Surgical Resection for Hepatocellular Carcinoma: Role of High-risk MRI Features. Transplantation. 2024
5. Combined Transarterial Chemoembolization and Radiofrequency Ablation for Hepatocellular Carcinoma Infeasible for Ultrasound-Guided Percutaneous Radiofrequency Ablation: A Comparative Study with General Ultrasound-Guided Radiofrequency Ablation Outcomes. Cancers (Basel). 2023

Advanced Imaging Modalities and Differential Diagnosis: A Radiologist's Perspective

Dong Ik Cha Sungkyunkwan University

Introduction

Benign liver lesions represent the most frequently encountered hepatic abnormalities in routine clinical imaging. Current evidence indicates that approximately 70-80% of incidentally detected liver lesions are benign rather than malignant.^{1,2} Simple cysts and hemangiomas account for the majority of these findings. Despite this high prevalence of benignity, establishing an accurate diagnosis remains clinically important. When radiologists can confidently identify benign lesions through imaging, several benefits follow: patients avoid invasive biopsy procedures, receive immediate reassurance, and do not undergo unnecessary additional testing. This approach also optimizes healthcare resource utilization.³ This lecture presents a systematic approach to diagnosing benign liver lesions using multiple imaging modalities while integrating essential clinical information.

Learning Objectives

- 1) Recognize that benign liver lesions are the most common hepatic findings in clinical practice
- 2) Understand the radiologist's role in preventing unnecessary invasive procedures
- 3) Evaluate clinical context systematically before interpreting hepatic imaging studies
- 4) Compare the diagnostic capabilities and limitations of CT, MRI, and CEUS
- 5) LI-RADS and its ancillary features for benign lesions^{4,5}
- 6) Identify characteristic MRI patterns of common benign lesions including cysts, hemangiomas, focal nodular hyperplasia, hepatic adenomas, and angiomyolipomas
- 7) Utilize hepatobiliary phase analysis for enhanced diagnostic confidence
- 8) Interpret CEUS findings including enhancement patterns and washout characteristics⁶
- 9) Implement a resource-conscious diagnostic strategy

Content Overview

1. Benign Liver Lesions: Understanding the Clinical Context

Benign liver lesions are not unusual findings but rather represent the typical case in hepatic imaging. This high baseline prevalence establishes an important starting point for diagnosis. Simple cysts and

cavernous hemangiomas together constitute the majority of benign findings, followed by focal nodular hyperplasia (FNH) and hepatic adenomas.⁷ Understanding this epidemiological pattern helps prevent overdiagnosis and unnecessary intervention.

2. The Radiologist’s Essential Role

Radiologists serve a critical function in patient care by accurately diagnosing benign lesions. Correct identification prevents unnecessary liver biopsies, which carry risks of bleeding and infection. Additionally, confident diagnosis provides immediate patient reassurance. Perhaps most importantly, appropriate imaging use prevents over-investigation—knowing when CT alone suffices without proceeding to MRI or CEUS represents efficient, evidence-based practice.³

3. Clinical Context: The First Step

Before interpreting any liver imaging study, radiologists must review relevant clinical information. Important factors include patient age and sex, presence of liver cirrhosis or chronic hepatitis B, liver function status, recent fever or inflammatory symptoms, dietary habits, travel history, prior malignancy, and oral contraceptive use.⁸ These clinical details fundamentally influence the differential diagnosis and interpretation strategy.

4. Strategic Use of Imaging Modalities

Each imaging modality offers distinct advantages. Understanding these differences enables optimal selection.

Multiphase Liver CT serves as the primary screening tool. It provides wide availability, cost-effectiveness, and excellent spatial resolution. Three phases—arterial, portal venous, and delayed—allow evaluation of enhancement patterns. Simple cysts show water attenuation without enhancement, while hemangiomas demonstrate peripheral nodular enhancement with progressive centripetal filling.⁹ However, CT has limitations including moderate soft tissue contrast and radiation exposure. The key decision point involves recognizing when lesions require MRI for definitive characterization.

Gadoxetic Acid-Enhanced MRI functions as the problem-solving modality. MRI provides superior soft tissue contrast through multiple complementary sequences: dynamic contrast phases, T2-weighted imaging, diffusion-weighted imaging, and hepatobiliary phase imaging at 20 minutes. LI-RADS ancillary features list the findings that are suggestive of benign lesions.^{4,5} Important features suggesting benignity include marked T2 brightness, hepatobiliary phase isointensity or hyperintensity, size stability over two years, and absence of diffusion restriction.

Contrast-Enhanced Ultrasound (CEUS) provides real-time vascular assessment. CEUS evaluates arterial phase hyperenhancement and washout characteristics. Absence of washout supports benignity, while early or marked washout raises concern for malignancy.⁶ CEUS offers unique advantages: real-time visualization of enhancement patterns, no nephrotoxicity, and ability to repeat scanning. Hemangiomas

show characteristic peripheral nodular enhancement, while FNH demonstrates spoke-wheel arterial enhancement.¹⁰

References

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2. Horta G, Lopez M, Dotte A, et al. Benign focal liver lesions detected by computed tomography: review of 1,184 examinations. Rev Med Chil. 2015;143(2):197-202.

3. Bonder A, Afdhal N. Evaluation of liver lesions. Clin Liver Dis. 2012;16(2):271-283.

4. Chernyak V, Fowler KJ, Kamaya A, et al. Liver Imaging Reporting and Data System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. Radiology. 2018;289(3):816-830.

5. American College of Radiology. CT/MRI Liver Imaging Reporting and Data System version 2018. Available at: <https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS>

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Euisoo Han
The Catholic University of Korea

Self Introduction

Education

- 2014.03-2020.02 M.S. & Ph.D., Graduate School of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
- 2007.03-2011.02 M.D., College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
- 2005.03-2007.02 Premedical Course, The Catholic University of Korea, Seoul, Republic of Korea

Professional Appointments

- 2024 .03-Present Assistant Professor, Division of HBP Surgery & Transplantation, Department of Surgery Seoul St. Mary's Hospital, The Catholic University of Korea
- 2022.03-2024.02 Assistant Professor, Division of HBP Surgery, Department of Surgery, Uijeongbu St. Mary's Hospital, The Catholic University of Korea
- 2021.03-2022.02 Clinical Assistant Professor, Division of HBP Surgery, Department of Surgery, Seoul National University Hospital
- 2019.05-2021.02 Clinical Fellow, Division of HBP Surgery, Department of Surgery, Seoul National University Hospital

Society Committee Positions

Korean Association of Robotic Surgeons (KAROS)	• Vice Secretary
Korean Society of Surgical Oncology (KSSO)	• Vice Secretary
Korean Surgical Infection Society (KSIS)	• Vice Secretary
Korean Association of Hepato-Biliary-Pancreatic Surgery (KAHBPS)	• Member, Examination Committee
	• Member, Research Committee
Korean Society of Endoscopic & Laparoscopic Surgeons (KSELS)	• Member, Research Committee
The Korean Association of Liver Surgery	• Member, Research Committee
	• Member, Information Committee
Korean Association for the Study of the Liver (KASL)	• Member, Information Technology Committee
Korean Liver Cancer Association (KLCA)	• Member, Legislation Committee
Korean Society for Transplantation (KST)	• Member, Academic & Research Committee
	• Member, Information Committee
Korean Liver Transplantation Society (KLTS)	• Member, Education Committee
	• Member, International Affairs Committee

Research Interests

- Liver Transplantation (Living-Donor and Deceased-Donor)
- Hepatic Resection for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma
- Minimally Invasive (Laparoscopic and Robotic) Hepatobiliary Surgery
- Pancreaticobiliary Surgery
- Surgical Outcomes and Translational Research in HBP Malignancies

Risk Stratification and Indication for Surgical Resection: A Surgeon's Perspective

Euisoo Han The Catholic University of Korea

Benign liver lesions are identified in approximately 20% of adults undergoing cross-sectional imaging, yet fewer than 5% represent hepatocellular adenoma (HCA)—the only entity that routinely demands surgical judgment. The central clinical question is therefore not whether we can operate, but whether we should.

A structured diagnostic approach begins with gadoxetate-enhanced MRI, which characterizes more than 90% of lesions non-invasively; biopsy is reserved for cases where the result will change management. Hemangioma and focal nodular hyperplasia (FNH) are observation diseases regardless of size. Mucinous cystic neoplasm of the liver (MCN-L) is the important exception requiring complete resection due to its premalignant potential.

For HCA, risk stratification rests on three pillars: sex, size, and molecular biology. Any adenoma in a male patient warrants resection given the aggressive behavior of male HCA. Lesions ≥ 5 cm carry a substantially elevated bleeding risk. Most importantly, β -catenin exon 3 mutations—present in roughly 10% of HCAs—confer a malignant transformation risk approaching 40%, mandating resection irrespective of size or sex. The Bordeaux molecular classification (H-HCA, I-HCA, b-HCA, sh-HCA) provides the biological framework that guides these decisions.

When surgery is indicated for benign disease, five principles are non-negotiable: parenchyma-sparing resection, preference for enucleation over major hepatectomy, minimally invasive surgery (MIS) by default, multimodal intra-operative navigation combining IOUS with pre-operative 3D volumetric reconstruction and ICG fluorescence imaging, and a standard of zero mortality. ICG fluorescence compensates for the loss of tactile feedback in laparoscopic and robotic approaches, enabling precise identification of the resection plane and aberrant biliary anatomy.

In our institutional experience at Seoul St. Mary's Hospital (4,098 liver resections, March 2010–December 2025), only 31 cases (0.8%) were for benign tumors, reflecting a deliberately high threshold for intervention. HCA was the most common indication (32.3%), followed by hemangioma (22.6%), MCN-L (19.4%), and FNH (19.4%). MIS became the dominant approach after 2018, and operative mortality was 0%.

In summary, a disciplined framework—MRI first, biopsy almost never, molecular subtyping for all HCA, and MIS with advanced navigation when surgery is warranted—ensures that we operate on fewer patients but on the right ones, with outcomes that meet the zero-mortality standard that benign disease demands.



Kyeong Sik Kim
Hanyang University

Self Introduction

Dr. Kyeong Sik Kim is an Assistant Professor of the Department of Surgery, Hanyang University College of Medicine, Seoul, Republic of Korea. He specializes in hepatobiliary-pancreatic surgery and liver transplantation.

Dr. Kim received his medical degree from Kyungpook National University School of Medicine in 2011 and completed his surgical residency at Samsung Medical Center in 2016. He then undertook a clinical fellowship in hepatobiliary surgery and transplantation at Samsung Medical Center (2016–2019). He subsequently served as Assistant Professor at Soonchunhyang University Seoul Hospital (2020–2022) before joining Hanyang University College of Medicine, where he has served as Clinical Assistant Professor (2022–2023) and Assistant Professor (2024–present). He is currently pursuing his Ph.D. in Surgery at Sungkyunkwan University School of Medicine.

Research Interests

- Minimally Invasive Hepatobiliary Surgery: Laparoscopic and Robotic Liver Resection, Laparoscopic Living Donor Hepatectomy
- Hepatocellular Carcinoma: Surgical Treatment Including Portal Vein Tumor Thrombosis, Interventional Radiology for Post-Transplant Vascular Complications
- Transplant Immunology: Animal Models, Immune Monitoring, and Regenerative Medicine

Representative Publications

1. Kim KS*, Choi GS, Rhu J, Kim JM. Comparison between laparoscopic liver resection and open liver resection in patients with hepatocellular carcinoma with portal vein tumor thrombosis. *Annals of Surgical Oncology*. 2024.
2. Kim KS*, Jun DW. Is it now possible to transition from laparoscopic liver resection to robotic liver resection? *Hepatobiliary Surgery and Nutrition*. 2024;13(3):55759-55559.
3. Kim KS*, Kim JM, Lee JS, Choi GS, Joh JW. Long-term Outcome of the Rendezvous Technique in Patients With Severe Biliary Anastomotic Stricture That Cannot Cannulate After Living Donor Liver Transplantation. *Liver Transplantation*. 2022.
4. Kim KS*, Lee JS, Choi GS, Cho JW, Lee SK, Kim JM. Long-term outcomes after stent insertion in patients with portal vein stenosis after liver transplantation. *Diagnostic and Interventional Radiology*. 2019;25:392-397.

Minimally Invasive Approaches in the Management of Benign Liver Tumors

Kyeong Sik Kim Hanyang University

Introduction

The role of minimally invasive surgery (MIS) for benign liver tumors has evolved profoundly since the first laparoscopic liver resection was reported in 1991.¹ Through the Louisville (2008), Morioka (2014), and Southampton (2018) consensus conferences, MIS has matured into the standard approach.^{2,3} The 2024 American College of Gastroenterology (ACG) guideline now endorses laparoscopic liver resection (LLR) as the “strongly preferred” modality for benign tumors requiring resection.⁴ Despite this technical maturation, the most clinically consequential questions remain inadequately addressed: when surgery should be performed, and how anatomical position influences operative risk. This lecture revisits these unsettled questions in the contemporary MIS era.

Classification and Surgical Indications

Per the WHO Classification of Tumours, 5th edition (2019),⁵ this lecture focuses on four surgically relevant entities: hemangioma, hepatocellular adenoma (HCA), focal nodular hyperplasia (FNH), and mucinous cystic neoplasm (MCN). Non-neoplastic cysts are excluded, as their surgical principle (fenestration) differs fundamentally from parenchymal resection. Contemporary guidelines (ACG 2024, EASL 2016, AISF 2022) converge on four general indications: persistent symptoms; risk of malignant transformation; rupture, hemorrhage, or consumptive coagulopathy; and significant size increase or diagnostic uncertainty.^{4,6,7} Notable paradigm shifts include the ACG 2024 recommendation that size alone is no longer an indication for hemangioma resection — even for lesions exceeding 10 cm.⁴ For HCA, β -catenin-activated subtype, male sex, and lesions ≥ 5 cm warrant resection regardless of symptoms.^{8,9} FNH rarely requires surgery, while MCN is premalignant and mandates complete resection in all cases.

The Settled Question: Laparoscopic versus Open Resection

The MIS-versus-open debate has been resolved. The meta-analysis by Ciria et al. (n = 9,527 LLR cases) demonstrated significant reductions in blood loss, length of stay, and morbidity with equivalent oncologic outcomes.¹⁰ For hemangioma specifically, He and Li’s meta-analysis (12 RCTs + 12 observational studies) confirmed LLR superiority in operative time, blood loss, and complications.¹¹ AISF 2022 explicitly recommends laparoscopic resection on the basis of better postoperative outcomes, quality of life,

and length of stay.⁷ Economic analyses further demonstrate that LLR saves US\$1,527–2,939 per patient compared with open resection.¹²

The Unsettled Questions: Timing and Anatomy

The surgical decision itself remains the principal challenge. For hemangioma, the Mayo cohort (n = 492) by Schnelldorfer et al. showed comparable adverse event rates between operative and nonoperative groups, and — critically — size was not a predictor of adverse events.¹³ The meta-analysis by Tuxun et al. (n = 1,485) likewise suggested that surgery may carry more risk than benefit in non-emergency patients.¹⁴ However, these data predate the LLR era and may no longer reflect contemporary risk-benefit balance.

More importantly, anatomical position emerges as a critical determinant of surgical risk. Xie et al. (PLOS One, 2025; n = 309) demonstrated that proximity to major central hepatic vasculature — within 1 cm of first-order portal vein branches, hepatic venous confluence, or IVC — independently and significantly worsens operative time, blood loss, transfusion need, length of stay, and complications, irrespective of tumor size.¹⁵ Where a tumor grows may matter more than how large it grows. A small, peripheral lesion observed today may become a centrally invasive lesion years later — the optimal surgical window may close silently.

The Hidden Cost of Watchful Waiting

Guidelines rarely quantify the long-term costs of conservative management: lifetime imaging surveillance, anxiety regarding malignant transformation or rupture, decision fatigue, and — most consequentially — the risk of losing the optimal surgical window. Klompenhouwer et al. documented the substantial surveillance burden in HCA.¹⁶ In appropriately selected patients, a single MIS resection may resolve these cumulative burdens at lower total cost than indefinite observation.

Conclusion

In benign liver tumor surgery, the question is no longer “MIS or open” — MIS is the established standard. The unresolved questions are when, where, and at what cumulative cost. Once the indication is established, MIS resection ends what observation merely postpones — for the surgeon, the patient, and the healthcare system.

Keywords: Benign liver tumor; Laparoscopic liver resection; Hepatic hemangioma; Hepatocellular adenoma; Surgical decision-making

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4. Frenette C, et al. ACG Clinical Guideline: Focal Liver Lesions. Am J Gastroenterol. 2024;119:1235-71.

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16. Klompenhouwer AJ, et al. Retrospective study on timing of resection of hepatocellular adenoma. Br J Surg. 2017;104:1695-1703.



Min-Su Park
Kyung Hee University

Self Introduction

Educational

- 2013.2 Ph.D., Degree, College of Medicine, Kyung Hee University, Seoul, South Korea
- 2008.2 M.S., Degree, College of Medicine, Kyung Hee University, Seoul, South Korea
- 2003.2 M.D., Degree, College of Medicine, Kyung Hee University, Seoul, South Korea

Professional Experience

- 2023.9-Present Professor, Division of Hepatobiliary Surgery and Organ Transplantation
Department of Surgery, Kyung Hee University Medical Center, Seoul, South Korea
- 2018.9-2023.8 Associate Professor, Division of Hepatobiliary Surgery and Organ Transplantation
Department of Surgery, Kyung Hee University Medical Center, Seoul, South Korea
- 2014.9-2018.8 Assistant Professor, Division of Hepatobiliary Surgery and Organ Transplantation
Department of Surgery, Kyung Hee University Medical Center, Seoul, South Korea

Research Interests

- HCC Biomarker
- HCC Prognosis Predictive Model
- Ischemic-Reperfusion Injury Prevention

Representative Publications

1. Surgical treatment of hepatocellular carcinoma: an expert consensus-based practical recommendation from the Korean Liver Cancer Association, ASTR 2025
2. Protective Role of Rapamycin in Fibrotic Liver Ischemia/Reperfusion Injury, Trans proc, 2024

Surveillance after Surgery Outcomes and Recurrence:
A Surgeon's Perspective

Min-Su Park *Kyung Hee University*

Benign liver tumors are increasingly detected due to widespread use of high-resolution imaging. Although many lesions can be managed conservatively, surgical resection is indicated in selected patients with symptoms, diagnostic uncertainty, malignant potential, hemorrhagic risk, or progressive growth. However, optimal postoperative surveillance strategies remain controversial and differ according to tumor biology and recurrence risk.

This presentation reviews current surgical outcomes and postoperative surveillance strategies for major benign liver tumors, including hepatocellular adenoma, focal nodular hyperplasia, hepatic hemangioma, and biliary cystic neoplasms. Particular emphasis is placed on recurrence patterns, risk stratification, imaging follow-up, and surgeon-centered decision-making after hepatic resection.

Postoperative outcomes following resection of benign liver tumors are generally excellent, with low mortality and favorable long-term quality of life. However, recurrence risk varies substantially according to tumor subtype and underlying molecular characteristics. Hepatocellular adenoma, particularly β -catenin-activated and inflammatory subtypes, may demonstrate recurrence or malignant transformation, warranting structured imaging surveillance. In contrast, recurrence after complete resection of focal nodular hyperplasia or hemangioma is extremely uncommon, and routine long-term surveillance is usually unnecessary. In biliary cystic neoplasms, incomplete excision is associated with recurrence and malignant progression, emphasizing the importance of complete surgical resection and tailored postoperative follow-up.

Surveillance after surgery for benign liver tumors should be individualized based on pathology, biological behavior, completeness of resection, and patient-specific risk factors. Surgeons play a critical role not only in operative management but also in long-term postoperative surveillance planning. A risk-adapted surveillance strategy may reduce unnecessary imaging while ensuring early detection of clinically significant recurrence.

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KASL BRANCH EARLY MORNING WORKSHOP 5

[Busan-Ulsan-Gyeongnam] Functional Cure-Paradigm Shift in CHB Treatment

Chair
Sung Jae Park (Inje Univ.)





Sang Yi Moon
Dong-A University

Self Introduction

Education

2004-2010	M.D., Degree from Dong-A University, College of Medicine, Busan, Republic of Korea
2020-2022	Master's Degree in Internal Medicine form Dong-A University, College of Medicine, Busan, Republic of Korea
2023-2026	Ph.D., in Applied Data Sciences, Department of Data Sciences Convergence, Dong-A University, Busan, Republic of Korea

Carrier

2010-2011	Internship in Dong-A University College of Medicine
2011-2015	Residency of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea
2018-2019	Clinical Fellowship of Gastroenterology and Hepatology, Dong-A University College of Medicine, Busan, Republic of Korea
2019-2022.02	Hepatology Division, Department of Internal Medicine, On hospital, Busan, Republic of Korea
2022.09-	Assistant Professor of Gastroenterology and Hepatology, Dong-A University College of Medicine, Busan, Republic of Korea

Research Interests

Big Data Analysis, Machine Learning, Hepatocellular Carcinoma

Representative Publications

1. Impact of gastrectomy on the risk of alcohol-associated liver disease in patients with gastric cancer. Scientific Reports. 2026 Feb 17. doi: 10.1038/s41598-026-40073-w.
2. Metabolic Dysfunction–Associated Steatotic Liver Disease, Alcohol Consumption, and the Risk of Atrial Fibrillation: A Nationwide Population – Based Study. Journal of the American Heart Association. 2025 Jul 15.
3. Steatotic Liver Disease Subtypes and Their Association with Colorectal Cancer Risk in Korea: A Nationwide Population-Based Study. Digestion. 2025 May 28. doi: 10.1159/000546376.
4. Association Between Metabolic Dysfunction-Associated Steatotic Liver Disease and Thyroid Cancer. Thyroid. 2024 Dec 18. doi: 10.1089/thy.2024.0522.
5. Association between ursodeoxycholic acid use and COVID-19 in individuals with chronic liver disease: a nationwide case-control study in South Korea. Virology Journal. 2024 Aug 27. doi: 10.1186/s12985-024-02464-1.

Unmet Needs in Current Treatment of Chronic Hepatitis B

Sang Yi Moon Dong-A University

Background

Chronic hepatitis B (CHB) remains a major global health burden, affecting approximately 254 million individuals worldwide as of 2022, with two-thirds residing in the Asia-Pacific region. Despite available antiviral therapies, a functional cure — defined as durable loss of hepatitis B surface antigen (HBsAg) with undetectable HBV DNA — is rarely achieved. This review addresses four critical unmet needs in current CHB management.

Unmet Need ①: Barriers to Functional Cure

Three structural barriers prevent functional cure. First, episomal covalently closed circular DNA (cccDNA) persists as a stable minichromosome maintained by histones, transcription factors, and chromatin-modifying enzymes. HBV exploits the host MRN complex (MRE11–RAD50–NBS1) for cccDNA formation, and nucleocapsid recycling continuously replenishes the cccDNA pool; no current therapy eliminates it directly. Second, massive release of subviral particles induces antigen overload, driving functional exhaustion of HBV-specific T and B cells. Third, this immune exhaustion — characterized by inhibitory receptor overexpression and impaired cytokine production — cannot be reversed by nucleos(t)ide analogues (NAs) alone; PEGIFN α also fails to restore HBV-specific CD8+ T cell responses.

Unmet Need ②: Long-Term NA Burden and Unclear Stopping Criteria

Current guidelines conflict on NA discontinuation. The 2025 AASLD guidelines conditionally recommend against stopping NAs prior to HBsAg seroclearance, while the 2025 EASL guidelines permit cessation under strict monitoring conditions. The RETRACT-B cohort (n=1,552) demonstrated that HBsAg seroclearance at 48 months was only 13.0% overall, with Asians showing a 6.8-fold lower likelihood than Caucasians; virologic relapse reached 91.4% at 48 weeks following entecavir discontinuation in Asian HBeAg-negative patients. Optimal cessation candidates require undetectable HBV DNA, no cirrhosis, and qHBsAg <100 IU/mL (Asian patients). The belief that retreatment diminishes HBsAg loss opportunity lacks sufficient evidence and should not delay retreatment.

Unmet Need ③: Residual HCC Risk after HBsAg Seroclearance

HBsAg loss does not eliminate HCC risk. Integrated HBV DNA, found in 85–90% of HBV-related HCC cases, induces genomic instability even after seroconversion. In a Korean cohort (n=829), annual HCC incidence after HBsAg seroclearance was 0.55%, with independent predictors including cirrhosis (HR 10.80), male sex (HR 8.96), and age ≥50 at seroclearance (HR 12.14). Surveillance with ultrasonography and AFP every six months should be maintained in high-risk patients. The 2025 EASL guidelines emphasize that HBsAg loss before age 50 yields greater clinical benefit, underscoring early functional cure as the primary treatment goal.

Unmet Need ④: Diagnosis and Treatment Access Gap

Globally, only 13% of CHB patients were diagnosed and 2.6% received treatment as of 2022, with annual hepatitis deaths reaching 1.3 million — an increase from 2019. No country has met the WHO 2025 treatment target of 50%. In Korea, despite achieving pediatric HBsAg prevalence ≤0.1%, the linkage-to-care rate remains at 39.4% and the treatment rate at 67.3%. The 2024 WHO guidelines expanded eligibility to include patients with significant fibrosis (APRI >0.5 or transient elastography >7 kPa) regardless of HBV DNA or ALT, and lowered the HBV DNA threshold to >2,000 IU/mL, expanding the treatment-eligible population to at least 50% of HBsAg-positive individuals.

Conclusion

Achieving functional cure in CHB requires simultaneously addressing cccDNA persistence, antigen overload, and immune exhaustion — challenges unmet by current therapies. Stricter NA cessation criteria are warranted for Asian patients, and HCC surveillance must continue after HBsAg seroclearance in high-risk groups. Expanding treatment access in alignment with the 2024 WHO guidelines is urgently needed.

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**Jeong Heo***Pusan National University*

Self Introduction

Jeong Heo, M.D., Ph.D., is a full professor of Internal Medicine, Pusan National University and Digestive Disease Center, Pusan National University Hospital. He is a medical doctor and scientist, having received his medicinae doctor and doctoral (Internal Medicine) degrees from College of Medicine, Pusan National University, in Busan Republic of Korea.

During his career, Prof. Heo held a number of academic positions, university and hospital appointments as well as principal investigator in many clinical trials for Phase I-IV of hepatitis B, C and hepatocellular carcinoma. He has also received research grants from the Korean Ministry of Education, Science and Technology. Prof. Heo has published more than 300 peer-reviewed manuscripts.

Research Interests

- Cure of Chronic Hepatitis B
- Immunotherapy of Hepatocellular Carcinoma

Representative Publications

1. Buti M, Heo J, Tanaka Y, et al. Sequential Peg-IFN after bepirovirsen may reduce post-treatment relapse in chronic hepatitis B. *J Hepatol*. 2025 Feb;82(2):222-234.
2. Lim HY, Heo J, Peguero JA, et al. Efficacy and safety of bintrafusp alfa in 2 phase I expansion cohorts with advanced HCC. *Hepatology*. 2025 Jan 1;81(1):32-43.
3. Hwang SY, Woo HY, Heo J, et al. Outcome of Atezolizumab Plus Bevacizumab Combination Therapy in High-Risk Patients with Advanced Hepatocellular Carcinoma. *Cancers (Basel)*. 2024 Feb 19;16(4):838.
4. Heo J, Liang JD, Kim CW, et al. Safety and dose escalation of the targeted oncolytic adenovirus OBP-301 for refractory advanced liver cancer: Phase I clinical trial. *Mol Ther*. 2023 Jul 5;31(7):2077-2088.
5. Yuen MF, Heo J, Jang JW, et al. Safety, tolerability and antiviral activity of the antisense oligonucleotide bepirovirsen in patients with chronic hepatitis B: a phase 2 randomized controlled trial. *Nat Med*. 2021 Oct;27(10):1725-1734.

Working Toward Functional Cure of Chronic Hepatitis B

Jeong Heo*Pusan National University*

Functional cure of chronic hepatitis B (CHB)—defined as sustained HBsAg loss with undetectable HBV DNA for ≥ 24 weeks off treatment—represents the highest attainable therapeutic goal, as it is associated with a significant reduction in the risk of hepatocellular carcinoma (HCC) and liver-related complications. Current standard-of-care nucleos(t)ide analogues (NAs) achieve functional cure in fewer than 1–2% of patients. Long-term TDF/TAF treatment data (Heo et al., AASLD 2024) demonstrate that 8 years of tenofovir-based therapy progressively shifts patients toward lower HBsAg strata. The proportion of patients with HBsAg $< 1,000$ IU/mL reaches 45% in HBeAg-negative patients and 30% in HBeAg-positive patients by year 8, continuously populating a “strike zone” favorable for targeted finite therapies.

Bepirovirsen is a novel, unconjugated antisense oligonucleotide (ASO) targeting all HBV RNAs, including pregenomic RNA and mRNAs. Unlike siRNA-based agents, bepirovirsen exerts a dual mechanism: gene silencing through RNase H-mediated degradation of viral transcripts to reduce HBsAg and HBV DNA production, and innate immune activation via TLR8 stimulation in non-parenchymal liver cells, which potentially reverses HBV-related immune exhaustion. This dual action is hypothesized to underlie its more durable responses compared with siRNA approaches. In the Phase 2b B-Clear trial (N=457), bepirovirsen 300 mg for 24 weeks with a loading dose achieved the primary endpoint in 9–10% of participants on background NA therapy with baseline HBsAg $\leq 1,000$ IU/mL. Critically, functional cure rates were markedly higher in this low-HBsAg subgroup, establishing baseline HBsAg as the dominant predictive biomarker. The Phase 2 B-Together trial showed that sequential therapy with pegylated interferon (PegIFN) following bepirovirsen did not meaningfully augment functional cure rates compared with bepirovirsen alone. However, long-term follow-up in the Phase 2 B-Sure trial demonstrated strong durability: among B-Clear on-NA complete responders who discontinued NAs, 71–78% achieved functional cure, which was maintained in 80–100% through 12–18 months. Currently, the ongoing global registrational Phase 3 program, B-Well 1 & 2 (N=1,800), is evaluating bepirovirsen in on-NA patients with baseline HBsAg $\leq 3,000$ IU/mL, with estimated completion in May 2026; results will determine the regulatory trajectory of the first approved functional cure therapy for CHB.

Bepirovirsen currently leads the CHB functional cure pipeline. The emerging paradigm of a “Priming

and Finishing” strategy—leveraging long-term NA therapy to progressively reduce HBsAg into the eligible range ($<1,000$ IU/mL), followed by a finite course of bepirovirsen—offers a rational, evidence-based framework for real-world implementation. Routine annual quantitative HBsAg (qHBsAg) monitoring in all patients on NA therapy for ≥ 3 –4 years is recommended to identify candidates approaching the therapeutic “strike zone.”

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KASL BRANCH EARLY MORNING WORKSHOP 6

[Gangwon]

Chair
Gab Jin Cheon (Univ. of Ulsan)





Minjong Lee
Ewha Womans University

Self Introduction

Prof. Minjong Lee is an Associate Professor of the Division of Gastroenterology and Hepatology in the Department of Internal Medicine, Ewha Womans University College of Medicine.

Prof. Lee graduated from Seoul National University College of Medicine with his medical degree in 2005 and Ph.D. in 2016 and completed his internship, residency, and fellowship at the Department of Internal Medicine at Seoul National University Hospital.

Since 2016, Prof. Lee has participated in the publication committee of the Korean Association of the Study of the Liver (2017-2023) and currently, in the research committee of the Korean Association of the Study of the Liver and the publication committee of the Korean Association of Gastroenterology (2024-).

Research Interests

Cirrhosis, Chronic Hepatitis B, Hepatocellular Carcinoma, MASLD

Representative Publications

- 1. A Novel Risk Prediction Model for Hepatocellular Carcinoma in MASLD: A Multinational, Multicenter Cohort Study. Clin Gastroenterol Hepatol. . 2026 Mar;24(3):688-700.e17.
- 2. PAGE-B incorporating moderate HBV DNA levels predicts risk of HCC among patients entering into HBeAg-positive chronic hepatitis B. Journal of Hepatology. 2024; 80(1):20-30.
- 3. Identification of patients with favorable prognosis after resection in intermediate-stage-hepatocellular carcinoma. International Journal of Surgery. 2024; 110(2):1008-1018.
- 4. Risk Stratification for Sarcopenic Obesity in Subjects With Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2023; 21(9):2298-2307.e18.
- 5. Association of Physical Activity With Risk of Liver Fibrosis, Sarcopenia, and Cardiovascular Disease in Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2023; 21(2):358-369.e12.
- 6. Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. Journal of Hepatology. 2018; 69(5):1066-1073.

Recent Progress in Treatment of Portal Hypertension

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Liver cirrhosis affects an estimated 58.4 million people worldwide, accounting for 4% of global annual deaths.¹ Despite advances in antiviral therapy and metabolic management, global prevalence has plateaued, underscoring the need for disease-modifying interventions.² Earlier regenerative approaches assumed transplanted stem cells would directly differentiate into hepatocytes; current evidence indicates this mechanism is not dominant. Most strategies now focus on modifying the hepatic repair microenvironment through paracrine signaling, immune modulation, macrophage-mediated fibrosis resolution, and metabolic remodeling.^{2,3} This shift has catalyzed several emerging therapeutic approaches reviewed below. Recent advances were introduced across eight emerging domains: MKK4 inhibition, autologous macrophage therapy, MSC-derived exosomes, IL-22 agonists, FXR agonists and FGF21 analogues, liver organoids, nanomedicine, and gut microbiome modulation including fecal microbiota transplantation (FMT).

1. MKK4 Inhibition

MAP kinase kinase 4 (MKK4/MAP2K4) is a signaling checkpoint that limits hepatocyte regenerative capacity. The first-in-class MKK4 inhibitor HRX215 enhanced liver regeneration in murine and porcine hepatectomy models and demonstrated favorable safety in a first-in-human Phase 1 study.⁴ Current development focuses on post-hepatectomy liver failure and small-for-size graft transplantation; applicability to established cirrhosis awaits dedicated trials.

2. Autologous Macrophage Therapy

Macrophages play a bidirectional role in hepatic fibrosis: M1-polarized macrophages drive stellate cell activation via TNF- α , IL-1 β , and TGF- β , whereas M2-polarized macrophages secrete IL-10 and MMPs to promote ECM degradation and HSC apoptosis.³ Autologous macrophage therapy ex vivo differentiates patient monocytes into regenerative macrophages for portal re-infusion. The MATCH Phase 2 trial in compensated cirrhosis provided encouraging safety data and suggested fewer liver-related severe adverse events.⁵ At AASLD 2025, Resolution Therapeutics reported that their engineered product RTX001 significantly reduced all-cause mortality and increased transplant-free survival at three years, with early INR and MELD improvement at 90 days predicting long-term benefit.⁶

3. MSC-Derived Exosomes: Cell-Free Regenerative Therapy

MSC therapy remains the most widely studied regenerative approach, with multiple studies reporting improvements in MELD score, albumin, and coagulation parameters.^{7,8} However, heterogeneity in cell source, dose, and route limits conclusions; robust evidence for long-term survival benefit is still lacking. MSC-derived exosomes offer a cell-free alternative that preserves paracrine benefits while eliminating risks of immune rejection and tumorigenesis. Key mechanisms include: exosomal miR-148a suppression of HSC activation via KLF6/STAT3;⁹ miR-26a-induced ferroptosis in HSCs through SLC7A11 modulation;¹⁰ and Wnt/ β -catenin activation by placenta-derived MSC exosomal CRP to promote angiogenesis and hepatocyte proliferation.¹¹ Wharton's jelly MSC-Exos show dose-dependent reductions in α -SMA, COLA1, and phosphorylated AKT.¹² Over 6,000 participants are enrolled in ongoing MSC-related Phase 1/2 trials globally.⁸

4. IL-22 Agonists

IL-22 activates STAT3 signaling to promote hepatocyte survival, reduce apoptosis, and stimulate repair. The recombinant fusion protein F-652 showed acceptable safety and potential liver function improvement in alcohol-associated hepatitis.^{13,14} To date, IL-22-based therapy has been evaluated primarily in acute inflammatory settings; its role in stable compensated cirrhosis or long-term fibrosis regression requires further study.

5. FXR Agonists and FGF21 Analogues

FXR agonists modulate bile acid homeostasis, lipid metabolism, and stellate cell activation. Obeticholic acid (OCA) achieved 23–35% fibrosis regression in Phase 3 trials, though pruritus remains dose-limiting.¹⁵ Cilofexor (GS-9674), a gut-restricted non-steroidal FXR agonist, significantly reduced hepatic steatosis and liver biochemistry in a 24-week Phase 2 study with improved tolerability.¹⁶ FGF21 analogues address metabolic contributors: efruxifermin demonstrated histological antifibrotic activity in MASH-related compensated cirrhosis in a Phase 2b RCT (NEJM, 2025),¹⁷ and aldafermin reduced ELF scores in compensated NASH cirrhosis and PSC.¹⁸ A pooled meta-analysis (73 studies, 2018–2025) found fibrosis regression rates of 30% for FXR agonists, 40% for FGF21 analogues, and up to 45% for combined pharmacologic-regenerative regimens.¹⁹

6. Liver Organoids and Nanomedicine

Three-dimensional liver organoids recapitulate hepatocyte polarity and inflammatory responses. Yuan et al. (Cell Stem Cell, 2024) showed that alginate-encapsulated proliferating human hepatocyte organoids (eLOs) restored albumin production, ammonia detoxification, and glycemic regulation after intraperitoneal transplantation in murine liver failure models, improving survival and accelerating endogenous regeneration.²⁰ Advanced GelMA-based co-culture systems (HepaRG + LX-2 HSCs + THP-1 monocytes) preserve hepatocyte function 5–10-fold longer than 2D models,²¹ and CRISPR/Cas9 integra-

tion enables personalized disease correction.²²

Nanomedicine overcomes the poor hepatic specificity of conventional antifibrotics. Biodegradable nanoparticles (10–200 nm) exploit fibrotic liver vascular fenestration for passive targeting; FAP- or vitamin A receptor-directed surface ligands enable active HSC-targeted delivery of anti-HSP47 siRNA, microRNA mimics, and CRISPR constructs, demonstrating potent antifibrotic effects in rodent models.²³ Enzyme-responsive FAP-cleavage systems promise near-zero off-target release.

7. Gut Microbiome Modulation and FMT

Cirrhosis causes profound gut dysbiosis—reduced microbial diversity, pathobiont overgrowth, and intestinal hyperpermeability—driving bacterial translocation and systemic inflammation.²⁴ FMT restores eubiosis by transferring a healthy donor microbiome. The THEMATIC Phase 2 trial (J Hepatol, 2025) demonstrated FMT safety without serious adverse events and reduced hepatic encephalopathy (HE) recurrence regardless of dose or route.²⁵ A prospective alcohol-related cirrhosis trial (JCM, 2025) confirmed improvements in HE severity (p=0.014), liver stiffness (p=0.027), steatosis (p=0.025), and CRP at one month.²⁶ The ChiFT Phase 2/3 RCT (NCT04932577; n=220) is currently recruiting to assess FMT's impact on complications, progression, and mortality.²⁷

Regenerative therapy for cirrhosis has undergone a paradigm shift—from direct cell replacement toward sophisticated modulation of the hepatic repair microenvironment. MKK4 inhibitors, macrophage reprogramming, MSC-derived exosomes, IL-22 agonists, FXR/FGF21 agents, organoid transplantation, targeted nanomedicine, and FMT each address distinct pathophysiological nodes. The field is converging toward combinatorial pharmacologic-regenerative strategies augmented by AI-driven patient stratification and non-invasive biomarker monitoring (circulating extracellular vesicles, non-coding RNAs). Nonetheless, large multicenter RCTs with important endpoints remain essential before any of these approaches can be considered standard of care for cirrhosis.

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KASL BRANCH EARLY MORNING WORKSHOP 7

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Self Introduction

2008	Doctor of Medicine, Jeonbuk National University Medical School
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2024-2027	Member, Medical Policy Committee, KASL
2026-2027	Member, Scientific Committee, KASL

Research Interests

- Hepatology
- Alcoholic Liver Disease
- Nonalcoholic Fatty Liver Disease
- Viral Hepatitis

Representative Publications

1. Lee CH, Lee YC, Seo SY, You GR, Jo HG, Cho SB, Cho EY, Kim IH, Choi SK, Yoon JH. Pre- and postoperative predictors of extrahepatic recurrence after curative resection for hepatocellular carcinoma. BMC Cancer. 2025 Aug 23;25(1):1368.
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Risk Stratification for Hepatocellular Carcinoma in MASLD: Who Should Be Screened?

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide, affecting over 30% of the global population, and has emerged as the fastest growing cause of hepatocellular carcinoma (HCC). While the burden of viral hepatitis-related HCC has declined due to effective antiviral therapies and vaccination programs, the global epidemics of obesity and type 2 diabetes have driven a rapid increase in MASLD-related HCC. Notably, up to 30–50% of MASLD-related HCC develops in the absence of cirrhosis, posing a major challenge for surveillance strategies.

Although HCC surveillance enables early detection and improves survival, current guidelines from major societies, including the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the American Gastroenterological Association, recommend surveillance only for patients with cirrhosis or advanced fibrosis, primarily based on cost-effectiveness considerations. In non-cirrhotic MASLD, the annual incidence of HCC is generally reported to be below 0.1%, making universal surveillance impractical. However, given the enormous global prevalence of MASLD, even this low incidence translates into a substantial absolute number of HCC cases. Furthermore, patients with non-cirrhotic MASLD who are not included in surveillance programs are more likely to be diagnosed at advanced stages, limiting curative treatment options.

In this session, we will review current evidence on risk stratification for HCC in MASLD and discuss practical strategies to identify high-risk individuals who may benefit from targeted surveillance.

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PLENARY PRESENTATION 1

Chairs

Kyung Sik Kim (Yonsei Univ.)

Yoon Jun Kim (Seoul National Univ.)

Dong-Sik Kim (Korea Univ.)



PP 1-1

Early Antiviral Therapy Reduces the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B: Causal Evidence from a Multinational Regression Discontinuity Study

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Aims: Observational studies suggest that antiviral therapy reduces the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB), but establishing its causal effect remains challenging because treatment decisions are strongly influenced by disease severity and other confounders. Several practice guidelines recommend treatment when alanine aminotransferase (ALT) levels exceed 80 U/L, creating a treatment threshold that can be leveraged as a natural experiment. This study aimed to estimate the causal effect of early antiviral therapy on HCC risk using this treatment threshold.

Methods: We employed a fuzzy regression discontinuity design using data from a multinational cohort of treatment-naïve CHB patients. This study included 10,776 patients from 19 centers across eight countries in Asia, Europe, and the United States, with baseline ALT levels spanning several international guideline thresholds (60–100 U/L). [GW1] The primary exposure of interest was early antiviral therapy initiation within 3 months of the index ALT measurement. The causal effect on HCC risk was estimated using local linear regression within a narrow ALT bandwidth of 4 U/L around the cutoff (76–84 U/L), effectively mimicking a randomized controlled trial (RCT) for patients marginally below and above the threshold who were otherwise expected to be clinically comparable.

Results: Baseline characteristics were continuous across the ALT 80 U/L threshold, supporting the validity of the quasi-experimental framework. Patients just below the cutoff (ALT 76–80 U/L), who had a significantly lower rate of early treatment (33.5% vs. 66.7%, $P < 0.001$), exhibited a substantially higher 5-year cumulative HCC risk compared to those just above the cutoff (80–84 U/L) (9.55% vs. 1.23%, reduced-form risk difference [RD] = -10.30 percentage points [pp], 95% confidence interval [CI] = -18.80–-1.80, $P = 0.017$). Fuzzy RDD estimates demonstrated that early antiviral therapy causally reduced the overall risk of HCC (RD = -41.25 pp, 95% CI = -73.45–-9.06, $P = 0.012$), with consistent preventive effects observed at 5 years (RD = -35.57 pp, 95% CI = -59.68–-11.45, $P = 0.003$) and 7 years (RD = -36.72 pp, 95% CI = -62.78–-10.66, $P = 0.006$). These findings remained consistent across various sensitivity analyses using different bandwidths (5 U/L: RD = -37.66 pp, 95% CI = -65.63–-9.70, $P = 0.008$; 6 U/L: RD = -48.61 pp, 95% CI = -70.58–-26.64, $P < 0.001$). In stratified analyses, the therapeutic benefit remained robust among patients without cirrhosis (RD = -37.85 pp, 95% CI = -68.95–-6.75, $P = 0.017$), HBeAg-negative patients (RD = -75.04 pp, 95% CI = -128.10–-21.99, $P = 0.006$), and those with low-to-intermediate viral load ($< 6 \log \text{ IU/mL}$; RD = -82.43 pp, 95% CI = -131.00–-33.85, $P < 0.001$). Placebo threshold tests at artificial thresholds (ALT 70 and 90 U/L) confirmed no significant discontinuity in HCC risk.

Conclusions: Using a regression discontinuity framework that closely approximates an RCT, this study provides causal evidence that early antiviral therapy substantially reduces the risk of HCC among patients near the conventional ALT treatment threshold. These findings provide causal evidence supporting earlier antiviral intervention and suggest that strict reliance on the ALT 80 U/L criterion may exclude patients who could benefit from treatment.

Keywords: Regression Discontinuity Design, DNA, Antiviral Treatment

PP 1-2

Sustained Enrichment of Butyrate- and Acetate-Producing Microbes Is Associated with Better Outcomes to Atezolizumab Plus Bevacizumab in Advanced Hepatocellular Carcinoma

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Aims: We conducted a prospective, multicenter study to identify functional microbial signatures and metabolite profiles associated with treatment response and to evaluate their potential as predictive biomarkers of clinical outcomes following atezolizumab plus bevacizumab (Ate/Bev) therapy in advanced hepatocellular carcinoma (HCC).

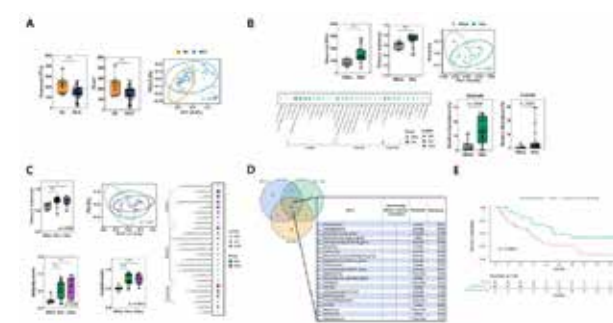
Methods: We prospectively enrolled 71 patients (discovery cohort) with advanced HCC who received Ate/Bev as first-line systemic therapy between July 2022 and December 2024 at two tertiary university hospitals. Baseline (pre-treatment) fecal microbiome samples and follow-up samples obtained at the time of the first radiologic response assessment were serially collected to evaluate treatment response-associated changes in the gut microbiome and metabolite profiles. Age-matched healthy controls (HC; $n = 10$) were included for comparison of baseline fecal microbiome composition. For validation, fecal microbiome samples were obtained from patients with long-term response (LRes; $n = 12$) treated with Ate/Bev at an independent hospital. LRes was defined as a sustained treatment response for more than 12 cycles of therapy. In addition, *in vitro* experiments using PBMCs from patients with HCC were performed to assess the effects of microbial metabolites on exhausted CD8⁺ T cells.

Results: At baseline, patients with advanced HCC exhibited significantly reduced gut microbial diversity compared with healthy controls (HC) (Fig. A). Only subtle differences were observed between responders (Res) and non-responders (NRes) at baseline. However, post-treatment microbiome analysis revealed that the Res group demonstrated a significant increase in gut microbial diversity along with distinct compositional changes. Notably, responders were enriched in bacterial taxa with short-chain fatty acid (SCFA)-producing potential (Fig. B). The increased microbial diversity observed in the Res group was consistently maintained in the LRes group

in the validation cohort. Moreover, the LRes group exhibited further enrichment of key acetate- and butyrate-producing genera compared with the Res group (Fig. C). *In vitro* experiments demonstrated that treatment with acetate or butyrate significantly reduced the expression of TIGIT⁺ and PD-1⁺ CD8⁺ T cells. Venn diagram analysis across NRes, Res, and LRes groups identified a consensus set of 22 bacterial taxa associated with favorable response, including enrichment of 20 SCFA-producing taxa and depletion of *[Ruminococcus]_gnavus_group* (Fig. D). Microbial signature-based stratification using the top 20%–50% most prevalent taxa derived from these 22 taxa consistently discriminated overall survival outcomes (Fig. E).

Conclusions: Our findings indicate that a responder-specific microbial signature, marked by enrichment of SCFA-producing taxa and depletion of dysbiosis-associated markers, is associated with improved treatment response and may represent a potential predictive biomarker for survival in advanced HCC.

Keywords: Microbiome, Survival, Metabolite, Atezolizumab



PP 1-3

Tailored Surgical Approaches for Hepatocellular Carcinoma in Caudate Lobe

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Aims: To recommend and validate a tailored resection protocol for hepatocellular carcinoma (HCC) in caudate lobe. Standardized surgical guidelines for optimal resection strategy of caudate lobe HCC are currently lacking.

Methods: We retrospectively reviewed 205 patients who underwent caudate lobectomy (CL) for HCC (2003–2022). A comprehensive protocol for CL was established based on tumor size and location within the three anatomical portions: the Spiegel lobe, the paracaval portion, and the caudate process. This protocol prioritizes anatomical en bloc resection for tumors infiltrating or abutting adjacent segments, and the extent of resection (partial vs. total CL) was determined based on tumor characteristics. Additionally, specific indications for pre-

operative transarterial chemoembolization (TACE) to downsize tumor were established to ensure clear resection margins and optimize oncologic outcomes.

Results: The tailored CL group (n=133), treated according to our protocol, showed significantly better 5-year overall survival (OS) (82.0% vs. 59.3%; $P<0.001$) and recurrence-free survival (RFS) (48.4% vs. 28.2%; $P<0.001$) than the non-tailored CL group (n=72). These survival benefits were consistently observed across three portions. In a resectable large ($\geq 5\text{cm}$) HCC without vascular invasion, preoperative TACE showed potential survival advantages, particularly in paracaval portion (5-year OS: 100.0% vs. 80.0%; $P=0.69$) and caudate process (3-year OS: 100.0% vs. 33.3%; $P=0.22$). In multivariate analysis, tailored CL remained significant favorable prognostic factor for both OS (HR: 0.33; 95% CI: 0.20–0.54; $P<0.001$) and RFS (HR: 0.63; 95% CI: 0.42–0.95; $P=0.03$).

Conclusions: Our protocol-based tailored CL is recommended for caudate lobe HCC due to its long-term survival benefits.

Keywords: Caudate Lobectomy, Hepatocellular Carcinoma, Tailored Resection, Long-Term Outcome

Figure 1. AMC protocol for tailored resection of HCC in the caudate lobe. (A) Flowchart of the AMC protocol. Recommended tailored resection strategies for HCC located in (B) Spiegel lobe, (C) paracaval portion, and (D) caudate process.

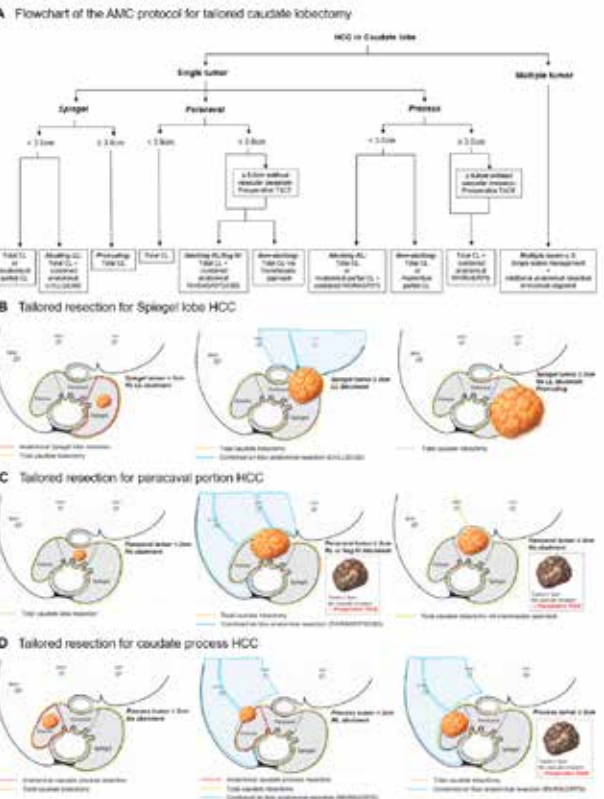


Figure 2. Survival outcomes after resection for caudate lobe HCC. (A) OS and (B) RFS for the entire cohort. (C) OS and (D) RFS according to caudate lobe sublocations, including the Spiegel lobe, paracaval portion, and caudate process. (E) OS and (F) RFS comparing tailored and non-tailored caudate lobectomy.

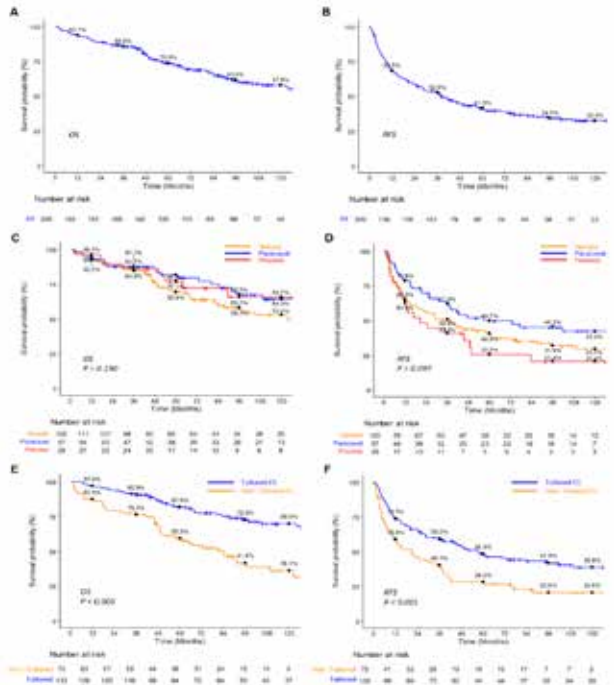
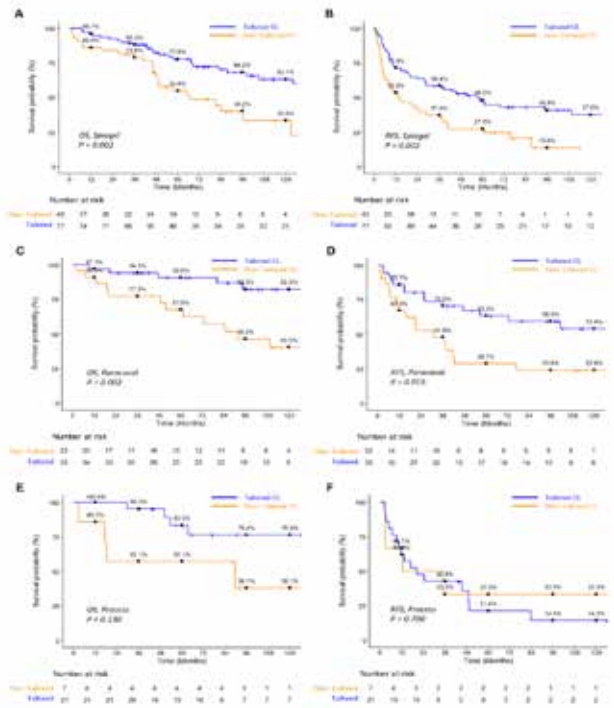


Figure 3. Survival outcomes comparing tailored and non-tailored caudate lobectomy. Overall survival and recurrence-free survival according to anatomical location: (A, B) Spiegel lobe, (C, D) paracaval lobe, and (E, F) caudate process.



PP 1-4

Early Post-Transplant Recipient-Derived Cell-Free DNA Predicts One-Year Graft Survival in Liver Transplant Recipients

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Aims: Early identification of liver transplant (LT) recipients at risk for graft failure remains challenging. Cell-free DNA (cfDNA) may capture both allograft injury and recipient tissue injury; however, its prognostic relevance after LT has been underexplored.

Methods: We retrospectively analyzed 172 LT recipients with prospectively collected cfDNA samples at postoperative day (POD) 7 and POD14. Total cfDNA, donor-derived cfDNA (dd-cfDNA), recipient-derived cfDNA (rd-cfDNA), and the percentage of dd-cfDNA (%dd-cfDNA) were quantified using low-depth whole-genome sequencing based on genotyping. Multivariable regression models were used to assess associations between cfDNA metrics and the primary outcome of 1-year graft loss and secondary outcomes.

Results: During 1-year follow-up, 21 recipients experienced graft loss. Among cfDNA-derived metrics, POD14 rd-cfDNA (log10-transformed) demonstrated the strongest association with 1-year graft loss (adjusted hazard ratio [HR] 8.81, 95% confidence interval [CI] 3.57–21.73; $P<0.001$) and the highest discrimination (adjusted C-index 0.878). Restricted cubic spline analysis confirmed a significant association between POD14 rd-cfDNA (log10) and 1-year graft loss (overall $P<0.001$). Using a cutoff derived from time-dependent receiver operating characteristic analysis (POD14 rd-cfDNA $\geq 32,839.25$ pg/mL), the high rd-cfDNA group (n=56) had markedly worse 1-year graft survival (adjusted HR 10.68, 95% CI 3.48–32.81; $P<0.001$; adjusted C-index 0.891). The high rd-cfDNA group also showed higher incidence of post-transplant sepsis and biliary complications than the low rd-cfDNA group (n=116) ($P=0.02$ and $P=0.003$, respectively).

Conclusions: POD14 rd-cfDNA is a strong early biomarker for predicting 1-year graft loss after LT and is associated with clinically relevant complications, supporting its role in early risk stratification.

Keywords: Cell-Free DNA, Biomarker, Liver Transplantation

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June 11-13, 2026 | Conrad Seoul, Korea

THE LIVER WEEK 2026

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PLENARY PRESENTATION 2

Chairs

June Sung Lee (Inje Univ.)

Jong Eun Yeon (Korea Univ.)

Kwang-Woong Lee (Seoul National Univ.)



PP 2-1

Clinically Meaningful Rates of Functional Cure in Patients with Chronic Hepatitis B Infection Treated with Bepirovirsen: B-Well Phase 3 Trials

Jinlin Hou¹, Seng-Gee Lim², Robert Elston³

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Aims: Functional cure (FC), hepatitis B surface antigen (HBsAg) loss and hepatitis B virus (HBV) DNA <lower limit of quantification (LLOQ) 24 weeks off therapy, is the treatment goal in chronic HBV infection. Bepirovirsen, an antisense oligonucleotide, is the first anti-HBV therapy in global Phase 3 trials with FC as the primary outcome.

Methods: B-Well 1 and 2 are global double-blind Phase 3 trials. Non-cirrhotic adults with nucleos(t)ide analogue (NA)-suppressed chronic HBV infection (HBV DNA <90 IU/mL) and HBsAg >100–≤3000 IU/mL were randomised 2:1 to bepirovirsen 300 mg or placebo weekly for 24 weeks. Participants discontinued NAs at Week 48, if eligible. The primary outcome was FC response rate at Week 72 for all participants; defined as HBsAg not detected (qualitative; <0.05 IU/mL) and HBV DNA <LLOQ (<20 IU/mL or target not detected) 24 weeks after discontinuing all HBV treatment. Key secondary outcomes included FC response rate for participants with baseline HBsAg ≤1000 IU/mL. Safety was assessed via adverse event and laboratory monitoring.

Results: Data are embargoed. B-Well 1 and 2 met the primary endpoint, and bepirovirsen demonstrated a statistically significant and clinically meaningful FC rate. FC rates were significantly higher with bepirovirsen plus standard of care compared with standard of care alone. Results were statistically significant across all ranked endpoints, including in patients with HBsAg ≤1000 IU/ml where an even greater effect was demonstrated. The trials demonstrated an acceptable safety and tolerability profile consistent with what was reported in other studies.

Conclusions: 24-week bepirovirsen treatment induced clinically meaningful and statistically significant FC rates versus placebo in virologically suppressed participants with chronic HBV infection, with an acceptable safety profile, showing the potential for bepirovirsen to be a first-in-class finite therapy for FC.

Keywords: Chronic Hepatitis B, Functional Cure, HBSAG Loss, Bepirovirsen, Antisense Oligonucleotide, Phase 3 Clinical Trial, Bwell

PP 2-2

Efficacy and Safety Results from Emerald-3: A Phase 3, Randomized Study of Tremelimumab plus Durvalumab with or without Lenvatinib Combined with Transarterial Chemoembolization (TACE) in Participants (pts) with Unresectable Embolization-Eligible Hepatocellular Carcinoma (eeHCC)

Jeong Heo¹, Zhenggang Ren², Joseph P. Erinjeri³, Ghassan K. Abou-Alfa^{4,6}, Riccardo Lencioni⁷, Yasuaki Arai⁸, Mohamed Bouat-tour⁹, Maria A. González-Carmona¹⁰, Yabing Guo¹¹, Ai-Bing Xu¹², Gustavo Vasconcelos Alves¹³, Arunee Dechaphunkul¹⁴, Gwo Fuang Ho¹⁵, Yueh Ni Lim¹⁶, Hong-Tao Hu¹⁷, Sri Harsha Tekumalla¹⁸, Vimal Dave¹⁹, Xavier Monzonis²⁰, Masatoshi Kudo²¹, Jia Fan²²

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Aims: TACE, a global standard of care (SoC) for unresectable eeHCC, induces a tumor immune response. STRIDE (Single Tremelimumab [T] Regular Interval Durvalumab [D]) has shown OS benefit at 6-year follow-up and is a SoC for unresectable advanced HCC. We report preplanned analyses from EMERALD-3 (NCT05301842; phase 3), which combined STRIDE ± lenvatinib (L) with TACE.

Methods: Eligible pts (≥18 yr) with confirmed eeHCC were randomized 1:1:1 to STRIDE (T 300 mg + D 1500 mg on Day 1 then D 1500 mg Q4W) + L (8 or 12 mg QD) + TACE; STRIDE + TACE; or TACE until reaching 175 pts/arm. Randomization con-

tinued 1:1 until STRIDE + L + TACE and TACE reached 275 pts/arm. D and L continued for ≤36 months (mo) or until disease progression, unacceptable toxicity, or withdrawn consent. Pts were stratified by region, any prior palliative embolization, and baseline tumor burden by up-to-7 criteria. The primary endpoint was PFS for STRIDE + L + TACE vs TACE by a stratified Cox proportional hazards model and stratified log-rank test. Key secondary endpoints were OS (STRIDE + L + TACE vs TACE) and PFS and OS (STRIDE + TACE vs TACE).

Results: As of Feb 23, 2026, 293 pts were randomized to STRIDE + L + TACE, 175 to STRIDE + TACE, and 292 to TACE. Baseline characteristics were broadly balanced across arms. STRIDE + L + TACE showed a statistically significant improvement in PFS vs TACE (HR, 0.70; 95% CI, 0.57–0.86; p=0.0007). A positive OS trend (HR, 0.84; 95% CI, 0.65–1.09; p=0.1814) was noted. STRIDE + TACE also improved PFS (HR, 0.71; 95% CI, 0.56–0.91) and OS (HR, 0.70; 95% CI, 0.51–0.95) vs TACE. STRIDE ± L + TACE showed higher 24-mo OS rates vs TACE (Table). The incidence of treatment-related AEs of max Grade 3/4 was 62.7% for STRIDE + L + TACE, 48.6% for STRIDE + TACE, and 18.6% for TACE..

Conclusions: STRIDE + L + TACE significantly improved PFS vs TACE. At the interim OS, with ≤45% maturity, a positive trend for OS with STRIDE ± L + TACE vs TACE was observed. STRIDE + TACE also improved PFS vs TACE. AEs were aligned with known safety profiles of individual therapies. The EMERALD-3 results support STRIDE ± L + TACE as potential new treatment options in unresectable eeHCC.

Table

	STRIDE + L + TACE (n=293)	TACE (n=292)	STRIDE + L + TACE (n=first 175)	STRIDE + TACE (n=175)	TACE (n=first 175)
PFS (95% CI)					
HR	0.70 (0.57–0.86)			0.71 (0.56–0.91) [†]	
p-value	0.0007 [*]			75% [‡]	
Median, mo	13.0 (12.2–16.7) [*]	9.8 (8.0–11.4) [*]	13.1 (11.0–17.7) [†]	12.9 (10.2–15.9) [†]	8.1 (6.5–10.2) [†]
OS (95% CI)					
HR	0.84 (0.65–1.09)			0.70 (0.51–0.95) [†]	
p-value	0.1814 [†]			45% [‡]	
Median, mo	39.5 (34.1–NC) [†]	34.7 (28.8–NC) [†]	39.5 (32.6–NC) [†]	NC (37.7–NC) [†]	32.9 (24.1–43.2) [†]
24-mo rate, %	66.9 (61.0–72.2) [†]	61.5 (55.4–67.0) [†]	67.8 (60.3–74.2) [†]	68.0 (60.4–74.5) [†]	57.8 (50.1–64.9) [†]

NC, not calculable.

Based on data cutoff: ^{*}1, 2 Sep 2025; [†]2, 23 Feb 2026

Keywords: Hepatocellular Carcinoma, Transarterial Chemo-embolization, Immune Checkpoint Inhibitors, Target Agent

PP 2-3

Development and Validation of a Machine-Learning Model for Waitlist Mortality Using the Largest Global Cohort of Over 195,000 Subjects

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Won-Mook Choi⁵, Young-In Yoon¹⁴, Dong Hyun Sinn⁶, Jong Man Kim¹⁵, Sangbin Han¹⁶, Jaehong Jeong¹⁷, Jun Yong Park⁸, Deok-Gie Kim¹⁸, Jae-Geun Lee¹⁸, Ho Joong Choi¹⁹, Eunice Xiang-Xuan Tan²⁰, Mark D. Muthiah²⁰, Hong-Yi Lin²¹, Oliver Tavabie²², Salim I Khakoo³, Yoon Jun Kim¹, Jung-Hwan Yoon¹, Jeong-Hoon Lee¹

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Aims: Under the current liver transplant (LT) allocation policy, deceased donor organs are prioritized for candidates at the greatest risk of short-term waitlist mortality. We aimed to develop and validate a machine-learning (ML) model for 90-day waitlist mortality using the largest and most geographically diverse LT cohort assembled to date.

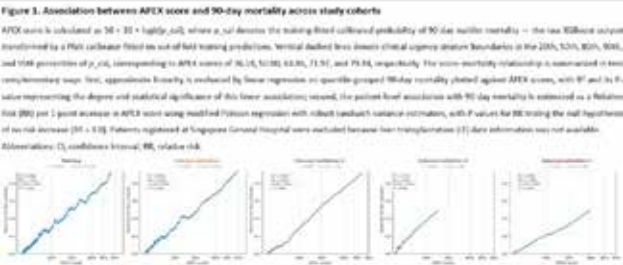
Methods: A total of 195,151 adult registrants from two national registries and 12 centers across six countries were included. The derivation cohort (n=131,820), comprising two Korean centers and the US Organ Procurement and Transplantation Network (OPTN, 2004–2023), was randomly partitioned into training (n=92,274) and internal validation (n=39,546) sets. External validation was performed in three independent cohorts: (1) a temporal OPTN cohort (2024–2025; n=21,009), (2)

the UK Transplant Registry (n=9,730), and (3) a multinational cohort (Korea, China, Singapore, and Brazil; n=6,416). Multiple ML algorithms were trained and benchmarked against MELD, MELD-Na, MELD 3.0, GEMA, and other established models.

Category	Model	AUC	Calibration	Discrimination	Calibration	Discrimination	Calibration	Discrimination	Calibration	Discrimination	Calibration	Discrimination
Discrimination	MELD	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81
	MELD-Na	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	
	MELD 3.0	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	
	GEMA	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	
	APEX	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	
	Discrimination	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
Discrimination	MELD	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	MELD-Na	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	
	MELD 3.0	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	
	GEMA	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	
	APEX	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	
	Discrimination	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
Discrimination	MELD	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	MELD-Na	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	
	MELD 3.0	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	
	GEMA	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	
	APEX	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	
	Discrimination	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
Discrimination	MELD	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	MELD-Na	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	0.82	0.96	
	MELD 3.0	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	0.83	0.97	
	GEMA	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	0.84	0.98	
	APEX	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	0.91	0.99	
	Discrimination	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	
	Calibration	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	0.95	0.81	

Table 2. Risk of 90-day mortality stratified by APEX score clinical grades

APEX score Grade	Training HR (95% CI)	Internal validation HR (95% CI)	External validation 1 HR (95% CI)	External validation 2 HR (95% CI)	External validation 3 HR (95% CI)
Grade 1 (1-10%)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Grade 2 (11-20%)	1.10 (1.05-1.15)	1.10 (1.05-1.15)	1.10 (1.05-1.15)	1.10 (1.05-1.15)	1.10 (1.05-1.15)
Grade 3 (21-30%)	1.20 (1.15-1.25)	1.20 (1.15-1.25)	1.20 (1.15-1.25)	1.20 (1.15-1.25)	1.20 (1.15-1.25)
Grade 4 (31-40%)	1.30 (1.25-1.35)	1.30 (1.25-1.35)	1.30 (1.25-1.35)	1.30 (1.25-1.35)	1.30 (1.25-1.35)
Grade 5 (41-50%)	1.40 (1.35-1.45)	1.40 (1.35-1.45)	1.40 (1.35-1.45)	1.40 (1.35-1.45)	1.40 (1.35-1.45)
Grade 6 (51-60%)	1.50 (1.45-1.55)	1.50 (1.45-1.55)	1.50 (1.45-1.55)	1.50 (1.45-1.55)	1.50 (1.45-1.55)
Grade 7 (61-70%)	1.60 (1.55-1.65)	1.60 (1.55-1.65)	1.60 (1.55-1.65)	1.60 (1.55-1.65)	1.60 (1.55-1.65)
Grade 8 (71-80%)	1.70 (1.65-1.75)	1.70 (1.65-1.75)	1.70 (1.65-1.75)	1.70 (1.65-1.75)	1.70 (1.65-1.75)
Grade 9 (81-90%)	1.80 (1.75-1.85)	1.80 (1.75-1.85)	1.80 (1.75-1.85)	1.80 (1.75-1.85)	1.80 (1.75-1.85)
Grade 10 (91-100%)	1.90 (1.85-1.95)	1.90 (1.85-1.95)	1.90 (1.85-1.95)	1.90 (1.85-1.95)	1.90 (1.85-1.95)



Results: Among all registrants, 64,112 underwent LT and 12,688 died within 90 days. Across cohorts, mean age was 51.8–53.5 years, female proportion was 34.7–44.8%, mean MELD was 16.1–20.1, and 90-day mortality was 7.5–11.5%. An XGBoost-based model incorporating seven variables—prothrombin time, age, creatinine, sodium, bilirubin, albumin, and dialysis status—selected from 18 candidates, demonstrated the best performance and was designated the Artificial Intelligence Priority Expert System for LT (APEX). APEX achieved AUROCs of 0.913 (training) and 0.910 (internal validation), significantly outperforming all conventional models (all $P<0.001$). Across external cohorts, APEX maintained superior discrimination (AUROC 0.866–0.929; all $P<0.05$) compared to preexisting models (Table 1). Logit transformation produced the APEX score, which showed a near-linear association with 90-day mortality ($R^2=0.976$ – 0.998 , all $P<0.001$; relative risk 1.054–1.060 per APEX score), consistently across all cohorts (Figure 1).

Stratification into six risk grades according to expected 90-day mortality (<20%, 20–50%, 50–80%, 80–90%, 90–95%, and $\geq 95\%$) showed progressively increasing hazards across all cohorts (Table 2). Substituting creatinine with CKD-EPI formula or adding sex as another covariate yielded no significant performance gain, indicating no substantial gender-related disparity. Sensitivity analyses confirmed robustness across sex, geographical regions, ethnicities, and disease etiologies.

Conclusions: In this largest global cohort, APEX represents a robust and equitable model for LT prioritization, consistently outperforming legacy allocation models for LT prioritization.

Keywords: Liver Transplantation, Machine Learning, Waitlist Mortality, Extreme Gradient Boosting

PP 2-4

Phase 3 Trial of Survodutide in Adults with Obesity and MASLD

Kyung Moon Kim¹, on behalf of the SYNCHRONIZE™-MASLD Committees , Investigators

¹Boehringer Ingelheim Korea, Seoul, Republic of Korea

Aims: Obesity is the leading cause of metabolic dysfunction–associated steatotic liver disease (MASLD). The high global prevalence and burden of obesity and MASLD, including its inflammatory phenotype, metabolic dysfunction–associated steatohepatitis (MASH), has created an urgent need for effective treatments for these diseases. Early treatment for MASLD is needed to reduce inflammation and alleviate the risk of cardiometabolic conditions. In previous phase 2 trials, survodutide, an investigational glucagon receptor/glucagon-like peptide-1 receptor dual agonist, induced substantial weight reduction in adults with obesity without type 2 diabetes (NCT04667377), and reduced liver fat content and improved liver histology in adults with biopsy-confirmed MASH and stage 1–3 liver fibrosis (NCT04771273; N=293).

Methods: This phase 3 trial (SYNCHRONIZE™-MASLD; NCT06309992) included 218 adults aged ≥ 18 years with a body mass index of ≥ 30 kg/m² or ≥ 27 kg/m² with ≥ 1 metabolic obesity complication and presumed or confirmed MASH, defined using imaging-based and non-invasive test criteria, or histology from a recent liver biopsy. Participants (N=216) were randomized 2:1 to receive once- weekly, subcutaneous survodutide at a dose of 6.0 mg or placebo. The two co-primary endpoints were achievement of a $\geq 30\%$ reduction in liver fat content (assessed by magnetic resonance imaging proton density fat fraction) and relative change in body weight (%) from baseline to Week 48. Safety was evaluated throughout the study.

Results: Enrollment and follow-up of all participants in the trial

have been completed. The final patient visit occurred in December 2025. Results will be available in June 2026. (following their presentation at the ADA on June 8, KST, before Mid-day of 10th June)

Conclusions: SYNCHRONIZE™-MASLD will provide a robust evaluation of the efficacy, safety and tolerability of survodutide in adults with obesity and MASLD.

Keywords: MASLD, MASH, Obesity, Survodutide

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FREE PAPER PRESENTATION 1

FP-1~FP-8	LC, Liver Failure & Autoimmune Diseases 1
FP-9~FP-15	Surgery, Technical Issues
FP-16~FP-22	HCC, Clinical 1
FP-23~FP-30	MASLD & ALD, Clinical
FP-31~FP-38	HBV 1
FP-39~FP-46	HCC, Basic
FP-47~FP-54	MASLD & ALD, Basic



Friday, June 12, 2026, 09:10-10:30

1. LC, Liver Failure & Autoimmune Disease 1

FP-1

Multimodal Computed Tomography–Clinical Integration for Noninvasive Grading of Hepatic Venous Pressure Gradient**Seul Ki Han**¹, Jin Gyo Jeong², JangHoon Ru², Jung Hyung Jung¹, Sejung Yang², Sang Gyune Kim⁴, Jhii-Hyun Ahn³, Moon Young Kim¹¹Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea; ²Department of Precision Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea; ³Department of Radiology, Yonsei University Wonju College of Medicine, Wonju, Korea; ⁴Department of internal medicine, Soonchunhyang college of medicine, Soonchunhyang university Bucheon hospital, Bucheon, Korea**Aims:** Portal hypertension is a central hemodynamic consequence of liver cirrhosis and a major determinant of hepatic decompensation and prognosis. The hepatic venous pressure gradient (HVPG) is the gold standard for measuring portal pressure and identifying clinically significant portal hypertension (CSPH), defined as HVPG greater than or equal to 10 mmHg. However, HVPG measurement is invasive, technically demanding, and limited to specialized centers. Existing noninvasive tests primarily reflect hepatic fibrosis or indirect consequences of portal hypertension rather than portal hemodynamics itself. We aimed to develop and validate a multimodal framework integrating abdominal computed tomography (CT) imaging and clinical data for noninvasive grading of HVPG.**Methods:** We retrospectively analyzed 603 individuals from Wonju Severance Christian Hospital, including 298 patients with portal hypertension confirmed by HVPG measurement and 305 controls. HVPG was measured as the mean of three standardized readings by an experienced radiologist. Abdominal CT images were spatially standardized, and fifteen routinely available clinical variables were incorporated, including age, sex, albumin, total bilirubin, aminotransferases, white blood cell count, hemoglobin, platelet count, sodium, creatinine, liver volume, spleen volume, and liver to spleen volume ratio. A multimodal deep learning framework was constructed using a Swin Transformer for image feature extraction and a language image pretraining model to encode clinical data. The model was trained to classify CSPH and to estimate HVPG as a continuous variable. Performance was assessed using five fold cross validation.**Results:** The multimodal model demonstrated robust performance for CSPH classification, achieving an accuracy of 0.79, precision of 0.85, recall of 0.83, F1 score of 0.79, and area

under the receiver operating characteristic curve of 0.87. This significantly outperformed a CT only unimodal model, which showed lower accuracy and discrimination. In regression analysis, predicted HVPG showed a strong correlation with measured HVPG, with a Pearson correlation coefficient of 0.71 and good agreement across the measurement range. These findings indicate that integrating anatomical information from CT imaging with functional clinical markers substantially improves noninvasive assessment of portal pressure.

Conclusions: We developed a multimodal CT and clinical data framework that enables accurate noninvasive grading of HVPG and identification of CSPH. By combining imaging derived anatomical features with routinely available laboratory markers, this approach overcomes key limitations of invasive HVPG measurement and indirect surrogate tests. This framework has the potential to improve risk stratification, reduce patient burden, and expand access to portal hypertension assessment, particularly in non specialized centers.**Keywords:** Portal Hypertension, Precision Medicine, Hepatic Venous Pressure Gradient, Non Invasive Test

FP-2

CT-Based Spleen Volume and Laboratory Markers Differentiate Porto-Sinusoidal Vascular Disorder from Cirrhosis across Global Cohorts**Subin Heo**¹, Maxime Ronot², Seung Soo Lee¹, Won-Mook Choi³¹Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Korea, ²Université Paris Cité, UMR 1149, CRI, Paris & Service de Radiologie, Hôpital Beaujon, France, ³Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Korea**Aims:** Porto-sinusoidal vascular disorder (PSVD) is an under-recognized cause of portal hypertension often misdiagnosed as cirrhosis. This study aims to compare CT-derived volumetric data and laboratory features between PSVD and cirrhosis and to develop and validate a noninvasive model to facilitate the clinical suspicion of PSVD.**Methods:** This retrospective study included an Eastern cohort (Korea; 101 PSVD, 202 cirrhosis) and a Western cohort (France; 45 PSVD, 100 cirrhosis). All patients exhibited signs of portal hypertension and were matched for its severity. Spleen volumes were automatically quantified on CT and normalized to personalized reference volumes. Volumetric and laboratory features were compared between the two disease groups. A multivariable conditional logistic regression model (PSVD-VL), incorporating standardized spleen volume, aspartate aminotransferase, platelet count, and international normalized ratio, was developed in the Eastern cohort and validated in the Western cohort.**Results:** Median standardized spleen volume was significantly greater in PSVD than in cirrhosis across both Eastern (5.14 vs. 3.59, $P < 0.001$) and Western (5.20 vs. 3.46, $P < 0.001$) cohorts. Conversely, hepatic synthetic function and hepatocellular injury markers were better preserved in PSVD. The PSVD-VL model demonstrated robust diagnostic performance with an area under the receiver operating characteristic curve of 0.86 (95% CI: 0.81–0.91) in the Eastern cohort and 0.79 (95% CI: 0.71–0.87) in the Western cohort.**Conclusions:** PSVD exhibits disproportionately larger spleen volumes despite more preserved liver function compared to cirrhosis of similar portal hypertension severity. Integration of CT-derived spleen volume and routine laboratory parameters may serve as an effective clinical trigger to prompt diagnostic liver biopsy.**Keywords:** Non-Cirrhotic Portal Hypertension, Liver Cirrhosis, Portal Hypertension

FP-3

Increased CD169 Expression on Peripheral Monocytes is Associated with Liver Damage in Autoimmune Hepatitis**Ga Won Han**^{1,2}, Mi Hyun Kwon^{1,2}, Kwon Yong Tak^{2,3}, Hee Sun Cho^{2,3}, Ji Won Han^{2,3}, Jeong Won Jang^{2,3}, Pil Soo Sung^{2,3}¹Department of Biomedicine & Health Sciences, The Catholic University Liver Research Center, College of Medicine, POSTECH-Catholic Biomedical Engineering Institute, Seoul, Republic of Korea; ²The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Korea; ³Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea**Aims:** Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by immune-mediated hepatocellular injury; however, the contribution of innate immune cells to disease activity remains incompletely understood. This study aimed to investigate the functional characteristics, and clinical relevance of CD169⁺ monocytes in patients with AIH.**Methods:** Peripheral blood mononuclear cells (PBMCs) and liver samples were obtained from biopsy AIH patients. Immunohistochemistry (IHC) was performed to assess immune cell infiltration in liver tissues. Single-cell RNA sequencing was conducted on peripheral blood mononuclear cells from one individual per group (healthy control and treatment-naïve AIH). Flow cytometry was used to determine the frequency of CD169⁺ monocytes in PBMCs. Serum IFN- γ levels were measured by ELISA, and IFN- γ expression in liver biopsy samples was analyzed by qRT-PCR. In addition, normal PBMCs were stimulated with recombinant IFN- γ to evaluate CD169⁺ monocyte induction.**Results:** IHC revealed marked immune cell infiltration in AIH patients with more severe portal and periportal inflamma-tion. Flow cytometric analysis showed a significantly higher frequency of CD169⁺ monocytes in PBMCs from AIH patients than in healthy controls ($P = 0.0259$). CD169 expression on total monocytes positively correlated with serum AST ($P = 0.0238$), ALT ($P = 0.0171$), and Total bilirubin levels ($P = 0.0125$). Single-cell RNA sequencing demonstrated increased CD163 expression and decreased CXCL8 expression in monocytes, suggesting functional reprogramming under chronic inflammatory conditions. Furthermore, recombinant IFN- γ treatment increased the frequency of CD169⁺ monocytes in normal PBMCs.**Conclusions:** Collectively, these findings suggest that increased IFN- γ production in the liver drives the expansion of circulating CD169⁺ monocytes in autoimmune hepatitis, thereby contributing to liver injury.**Keywords:** Autoimmune Hepatitis, Inflammation

FP-4

Multimodal Clinical DILI Prediction with Quantum-Derived Molecular Representation**Yujin Kim**¹, Seoeun Park¹, Soon Sun Kim², Ji Eun Han², Hyo Jung Cho², Jae Youn Cheong², Charmgil Hong¹¹Department of Computer Science and Electrical Engineering, Handong Global University, Pohang, Korea; ²Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea**Aims:** Drug-induced liver injury (DILI) is challenging to predict, particularly in clinical settings, as hepatotoxicity arises from both drug-specific properties and patient-specific susceptibility. Its idiosyncratic nature reflects this complexity, as the same drug may cause liver injury in one patient but not in another. Previous studies have focused on non-clinical, drug-level prediction, whereas patient-level clinical DILI prediction remains underexplored. Conventional drug representations often emphasize structural information and may not fully capture molecular characteristics relevant to reactivity and toxicity. This study proposes a multimodal framework for individualized clinical DILI risk prediction through integration of quantum-derived molecular features with patient electronic medical record (EMR) data.**Methods:** The dataset included 59 antibiotics administered to 6,028 patients between 2016 and 2020, with DILI labels assigned according to the Council for International Organizations of Medical Sciences (CIOMS) criteria. Patient-level EMR data, such as demographics, laboratory results, comorbidities, and concomitant medications, were encoded with a Feature Tokenizer Transformer. To represent drug-specific properties beyond clinical variables, two complementary molecular modalities were incorporated. Electron Localization Function (ELF) maps derived from density functional theory calculations were encoded with a Video Vision Transformer to represent

electronic features associated with molecular reactivity and toxicity. Three-dimensional structural drug embeddings were obtained from UniMol. These multimodal representations were integrated through cross-attention to model drug–patient interactions.

Results: On the test set, the full multimodal model achieved the best performance, with AUROC 0.8615 ± 0.1000 , AUPRC 0.5096 ± 0.2293 , and MCC 0.4612 ± 0.1571 . In comparison, the EMR-only baseline achieved AUROC 0.6403 ± 0.0249 , AUPRC 0.1791 ± 0.0183 , and MCC 0.1456 ± 0.0259 . Ablation analyses confirmed incremental performance gains with each added modality.

Conclusions: Multimodal integration of quantum-derived molecular features, three-dimensional drug representations, and patient EMR data substantially improved individualized clinical DILI prediction. These findings highlight the importance of jointly modeling drug-specific and patient-specific factors and suggest potential utility for clinical risk stratification in hepatotoxicity.

Table 1: Ablation study on modality contributions for multimodal clinical DILI prediction. Model performance was evaluated using five-fold cross-validation and assessed with accuracy, F1-score, Matthews correlation coefficient (MCC), area under the receiver operating characteristic curve (AUROC), and area under the precision-recall curve (AUPRC).

Model	Accuracy	F1-score	MCC	AUROC	AUPRC
EMR only	0.7907 ± 0.0217	0.2605 ± 0.0339	0.1456 ± 0.0259	0.6403 ± 0.0249	0.1791 ± 0.0183
w/o Unimol	0.7324 ± 0.3184	0.2020 ± 0.1353	0.1740 ± 0.2306	0.6916 ± 0.1865	0.3177 ± 0.2371
w/o ELF	0.8083 ± 0.0618	0.2080 ± 0.1043	0.1235 ± 0.0908	0.6900 ± 0.0606	0.2096 ± 0.0601
Full model	0.9015 ± 0.0258	0.5133 ± 0.1412	0.4612 ± 0.1571	0.8615 ± 0.1000	0.5096 ± 0.2293

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Keywords: DILI, Quantum Chemical Descriptor, Multi-Modality, Machine Learning

FP-5

Urgent Liver Transplantation for Acute-on-Chronic Liver Failure in National Data: Impact of Dynamic MELD Change and Donor Type on Survival

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Aims: Acute-on-chronic liver failure (ACLF) carries high short-term mortality without liver transplantation (LT). This study compared outcomes between living-donor (LDLT) and deceased-donor liver transplantation (DDLT) for ACLF patients and evaluated dynamic MELD score changes as prognostic indicators.

Methods: We retrospectively analyzed 199 adult ACLF patients who underwent emergency LT between 2017 and 2021 using the national KONOS registry. Patients were stratified by ACLF grade (I–III) and donor type. Dynamic change in MELD score (Δ MELD > 10%) from listing to transplantation was examined as a prognostic marker. Survival analysis and multivariate regression were performed to identify risk factors for mortality.

Results: Among 219 ACLF candidates, 199 underwent LT (LDLT = 167, DDLT = 32). Without LT, all ACLF grade III patients died. Overall survival was comparable between LDLT and DDLT for the entire cohort ($P=0.866$) and ACLF grade I ($P=0.642$). However, LDLT demonstrated superior survival for ACLF grade II ($P=0.042$) and III ($P=0.036$) patients. The mean waiting time was significantly shorter for LDLT (2.3 days) versus DDLT (4.1 days) in grade III patients. Δ MELD > 10% independently predicted mortality (adjusted OR = 2.50, 95% CI 1.14–5.52, $P=0.023$). Fungal infection (OR = 2.41, $P=0.012$), postoperative complications (OR = 2.42, $P=0.021$), and longer ICU stay (OR = 1.03 per day, $P<0.001$) were additional risk factors.

Conclusions: Timely LDLT neutralizes the prognostic disadvantage of higher ACLF grades. A rising MELD (> 10%) before LT is a key dynamic predictor of mortality. LDLT provides survival equivalence across ACLF grades and superior outcomes for grades II–III compared to DDLT, likely due to shorter waiting times. Vigilant perioperative care and early LDLT are essential to optimize outcomes.

Keywords: Acute Liver Failure, Living Liver Donors, Outcomes, Meld

FP-6

Clinical and Epidemiologic Characteristics of Autoimmune Hepatitis in Korea: Treatment Patterns and Outcomes

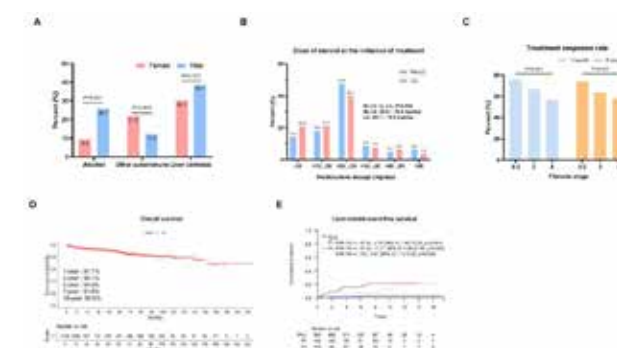
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Aims: This study aimed to evaluate the prevalence, baseline demographic characteristics, treatment strategies, and clinical outcomes of patients with autoimmune hepatitis (AIH) in Korea using a multicenter cohort.

Methods: A total of 1,401 patients newly diagnosed with autoimmune hepatitis (AIH) between January 2010 and December 2021 at 14 Korean centers were enrolled. Among them, 1,133 patients (including 867 with liver histology, biopsy group) were analyzed to evaluate prevalence, baseline demographic characteristics, treatment strategies, and clinical outcomes in Korea, with particular focus on differences according to sex and histologic fibrosis stage. Treatment outcomes included biochemical response at 6 months, overall survival, and liver-related event-free survival.

Results: The median age at diagnosis was 60 years, with the highest proportion of patients in their 50s (26.5%) and 60s (27.3%). Histologic fibrosis stages were similarly distributed between male and female patients. However, the presence of liver cirrhosis (LC) was significantly higher in male patients ($P=0.031$), who also had a higher proportion of alcohol consumption ($P<0.001$). Approximately 20% of patients had concurrent autoimmune diseases, which were significantly more common in female patients ($P<0.005$) (Fig. A). Regarding treatment strategies, combination therapy with steroids and azathioprine (42.7%) was most commonly administered, followed by steroid monotherapy (36.1%). Approximately half of the patients received an initial steroid dose of 20–30 mg/day; however, patients with LC received significantly lower steroid doses compared to those without LC ($P=0.006$) (Fig. B). As histologic fibrosis stage progressed, the rate of biochemical response at 6 months significantly decreased ($P<0.001$) (Fig. C). The overall 10-year survival probability was 89.6%, with no significant difference between male and female patients (Fig. D). The incidence of liver-related events was significantly higher in patients with F4 fibrosis, followed by those with F3 fibrosis, compared with patients with F0–2 fibrosis ($P<0.05$) (Fig. E).



Conclusions: Utilizing a large multicenter cohort, this study comprehensively characterized the demographic features, treatment patterns, and clinical outcomes of patients with AIH in Korea, providing valuable epidemiologic insights into AIH in the Korean population.

Keywords: Autoimmune Hepatitis, Sex, Liver Cirrhosis, Demographics

FP-7

Efficacy and Safety of Seladelpar in the Asian Subpopulation of Patients with Primary Biliary Cholangitis: Results from RESPONSE and ASSURE

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Aims: In the Phase 3, placebo-controlled RESPONSE (NCT04620733) and ongoing OLE ASSURE (NCT03301506), seladelpar, a first-in-class delpar (selective PPAR δ agonist), caused improvements in cholestasis, was safe/well-tolerated in patients with primary biliary cholangitis (PBC). We report the efficacy and safety of seladelpar in the Asian subpopulation.

Methods: Patients with PBC and inadequate response/intolerance to UDCA received daily oral seladelpar 10mg or placebo (2:1) for 12 months (M) in RESPONSE. Patients participating in earlier studies receiving open-label seladelpar 10mg daily in ASSURE were also analyzed (data cutoff: 31-Jan-2024). Patients self-identifying as Asian were included in this subgroup analysis and compared to non-Asian patients. Endpoints included composite response (ALP $<1.67 \times$ ULN, ALP decrease $\geq 15\%$, TB $\leq$ ULN)/ALP normalization/ALP change; safety was also assessed.

Results: In RESPONSE, 7/128 seladelpar-treated and 4/65 placebo-treated patients were Asian; mean (SD) baseline ALP (U/L) in Asian patients was 241 (53) and 324 (81) for seladelpar and placebo, respectively, vs in non-Asian patients 319 (125) and 313 (120). In ASSURE, 13/174 patients were Asian. At M12 in RESPONSE, 7/7 (100.0%) and 0/4 Asian patients achieved composite response with seladelpar and placebo, respectively, vs 72/121 (59.5%) and 13/61 (21.3%) non-Asian patients. In ASSURE, 6/8 (75.0%) vs 98/140 (70.0%) Asian vs non-Asian patients met the composite endpoint. M12 in RESPONSE, 5/7 (71.4%) Asian vs 27/121 (22.3%) non-Asian patients reported ALP normalization with seladelpar, compared with no placebo patients; in ASSURE, 2/8 (25.0%) Asian vs 53/140 (37.9%) non-Asian patients reported ALP normalization. ALP was similarly reduced in all patients receiving seladelpar. Overall, 6/7 seladelpar-treated Asian patients, 3/4 placebo-treated Asian patients in RESPONSE, and 7/13 seladelpar-treated patients in ASSURE experienced AEs. No serious AEs were reported among Asian patients.

Conclusions: Seladelpar reduced biomarkers of cholestasis among Asian and non-Asian patients in the RESPONSE and ASSURE trials. Seladelpar was overall safe/well tolerated in Asian patients.

Keywords: Primary Biliary Cholangitis, Seladelpar, Peroxisome Proliferator-Activated Receptor Delta (PPAR δ), Pruritus

Figure 1. (A) Composite Response Rate, (B) Alkaline Phosphatase Normalization, and (C) Alkaline Phosphatase Percentage Change From Baseline Through Month 12 in RESPONSE Patients Receiving Seladelpar 10 mg or Placebo (Asian and Non-Asian Subgroups)

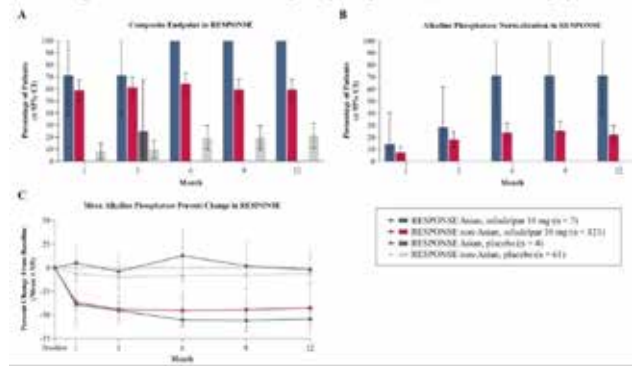
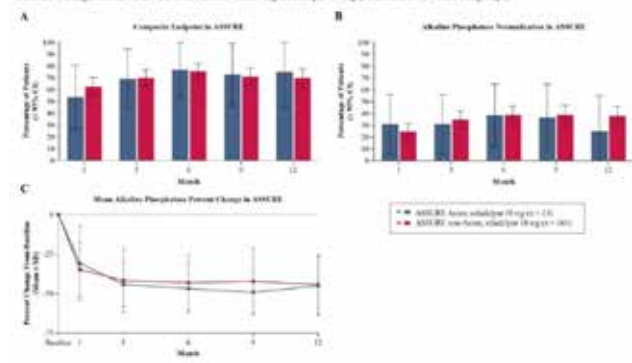


Figure 2. (A) Composite Response Rate, (B) Alkaline Phosphatase Normalization, and (C) Alkaline Phosphatase Percentage Change From Baseline Through Month 12 in ASSURE Patients Receiving Seladelpar 10 mg (Asian and Non-Asian Subgroups)



FP-8

Shear Wave Elastography Combined with ALBI Score Enhances Prediction of Hepatic Decompensation in Advanced Chronic Liver Disease

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Aims: Hepatic decompensation (HD) is a key determinant of prognosis in advanced chronic liver disease (ACLD). Shear wave elastography (SWE) is widely used to assess fibrosis, but its prognostic value for HD remains uncertain. We evaluated SWE alone and combined with ALBI for risk prediction.

Methods: 2,759 patients with ACLD who underwent SWE between 2019 and 2025 were analyzed. The endpoint was time to first HD event. Predictive performance of SWE, alone and with ALBI, was evaluated in training (n=1,839) and test (n=920)

sets.

Results: SWE alone showed good performance for predicting HD (C-index 0.760) and OS. A 10-kPa threshold effectively stratified risk, with high-risk patients having higher hazards of HD and death ($P<0.001$). SWE and ALBI showed no statistical interaction, supporting their potential for complementary synergistic effects when combined. Integrating SWE with ALBI grade created a simple three-tier classification that further improved stratification, with high-risk patients (SWE >10 kPa and ALBI grade 2/3) having a 16.6-fold risk of HD and a 21.4-fold risk of death compared with low-risk patients ($P<0.001$). A Cox model in the training set generated a weighted linear formula (SWE + $20 \times$ ALBI), termed the SALBI score, achieving the highest accuracy (C-index: training 0.802, test 0.820), outperforming SWE, ALBI, FIB-4, and MELD. The SALBI score stratified high- versus low-risk groups with 13.0-fold and 15.0-fold risks in train and test sets ($P<0.001$).

Conclusions: SWE is a robust prognostic marker for HD. A linear score combining SWE with ALBI further improves prediction and provides a practical tool for stratification.

Keywords: Shear Wave Elastography, Hepatic Decompensation, Chronic Liver Disease

Friday, June 12, 2026, 09:10-10:20

2. Surgery, Technical Issues

FP-9

Treatment Outcomes of Liver Abscesses: Efficacy of Ultrasound-Guided Percutaneous Drainage and Surgical Interventions in a Consecutive Case Series (2019–2025)

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Aims: Liver abscesses remain a significant challenge in hepatopancreatobiliary surgery, being associated with a risk of severe complications. Despite the implementation of international protocols that prioritize minimally invasive surgery, analysis of real-world clinical practice is necessary to validate surgical treatment strategies. The aim of this study is to evaluate the etiological profile, tactical approaches, and immediate treatment outcomes in a consecutive series of patients with liver abscesses.

Methods: A retrospective analysis was conducted on the treat-

ment of 75 patients between 2019 and 2025. The study assessed the etiology and the effectiveness of surgical strategies.

Results: 75 patients were included in the study; the median age was 52 years [35–65]. The cohort was predominantly male (61.3%; n = 46). The leading etiological factor was biliary tract disease (52.0%), followed by cryptogenic abscesses (29.3%) and portal spread of infection (12.0%). The success rate of primary ultrasound-guided drainage was 94.7%. No statistically significant differences in treatment efficacy were observed by etiology ($P>0.05$). A right hemihepatectomy was required in one case due to multiple abscesses of the right hepatic lobe. The overall rate of interventional and surgical management was 96.0%. Mortality was 1.33% (1 case).

Conclusions: In this clinical series, liver abscesses were predominantly of biliary origin and were successfully treated using minimally invasive ultrasound-guided drainage. Widespread use of percutaneous drainage was associated with a low complication rate and high treatment effectiveness. These findings support the rationale for using minimally invasive surgery as the first-line approach in the modern management of liver abscesses.

Keywords: Liver Abscess, Drainage, Minimally Invasive Surgery

FP-11

A Retrospective Comparative Study on Cone Unit-Based Wide-Margin Laparoscopic Anatomical Hepatectomy and Conventional Laparoscopic Anatomical Hepatectomy in the Treatment of Hepatocellular Carcinoma

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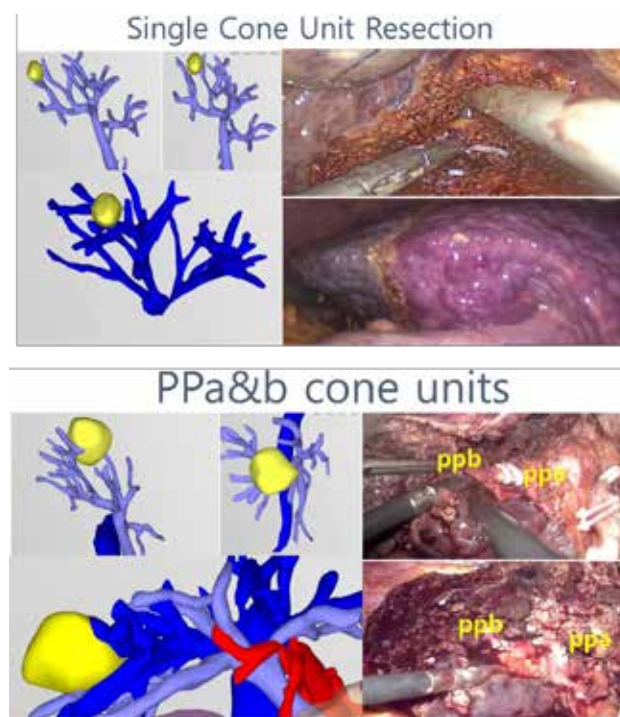
Aims: This study aims to compare the cone unit resection with wide-margin clearance against classical anatomical resection, including segmentectomy or hemihepatectomy.

Methods: A retrospective analysis was conducted with CNLC stage Ia–IIa hepatocellular carcinoma (HCC). Patients were divided the Cone Unit plus wide-margin group (cone-unit AR, CU group) and the classical group (classical AR, AR group). Perioperative outcomes were compared, including operative time, blood loss, alanine aminotransferase (ALT), aspartate aminotransferase (AST), presence of cirrhosis, antiviral therapy status, body mass index (BMI), length of hospital stay and total hospital costs. Overall survival (OS) and the Cox proportional hazards regression model, with intergroup comparisons performed using the log-rank test.

Results: A total of 64 patients were included in the analysis. Postoperative ALT and AST levels were significantly lower in

the CU group ($P<0.05$); The operative time was slightly longer in the CU group (120.50 minutes vs 95.00 minutes, $P>0.05$), and intraoperative blood loss was marginally greater (380 mL vs 330 mL, $P>0.05$); however, neither difference was statistically significant. The median follow-up period ranged from 12 to 36 months. The mean survival time was 35.00 ± 1.07 months in the CU group and 30.00 ± 0.85 months in the AR group ($P>0.05$), with no statistically significant difference observed.

Conclusions: Laparoscopic anatomical liver resection based on the Cone Unit theory combined with a wide surgical margin is both safe and feasible in patients with CNLC stage Ia–IIa hepatocellular carcinoma, and is particularly suitable for patients with cirrhosis or impaired hepatic reserve. It is associated with a reduced incidence of postoperative liver dysfunction and offers favourable clinical applicability.



Keywords: Hepatocellular Carcinoma, Laparoscopic Liver Resection, Cone Unit With Wide Surgical Margin

FP-12

Surgical Resection Beyond BCLC Recommendations Improves Survival in Intermediate and Advanced HCC: Nationwide Evidence from Korea

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Aims: BCLC recommends TACE for intermediate (B) and sys-

temic therapy for advanced (C) HCC, yet surgical resection may benefit selected patients. We evaluated real-world outcomes of upward treatment deviation using a nationwide registry with propensity-score adjustment.

Methods: We analyzed 10,517 HCC patients with valid BCLC staging in the Korea Central Cancer Registry (2008–2018). Treatments were categorized as guideline-concordant, upward deviation (more aggressive), or downward deviation (less aggressive). Outcomes were overall survival (OS) and cancer-specific survival (CSS). Selection bias was addressed using inverse probability of treatment weighting (IPTW), and Cox regression identified prognostic factors.

Results: Resection rates increased over time in both BCLC-B (25.6%→39.1%) and BCLC-C (9.9%→16.9%). In BCLC-B, IPTW-adjusted 5-year CSS was higher with resection than TACE (67.9% vs 42.9%; HR 0.27, 95% CI 0.25–0.30; $P<0.001$). Independent prognostic factors included Child-Pugh score (HR 1.14), tumor size (HR 1.08 per cm), multiple tumors (HR 1.12), and AFP (HR 1.06 per log increase). In BCLC-C, IPTW-adjusted 5-year CSS was also better with upward deviation than systemic therapy (35.2% vs 9.3%; HR 0.59, 95% CI 0.52–0.66; $P<0.001$). Benefit was attenuated with lymph node metastasis (HR 1.68), distant metastasis (HR 1.66), or portal vein invasion (HR 1.49), indicating patient selection is crucial.

Conclusions: Surgical resection provides significant survival benefit over guideline-recommended treatments in both BCLC-B and selected BCLC-C patients after adjusting for selection bias. Optimal candidates include those with preserved liver function, limited tumor burden, and absence of extrahepatic spread. These findings support expansion of surgical indications beyond current BCLC recommendations in experienced centers.

Keywords: Hepatocellular Carcinoma, BclC Stage, Surgical Resection

FP-13

Clinical Feasibility of Living Donor Liver Transplantation in Patients with Acute-On-Chronic Liver Failure: An International Multicenter Study

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Aims: Acute-on-chronic liver failure (ACLF) is associated with high mortality, and liver transplantation is often the only life-saving treatment. However, the clinical outcomes of liv-

ing donor liver transplantation (LDLT) in patients with ACLF remain controversial. This study aimed to evaluate the clinical feasibility of LDLT in ACLF patients.

Methods: This international multicenter retrospective study analyzed 236 ACLF patients who underwent LDLT at six transplant centers within the International Living Donor Liver Transplantation Group. ACLF was defined according to the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium criteria and graded based on the number of organ failures.

Results: A total of 236 patients were stratified by ACLF grade: ACLF-1 ($n=109$, 46.2%), ACLF-2 ($n=68$, 28.8%), and ACLF-3 ($n=59$, 25.0%). Pre-transplant organ failure rates and MELD scores increased significantly with higher ACLF grade (all $P<0.001$). However, GRWR was comparable between the three groups (1.05 [0.81–1.30] vs. 1.05 [0.87–1.21] vs. 0.93 [0.83–1.16], $P=0.269$). Early allograft dysfunction (6.4% vs. 10.3% vs. 25.4%, $P=0.001$) and 90-day mortality (1.5% vs. 1.8% vs. 20.3%, $P<0.001$) were significantly higher in ACLF-3 group. Multivariate analysis identified ACLF grade 3 (OR 13.66, 95% CI 2.94–63.45, $P=0.001$), prolonged warm ischemic time ≥ 30 minutes, and non-right liver grafts as independent risk factors for 90-day mortality. Furthermore, post-transplant 90-day survival decreased with increasing number of organ failures ($P=0.003$).

Conclusions: ACLF grade 3 was associated with significantly worse short- and long-term outcomes. Given LDLT's advantage of controlled timing, careful patient selection and pre-transplant optimization should be performed considering ACLF grade and associated risk factors.

Keywords: Acute-On-Chronic Liver Failure, Living Donor Liver Transplantation

FP-14

Hierarchical Quantification of Surgical Workflow of Laparoscopic Left Lateral Sectionectomy Using Step–Task–Action Triplets: Experimental Analysis of the LLS48 Dataset

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Aims: Laparoscopic left lateral sectionectomy (LLS) is a standardized anatomical liver resection that is widely performed. Despite routine video recording of minimally invasive procedures, objective and hierarchical documentation of intraoperative workflow remains limited.

Methods: We retrospectively analyzed 48 laparoscopic LLS procedures performed at a tertiary referral center between February 2020 and March 2022. Surgical videos were sampled

into 5-second clips every 90 seconds and annotated at three hierarchical levels—step, task, and action—according to the SAGES consensus guideline. Actions were represented as triplets <instrument, verb, target>. A deep learning model based on a Swin Transformer backbone was trained to recognize action triplets from single frames using a curriculum-based contrastive learning strategy (CurConMix). Learned representations were further evaluated for transfer learning in step and task recognition.

Results: The LLS48 dataset comprised 1,912 video clips (9,560 frames), corresponding to 2 h 39 min of annotated video. Five procedural steps and 18 tasks were defined. Parenchymal transection was the dominant step, accounting for 52.0% of annotated frames, followed by left liver mobilization (21.7%), hemostasis after transection (11.2%), extraction and drainage (8.8%), and trocar placement (6.3%). At the action level, 17 instruments, 16 verbs, and 38 targets formed 195 unique triplets with a pronounced long-tail distribution. Frame-level average precision for triplet recognition reached $51.7 \pm 2.4\%$. Using transferred features, step and task recognition achieved accuracies of $85.8 \pm 0.6\%$ and $69.1 \pm 2.3\%$, respectively.

Conclusions: We present the first hierarchically quantified dataset of laparoscopic LLS, demonstrating that fine-grained action triplet representations can reliably support higher-level workflow analysis.

Keywords: Surgical Video, Surgical Action Triplet Recognition, LLS48

FP-15

Adequate Surgical Margin, Not Resection Type, Determines Long-Term Outcomes after Liver Resection for Hepatocellular Carcinoma

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Aims: Although anatomical resection (AR) is often considered oncologically superior to nonanatomical resection (NAR) for hepatocellular carcinoma (HCC), it remains unclear whether reported survival benefits are attributable to the resection type itself or to its association with wider surgical margins. This study aims to determine whether long-term oncologic outcomes after liver resection for HCC are more strongly associated with resection type or with surgical margin adequacy.

Methods: This retrospective cohort study included 1,349 patients who underwent liver resection for HCC between 2004 and 2022. Surgical margin width was defined as the shortest pathological distance from the tumor to the resection margin, with a margin of at least 1 cm considered adequate.

Recurrence-free survival (RFS) and overall survival (OS) were analyzed according to resection type and margin status using propensity score matching and multivariable Cox regression, with subgroup analyses by tumor size.

Results: AR was associated with a higher rate of achieving a margin ≥ 1 cm than NAR (38.5% vs 26.4%; $P < 0.001$). After propensity score matching, OS (5-year OS, 54.5% vs 60.9%; $P = 0.087$) and RFS (5-year RFS, 33.3% vs 38.5%; $P = 0.537$) did not differ between resection types. In tumors < 5 cm, a margin < 1 cm was independently associated with worse RFS (hazard ratio, 1.45; 95% CI, 1.10–1.90; $P = 0.015$). In tumors ≥ 5 cm, neither margin width nor resection type was associated with OS or RFS.

Conclusions: Long-term oncologic outcomes after liver resection for HCC are more strongly associated with surgical margin adequacy than with resection type, particularly in small tumors.

Keywords: Hepatocellular Carcinoma, Anatomical Liver Resection, Surgical Margin

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3. HCC, Clinical 1

FP-16

Longitudinal Elevation of IL-10 Following Atezolizumab plus Bevacizumab Is Associated with Favorable Response and Survival in Advanced Hepatocellular Carcinoma

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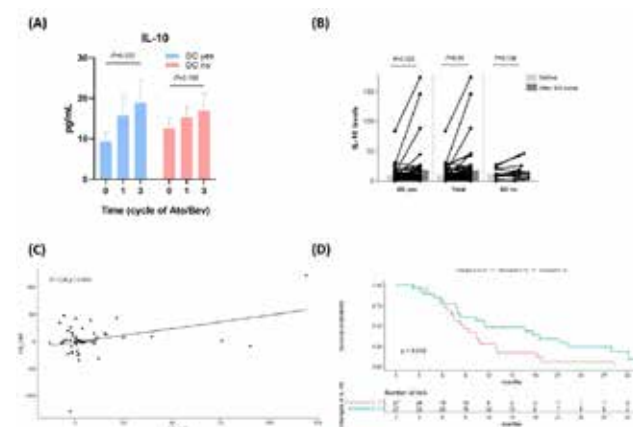
Aims: We previously reported that early increases in interleukin-10 (IL-10) and tumor necrosis factor- α (TNF- α) levels following atezolizumab plus bevacizumab (Ate/Bev) therapy predict survival in patients with advanced hepatocellular carcinoma (HCC). In this study, we aimed to longitudinally assess serial cytokine changes and evaluate their association with outcome in advanced HCC patients receiving Ate/Bev.

Methods: We prospectively enrolled 154 consecutive patients with advanced HCC who were treated with Ate/Bev between July 2022 and June 2025. Of these, 54 patients who provided blood samples at three time points—before initiation of Ate/Bev, prior to the second cycle, and prior to the fourth cycle—were included in the cytokine analysis. Serum levels of IL-2, IL-6, IL-10, IL-12, IL-17, interferon- γ (IFN- γ), and TNF- α were measured at each time point, and temporal changes

in cytokine levels were examined. The primary endpoint was overall survival, while secondary endpoints included treatment response.

Results: During a mean follow-up of 11.4 months, 42 patients (77.7%) died. The median age was 66.0 years, with most patients being male (92.6%), and the predominant etiology was viral-related HCC (85.2%). Serial changes in IL-2, IL-6, IL-12, IL-17, IFN- γ , and TNF- α levels were not significantly associated with overall survival. In contrast, IL-10 levels significantly increased following Ate/Bev treatment ($P = 0.01$), particularly among patients who achieved disease control ($P = 0.022$) (Figure A,B). Changes in IL-10 levels were positively correlated with changes in the CRP levels ($r = 0.38$, $P = 0.004$) (Figure C). Notably, patients exhibiting an increase in IL-10 levels demonstrated significantly better survival compared with those showing a decrease ($P = 0.042$) (Figure D). In multivariable analysis, an increase in IL-10 levels and CRP levels remained an independent predictor of overall survival in advanced HCC patients treated with Ate/Bev.

Conclusions: Our findings suggest that serial changes in cytokine levels—particularly IL-10—following Ate/Bev therapy may serve as a useful biomarker for monitoring treatment response and predicting clinical outcomes in patients with advanced HCC.



Keywords: Cytokine, Survival, Atezolizumab, IL-10

FP-17

Outcomes of Continuing Atezolizumab–Bevacizumab Beyond 2 Years in Patients with Advanced HCC: Preliminary Report of a Multicenter Retrospective Cohort Study using Landmark Analysis

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Aims: Atezolizumab plus bevacizumab (Atezo/Bev) is the established first-line standard of care for advanced hepatocellular carcinoma (HCC). The optimal treatment duration in patients remaining progression-free beyond 2 years has not been defined. This study evaluated the impact of continuing versus discontinuing Atezo/Bev at a 2-year landmark.

Methods: In this multicenter retrospective cohort study, patients with advanced HCC receiving first-line Atezo/Bev who remained progression-free at 2 years were classified into Maintenance ($n = 36$) and Discontinuation ($n = 50$) groups. The primary outcome was post-landmark PFS (PL-PFS); secondary outcomes were time to post-landmark progression (TT-PLP) and post-landmark OS (PL-OS). Exploratory subgroup analyses were performed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and modified RECIST (mRECIST) response, ALBI grade, and neutrophil-to-lymphocyte ratio (NLR) at landmark.

Results: At the 2-year landmark, RECIST v1.1 response comprised CR in 30 patients (35%; Discontinuation 19, Maintenance 11), PR in 32 (37%; 17, 15), and SD in 24 (28%; 14, 10); by mRECIST, 44 achieved CR (25, 19) and 42 were non-CR (25, 17). Overall, no significant difference was observed in median PL-PFS (417 vs. 523 days; $P = 0.43$) or PL-OS ($P = 0.77$). Piecewise Cox regression showed comparable risks at 0–300 days (PL-PFS HR 1.24, $P = 0.64$; TT-PLP HR 1.40, $P = 0.45$), with a non-significant trend favoring maintenance beyond 300 days (PL-PFS HR 0.40, $P = 0.13$; TT-PLP HR 0.33, $P = 0.13$). Subgroup analyses stratified by RECIST v1.1 response category and mRECIST-based CR versus non-CR showed no significant between-group differences. Among patients with ALBI grade 2–3, maintenance was associated with substantially lower risk of progression and death beyond 300 days (PL-PFS HR 0.15, $P = 0.02$; TT-PLP HR 0.09, $P = 0.04$), with no difference in the initial 300-day period (HR 1.09, $P = 0.85$). No such effect was seen in ALBI grade 1 or NLR-based subgroups.

Conclusions: Routine Atezo/Bev maintenance beyond 2 years did not improve outcomes overall, and radiologic response at landmark did not identify benefiting patients. However, those with ALBI grade 2–3 may derive a delayed benefit from continued treatment, supporting individualized de-escalation strategies in long-term responders.

Keywords: Hepatocellular Carcinoma, Atezolizumab–Bevacizumab, Recist

FP-18

Association of Radiotherapy with Atezolizumab plus Bevacizumab with Survival in Advanced Hepatocellular Carcinoma

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Aims: Immunotherapy is the standard first-line therapy for advanced hepatocellular carcinoma (HCC). Radiotherapy (RT) is well established for achieving local control and may also induce systemic immune effects, thereby augmenting the efficacy of immunotherapy. We evaluated the association of RT with outcomes in patients receiving atezolizumab plus bevacizumab (Ate+Bev).

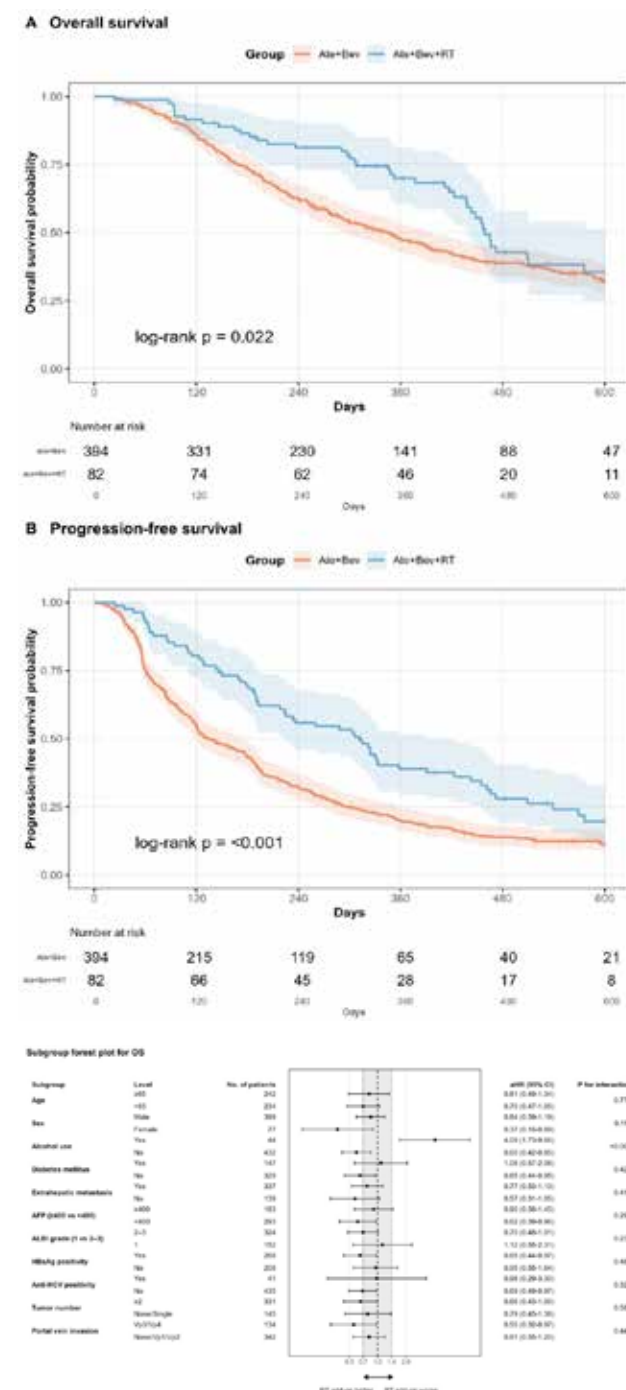
Methods: Patients who received RT during Ate+Bev therapy ($n = 82$) in 2021–2023 were compared with patients treated with Ate+Bev alone ($n = 394$). Overall survival (OS) and progression-free survival (PFS) were analyzed with multivariable Cox proportional hazards models.

Results: Median follow-up was 18.0 months and the median interval from Ate+Bev initiation to RT was 40 days. Baseline tumor characteristics and liver function were comparable between the two groups. Compared with Ate+Bev alone, Ate+Bev+RT was associated with longer OS (aHR=0.73, 95% CI=0.53–1.00, $P = 0.049$) and PFS (aHR=0.57, 95% CI=0.44–0.74, $P < 0.001$). Effects were consistent across subgroups for PFS (all interaction $P > 0.05$). In RT recipients, OS (aHR=1.41, 95% CI=0.58–3.45, $P = 0.45$) and PFS (aHR=1.15, 95% CI=0.64–2.06, $P = 0.45$) did not differ based on the timing of RT. In patients with extrahepatic RT targets, OS (aHR=13.8, 95% CI=3.30–57.7, $P < 0.001$) and PFS (aHR=5.50, 95% CI=2.15–14.0, $P < 0.001$) were inferior to those with intrahepatic RT targets. RT-related adverse events occurred in 1.2% of patients, and the overall incidence of adverse events was comparable between the two groups ($P = 0.20$).

Conclusions: Combining RT with Ate+Bev was associated with longer OS and PFS, particularly in patients with intrahepatic RT

targets. These findings support the potential role of RT as an effective adjunct to immunotherapy and warrant prospective validation.

Keywords: Liver Cancer, Immunotherapy, External Beam Radiotherapy, Immune Checkpoint Inhibition



FP-19

Differential Therapeutic Effectiveness of Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma by Chronic Hepatitis B Viral Activity

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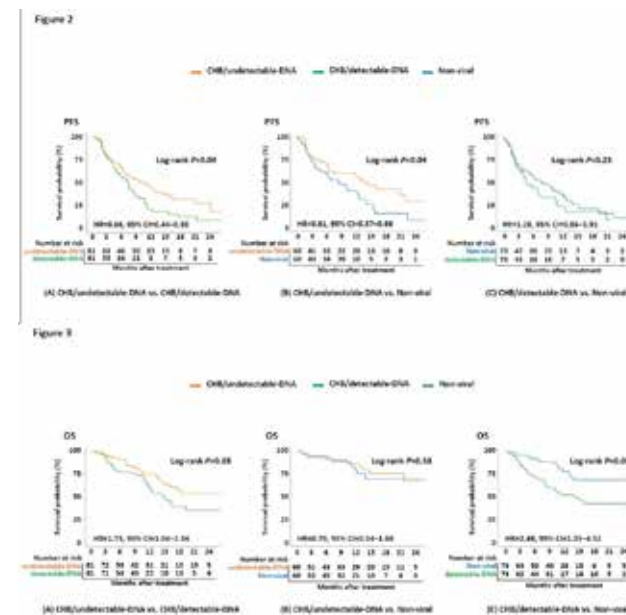
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Aims: Atezolizumab plus bevacizumab (Atezo/Bev) is recommended as the first-line therapy for unresectable hepatocellular carcinoma (uHCC). Previous studies suggested differential immunotherapy responses between viral and non-viral HCC; however, the mechanisms remained unclear. We investigated the impact of hepatitis B virus (HBV) DNA detectability, an indicator of viral replication activity that may influence the intrahepatic immune microenvironment, on Atezo/Bev outcomes.

Methods: This retrospective study included patients with uHCC, initially treated with Atezo/Bev at three hospitals in Korea. Patients were categorized as chronic hepatitis B (CHB) with undetectable HBV DNA (CHB/undetectable-DNA), CHB with detectable HBV DNA (CHB/detectable-DNA), or non-viral. Primary and secondary outcomes were progression-free survival (PFS) and overall survival (OS).

Results: We included 549 consecutive patients: CHB/undetectable-DNA (n=216), CHB/detectable-DNA (n=171), and non-viral groups (n=162). After propensity score matching, baseline characteristics were well-balanced. CHB/undetectable-DNA group had significantly longer PFS than both CHB/detectable-DNA (hazard ratio [HR]=0.66, 95% confidence interval [CI]=0.44–0.98, $P=0.04$) and non-viral groups (HR=0.61, 95% CI=0.37–0.98, $P=0.048$). PFS did not differ between CHB/detectable and non-viral groups (HR=1.28, 95% CI=0.86–1.91, $P=0.23$). CHB/detectable-DNA group showed significantly shorter OS than both CHB/undetectable-DNA (HR=1.75, 95% CI=1.04–2.94, $P=0.03$) and non-viral groups (HR=2.48, 95% CI=1.35–4.52, $P=0.003$). OS was comparable between CHB/undetectable-DNA and non-viral groups (HR=0.79, 95% CI=0.34–1.84, $P=0.58$).

Conclusions: Undetectable HBV DNA was associated with longer PFS and OS than detectable HBV DNA in CHB patients with uHCC receiving first-line Atezo/Bev. These findings suggest that HBV DNA detectability may negatively influence immunotherapy outcomes. Antiviral treatment may mitigate this effect and improve the therapeutic effectiveness of Atezo/Bev.



Keywords: Immunotherapy, Atezolizumab Plus Bevacizumab, HBV DNA, Liver Cancer

FP-20

Refining Patient Selection for Proton Beam Therapy in Hepatocellular Carcinoma: Utility of mALBI Grade and Quantitative ALBI Score Increments

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Aims: Proper patient selection is vital to maximize the therapeutic benefits of proton beam therapy (PBT) for hepatocellular carcinoma (HCC). This study aimed to evaluate the prognostic significance of post-treatment albumin-bilirubin (ALBI) score changes and identify the most robust baseline assessment tool for predicting liver function deterioration after PBT.

Methods: We retrospectively analyzed 1,812 HCC patients treated with PBT between 2015 and 2024. Post-treatment liver function was defined by the worst ALBI score recorded within 4 months. We investigated absolute ALBI increments (≥ 0.25 [1QE], ≥ 0.5 [2QE]) and relative percentage aggravation (ALBI-RA). Spline-based regression determined the optimal ALBI-RA threshold. A sensitivity analysis was conducted on a non-progressive disease (non-PD) subgroup (n=1,321) to isolate PBT-induced liver function deterioration from tumor-related decline. The predictive performance of baseline modified

ALBI (mALBI, 1+2a vs. 2b+3) grade was compared against the traditional Child-Pugh score (≤ 7 vs. ≥ 8) using Harrell's C-index and area under the curve [AUC].

Results: Both absolute ALBI increments and ALBI-RA significantly predicted overall survival (OS). Specifically, ALBI-RA ($\geq 12\%$ aggravation) exhibited the highest prognostic accuracy (C-index 0.777), outperforming absolute increments. In the non-PD subgroup, ALBI-RA remained a robust independent predictor of mortality (hazard ratio [HR] 2.064, $P<0.001$). Furthermore, the binary mALBI grade showed superior predictive accuracy for ALBI-RA (AUC 0.666; 95% confidence interval [CI] 0.639-0.693) compared to the binary Child-Pugh score (AUC 0.641; 95% CI 0.614-0.669).

Conclusions: Quantitative ALBI changes, particularly the 12% ALBI-RA threshold, are sensitive indicators of post-PBT hepatic deterioration and long-term survival. The mALBI grade offers a more objective and refined framework than the Child-Pugh system for identifying optimal PBT candidates, enabling personalized dose-volume constraints to preserve functional liver reserve.

Keywords: Hepatocellular Carcinoma, Proton Beam Therapy, ALBI Score, Prognosis

FP-21

Genomic Profiles as Determinants of Therapeutic Efficacy in Hepatocellular Carcinoma: Towards Precision Medicine

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Aims: As therapeutic options for hepatocellular carcinoma (HCC) expand, optimizing treatment selection based on individualized genomic profiles remains a clinical challenge. We hypothesized that patient-specific mutational landscapes and associated biological characteristics significantly influence treatment efficacy and tumor burden.

Methods: We analyzed 42 patients treated for HCC between January 2025 and February 2026 who had available tumor biopsy samples. Targeted Next-Generation Sequencing (NGS) was performed to identify genomic alterations. These profiles were correlated with etiology, pathological features (CK19, GPC3, PD-L1 CPS), initial tumor markers, and therapeutic responses across systemic and localized modalities. PD-L1 expression was specifically analyzed using a threshold of CPS ≥ 10 . Genomic instability was assessed using the HRD sum score.

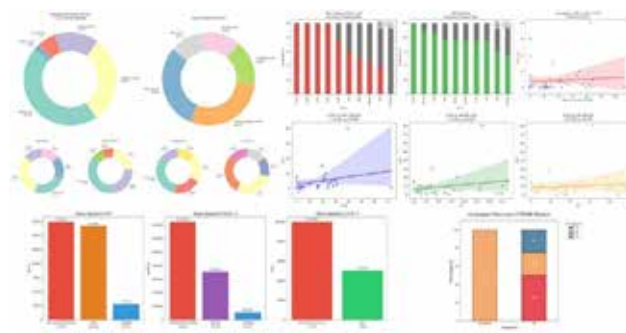
Results: In the overall cohort (N=42), chronic hepatitis B (HBV) was the most prevalent etiology (50.0%), followed by MASLD (31.0%, n=13), alcohol (16.7%), and intrahepatic CCC (7.1%),

n=3). In the overall cohort (N=42), the most frequent genomic alterations were mutations in TP53 (45.2%), TERT promoter (45.2%), and CTNNB1 (23.8%). In HBV-related HCC, the top 3 alterations were TP53 (42.9%), TERT promoter (33.3%), and RIT1 (23.8%). MASLD-related HCC was characterized by a high prevalence of TERT promoter (69.2%), CTNNB1 (46.2%), and TP53 (38.5%), highlighting the dominance of CTNNB1 in this subgroup. Pathological analysis of pure CCC cases (N=3) revealed frequent ERBB2 (66.7%) and TP53 (66.7%) alterations. Pathological analysis of pure CCC cases (N=3) revealed frequent ERBB2 (66.7%) and TP53 (66.7%) alterations. Regarding tumor burden, baseline markers were notably high in cases with FGF-family amplifications (Median AFP 4,601) or AXIN1 mutations (Median AFP 2,324), whereas CTNNB1 mutations were associated with a significantly lower baseline tumor burden (Median AFP 40.8). Furthermore, TP53 mutations and FGF-family amplifications were strongly associated with PD-L1 expression (CPS $\geq$ 10: 52.6% and 75.0%, respectively) and GPC3 positivity (78.9% and 75.0%, respectively). PD-L1 CPS also showed a positive correlation trend with the HRD sum score ($r=0.26$, $P=0.32$).

Regarding treatment response, AXIN1 mutations and RIT1 amplifications were consistently associated with refractory disease, with AXIN1 mutants showing rapid progression and a severe AFP/PIVKA-II surge under ICI (Mean Delta AFP +2,658.6 ng/mL), and RIT1 amplifications also exhibiting marker elevation (Mean Delta AFP +1,939.6 ng/mL). ARID1A mutants exhibited response dissociation, showing better extrahepatic control (Complete Response) under ICI despite intrahepatic progression. CTNNB1 mutants showed poor response to ICI (PD-Ref 25.0%) but achieved exceptional clinical stability under Lenvatinib (100% SD, Mean Delta AFP +0.27). Comprehensive analysis suggests that ARID1A alterations are favorable for ICI, while CTNNB1 is best managed with Lenvatinib or HAIC. Conversely, TP53 and AXIN1 mutations indicate high resistance to ICI (TP53: Mean Delta AFP +2,290.3 ng/mL) but remain sensitive to HAIC, which induced significant marker reduction (TP53: Mean AFP -2,912.1 ng/mL). Notably, a patient with CD274 amplification achieved a confirmed Partial Response with a significant decline in AFP levels from 13,585 to 9,517 ng/mL during Durvalumab/Tremelimumab treatment.

Conclusions: Genomic profiling via targeted NGS provides critical insights into HCC tumor burden and treatment-specific outcomes. The dominance of CTNNB1 in NBNC HCC, its association with lower tumor burden, and the clinical stability of Lenvatinib and HAIC highlight the importance of genotype-directed strategies. Integration of mutational data into clinical decision-making enables optimized, personalized treatment in HCC.

Keywords: Next Generation Sequencing, Hepatocellular Carcinoma, Individualized Therapy, Genetic Mutation



FP-22

Ambient Particulate Matter Exposure and Liver Cancer Incidence and Post-Diagnosis Mortality: A Nationwide Cohort Study

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Aims: Air pollution has been linked to various cancers, but evidence for liver cancer is limited by small sample sizes, lack of viral hepatitis data, and inability to distinguish hepatocellular carcinoma (HCC) from intrahepatic cholangiocarcinoma (ICC). We investigated the associations between ambient particulate matter (PM) exposure and liver cancer incidence and post-diagnosis mortality.

Methods: Using the Korean National Health Insurance Service database, we assembled a nationwide cohort of 8,259,460 individuals aged ≥ 30 years from the Air Impact Research cohort (2006–2022). Annual residential $PM_{2.5}$ and PM_{10} concentrations were estimated using the Community Multiscale Air Quality modeling system (1 km resolution). We evaluated incident liver cancer (C22 overall, HCC [C22.0], and ICC [C22.1]) and post-diagnosis all-cause mortality. Time-varying Cox models were adjusted for demographic, lifestyle, and clinical factors including individual-level hepatitis B virus (HBV) and hepatitis C virus (HCV) status. Stratified analyses were performed by HBV and HCV status.

Results: During a median follow-up of 12.5 years, 50,311 incident liver cancers occurred (37,330 HCC; 10,738 ICC). Each $10 \mu g/m^3$ increase in $PM_{2.5}$ was associated with increased liver cancer incidence (HR 1.34, 95% CI 1.30–1.39), with consistent associations for both HCC (HR 1.35, 1.29–1.40) and ICC (HR 1.36, 1.28–1.44). The association was stronger in HBV-positive individuals for cancer incidence (p for interaction=0.02 for $PM_{2.5}$). Among 50,311 liver cancer patients, higher PM exposure was associated with increased post-diagnosis mortality ($PM_{2.5}$ HR 1.13, 1.10–1.16 per $10 \mu g/m^3$).

Conclusions: Ambient PM exposure was independently associ-

ated with increased liver cancer incidence and post-diagnosis mortality, even after adjusting for individual viral hepatitis status, suggesting that air quality improvement and targeted protection for high-risk groups may be effective strategies to reduce the global liver cancer burden.

Keywords: Air Pollution, Liver Cancer, Hepatocellular Carcinoma, Particulate Matter

Friday, June 12, 2026, 09:10-10:30

4. MASLD & ALD, Clinical

FP-23

Alcohol-Use Trajectories and Major Adverse Liver Outcomes in MetALD: A Nationwide Longitudinal Cohort Study

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Aims: Alcohol contributes to the progression of steatotic liver disease. However, in individuals with MetALD, the impact of changes in drinking behavior on disease progression remains unclear. We investigated whether longitudinal changes in alcohol consumption were associated with the risk of major adverse liver outcomes in people with MetALD.

Methods: Data were obtained from the Korean National Health Screening Program. Adults with MetALD who completed three screening examinations (2009–2010, 2011–2012, and 2013–2014) were included ($n = 58,434$). Participants were categorized by alcohol consumption trajectories: Group 1 (sustained consumption), Group 2 (fluctuating consumption), and Group 3 (consistent reduction). The primary outcome was major adverse liver outcomes. Changes in cardiometabolic risk factors from baseline to the last examination were also evaluated.

Results: Over a median follow-up of 8.1 years, 33.2% of participants were classified as Group 1, 34.8% as Group 2, and 32.0%

as Group 3. After multivariable adjustment, Group 3 had a lower risk of major adverse liver outcomes than Group 1 (adjusted HR, 0.84; $P=0.032$). For liver-related mortality, risk was lower in Group 2 (adjusted HR, 0.73; $P=0.023$) and Group 3 (adjusted HR, 0.65; $P=0.004$). This protective association was evident among individuals with fewer than four cardiometabolic risk factors but was attenuated among those with four or more cardiometabolic risk factors. Consistent alcohol reduction was accompanied by greater resolution of hypertriglyceridemia and hypertension compared with sustained consumption.

Conclusions: Alcohol use in MetALD is highly dynamic, and hepatic risk is better captured using longitudinal drinking trajectories. Sustained alcohol reduction appears to confer cardiometabolic benefits, largely through improvements in hypertriglyceridemia and hypertension.

Keywords: MetALD, Trajectory, Alcohol

FP-24

Phase 3 ESSENCE Trial: Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Aims: Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). Semaglutide is being investigated for its potential to treat MASH in the phase 3 ESSENCE trial.

Methods: ESSENCE, an ongoing multi-center, phase 3 randomized, double-blind, placebo-controlled outcome trial involving 1200 participants with biopsy-defined MASH and fibrosis stage F2/F3, randomized participants 2:1 to once-weekly subcutane-

ous semaglutide 2.4 mg or placebo for 240 weeks. A planned interim analysis at week 72 of the first 800 participants evaluated the trial's primary endpoints: resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis.

Results: Among the 800 participants (semaglutide [n=534; 169 F2, 365 F3] or placebo [n=266; 81 F2, 185 F3]), mean (standard deviation [SD]) age was 56.0 (11.6) years and body mass index was 34.6 (7.2) kg/m². Most participants were White (67.5%), female (57.1%) and 55.9% had type 2 diabetes at baseline; 250 (31.3%) participants had F2 and 550 (68.8%) had F3. Resolution of steatohepatitis with no worsening of fibrosis was achieved by 62.9% of participants in the semaglutide group vs 34.3% receiving placebo, with an estimated difference in responder proportions (EDP) of 28.7% (95% CI, 21.1 to 36.2; $P<0.001$). Improvement in liver fibrosis with no worsening of steatohepatitis was achieved by 36.8% (semaglutide) and 22.4% (placebo) (EDP, 14.4%; 95% CI, 7.5 to 21.3; $P<0.001$), while 32.7% (semaglutide) and 16.1% (placebo) achieved combined resolution of steatohepatitis with improvement in liver fibrosis (EDP, 16.5%; 95% CI, 10.2 to 22.8; $P<0.001$). There were improvements in liver enzymes and non-invasive fibrosis markers. As expected, improvements in body weight and cardiometabolic parameters were also observed. The incidence of serious adverse events in the safety analysis set was similar in both arms.

Conclusions: In participants with MASH and moderate to advanced liver fibrosis, semaglutide 2.4 mg once-weekly demonstrated superiority vs placebo for improvement of histological activity and fibrosis markers, thus meeting both primary endpoints after 72 weeks of treatment. In addition, semaglutide improved MASH injury and fibrosis biomarkers and cardiometabolic features.

Keywords: MASH, MASLD, Semaglutide, Essence

FP-25

Shear Wave Elastography Is Comparable to Vibration-Controlled Transient Elastography for Predicting Liver-Related Events in a FIB-4–Based Two-Step Risk Stratification Strategy

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Aims: Two-step risk stratification combining the FIB-4 and

liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is widely used in metabolic dysfunction-associated steatotic liver disease (MASLD). However, the applicability of shear wave elastography (SWE) within this approach remains unclear. We compared the risk stratification performance of SWE and VCTE using two-step algorithms proposed by the Korean Association for the Study of the Liver (KASL) and the American Gastroenterological Association (AGA).

Methods: Patients with MASLD who underwent both VCTE and SWE during the same session between 2019 and 2025 were included. Risk stratification was performed using KASL- and AGA-based two-step approaches. The primary endpoint was liver-related events (LRE), defined as hepatocellular carcinoma (HCC), liver transplantation, liver-related death, and hepatic decompensation events, including ascites, variceal bleeding, and hepatic encephalopathy.

Results: Among 2,817 patients, 1,475, 721, 188, and 433 were classified as low-, intermediate-low, intermediate-high, and high-risk, respectively, using the KASL algorithm with SWE, whereas 2,196, 140, and 481 were classified as low-, intermediate-, and high-risk, respectively, using the AGA algorithm with SWE. The KASL-SWE algorithm effectively stratified LRE risk, with higher hazard ratios for intermediate-low (HR 2.98), intermediate-high (HR 10.80), and high-risk groups (HR 22.05) compared with the low-risk group. Using the AGA-SWE algorithm, intermediate- and high-risk groups showed increased risks of LREs (HR 7.58 and 11.49, respectively). The mean time-dependent area under the curve at 60 months was 0.785 for both KASL-SWE and KASL-VCTE, and 0.764 and 0.766 for AGA-SWE and AGA-VCTE, respectively, with no significant differences between SWE and VCTE in either algorithm. Net reclassification improvement did not differ between SWE- and VCTE-based KASL algorithms. SWE and VCTE demonstrated good concordance (Spearman's $\rho = 0.713$, $P<0.001$).

Conclusions: SWE-based two-step risk stratification showed predictive performance comparable to VCTE-based models in MASLD. These findings support SWE as a viable alternative for LSM within guideline-recommended two-step algorithms, warranting further multicenter validation.

Keywords: Shear Wave Elastography, Transient Elastography, MASLD, FIB-4

FP-26

Distinct Phenotype of Cryptogenic Steatotic Liver Disease and Its Unfavourable Long-Term Outcomes Including Liver-Related Death

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Aims: After renaming steatotic liver disease (SLD), cryptogenic SLD remains undefined. We aimed to investigate the clinical features and long-term outcomes of cryptogenic SLD, defined as lean SLD without cardiometabolic risk factors (CMRFs).

Methods: Clinical characteristics were evaluated in the United Kingdom Biobank (UKB) magnetic resonance proton density fat fraction (MR PDFF) cohort, defining SLD as PDFF $\geq 5\%$, and validated in four independent cross-sectional cohorts, including the National Health and Nutrition Examination Survey and the Korean National Health Insurance Service (KNHIS) health check-up cohort. Liver fibrosis was assessed in a health check-up magnetic resonance elastography cohort. Long-term outcomes were examined using Cox regression in two longitudinal cohorts: the UKB hepatic steatosis index cohort and the KNHIS cohort.

Results: Among participants who underwent MR PDFF (N = 30,847), 1,195 (3.4%) met the criteria for non-obese SLD (BMI < 25 kg/m²). Of these, 13.7% were classified as cryptogenic SLD and 86.3% as lean metabolic dysfunction-associated SLD (MASLD). Compared with the non-SLD/no CMRF group, cryptogenic SLD was predominantly male and associated with higher BMI and greater alcohol consumption despite lacking CMRFs. In the UKB PDFF cohort, cryptogenic SLD exhibited higher cT1 values, increased prevalence of PNPLA3 and TM6SF2 risk variants. Higher liver fibrosis rates were also observed in the MR elastography cohort. In longitudinal cohorts, cryptogenic SLD was independently associated with an increased risk of liver-related death (HR = 2.473, $P=0.002$).

Conclusions: Cryptogenic SLD accounts for a substantial proportion of lean SLD and represents a genetically susceptible, high-risk phenotype with advanced liver injury and increased liver-related mortality.

Keywords: Cryptogenic, Steatotic Liver Disease, Cardiometabolic Risk Factor, Liver-Related Death

FP-27

Moderate Alcohol Consumption and Liver-Related Events in MASLD: Risk Thresholds and the Impact of Cumulative Intake

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Aims: Although several studies have suggested potential health benefits of low-volume alcohol consumption, the findings remain controversial, particularly in patients with liver disease. This nationwide study aimed to investigate the association between various levels of alcohol intake and the risk of liver-related events (LRE) in individuals with steatotic liver disease (SLD).

Methods: We analyzed data from 2,951,003 adults (aged 40–64 years) in the Korean National Health Insurance Service database who underwent health examinations between 2009 and 2010. Hepatic steatosis was defined by a Fatty Liver Index ≥ 30 , and SLD was classified according to established criteria. Alcohol consumption was categorized as none, very low (1–49 g/week), low (50–99 g/week), moderate (100–139 g/week), increased (140–350 g/week), and heavy (>350 g/week). We evaluated how baseline and changes in alcohol consumption over a 4-year follow-up period influenced the long-term risk of LREs among individuals with SLD.

Results: Over a median follow-up of 13 years, the incidence rates (IR) of liver-related events (LREs) per 100,000 person-years were 132.7 in the non-SLD group, compared to 493.7, 435.7, 439.8, and 446.8 in the MASLD groups with no, very-low, low, and moderate alcohol intake, respectively. Compared to the MASLD group with none-to-low alcohol intake (0–99 g/week), the moderate alcohol intake group (100–139 g/week) had a significantly increased risk of LRE in both the multivariable-adjusted model (adjusted sub-distribution hazard ratio [aSHR]=1.035; 95% CI 1.011–1.059; $P=0.003$) and the IPTW-adjusted model (aSHR=1.071; 95% CI 1.057–1.084; $P<0.001$). Sex-specific analyses revealed a lower risk threshold for LRE in women than in men; significant risk elevation in men was observed only at the moderate level (aSHR=1.036; 95% CI 1.009–1.064; $P=0.009$), whereas women showed a markedly earlier onset of risk from low-volume intake (aSHR=1.093; 95% CI 1.022–1.169; $P=0.009$) and continuing through the moderate level (aSHR=1.122; 95% CI 0.997–1.264; $P=0.057$). The longitudinal analysis demonstrated that transitioning to moderate alcohol intake was associated with a significantly higher risk of LRE compared to sustained lower-volume drinking patterns (HR 1.393–1.509 for progression to moderate intake vs. HR 1.141–1.295 for maintaining or shifting within the low-volume range). Notably, among individuals initially categorized in the moderate alcohol group, the risk of LRE remained comparably high regardless of whether they reduced or maintained their consumption levels (HR 1.290–1.450 for reduction to low-vol-

ume vs. HR 1.312 for maintaining moderate volume).

Conclusions: Moderate alcohol intake (100–139 g/week) significantly increases the risk of LRE in individuals with MASLD, underscoring the critical need for strict alcohol limitation.

Keywords: Steatotic Liver Disease, Moderate Alcohol Consumption, Liver Related Event, Nationwide Study

FP-28

Redefining the “At-Risk” Population in MASLD: A Multi-center Cross-Cohort Analysis of Liver Injury and Long-term Outcomes using Non-Invasive Tests

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Aims: Current guidelines offer varying definitions for the “at-risk” population in metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to evaluate the prevalence of significant liver injury across different definitions and to identify key risk factors to establish a more refined definition of the at-risk population.

Methods: We conducted an analysis across five cohorts including 56,661 individuals: the Korean MRE cohort (N=9,506), V-LINK health screening cohort (N=12,341), V-LINK MASLD cohort (N=26,595), Japanese VCTE cohort (N=2,512), and US NHANES VCTE cohort (N=5,707). The prevalence of significant/advanced fibrosis, metabolic dysfunction-associated steatohepatitis (MASH), and major adverse liver outcomes (MALO) across various ‘at-risk’ MASLD definitions was evaluated using non-invasive tests (NITs).

Results: Across the five large-scale cohorts of 56,661 individuals, the prevalence of significant fibrosis (≥F2) and advanced fibrosis (≥F3) ranged from 1.3%–12.7% and 0.6%–7.7%, respectively, while the proportion of MASH varied from 44.8%–69.4% across the EASL, AASLD, AGA, ADA, and APASL criteria. We developed a newly proposed criteria incorporating key risk factors of liver injury: ultrasound-defined steatosis, ALT>40 U/L, type 2 diabetes, and metabolic syndrome. Our newly proposed criteria identified an at-risk population with a consistently higher prevalence of MASH, ranging from

56.2%–74.6% across all cohorts, while maintaining comparable detection rates for significant (1.5%–12.9%) and advanced fibrosis (0.6%–7.7%). The prevalence of MALO was evaluated to validate prognostic accuracy. In the US NHANES cohort, our new criteria had the highest incidence of MALO at 12.3%, surpassing other established guidelines (range: 10.5%–12.2%). In the VLINK-MASLD cohort, our new criteria maintained a high prognostic yield of 2.2%, which was comparable to the range observed across other criteria (2.1%–2.4%).

Conclusions: The current definitions of “at-risk” MASLD exhibit significant heterogeneity in the detection of liver injury. Our newly proposed criteria more effectively identify populations with a high prevalence of MASH and MALO.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease, At-Risk Population, Metabolic Dysfunction-Associated Steatohepatitis, Major Adverse Liver Outcome

FP-29

Cost-Effectiveness of Resmetirom Treatment for Suspected ‘At-Risk MASH’ Based on Transient Elastography without Biopsy

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Aims: In clinical practice, resmetirom treatment may be initiated for patients with suspected ‘at-risk MASH’ based on vibration-controlled transient elastography (VCTE) without liver biopsy. This study evaluated the cost-effectiveness of resmetirom treatment for suspected ‘at-risk MASH’ identified by VCTE without biopsy, accounting for diagnostic misclassification.

Methods: We conducted a cost-utility analysis from the United States healthcare payer perspective to evaluate resmetirom treatment for suspected ‘at-risk MASH’ identified by VCTE versus no pharmacologic treatment. Under an AASLD-aligned VCTE-based treatment algorithm (VCTE 8–15 kPa), we assumed substantial off-target treatment arising from false-positive eligibility. The base-case fibrosis distribution was anchored to the Hepamet registry and systematically varied in scenario analyses. Treatment efficacy on fibrosis progression and regression were based on MAESTRO-NASH relative risks, and cardiovascular benefit was conservatively modeled via

LDL-cholesterol-mediated risk reduction.

Results: In the base case, resmetirom generated 1.00 incremental QALYs and 1.06 incremental life-years at an incremental cost of \$137,151 per patient, resulting in an ICER of \$137,361 per QALY, and remained cost-effective versus no pharmacologic treatment with intensive lifestyle intervention. Scenario analyses showed that the ICER was highly sensitive to diagnostic misclassification, largely driven by the proportion of false-positive F0–F1 patients treated and the proportion of F4 patients misclassified by VCTE. Cost-effectiveness was no longer maintained when the proportion of F0–F1 exceeded 45%. In probabilistic sensitivity analysis, the probability that resmetirom was cost-effective was 65% at \$150,000 per QALY, with cost-effectiveness becoming more likely than no treatment at approximately \$130,000 per QALY.

Conclusions: Resmetirom treatment based on VCTE for suspected ‘at-risk MASH’ appears cost-effective under most plausible misclassification scenarios, although sensitive to the proportion of off-target F0–F1 patients included.

Keywords: Cost, Resmetirom, Biopsy

FP-30

Serum Osteoprotegerin Predicts Liver and Cardiometabolic Outcomes in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor receptor superfamily. We aimed to determine the clinical significance of OPG as a predictor of major adverse liver outcomes (MALO) as well as major adverse cardiovascular events (MACE) in metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: In UK biobank data (n=41,005), serum OPG levels were compared across steatotic liver disease (SLD) subgroups.

Findings were validated in an independent Asian hospital cohort (n=176) with transient elastography-derived liver stiffness measurement and controlled attenuation parameter. Hepatic OPG expression was evaluated using bulk RNA sequencing, single-nucleus RNA sequencing, and immunohistochemistry. Two-sample Mendelian randomization was performed to assess the causal effects of genetically predicted OPG on hepatocellular carcinoma and cirrhosis. Cox proportional hazards models were used to evaluate serum OPG as a predictor of MALO and MACE, and discrimination was assessed using Harrell’s C-index.

Results: Serum OPG levels were higher in individuals with MASLD than in those with non-SLD, were positively associated with major cardiometabolic risk factors, and increased stepwise with a greater number of risk factors. In the validation cohort, serum OPG rose in parallel with liver stiffness and MASLD disease severity; an OPG concentration of at least 150 pg/mL was the strongest independent predictor of clinically significant hepatic fibrosis. Higher OPG levels independently predicted both MALO (adjusted HR ~2.2–2.4) and MACE (fully adjusted HR ~1.33) across SLD subgroups. Mendelian randomization analyses supported a positive causal estimate of genetically predicted OPG on hepatocellular carcinoma risk. Bulk and single-nucleus transcriptomic analyses further suggested that elevated OPG in MASLD reflects upregulated endothelial OPG expression rather than hepatocyte-derived expression, with endothelial OPG increasing with histologic activity.

Conclusions: Serum OPG correlates with hepatic fibrosis and serves as a predictive biomarker to identify individuals with MASLD at high risk for both MACE and MALO.

Keywords: Osteoprotegerin, MASLD, MALO

Friday, June 12, 2026, 13:30-14:50

5. HBV 1

FP-31

Long-Term Persistence of the Parabolic Association Between Baseline HBV DNA and Hepatocellular Carcinoma Risk after Antiviral Therapy

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Aims: Previous studies have demonstrated a non-linear parabolic relationship between baseline hepatitis B virus (HBV) DNA levels and hepatocellular carcinoma (HCC) risk, regardless of antiviral treatment. However, it is unclear whether this association changes over time after treatment initiation. The present study aimed to assess the temporal evolution of the relationship between baseline HBV DNA levels and HCC risk using landmark analyses at predefined time points in patients with chronic hepatitis B (CHB).

Methods: We conducted a multicenter retrospective cohort study of 4,657 non-cirrhotic patients with CHB and baseline HBV DNA levels $\geq 2,000$ IU/mL who initiated antiviral therapy. Time-dependent landmark analyses were performed at 1-, 3-, 5-, and 7-years following cohort entry. The association between baseline HBV DNA levels, categorized into discrete groups, and HCC risk was evaluated at each time point using multivariable Cox regression models. Subgroup analyses were additionally performed to assess potential effect modification by other clinical factors.

Results: Among the 4,657 patients, the mean age was 45.0 years; 2,843 (61.0%) were male, and 2,891 (62.1%) were hepatitis B e antigen (HBeAg)-positive. During a median follow-up of 8.9 years, HCC developed in 225 (4.8%) patients. In multivariable Cox regression analyses, a parabolic association between baseline HBV DNA levels and HCC risk persisted across all landmark time points, although the magnitude of the peak risk gradually attenuated over time. The highest risk was observed among patients with baseline HBV DNA levels of $6.00\text{--}6.99 \log_{10}$ IU/mL (hazard ratio [HR], 4.01; $P < 0.001$ at the 1-year landmark; HR, 3.50; $P < 0.001$ at 3 years; HR, 3.05; $P < 0.001$ at 5 years; and HR, 2.13; $P = 0.03$ at 7 years), followed by those with baseline HBV DNA levels of $7.00\text{--}7.99 \log_{10}$ IU/mL (HR, 2.59; $P < 0.001$ at 1 year; HR, 2.75; $P < 0.001$ at 3 years; HR, 2.89; $P < 0.001$ at 5 years; and HR, 2.52; $P = 0.005$ at 7 years), compared with patients with baseline HBV DNA levels $\geq 8.00 \log_{10}$ IU/mL. In subgroup analyses, the effect size of baseline HBV DNA levels ($6.00\text{--}7.99$ vs. $\geq 8.00 \log_{10}$ IU/mL) on HCC risk was more pronounced among patients younger than 50 years, those who were HBeAg-positive, and those with a fibrosis-4 index < 2 .

Conclusions: Despite long-term antiviral therapy, baseline HBV DNA levels remained non-linearly and parabolically associated with HCC risk up to and beyond 7 years after treatment initiation. These findings suggest that, to further reduce long-term HCC risk, antiviral therapy should be initiated earlier, before HBV-related hepatocarcinogenic events accumulate.

Keywords: Antiviral Therapy, Hepatitis B, Hepatocellular Carcinoma

FP-32

Clinical Impact of Antiviral Therapy on Reducing HCC and Cirrhosis Risks in the Indeterminate Phase of Chronic Hepatitis B

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Aims: Many patients in the indeterminate phase chronic hepatitis B (CHB) remain untreated due to rigid criteria. We aimed to evaluate whether untreated indeterminate patients have higher risks of hepatocellular carcinoma (HCC) and liver cirrhosis (LC) compared to treated active phase patients, and to evaluate the clinical benefits of antiviral therapy (AVT) in indeterminate phase subgroups.

Methods: A total of 15,684 patients with HBV were analyzed from the VLINK HBV cohort, a multi-center database including data from seven tertiary-level hospitals. Patients with indeterminate phase was sub-stratified: Low-ALT (ALT < 40 U/L), moderate-level viremia (ALT $40\text{--}80$ IU/L, DNA $2,000\text{--}8\log$), and low-level viremia (DNA $< 2,000$, ALT > 40 IU/L) groups. We calculated incidence rates (IR) per 100 person-years (PY) and adjusted hazard ratios (aHR) using Cox proportional hazards models.

Results: In the HBeAg-positive group, untreated indeterminate patients showed a higher HCC IR (0.938) and LC IR (1.84) compared to treated active patients, who had an IR of 0 for both outcomes (aHR=1.85, 95% CI 1.24–2.76 for HCC; aHR=2.12, 95% CI 1.45–3.10 for LC). Similarly, untreated HBeAg-negative indeterminate patients had a higher HCC IR (0.532) than treated active patients (IR=0.218), representing a significantly elevated risk (aHR=1.42, 95% CI 1.08–1.87). Within the indeterminate phase, AVT significantly reduced the LC IR from 2.888 to 1.521 (aHR=0.52, 95% CI 0.38–0.71) and the HCC IR from 1.114 to 0.899 (aHR=0.68, 95% CI 0.45–0.92) in moderate-level viremia group. Furthermore, in the low-level viremia group, the AVT-treated group showed a significantly lower HCC IR (0.656) compared to the untreated group (0.947; aHR=0.58, 95% CI 0.35–0.96).

Conclusions: Untreated indeterminate phase patients have higher risk of HCC and LC development than patients receiving AVT in the active phase. A more proactive antiviral strategy for indeterminate phase patients is essential to overcome the

current treatment gap.

Keywords: Indeterminate Phase, Hepatocellular Carcinoma, Antiviral Therapy, Hepatitis B Virus

FP-33

Clinical Benefits of Antiviral Therapy in the Indeterminate Phase of Chronic Hepatitis B: A Systematic Review and Meta-Analysis

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Aims: The clinical phases of chronic hepatitis B (CHB) lack consistent criteria, leading to a significant “grey zone” or “indeterminate phase” that accounts for approximately 30% of patients. This systematic review and meta-analysis evaluated the clinical benefits of antiviral therapy (AVT) in this population.

Methods: A comprehensive systematic literature review and meta-analysis were conducted using the PubMed, EMBASE, and Cochrane Library databases. The primary outcome was the annual incidence and incidence rate ratios (IRRs) of hepa-

tocellular carcinoma (HCC).

Results: A total of 37 studies involving 56,379 patients were included in the final analysis. The overall annual incidence of HCC in indeterminate phase patients was 0.33 per 100 person-years (PY). The AVT group exhibited a significantly lower HCC incidence (0.30/100 PY) compared to the untreated group (0.35/100 PY), with an incidence rate ratio (IRR) of 0.41 (95% CI 0.29–0.59; $I^2 = 19.1\%$). Subgroup analysis revealed that the benefit of AVT was particularly prominent in patients with moderate level viremia (HBV DNA $2,000\text{--}8 \log_{10}$ IU/mL), showing an IRR of 0.30 (95% CI 0.19–0.47; $I^2 = 0.0\%$). Significant reductions in HCC risk were also observed in patients with ALT levels < 40 IU/L (IRR=0.32) and < 80 IU/L (IRR=0.36), as well as in both HBeAg-positive (IRR=0.66) and HBeAg-negative (IRR=0.56) cohorts. Furthermore, AVT significantly reduced the risk of liver cirrhosis (IRR=0.62, 95% CI 0.52–0.75; $I^2 = 22.2\%$). While the annual incidence of decompensated cirrhosis was 0.22/100 PY in the untreated group, no such events were reported in the AVT group.

Conclusions: Antiviral therapy is associated with a significant reduction in the risk of HCC and liver cirrhosis among CHB patients in the indeterminate phase, particularly those with moderate level viremia.

Keywords: Indeterminate Phase, Antiviral Therapy, Hepatitis B Virus, Hepatocellular Carcinoma

FP-34

NGS-Based X/Precore Genetic Heterogeneity Improves Identification of the True Immune Tolerant Phase in HBeAg-Positive Chronic Hepatitis B

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Aims: Clinical significance of hepatitis B virus (HBV) genetic variability in immune-driven inflammation, viral control, and phase progression in chronic hepatitis B (CHB) is incompletely understood. We evaluated whether X/precure mutations and intrahepatic HBV quasispecies heterogeneity better reflect virus–host interactions and improve phase stratification.

Methods: Intrahepatic HBV sequences were analyzed from liver tissue of 140 HBeAg-positive patients across the immune-tolerant (IT), gray zone (GZ), and immune-active (IA) phases using next-generation sequencing. Twelve predefined X/precure hotspot mutations were assessed, and viral diversity was quan-

tified using Shannon entropy and nucleotide diversity. Associations with serum and intrahepatic viral markers, inflammatory activity, cytokine levels, phase transition, HBeAg seroclearance, and sustained IT status were evaluated.

Results: The prevalence of X/precore hotspot mutations and viral diversity indices increased progressively from IT to GZ and IA phases, with the lowest mutation burden observed in IT. Cumulative mutation number and diversity indices were inversely correlated with HBeAg, HBcrAg, serum HBV DNA, intrahepatic total HBV DNA, and cccDNA levels, whereas individual X/precore mutations showed limited associations. Greater quasispecies heterogeneity was associated with higher aminotransferase levels, increased necroinflammatory grades, and elevated pro-inflammatory cytokines. Patients with higher diversity indices experienced earlier phase transition and HBeAg seroclearance. Mutation-based IT classification demonstrated superior discrimination of sustained IT at 1 year compared with conventional clinical or histologic criteria (AUC = 0.824), with high sensitivity and specificity.

Conclusions: In HBeAg-positive CHB, X/precore quasispecies heterogeneity reflects immune-mediated viral evolution and is closely linked to disease activity and phase transition. Incorporating mutation-based criteria may improve identification of patients with a stable IT phenotype and refine immune phase stratification.

Keywords: Hepatitis B Virus, Viral Quasispecies, Mutation, Immune Tolerant

FP-35

Higher Unglycosylated HBsAg Proportion May Predict Faster Decline Kinetics of HBsAg in Chronic Hepatitis B

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Aims: Functional cure for Chronic Hepatitis B (CHB), defined as sustained HBsAg loss, is a key treatment goal. N-linked glycosylation modification at N146 of HBsAg resulted in two forms of HBsAg: glycosylated (GpS) or unglycosylated (pS). In most CHB patients, pS/GpS ratios are 1:1. However, the relationship between HBsAg decline and HBsAg glycosylation levels is not well understood. In this study, the association between GpS levels and HBsAg decline in CHB patients was investigated.

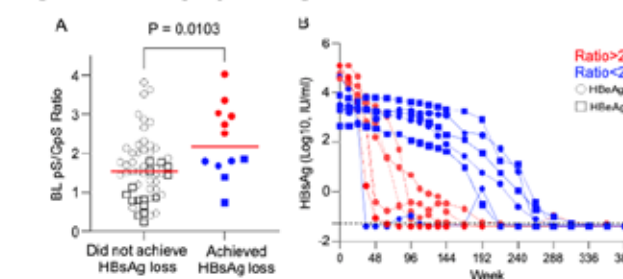
Methods: BL serum samples were analyzed from CHB patients enrolled in two phase 3 studies of tenofovir alafenamide and/or

tenofovir disoproxil fumarate. Western blot quantified GpS and pS, and pS/GpS ratios were calculated. Quantitative HBsAg was measured through week 384. HBsAg decline was analyzed from BL to week 384. N146 mutations were analyzed at baseline.

Results: 66 patients (48 HBeAg+, 18 HBeAg-; GT A-F) were analyzed. BL pS/GpS ratios ranged from 0.23–4.03. HBsAg decline at week 48 varied from 0 to 6.19 log. HBeAg+ CHBs had higher mean pS/GpS ratios than HBeAg- CHBs (1.99 vs 1.07; $P < 0.0001$). In HBeAg+ patients, BL pS/GpS ratio correlated positively with HBsAg decline at week 48 ($r = 0.52$, $P = 0.0002$) and persisted from weeks 96–196 ($r > 0.5$, $P < 0.001$). For example, the largest HBsAg decline from baseline (6.19 log) was observed at week 48 in a patient with BL pS/GpS as 2.95. Patients achieving HBsAg loss had higher pS/GpS ratios (Figure 1A). Among those who achieved HBsAg loss, faster S loss kinetics were associated with higher pS/GpS ratios (Figure 1B). No N146 mutations were detected.

Conclusions: The higher proportion of unglycosylated HBsAg correlated with faster HBsAg decline in HBeAg+ patients suggesting BL pS/GpS ratio could serve as a potential biomarker for predicting treatment response in HBeAg+ CHB patients. Further studies are warranted to elucidate the underlying mechanism of this correlation.

Figure 1. Baseline ratio pS/GpS vs. HBsAg loss



Keywords: Unglycosylated HBsAg, Chronic Hepatitis B, HBsAg Kinetics, HBsAg Glycosylated (GpS) Unglycosylated (pS) Ratio

FP-36

Changes to an Active Lifestyle and Risks of Mortality and Liver-Related Events in Adults with Chronic Hepatitis B: A Nationwide Cohort Study

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Aims: Physical activity (PA) confers several health benefits; however, whether increasing PA among physically inactive

adults with chronic hepatitis B (CHB) reduces adverse clinical outcomes remains unclear.

Methods: A nationwide cohort study was conducted using Korean National Health Insurance data. We included 318,131 adults with CHB who were physically inactive at the initial health screening (Exam 1) and completed a subsequent screening within 4 years (Exam 2). Among them, 58,703 initiated moderate-to-vigorous PA (MVPA), defined as vigorous activity ≥ 20 min/day on ≥ 3 days/week or moderate activity ≥ 30 min/day on ≥ 5 days/week. The primary outcome was all-cause mortality, and the secondary outcomes were liver-related events (hepatic decompensation, liver transplantation, hepatocellular carcinoma [HCC]) and HCC. Outcomes of MVPA initiators and those remaining inactive were compared using multivariable Cox and Fine-Gray competing risk models adjusted for demographic, clinical, and behavioral covariates.

Results: During a median 7.9-year follow-up (IQR, 5.2–9.5), 7,609 deaths occurred. MVPA initiation was associated with lower all-cause mortality (hazard ratio [HR], 0.89; 95% CI, 0.84–0.94), reduced risk of liver-related events (subdistribution HR [subHR], 0.94; 95% CI, 0.92–0.97), and lower risk of HCC (subHR, 0.95; 95% CI, 0.91–0.99) compared with those remaining inactive. Mortality reduction was consistent across subgroups analyzed.

Conclusions: Initiating MVPA among physically inactive adults with CHB was associated with significant reductions in mortality and liver-related outcomes. These findings provide large-scale epidemiologic evidence supporting PA promotion as a strategy to improve survival in physically inactive patients with CHB.

Keywords: Chronic Hepatitis B, Exercise, Mortality, Liver Diseases

FP-37

High Treatment Adherence Reduces HCC in Cirrhosis, with Additional Benefit from TAF

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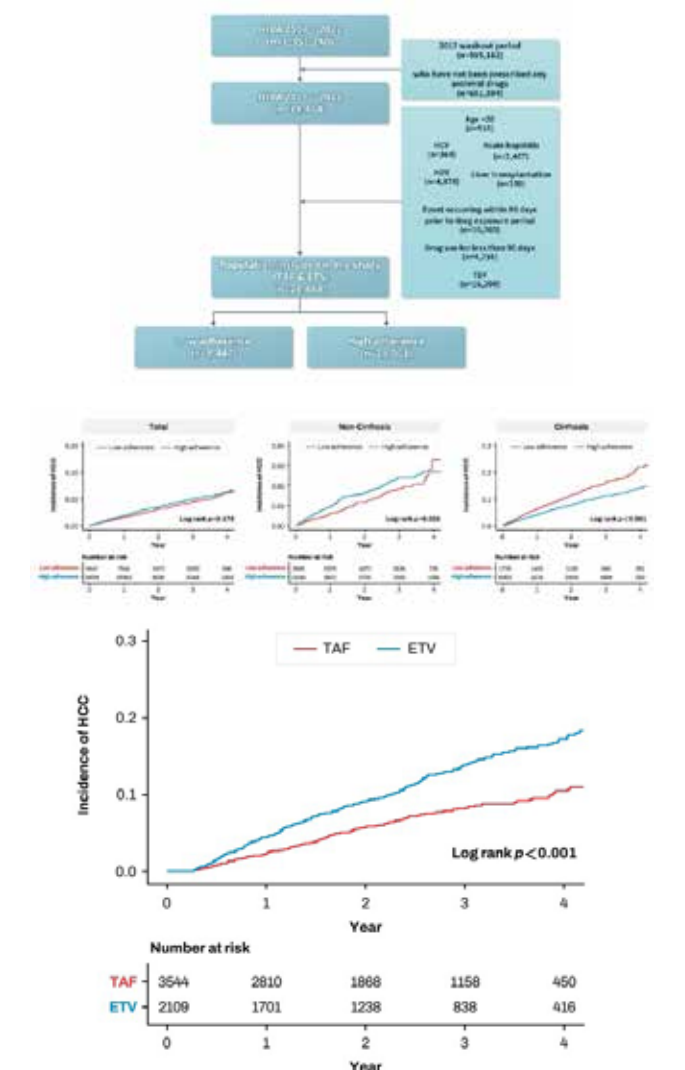
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Aims: Adherence to antiviral therapy is essential for viral suppression in chronic hepatitis B (CHB), yet its effect on hepatocellular carcinoma (HCC) remains uncertain. We examined the association between nucleos(t)ide analogue (NA) adherence and HCC risk, focusing on tenofovir alafenamide (TAF) versus entecavir (ETV).

Methods: Treatment-naïve adults with CHB initiating TAF or ETV were identified from the Korean National Health Insurance

Service database. Adherence was measured using the medication possession ratio, with high adherence defined as $\geq 90\%$. The primary outcome was HCC incidence.

Results: A total of 28,448 patients were included, of whom 19,001 (66.8%) showed high adherence and 9,447 (33.2%) low adherence. In the overall cohort, HCC incidence was comparable between high- and low-adherence groups (14.89 vs. 13.76 per 1,000 person-years; IRR 1.08, 95% CI 0.95–1.24). Among cirrhotic patients, however, high adherence was associated with substantially lower HCC incidence (32.92 vs. 49.59 per 1,000 person-years; IRR 0.66, 95% CI 0.57–0.78). Multivariate analysis confirmed high adherence as an independent protective factor (HR 0.77, 95% CI 0.66–0.90). Notably, within the high-adherence group, TAF was linked to a significantly lower HCC risk than ETV (HR 0.54 vs. 0.89; log-rank $P < 0.001$), whereas low adherence to either agent conferred no protection. Logistic regression further identified ETV use as a strong predictor of poor adherence (OR 2.80, 95% CI 2.65–2.96).



Conclusions: High adherence to antiviral therapy reduces HCC risk in cirrhotic CHB patients. TAF showed superior outcomes to ETV, reflecting both greater adherence and a potential intrinsic advantage.

Keywords: Chronic Hepatitis B, Hepatocellular Carcinoma, Antiviral Adherence, Tenofovir Alafenamide

FP-38

Long-Term Clinical Trajectories of Chronic Hepatitis B in the Lamivudine Era: Insights from a 25-Year Real-World Study

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Aims: Lamivudine, the first oral agent for chronic hepatitis B (CHB), marked the transition to effective oral antiviral therapy, offering favorable tolerability and reliable viral suppression. However, comprehensive evidence regarding its long-term clinical impact across diverse treatment courses is limited.

Methods: This real-world cohort study analyzed 1,134 patients with CHB initiated on lamivudine between 1997 and 2010. Clinical outcomes, including liver transplantation (LT)-free survival, hepatocellular carcinoma (HCC) incidence, and hepatitis B surface antigen (HBsAg) seroclearance, were evaluated according to treatment continuation, cessation, virologic response, and rescue therapy. Propensity score matching and landmark analyses were performed to minimize bias.

Results: Over a maximum follow-up period of 28 years (median, 14.8 years), the 25-year rates of LT-free survival, cumulative HCC incidence, and HBsAg seroclearance were 88.3%, 22.9%, and 20.9%, respectively. Treatment discontinuation significantly increased the probability of HBsAg seroclearance without negatively affecting survival or HCC incidence, when performed according to the stopping criteria. Virologic responders demonstrated superior long-term survival (25-year LT-free survival, 89.8%) and higher HBsAg seroclearance rates than non-responders. Among these responders, treatment discontinuation did not worsen LT-free survival or HCC risk compared with continued therapy, while achieving higher rates of HBsAg seroclearance in patients maintaining a sustained virologic response. Lamivudine resistance was significantly associated

with a higher HCC risk (hazard ratio [HR] 2.10, $P < 0.001$), whereas rescue therapy improved LT-free survival (HR 0.24, $P < 0.001$) and reduced HCC incidence (HR 0.57, $P = 0.017$).

Conclusions: Lamivudine therapy provided durable long-term survival and reduced HCC risk with safe cessation in selected patients and clear benefits of timely rescue therapy. These findings offer insights for optimizing CHB management strategies with currently available antiviral agents.

Keywords: HBV, Lamivudine, HCC

Friday, June 12, 2026, 13:30-14:50

6. HCC, Basic

FP-39

Secretory Nidogen 1 Triggers the Endocytic Recycling of $\beta 5$ Integrin in Hypoxia Induced Liver Cancer Metastasis

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Aims: The characteristic hypoxic region within the hepatocellular carcinoma (HCC) tumors has been recognized as the key driver of HCC malignance and treatment resistance. Delineating the mechanism by which hypoxia contribute to HCC progression and identifying effective intervention strategies targeting intratumoral hypoxia are therefore urgently needed. Nidogen 1 (NID1), a critical structural component of both the basement membrane and extracellular matrix, has been reported to play a critical role in driving liver cancer metastasis. However, if NID1 is involved in hypoxia induced HCC metastasis remains unknown.

Methods: Recombinant NID1 (rNID1) protein and NID1 neutralizing antibody were generated and adopted to study the functional role of secretory NID1 (sNID1). Co-immunoprecipitation and sitedirected mutagenesis were performed to validate the membrane receptor of sNID1 under hypoxic stress. *In vitro* functional assays and *in vivo* experimental lung metastasis were utilized to assess the HCC cell invasiveness and metastatic potential of HCC cells. Immunofluorescent staining was employed to examine the endocytosis of NID1.

Results: Hypoxia-induced NID1 secretion was found to be a key factor in enhancing HCC cell motility. rNID1 recapitulated the hypoxia-induced migratory capacity of HCC cells and promoted the lung metastasis, effects that were abrogated by the NID1 neutralizing antibody. $\beta 5$ integrin (ITG $\beta 5$) was identified

as the membranous receptor of sNID1, interacting via the RGD motif of NID1. The NID1-ITG $\beta 5$ complex was subsequently endocytosed, triggering the FAK-dependent cell motility pathway. Following sorting in the early endosomes, ITG $\beta 5$ -containing vesicles were transported along microtubules and subsequently recycled back to the plasma membrane at the migration front.

Conclusions: Our findings provide a novel mechanistic insight into hypoxia enhanced HCC cell motility and highlight NID1 as a potential therapeutic target for hypoxia-associated HCC metastasis.

Figure 1. Hypoxia-induced NID1 secretion played a key role in the enhancement of the HCC cell motility.

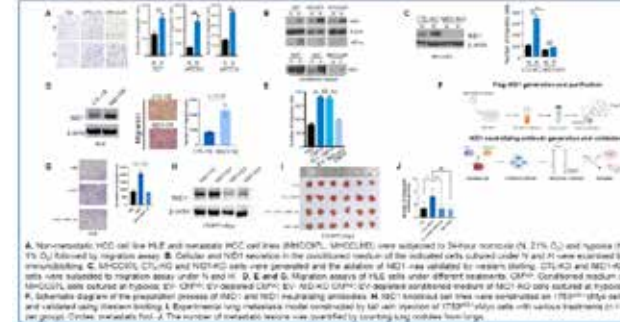


Figure 2. NID1 interacted with ITGβ5 through the RGD site.

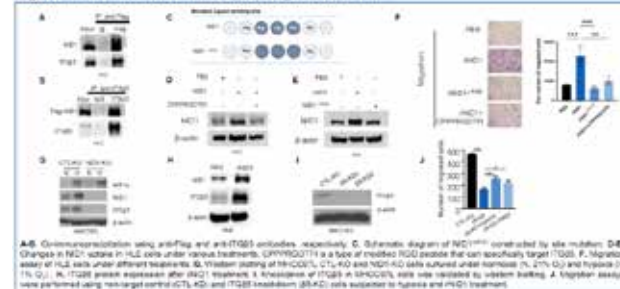
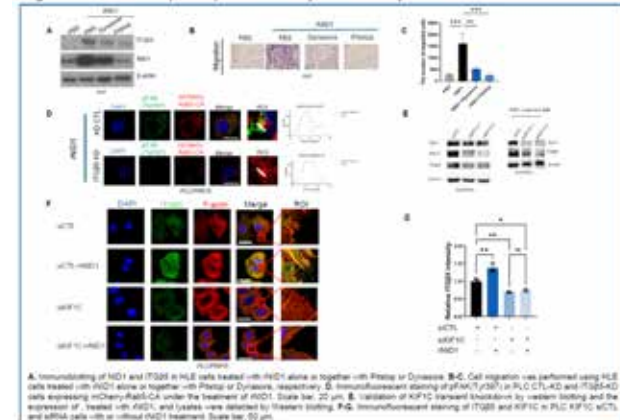


Figure 3. The NID1-ITGβ5 complex was endocytosed and recycled.



Keywords: Liver Cancer, Metastasis, Nidogen-1, $\beta 5$ Integrin

FP-40

Application of CRISPR/Cas9 Technology to Develop a Hepatocellular Carcinoma Model Using Human Primary Hepatocyte Organoids

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Aims: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality worldwide, driven by molecular complexity and heterogeneity. Patient-derived organoids offer a physiologically relevant platform for modeling HCC but are limited by cell scarcity and instability. CRISPR/Cas9 genome editing of human hepatocyte organoids offers a controllable approach to recreate oncogenic alterations.

Methods: We established a biobank of patient-derived hepatocellular carcinoma organoids (HCC PDOs) and validated them using PCR and immunofluorescence. Human hepatocyte organoids (h-HepOrg) were generated from liver tissue through collagenase perfusion and MACS-based EpCAM-negative sorting, followed by characterization to confirm their hepatocytic identity. CRISPR/Cas9-mediated TP53 knockout was introduced to model early hepatocarcinogenesis.

Results: We developed a robust library of HCC PDOs that preserve the architecture and molecular signature of the parental tumors. Histologically, HCC PDOs displayed solid, compact 3D structures with robust expression of HCC markers AFP, Hep-Par1, GPC3, and β -catenin. PAS staining confirmed glycogen storage, while PCR analyses revealed overexpression of AFP, GPC3, and cancer stem cell markers CD24 and CD44. h-HepOrg comprised pure hepatocyte populations expressing mature hepatocyte markers albumin and HNF4 α , with minimal expression of cholangiocyte markers CK7 and EpCAM. CRISPR/Cas9-mediated TP53 knockout in h-HepOrg achieved high editing efficiency, confirmed by PCR and Sanger sequencing, inducing morphological changes and enhanced proliferation consistent with early oncogenic transformation.

Conclusions: This study established robust *in vitro* hepatocellular carcinoma models using patient-derived organoids and CRISPR/Cas9-edited human hepatocyte organoids. These models recapitulate key histopathological and molecular features of HCC, with TP53-knockout h-HepOrg organoids providing a genetically defined baseline for disease modeling.

Keywords: Hepatocellular Carcinoma, Organoids, Disease Modeling

FP-41

The PLD2–APP–OTC Axis Regulates Urea Cycle Activation and Tumor Growth in Hepatocellular Carcinoma

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Aims: Phospholipase D2 (PLD2) is an enzyme responsible for hydrolyzing phosphatidylcholine into choline and phosphatidic acid (PA). While PLD2 is known to promote tumors in colorectal and lung cancers, its functional role in hepatocellular carcinoma (HCC) remains largely elusive.

Methods: The study utilized HCC cell lines (HepG2, Huh-7, SNU-398, and SNU-449) and a normal hepatocyte line (MIHA). A mouse HCC model was established using transposon technology to drive HCC development, and tumor tissues were subsequently analyzed via RNA sequencing (RNA-seq).

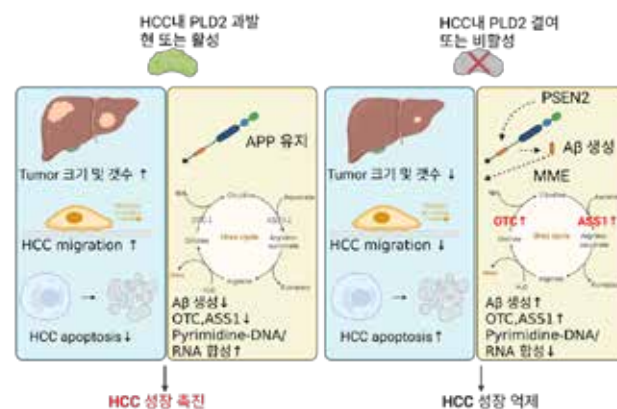
Results: PLD2 expression was significantly elevated in HCC cell lines compared to normal MIHA cells. Functional assays showed that PLD2 deficiency in HCC cells increased apoptosis and reduced proliferation, whereas PLD2 overexpression enhanced migratory capacity.

In vivo, liver-specific PLD2-deficient mice generated via the Sleeping Beauty transposon system exhibited a marked reduction in both tumor number and size. RNA-seq of these tumors revealed a significant upregulation of urea cycle-related genes, specifically ornithine transcarbamylase (OTC) and argininosuccinate synthetase 1 (ASS1), findings which were corroborated by TCGA dataset analysis.

Further investigation into the mechanism of OTC upregulation revealed that palmitate treatment induced a concomitant increase in amyloid precursor protein (APP) and PLD2 expression in HCC cells.

Conclusions: Collectively, these findings suggest that PLD2 deficiency may alter APP processing, potentially leading to increased amyloid- β production, which could enhance OTC expression and activate urea cycle pathways, thereby contributing to tumor suppression in HCC.

Keywords: PLD2, HCC, OTC, APP



FP-42

Soluble FAP Activates STAT3 and Induces IL-6 to Sustain Cancer-Associated Fibroblast Activation via a Positive Feedback Loop in Hepatocellular Carcinoma

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Aims: Cancer-associated fibroblasts (CAFs) critically shape the tumor microenvironment in hepatocellular carcinoma (HCC). Fibroblast activation protein (FAP), highly enriched in matrix CAFs, exists in both membrane-bound and soluble (sFAP) forms; however, the functional role of sFAP in sustaining CAF activation remains unclear. This study aimed to define FAP-positive CAF subsets and investigate whether sFAP promotes CAF activation via STAT3 signaling.

Methods: Single-cell RNA sequencing data from human HCC samples were analyzed and validated using patient-derived CAF and serum samples (HCC n = 110; controls n = 50). FAP-high and FAP-low CAF populations were isolated by fluorescence-activated cell sorting. CAFs were treated with recombinant human FAP, a FAP inhibitor or FAP-targeting siRNA. Phosphorylated STAT3 and IL-6 expression were assessed. *In vivo* validation was performed using a syngeneic Hepa1-6 model (vehicle n = 4; FAP inhibitor n = 4; 5 mg/kg intraperitoneally every 2 days for 14 days).

Results: Single-cell RNA sequencing analysis of patients with hepatocellular carcinoma revealed five distinct CAF clusters, with FAP predominantly enriched in matrix CAFs. Tumor-de-

rived CAFs exhibited higher FAP expression than non-tumor fibroblasts, and serum FAP levels were elevated in patients with HCC. FAP-high CAFs showed increased STAT3 and IL-6 expression compared with FAP-low CAFs. Recombinant FAP increased IL-6 secretion and enhanced phospho-STAT3, suggesting activation of an IL-6–STAT3 autocrine loop, whereas FAP inhibition or knockdown reduced phospho-STAT3. *In vivo*, FAP inhibition reduced intratumoral FAP-positive cells and decreased tumor volume.

Conclusions: Soluble FAP sustains CAF activation through a FAP–STAT3–IL-6 positive feedback loop, thereby promoting tumor progression in HCC. Targeting FAP disrupts this stromal signaling axis and represents a promising strategy for remodeling the tumor microenvironment.

Keywords: Cancer-Associated Fibroblast, FAP, STAT3, IL-6

FP-43

SFRP4⁺ Cancer-Associated Fibroblasts Drive EMT and an Immunosuppressive Tumor Microenvironment in Hepatocellular Carcinoma

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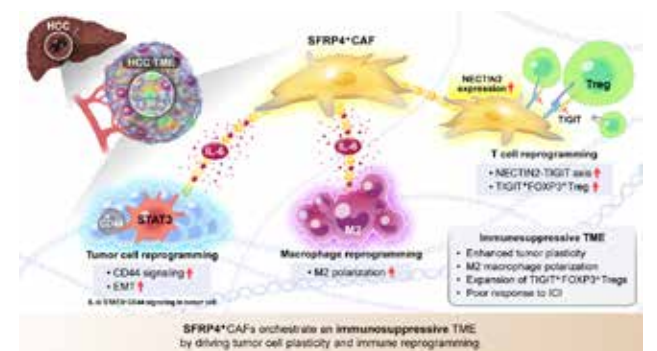
Aims: Cancer-associated fibroblasts (CAFs) are major stromal components that influence tumor progression and immune regulation in hepatocellular carcinoma (HCC). However, the specific CAF subtypes and signaling mechanisms that coordinate tumor cell plasticity and immune suppression remain incompletely defined. This study aimed to investigate the role of SFRP4⁺ CAFs in regulating HCC cell plasticity and the tumor immune microenvironment.

Methods: Primary CAFs and paracancer fibroblasts (PAFs) isolated from eight HCC patients underwent whole-transcriptome sequencing (WTS) and were integrated with publicly available bulk and single-cell RNA-sequencing datasets. CAF-enriched genes were identified through comparative transcriptomic analyses. Functional assays assessed the effects of CAF-derived signaling on HCC cell proliferation and epithelial–mesenchymal transition (EMT). Immune regulatory effects were assessed by analyzing macrophage polarization (M1/M2) and T cell-related interactions using transcriptomic and CellChat analyses.

Results: Integrated transcriptomic analyses identified secret-

ed frizzled-related protein 4 (SFRP4) as a CAF-enriched gene upregulated in HCC. SFRP4⁺ CAFs promoted HCC cell proliferation and induced EMT-associated programs. Mechanistically, these effects were mediated by activation of IL-6/STAT3 signaling and upregulation of CD44. In addition, CAF-derived IL-6 promoted macrophage polarization toward an M2-like phenotype. SFRP4⁺ CAFs also exhibited high NECTIN2 expression, enabling interactions with TIGIT-expressing T cells. Tumors enriched for SFRP4⁺ CAF signatures showed increased FOXP3⁺ regulatory T cell infiltration.

Conclusions: SFRP4⁺ CAFs represent a distinct stromal population that drives HCC progression by promoting EMT in HCC cells and shaping an immunosuppressive tumor microenvironment. These findings highlight SFRP4⁺ CAFs as a potential therapeutic target for HCC, offering new avenues for treatment strategies aimed at disrupting these tumor-promoting interactions.



Keywords: Hepatocellular Carcinoma, Cancer-Associated Fibroblasts, Secreted Frizzled-Related Protein 4, Tumor Immune Microenvironment

FP-44

Large-Scale Whole-Genome Sequencing Reveals the Mutagenic Processes Underlying Hepatocellular Carcinoma

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Aims: Mutational signature analysis using whole-genome sequencing (WGS) allows for the classification and quantification of various mutagenic processes. Although the liver is a primary target of diverse carcinogens, a comprehensive understanding of these mutagenic processes underlying hepatocellular carcinoma (HCC) remains incomplete.

Methods: We performed WGS and RNA-seq data from 456

Korean HCC patients to systematically investigate the mutagenic landscape. Comprehensive WGS analysis was conducted to identify single-base substitutions (SBS), indels (ID), double-base substitutions (DBS), copy-number alterations (CNA), and structural variations (SV). De novo mutational signature decomposition was employed to extract signatures for SBS, ID, DBS, and SVs.

Results: We identified 33 CNA and 16 non-CNA driver alterations present in over 5% of patients, covering four major functional modules: cell cycle regulation, lipid metabolism, WNT/beta-catenin signaling, and inflammatory response. In addition to recurrent drivers, actionable driver alterations reported in any cancer type were present in 70% of patients, whereas alterations reported specifically in pan-solid tumors or HCC were present in 45% of patients. Among them, *MET* (n=3) and *KRAS* (n=3) are examples of directly targetable alterations. Mutational signature analysis showed that smoking, aristolochic acid (AA), and alcohol contributed 11%, 7%, and 5% of the mutational burden, respectively. We discovered a novel liver-specific smoking signature and independently validated it in public datasets. Notably, carriers of the ALDH2-deficient “Asian flushing” germline variant exhibited more than 4-fold increase in alcohol-related mutations. Mutational timing analysis revealed an abrupt accumulation of AA-associated mutations occurring in early childhood in a subset of patients, implicating that remote AA exposure decades prior contributes to adult-onset HCC. Furthermore, we identified dense duplication or deletion signatures linked to driver mutations associated with homologous recombination deficiency (HRD), such as *RAD51B* and *ATM/ATR*, suggesting potential utility as biomarkers for HRD-targeted treatment.

Conclusions: This large-scale WGS analysis systematically demonstrates how diverse exogenous and endogenous factors drive mutational accumulation and oncogenic transformation in the liver. These findings provide a critical framework for improving HCC prevention and developing personalized therapeutic strategies.

Keywords: Hepatocellular Carcinoma, Mutagen, Mutational Process, Mutational Signature

FP-45

Longitudinal Single-Cell Profiling Reveals Distinct Immune Trajectories Associated with Response and Resistance to Atezolizumab–Bevacizumab in HCC

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Aims: Atezolizumab plus bevacizumab (atezo-bev) is the standard first-line therapy for unresectable hepatocellular carcinoma (HCC). However, the longitudinal immune dynamics underlying durable clinical benefit or the development of resistance are not yet fully characterized.

Methods: We performed longitudinal single-cell RNA sequencing and T-cell receptor (TCR) repertoire profiling of peripheral blood mononuclear cells (PBMCs) from 16 patients with HCC treated with atezo-bev. Samples were collected at baseline, after three cycles of treatment, and at disease progression or last follow-up. Patients were categorized into primary resistance, secondary resistance, and durable response groups.

Results: Distinct longitudinal immune trajectories were observed across the response groups. Durable responders showed progressive expansion of lymphoid populations with reduction of myeloid cells, whereas primary resistance patients exhibited the opposite pattern. Secondary resistance patients showed intermediate dynamics that shifted toward a resistance-like profile at progression.

At the T-cell subtype level, CD28⁺PD1⁺ CD8⁺ T cells were enriched in durable responders from baseline and maintained during treatment, accompanied by significant clonal expansion of the effector CD8⁺ GZMB⁺ T-cell population. BCR repertoire profiling revealed a distinct evolutionary trajectory within IGHMlo memory B-cells exclusive to durable responders. This was characterized by a rapid early surge in somatic hypermutation immediately post-treatment, followed by a robust expansion of class-switch recombination at the final follow-up. This stepwise genetic refinement suggests that strong T-B cell interactions drive the lymphocyte population. Myeloid cell analysis revealed enrichment of immune-activated monocyte clusters in durable responders, whereas resistance groups showed expansion of CD163⁺ monocyte populations associated with suppressive myeloid states. Notably, cell–cell interaction analysis identified chemokine–CCR5 signaling toward proliferating CD8⁺ T cells, which was enriched in durable responders.

Conclusions: These findings provide insights into immune dynamics in HCC following atezo-bev treatment. Durable responses were associated with sustained lymphoid activation and T-B cell clonal expansion, potentially supported by CCR5-mediated immune cell interactions.

Keywords: Atezolizumab–Bevacizumab, Single-Cell Rna Sequencing, Longitudinal Immune Dynamics, Immunotherapy Resistance

FP-46

Immune Cell Profiling and Real-World Long-Term Efficacy of Adjuvant Cytokine-Induced Killer Cell Therapy for Hepatocellular Carcinoma

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Aims: Despite the pressing need for adjuvant therapy for hepatocellular carcinoma (HCC), most approaches—including immune checkpoint inhibitor-based regimens—have failed to demonstrate a significant benefit on recurrence-free survival (RFS). Cytokine-induced killer (CIK) cells are a heterogeneous population enriched in CD3⁺CD56⁺ NKT-like effectors with both T cell and NK cell properties produced by ex vivo culture, conferring antitumor cytotoxicity in a non-MHC-restricted manner. In a prior randomized controlled trial, adjuvant immunotherapy utilizing autologous CIK cells improved RFS and overall survival. This study aimed to assess the long-term outcomes of CIK therapy in a real-world cohort and elucidate the underlying mechanisms of sustained effects of CIK cell treatment.

Methods: A retrospective real-world data (RWD) analysis was conducted involving 577 patients—251 in the CIK immunotherapy group and 326 controls— from two tertiary centers in Korea. Propensity score matching (PSM) was employed to adjust for baseline imbalances, and the primary endpoint was RFS. In parallel, a prospective immune monitoring study using flow cytometry analyzed post-treatment changes in peripheral blood immune cell subsets in 33 patients who received repeated CIK cell transfer after curative treatment for HCC.

Results: In the RWD study (median follow-up=57.2 months), the CIK group demonstrated significantly prolonged RFS both before PSM (median=101.2 vs. 64.7 months; HR=0.69, 95% CI=0.53–0.90, *P*=0.006) and after PSM (median=101.2 vs. 65.7 months; HR=0.64, 95% CI=0.45–0.91, *P*=0.01). Analysis of peripheral blood immune cells revealed that CIK therapy induced coordinated remodeling across both conventional and innate-like adaptive immune compartments. [JYP1] Within the innate-like T cells, the therapy significantly increased PLZF⁺ CD4 and CD8 double negative (DN) T cells (11.2 ± 3.3% vs. 21.9 ± 5.4%, *P*=0.039). This was accompanied by enhanced secretion of proinflammatory cytokines, such as perforin (25.4 ± 4.9% vs. 52.0 ± 6.5%, *P*=0.022), IFN- γ (6.1 ± 1.6% vs. 11.9 ± 1.5%, *P*=0.006) and TNF- α (7.9 ± 1.8% vs. 17.8 ± 2.5%, *P*=0.003) indicating that increased Th1 prone immune reaction by innated like T cells after CIK therapy. [LJ2] Within the conventional adaptive T cell compartment, the frequency of classical CD8⁺ memory T cells (CD45RO⁺/CD45RA⁻) were significantly elevated following repeated CIK cell transfer (25.5 ± 2.4% vs. 34.5 ± 2.7%, *P*=0.003). Collectively, these findings suggest that the Th1 prone cytokine milieu generated by innate-like DN T

cells, may be associated with longer survival of CD8⁺ memory T cells in the host. It can facilitate the expansion and long-term maintenance of a durable CD8⁺ memory T cell pool and related enhanced anti-HCC host immunity.

Conclusions: Adjuvant CIK cell therapy significantly improved RFS in a real-world cohort, supporting its reproducible and durable benefit in reducing HCC recurrence after curative treatment. The sustained off-treatment efficacy was mechanistically associated with dual immune remodeling: cytolytic activation of innate-like DN T cells and the establishment of a durable CD8⁺ memory T cell pool, likely bridged by an Th1 cytokine milieu. These findings warrant further investigation into larger, prospective studies.

Keywords: Cytokine-Induced Killer Cell, Adjuvant Therapy, CD8⁺ Memory T Cell, Real-World Data

Friday, June 12, 2026, 13:30-14:50

7. MASLD & ALD, Basic

FP-47

A Stage Specific NETs-Related Signature in Alcoholic Steatohepatitis: From Molecular Subtyping to Therapeutic Vulnerabilities

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Aims: Alcohol-associated steatohepatitis (ASH) is a globally prevalent liver disease, with robust evidence implicating neutrophil extracellular traps (NETs) as a central pathological phenomenon driving inflammation and progression. However, the core genomic signatures that govern NETs and underlying molecular mechanisms within the ASH microenvironment remain poorly defined. Therefore, this study aims to identify core NETs-related genomic signatures, elucidate their underlying molecular mechanisms, and explore therapeutic potential in the ASH microenvironment.

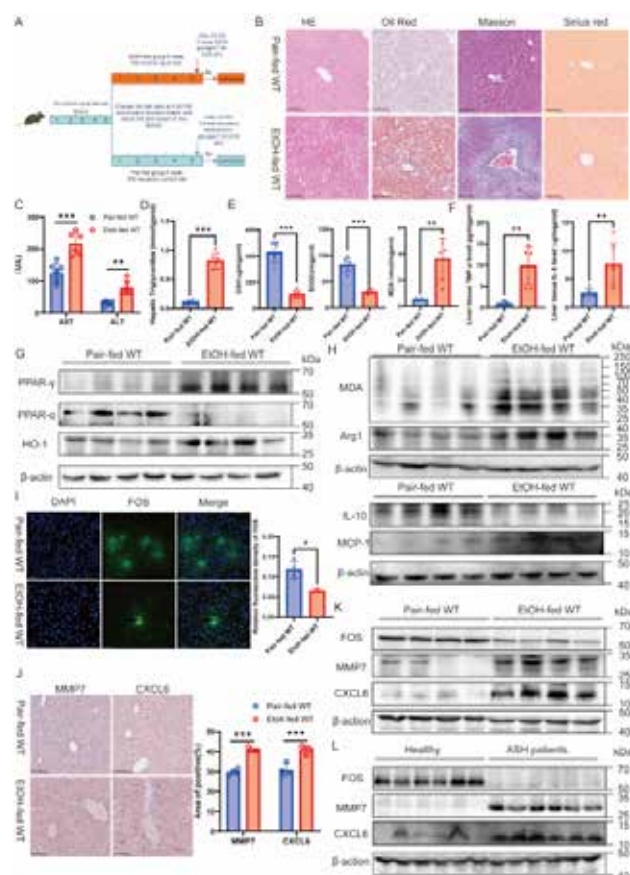
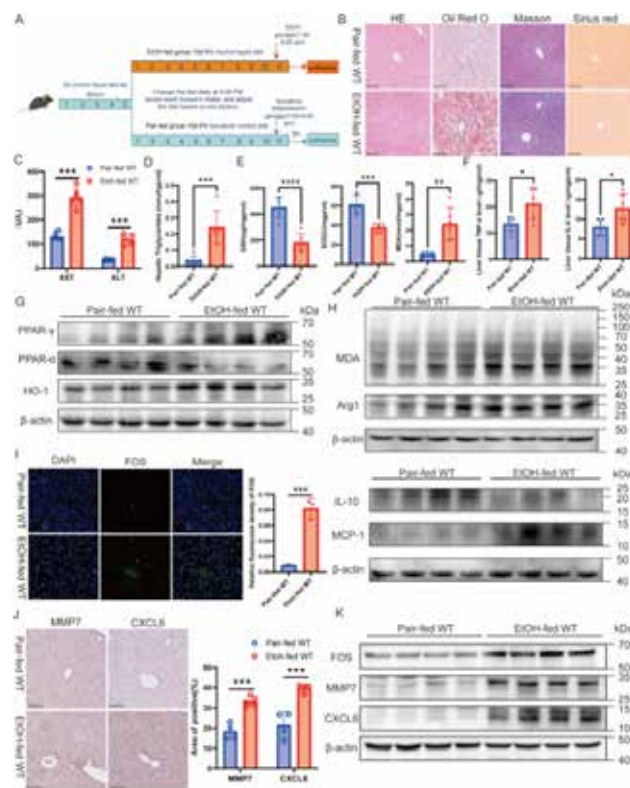
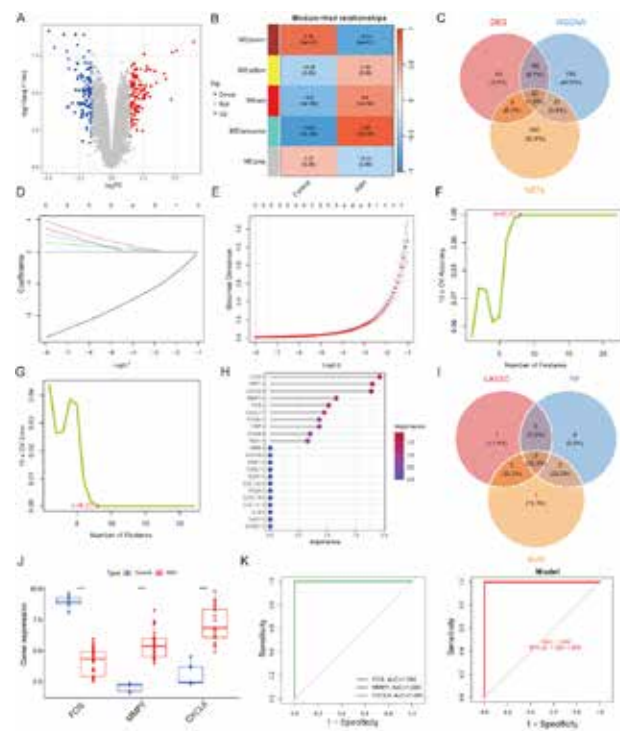
Methods: Building on the prominent NETs formation phenomenon in ASH, we established a core pool of NETs-related hub genes through intersection of ASH-derived differentially expressed genes (DEGs), key WGCNA modules, and a curated NETs gene set. From this NET-focused pool, a consensus of three machine learning algorithms (LASSO, SVM, RF) distilled

a final diagnostic signature, which was rigorously validated in training and external cohorts via ROC analysis and neural networks. Patient heterogeneity was then investigated using consensus clustering with this signature, followed by immune profiling and functional validation in human and mouse ASH models. Therapeutic potential was explored through drug database enrichment and molecular docking.

Results: A NETs-focused three-gene signature (FOS, MMP7, CXCL6) achieved exceptional diagnostic accuracy for ASH (AUC=1.00 in training; 0.983 in validation). It stratified ASH into a Metabolic-dominant (C1) subtype and a Pro-inflammatory (C2) subtype, the latter exhibiting higher MMP7/CXCL6, lower FOS, and enriched cytotoxic infiltration. *In vivo*, FOS rose in acute injury but declined in chronic models and human ASH, whereas MMP7/CXCL6 remained elevated, suggesting a temporal shift from acute FOS-dominant response to sustained MMP7/CXCL6-mediated inflammation. Finally, drug-gene interaction analysis identified several potential therapeutic modulators, including N-acetylcysteine (NAC), with predicted high binding affinities to FOS and MMP7.

Conclusions: FOS, MMP7, and CXCL6 constitute a clinically actionable signature capturing the stage-specific dynamics of NETs-driven inflammation in ASH. Beyond its diagnostic and stratifying utility, this signature highlights potential therapeutic avenues for clinical intervention.

Keywords: Alcoholic Steatohepatitis, Neutrophil Extracellular Traps, FOS-MMP7-CXCL6



FP-48

Single-Cell Transcriptomic Profiling Reveals Stage-Specific Reprogramming of Peripheral NK Cells from Compensatory Hyperactivation to Terminal Exhaustion during Alcohol-Associated Liver Disease Progression

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Aims: Alcohol-associated liver disease (ALD) is a leading cause of liver-related mortality. The immune mechanisms driving progression from alcoholic fatty liver (AFL) to irreversible cirrhosis remain poorly understood. Natural killer (NK) cells play a key anti-fibrotic role by eliminating activated hepatic stellate cells, but their function becomes impaired as disease advances.

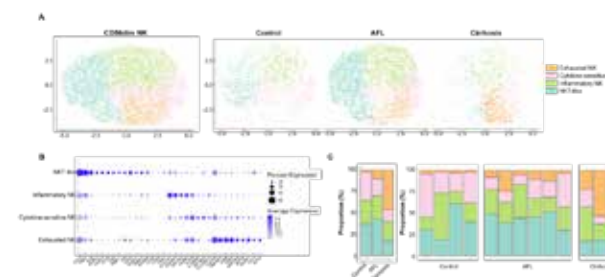
Methods: We performed single-cell RNA sequencing on peripheral blood mononuclear cells from 13 individuals (healthy controls, n=4; AFL, n=6; cirrhosis, n=3) to characterize the CD56dim NK cell compartment. Findings were validated by multi-color flow cytometry in an independent cohort (healthy controls, n=10; AFL, n=18; cirrhosis, n=11). Gene set enrichment analysis (GSEA) and module scoring were used to assess pathway-level changes.

Results: Analysis of 7,354 CD56dim NK cells identified four transcriptionally distinct subsets, including a terminally exhausted population marked by ZFP36, DUSP1, and BTG2. Disease progression was marked by expansion of this exhausted subset, which followed a biphasic trajectory: transient hyperactivation in AFL followed by terminal dysfunction in cirrhosis. Mechanistically, exhausted NK cells in cirrhosis showed upregulation of post-transcriptional regulators, transcriptional repressors, and inflammatory chemokines. GSEA identified 17 enriched Hallmark pathways, with TNF α /NF- κ B signaling as the top hit. Flow cytometry confirmed a sequential checkpoint acquisition pattern: TIGIT upregulation in AFL, followed by NKG2A elevation restricted to cirrhosis.

Conclusions: ALD progression involves stage-specific NK cell reprogramming, from compensatory hyperactivation in AFL to terminal exhaustion in cirrhosis. The sequential checkpoint model provides a framework for non-invasive disease staging and highlights AFL as a critical therapeutic window for preserving NK cell anti-fibrotic immunity.

Keywords: Alcohol-Associated Liver Disease, NK Cell, Single-Cell

Rna Sequencing, Cirrhosis



FP-49

Blocking the Gut-Liver IgA Axis Attenuates Macrophage-Mediated Inflammation and Injury in Alcohol-Associated Liver Disease

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Aims: Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity, yet therapies for severe inflammation remain limited. We examined whether circulating IgA, hepatic IgA deposition, and hepatic myeloid-cell binding are associated with IL-1 β -linked inflammation and hepatocyte injury in ALD.

Methods: In this single-centre cross-sectional study, we enrolled consecutive adults with ALD (n=220), chronic hepatitis B (CHB; n=147), and healthy controls (n=20). A clinically indicated liver-biopsy subcohort underwent flow cytometry, immunohistochemistry, and RT-qPCR. Mice received 16-day chronic-plus-binge ethanol feeding $\pm$ fingolimod (FTY720; 1 mg/kg/day). CD14⁺ monocytes were stimulated on platebound slgA $\pm$ LPS, and conditioned media were applied to Huh7 cells.

Results: Serum IgA was higher in ALD (median 323-412 mg/dL) than in healthy/CHB (194/211 mg/dL; $P<0.001$) and correlated with hepatic IgA+ area ($\rho=0.672$, $P<0.001$). IgA also correlated with IL-1 β transcripts normalized to CD68 ($\rho=0.487$, $P=0.02$) and with IgA binding on hepatic CD14⁺ cells ($P<0.05$). In mice, serum IgA correlated with frequency of IgA-bound macrophages (n=16, $\rho=0.844$, $P<0.001$). FTY720 reduced serum IgA ($P<0.01$), IgA-bound macrophages ($P<0.001$), and CD68-normalized IL1b transcripts ($P<0.01$), and attenuated EtOH-induced liver injury (ALT/AST; $P<0.05$). Spatial transcriptomics suggested reduction in monocyte-derived macrophage-enriched regions and IL-1-linked programs with FTY720. Monocyte supernatants from slgA+LPS stimulation contained higher

TNF- α /IL-1 β than LPS alone (Δ +280/+798 pg/mL, $P < 0.01$) and induced greater total apoptosis in Huh7 cells (Δ +2.96%, $P < 0.01$).

Conclusions: IgA binding to hepatic myeloid cells is associated with IL-1-linked inflammation in ALD, and in ethanol-fed mice pharmacologic trafficking blockade reduced IgA binding together with IL-1-linked readouts.

Keywords: Gut-Liver Axis, Alcohol-Associated Liver Disease, Macrophage, Immunoglobulin A

FP-50

Spatial Transcriptomics Reveals Macrophage–Fibroblast Crosstalk as a Driver of MASH Fibrosis and Guides CD47-Engineered Extracellular Vesicle Therapy

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Aims: Metabolic dysfunction-associated steatohepatitis (MASH) poses a major global health burden, affecting more than 100 million individuals, yet no approved therapy effectively reverses established fibrosis. We hypothesized that the physical microenvironment—specifically matrix stiffening and direct cell–cell interactions (CCI)—drives the fibrotic execution program, and that targeted delivery to the pathogenic cellular niche is essential for therapeutic efficacy. To address this, we employed spatial transcriptomic profiling to identify disease-relevant cellular targets and applied these findings to guide the development of extracellular vesicle-based therapeutic platforms.

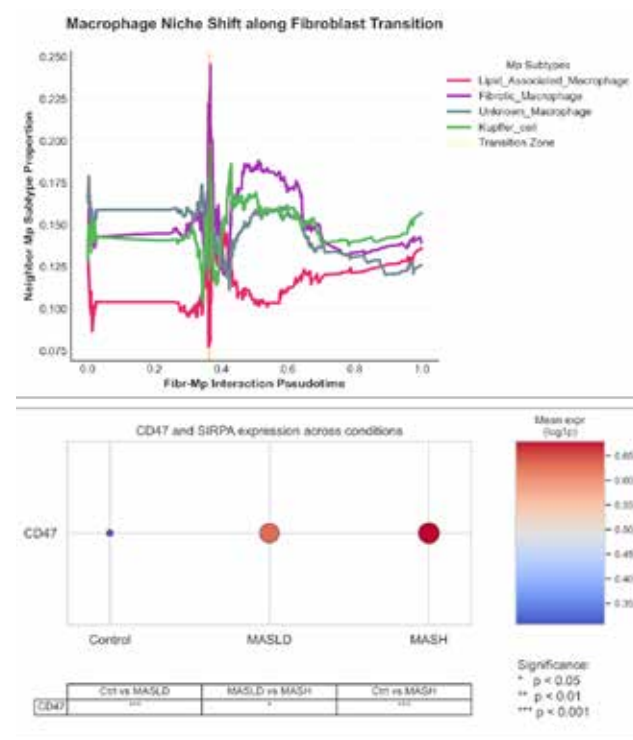
Methods: We performed integrated spatial transcriptomic profiling of human liver tissue spanning disease stages (Control, MASLD, MASH) using Visium and Xenium platforms. CCI signals were quantified with CellNeighborEX v2, which isolates interaction-induced transcriptional changes by computing residuals between observed spatial expression profiles and single-cell reference-based predictions. CCI-associated genes were systematically categorized using Adhesome/Reactome (ECM signaling potential) and MatrixDB (physical ECM interaction) databases. SIRP- α -engineered extracellular vesicles (SIRP-EVs) derived from mesenchymal stem cells were labeled with Cy5.5 for biodistribution assessment. *In vivo* validation was conducted in diet-induced MASH mouse models.

Results: CCI analysis uncovered a striking dissociation between fibrotic “potential” and fibrotic “execution” across disease stages: MASLD tissues harbored 2,043 ECM signaling genes yet ex-

hibited zero physical interaction genes, whereas MASH tissues displayed 315 MatrixDB-positive genes. This pattern suggests that physical ECM crosslinking—rather than transcriptional upregulation alone—may serve as the critical determinant of fibrosis execution. Pseudotime modeling revealed a discrete transition zone at approximately 0.35, at which fibrogenic scores shifted from negative to positive values, coinciding with marked expansion of fibrotic and lipid-associated macrophage populations. This inflection point appeared to demarcate the threshold of fibroblast-to-myofibroblast transdifferentiation. Both fibroblasts and macrophages exhibited progressive CD47 upregulation across disease stages from Control to MASH. SIRP-EV biodistribution analyses demonstrated significantly greater accumulation in fibrotic compared to normal liver tissue ($P < 0.01$), and flow cytometry confirmed selective delivery to fibroblasts and macrophages—the two-principal fibrosis-driving cell populations.

Conclusions: Our spatially resolved transcriptomic framework identifies physical macrophage–fibroblast crosstalk as a pivotal driver of MASH fibrosis progression, and establishes CD47 as a tractable surface target shared by both pathogenic cell types. SIRP-EVs demonstrate selective homing to the fibrotic niche, presenting a promising platform for precision therapeutic delivery. These findings offer a conceptual and translational basis for disease-modifying interventions that have thus far eluded systemic antifibrotic approaches.

Keywords: MASH, Spatial Transcriptomics, Fibrosis, CD47



FP-51

Hepatic CSE Deficiency Impairs Systemic Glutathione Homeostasis and Promotes Liver–Kidney Redox Imbalance in Obesity

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Aims: The liver is the major source of systemic glutathione (GSH) and plays a central role in whole-body redox homeostasis. Cystathionine γ -lyase (CSE), a key enzyme in the trans-sulfuration pathway, regulates cysteine availability for GSH synthesis. We investigated whether hepatic CSE deficiency disrupts systemic GSH homeostasis and contributes to liver–kidney redox imbalance under obese conditions.

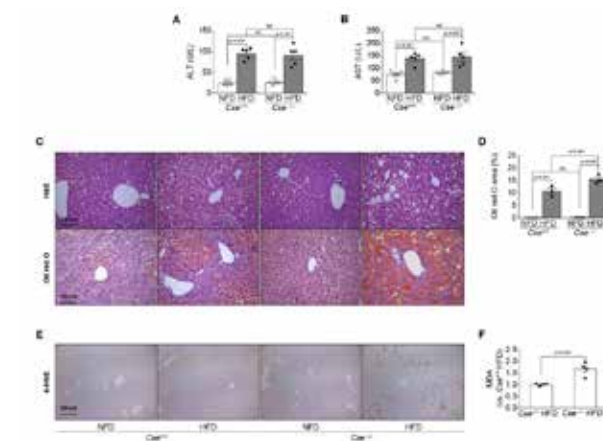
Methods: CSE-deficient ($Cse^{-/-}$) and wild-type ($Cse^{+/+}$) mice were fed a normal-fat diet (NFD) or a high-fat diet (HFD) for 16 weeks. Hepatic, plasma, and renal GSH metabolism were assessed, along with hepatic oxidative injury, steatotic change, renal oxidative stress, profibrotic signaling, fibrosis, and renal function.

Results: HFD significantly reduced hepatic total GSH levels, with greater depletion in $Cse^{-/-}$ mice than in $Cse^{+/+}$ mice. This hepatic GSH depletion was accompanied by parallel reductions in plasma and renal GSH levels, indicating impaired systemic antioxidant homeostasis. HFD increased hepatic 4-hydroxynonenal expression, malondialdehyde levels, vacuolization, and Oil Red O–positive lipid accumulation in both genotypes, with more pronounced changes in $Cse^{-/-}$ mice, indicating aggravated hepatic oxidative injury and steatotic change. Renal redox imbalance was markedly aggravated in HFD-fed $Cse^{-/-}$ mice, as evidenced by increased hydrogen peroxide accumulation, lipid peroxidation, and an elevated oxidized GSH-to-total GSH ratio. These changes were associated with upregulation of transforming growth factor- β 1, collagen I, and plasminogen activator inhibitor-1, along with increased collagen deposition, elevated plasma creatinine, and reduced creatinine clearance.

Conclusions: Hepatic CSE deficiency exacerbates HFD-induced hepatic oxidative injury and disrupts systemic glutathione homeostasis, accompanied by aggravated renal redox imbalance and fibrosis. These findings suggest that hepatic CSE-dependent glutathione metabolism is an important determinant of

metabolic organ crosstalk under obese conditions.

Keywords: Cystathionine γ -Lyase, Oxidative Stress, Obesity, Liver–Kidney Crosstalk



FP-52

The Single-Cell Landscape of MASLD-Specific Liver Sinusoidal Endothelial Cell Subclusters

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Aims: In metabolic dysfunction-associated steatosis liver disease (MASLD), liver sinusoidal endothelial cells (LSECs) play a pivotal role in the onset and progression of metabolic MASLD. However, the dynamics and roles of LSEC subclusters during MASLD progression remain largely unknown. This study aimed to analyze the molecular alterations and functions of LSEC subclusters as MASLD progressed, using single-cell analysis.

Methods: We analyzed single-cell RNA-seq (scRNA-seq) in 11 individuals to compare endothelial subclusters between MASLD patients and healthy controls, validated the findings with single-nucleus RNA-seq (snRNA-seq) in 14 individuals from an independent cohort, and further examined their association with histological severity and zonal distribution using

spatial transcriptomics in 12 individuals.

Results: Endo 4 subcluster, identified as the MASLD-specific LSEC subcluster, was significantly increased in patients with MASLD compared to healthy controls in both scRNA-seq and snRNA-seq cohorts. Gene expression analysis revealed that ANGPT2 was upregulated in the MASLD-specific LSEC subcluster compared to other LSEC cells. Furthermore, gene expressions related to extracellular matrix, TGF- β signaling, and HIF-1 signaling were increased in the MASLD-specific LSEC subcluster. Spatial transcriptomics showed MASLD-specific LSEC sub-clusters increased progressively with the severity of steatosis, ballooning, inflammation, and fibrosis. Notably, the MASLD-specific LSEC subcluster showed a higher degree of colocalization with scar-associated stellate cells than other subclusters. It also demonstrated increased interaction with hepatic stellate cells, T cells, and highest interaction with CD14⁺ CD16⁺ circulating monocytes.

Conclusions: The MASLD-specific LSEC subcluster, associated with disease severity, was characterized by activation of extracellular matrix remodeling, TGF- β and HIF-1 signaling, and showed enhanced interactions with hepatic T cells, stellate cells, and peripheral circulating monocytes.

Keywords: LSEC, MASLD, Single Cell Transcriptomics

FP-53

Metabolic Stress Transforms DNA Damaged Biliary Epithelial Cells into Hepatocellular Carcinomas

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Aims: Hepatocellular carcinoma (HCC) arising in metabolic dysfunction-associated steatotic liver disease (MASLD) is rapidly increasing worldwide. However, the mechanisms by which metabolic stress interacts with mutagenic injury to drive hepatocarcinogenesis remain incompletely understood. We investigated the cellular and molecular mechanisms underlying MASLD-associated hepatocarcinogenesis using a streptozotocin and high-fat diet (S⁺H⁺) mouse model.

Methods: Seven-week-old C57BL/6J mice were treated with low-dose streptozotocin (STZ) followed by high-fat diet (HFD) feeding to induce hepatocarcinogenesis. Longitudinal analyses

included bottleneck sequencing (BotSeq), single-cell RNA sequencing, and lineage tracing using Sox9-CreERT2;R26-LSL-td-Tomato mice to define mutational dynamics and the cell-of-origin of HCC. Functional experiments using organoids and pharmacologic inhibition evaluated the role of WNT signaling.

Results: The S⁺H⁺ mice developed HCC with markedly higher incidence than control groups, reaching 100% by 68 weeks. STZ induced somatic mutations in hepatocytes, whereas sustained HFD promoted selective expansion of hepatocytes with increased mutational impact from STZ. Single-cell transcriptomic analysis identified transitional liver progenitor cells bridging biliary epithelial cells (BECs) and hepatocytes, suggesting BEC-to-hepatocyte transdifferentiation during mutagenic injury followed by chronic metabolic stress. Lineage tracing demonstrated that BEC-lineage hepatocytes exhibited a modest increase in mutational burden and substantially higher tumorigenic potential (47.6-fold higher than non-BEC-lineage), accounting for a large fraction of HCCs. Endothelial cells in S⁺H⁺ livers showed increased expression of WNT-activating ligands, establishing a WNT-enriched hepatic microenvironment that supported expansion and malignant transformation of BEC-derived hepatocytes, reversed by pharmacologic inhibition.

Conclusions: Metabolic stress cooperates with mutagenic injury to promote hepatocarcinogenesis by enabling regeneration and malignant transformation of DNA-damaged BEC-derived hepatocytes within a WNT-enriched hepatic microenvironment. Our findings identify BEC-lineage as a major cell-of-origin for MASLD-associated HCC and highlight the tumor-promoting hepatic microenvironment as a potential therapeutic target.

Keywords: Hepatocarcinogenesis, MASLD, Cell of Origin, Liver Progenitor Cells

FP-54

Aging-Associated Clonal Hematopoiesis in TET2-Mutant HSCs Drives Myeloid Expansion and Accelerates Liver Inflammation and Fibrosis in MASH

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Aims: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-associated condition characterized by the expansion of clones of hematopoietic stem cell carrying somatic mutations. Among these mutations, alterations in TET2 are frequently observed and have been associated with altered inflammatory responses in myeloid cells. Although CHIP has been linked to several chronic inflammatory diseases, its role in

metabolic dysfunction-associated steatohepatitis (MASH) remains incompletely understood. In this study, we investigated whether TET2-mutant clonal hematopoiesis influences hepatic inflammation and fibrosis during MASH development.

Methods: To employ model of TET2-mutant clonal hematopoiesis, lethally irradiated CD45.1 recipient mice received competitive bone marrow transplantation consisting of wild-type and TET2-deficient bone marrow cells at a 7:3 ratio. After hematopoietic reconstitution, mice were fed a choline-deficient amino acid-defined high-fat diet (CDAA-HFD) to induce MASH. Immune cell populations in peripheral blood and liver tissues were analyzed by flow cytometry, and liver pathology was assessed by histological analyses including Sirius Red staining. In addition, spatial transcriptomics was performed to investigate transcriptional changes within the liver microenvironment.

Results: Following transplantation, TET2-deficient hematopoietic cells highly expanded relative to wild-type cells. Flow cytometric analysis revealed increased proportions of myeloid lineage cells, including neutrophils and monocytes, in mice harboring TET2-mutant hematopoiesis. In the CDAA-HFD model, these mice showed increased hepatic inflammatory foci and inflammation, accompanied by greater collagen deposition and more extensive liver fibrosis. Spatial transcriptomics identified liver regions with increased immune-response and fibrosis-related gene programs.

Conclusions: These findings suggest that aging-associated TET2-mutant clonal hematopoiesis promote MASH progression by altering hematopoietic-derived immune cell composition, supporting a potential link between clonal hematopoiesis and liver disease progression.

Keywords: Clonal Hematopoiesis, TET2, MASH, Liver Fibrosis

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FREE PAPER PRESENTATION 2

FP-55~FP-62	MASLD, Clinical
FP-63~FP-70	HCC, Clinical 2
FP-71~FP-78	HBV & HCV
FP-79~FP-85	Liver Transplantation 1
FP-86~FP-93	HBV 2
FP-94~FP-101	LC, Liver Failure & Autoimmune Diseases 2
FP-102~FP-107	Liver Transplantation 2



Saturday, June 13, 2026, 09:10-10:30

8. Liver Cancer, Clinical 2

FP-55

Proposal of a Body Mass Index-Based Subclassification for Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake

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Aims: Body mass index (BMI) is a fundamental clinical parameter in steatotic liver disease (SLD). However, metabolic dysfunction-associated steatotic liver disease with increased alcohol intake (MetALD) is currently subclassified mainly according to alcohol consumption. This study aimed to investigate the clinical characteristics of MetALD with a focus on BMI-based subclassification.

Methods: We analyzed two independent cohorts: a Japanese health-screening cohort (N=24,232) and a Korean multicenter hospital cohort (V-LINK, N=35,087). SLD was defined based on ultrasonography, cardiometabolic criteria, and alcohol consumption. Patients with MetALD were subclassified using two approaches: (1) BMI-based classification (lean MetALD [BMI < 23 kg/m²] vs. non-lean MetALD [BMI ≥ 23 kg/m²]) and (2) alcohol consumption-based classification (metabolic-predominant [140–245 g/week for females and 210–315 g/week for males] vs. alcohol-predominant [≥245 g/week for females and ≥315 g/week for males]).

Results: (1) BMI-based subclassification revealed clearly distinct clinical phenotypes that were consistent across both cohorts.

Patients with lean MetALD were significantly older, consumed less alcohol, and had fewer cardiometabolic risk factors (CMRFs) than those with non-lean MetALD (all $P < 0.01$). Despite this, the lean group exhibited significantly higher liver injury markers, including FIB-4 index (1.52 vs. 1.29 in Japanese cohort; 3.46 vs. 1.69 in Korean cohort), ALBI score (-2.81 vs. -2.90 in Japanese cohort; -2.64 vs. -2.97 in Korean cohort), and AST levels (31 vs. 28 U/mL in Japanese cohort; 107.9 vs. 43.0 U/mL in Korean cohort) (all $P < 0.05$). (2) In contrast, alcohol consumption-based subclassification showed no significant differences in age, BMI, or the number of CMRFs between metabolic- and alcohol-predominant groups. Moreover, markers of liver injury and metabolic burden were comparable across different levels of alcohol consumption.

Conclusions: This study provides robust evidence from two independent East Asian cohorts that MetALD is a heterogeneous condition. BMI-based subclassification identifies clinically meaningful differences in disease phenotype and severity, suggesting its potential utility beyond conventional alcohol consumption-based classification.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake, Body Mass Index, Fibrosis, Steatotic Liver Disease

FP-56

Serum Free Triiodothyronine to Free Thyroxine Ratio and Risk of Developing Metabolic Dysfunction-Associated Steatotic Liver Disease: A Large-Scale Cohort Study

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Aims: Thyroid hormones regulate hepatic lipid metabolism, and impaired thyroid hormone action has been implicated

in metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to investigate the association between the free triiodothyronine (FT3) to free thyroxine (FT4) ratio and MASLD risk in euthyroid individuals.

Methods: We followed a cohort of 209,729 apparently healthy individuals without MASLD at baseline for a median of 5.7 years (interquartile range, 2.7–9.2). Serum FT3, FT4 and thyroid-stimulating hormone (TSH) were measured and FT3/FT4 ratio was calculated. Incident MASLD was defined based on ultrasound findings and metabolic dysfunction criteria. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) by FT3/FT4 ratio quintiles, with FT3/FT4 and covariates updated over follow-up.

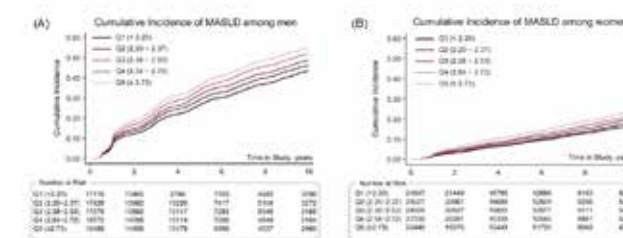
Results: Over 1,254,033.5 person-years of follow-up, 51,205 incident MASLD cases were identified (incidence rate: 40.8 per 1,000 person-years; men, 71.1; women, 21.5). Across FT3/FT4 quintiles, FT3 and TSH levels progressively increased, whereas FT4 levels decreased (p for trend <0.001). In time-dependent models, multivariable-adjusted HRs (95% CI) for MASLD incidence across FT3/FT4 quintiles (Q2–Q5 vs. Q1) were 1.10 (1.06–1.15), 1.17 (1.13–1.22), 1.24 (1.19–1.28) and 1.29 (1.25–1.34), respectively in men and 1.08 (1.02–1.14), 1.20 (1.14–1.26), 1.30 (1.24–1.37) and 1.44 (1.37–1.51) in women (p for interaction by sex <0.001).

Conclusions: A higher FT3/FT4 ratio within the euthyroid range is independently associated with an increased risk of developing MASLD in a dose-dependent manner. A higher FT3/FT4 ratio may identify individuals at increased risk of MASLD, potentially reflecting impaired hepatic thyroid hormone action despite normal circulating levels.

Keywords: Euthyroid, Thyroid Hormone Metabolism, THR-B, Hepatic Steatosis

Figure. Cumulative incidence of metabolic dysfunction-associated steatotic liver disease according to free triiodothyronine to free thyroxine ratio quintiles (A) men and (B) women.

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease.



FP-57

Dynamic Transitions in Steatotic Liver Disease Subtypes and Risk of Liver-related Events: A Nationwide Cohort Study

Yewan Park¹, Jooyi Jung², Seungbong Han², Gi-Ae Kim¹

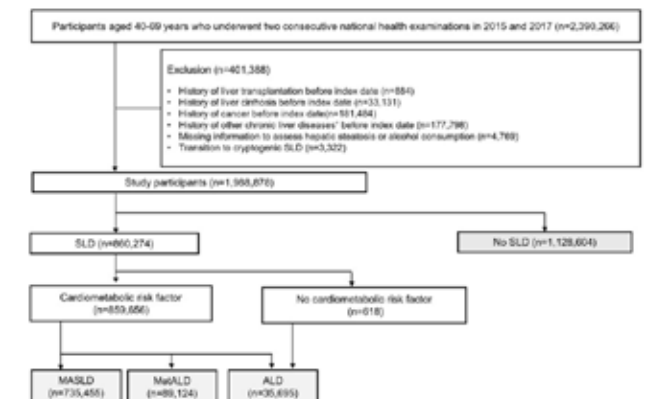
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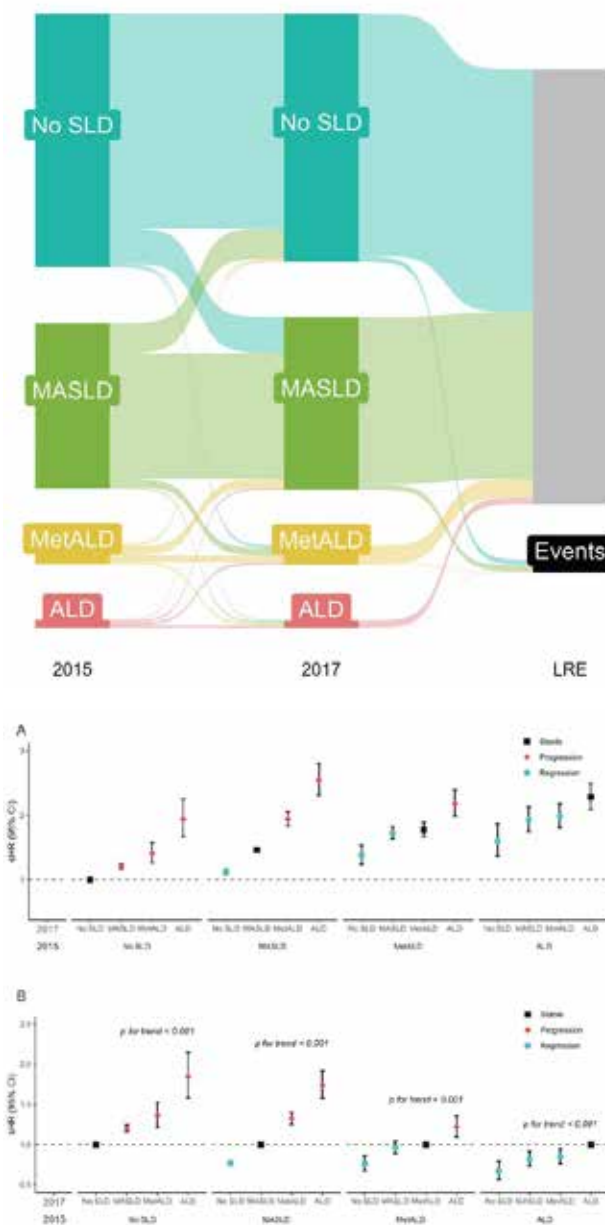
Aims: Steatotic liver disease (SLD) is a dynamic condition, yet most studies rely on single-time-point assessments, leaving the prognostic impact of its subtype transitions unclear. This study aimed to investigate the association between SLD subtype transitions and the risk of long-term liver-related events (LREs).

Methods: From the Korean National Health Insurance Service database, adults who underwent national health checkups in both 2015 and 2017 were recruited. SLD subtypes included metabolic dysfunction-associated SLD (MASLD), metabolic and alcohol-related SLD (MetALD), and alcohol-related liver disease (ALD). Transitions were classified into stable, regression, and progression. LREs included incident cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related mortality. Subdistribution hazard ratios (sHRs) were estimated using Fine-Gray competing-risk models.

Results: Among 1,988,878 individuals, 21.7% transitioned over two years: 11.3% progressed, whereas 10.4% regressed. The progression group showed an increased risk of LREs compared with the stable group (sHR, 1.33; 95% confidence interval [CI], 1.28–1.39), whereas the regression group showed attenuated risk (sHR, 0.86; 95% CI, 0.83–0.88). The findings were consistent across no SLD, MASLD, MetALD, and ALD groups. Sensitivity analyses stratified by sex, body mass index, and fatty liver index thresholds of >60 demonstrated comparable findings.

Conclusions: We found that progression to more advanced SLD subtypes were associated with increased risks of LREs, whereas regression to less advanced subtypes or no SLD was associated with substantial risk reduction. The findings can contribute to communicating the necessity of improving SLD subtypes through lifestyle modification, such as reducing alcohol intake or improving metabolic risk factors.





Keywords: Steatotic Liver Disease, Subtype Transition, Liver-Related Events, Longitudinal Assessment

FP-58

Development and Validation of M-SLD: A Novel Non-invasive Model for Steatotic Liver Disease Referenced Against Histology and MRI-PDFF

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Aims: While the Fatty Liver Index (FLI) is a standard noninvasive tool for hepatic steatosis, its accuracy is limited by its original reliance on ultrasonography. We aimed to develop and validate M-SLD, a novel predictive model for steatotic liver disease (SLD) anchored by gold-standard liver biopsy and MRI-proton density fat fraction (MRI-PDFF).

Methods: This retrospective diagnostic accuracy study was conducted at a single tertiary center. We included adults (n=2,699) who underwent simultaneous liver biopsy and MRI-PDFF within 30 days between January 2015 and March 2023. The dataset was temporally split into derivation (pre-2021, n=1,787) and validation (2021 onwards, n=912) cohorts. The M-SLD model was developed via multivariable logistic regression using: body mass index, waist circumference, age, sex, diabetes, high-density lipoprotein, and natural log-transformed triglycerides, gamma-glutamyltransferase, and alanine aminotransferase. The performance of M-SLD was compared against FLI across all cohorts. External validation was performed in a large health-screening cohort (n=120,785) collected between January 2010 and December 2025, using ultrasonography as the reference standard.

Results: In both derivation and validation cohorts, M-SLD significantly outperformed FLI (AUROC 0.772 and 0.760 vs. 0.710 and 0.683, respectively; $P<0.001$). M-SLD showed moderate correlation with histologic grade ($r=0.455-0.475$) and MRI-PDFF ($r=0.515-0.542$). The model demonstrated superior discriminatory power for early-stage steatosis (S0 vs. S1 and S1 vs. S2, $P<0.001$), though not for S2 vs. S3. In patients with MASLD-range alcohol intake, MSLD remained superior to FLI in both derivation (AUROC 0.777 vs 0.714) and validation (AUROC 0.761 vs 0.684) cohorts (both $P<0.001$). External validation confirmed high transportability with an AUROC of 0.871, significantly outperforming FLI (0.865, $P<0.001$).

Conclusions: M-SLD provides superior and reproducible discrimination of SLD compared to FLI when referenced against histology and MRI-PDFF. Given its robust performance across multiple diagnostic modalities and large-scale cohorts spanning 15 years, M-SLD serves as a refined noninvasive tool for case ascertainment in MASLD research and clinical screening.

Keywords: Steatotic Liver Disease, Fatty Liver Index, Mri-Pdff, Noninvasive Prediction Model

FP-59

Metabolic-Alcohol Spectrum of Steatotic Liver Disease and Risk of Incident Gout: A Multi-National Cohort Study in Korea, Japan, and the United Kingdom

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a systemic metabolic disorder closely linked to insulin resistance and cardiometabolic abnormalities that may predispose individuals to hyperuricemia and gout. However, large-scale cross-national validation across the metabolic-alcohol spectrum of steatotic liver disease (SLD) remains limited. We investigated the association between the SLD spectrum and incident gout using three large population-based cohorts from Korea, Japan, and the United Kingdom.

Methods: We conducted a retrospective cohort study using the Korean National Health Insurance Service-Health Screening Cohort, the Japanese Medical Data Center database, and the UK Biobank. SLD was classified as no SLD without cardiometabolic risk factors, no SLD with risk factors, MASLD with no alcohol, MASLD with alcohol use, metabolic dysfunction-associated alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD). Incident gout was defined using diagnostic codes, and hyperuricemia was additionally evaluated in the Japanese cohort. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) for gout after adjustment for demographic factors, comorbidities, kidney function, smoking, and physical activity.

Results: Across all three cohorts, the risk of gout increased progressively across the metabolic-alcohol spectrum of SLD. In the Korean cohort, compared with individuals without SLD and without risk factors, adjusted HRs for gout were 2.33 (95% CI 2.09–2.59) for MASLD without alcohol, 2.62 (2.35–2.93) for MASLD with alcohol, 3.02 (2.67–3.42) for MetALD, and 3.11 (2.66–3.64) for ALD. Similar graded associations were observed in the Japanese and UK cohorts, where MASLD, MetALD, and ALD were consistently associated with progressively higher risks of gout. In additional analyses from the Japanese cohort, the associations were even stronger when hyperuricemia was included as an outcome. Furthermore, a significant interaction between MASLD and alcohol consumption was observed ($P<0.001$), suggesting a synergistic effect on gout risk.

Conclusions: In three large population-based cohorts from Asia and Europe, SLD across the metabolic-alcohol spectrum was independently associated with an increased risk of incident gout. These findings suggest that the metabolic-alcohol spectrum of SLD may play an important role in gout development.

Keywords: Fatty Liver, Gout, Hyperuricemia, Cohort Studies

Figure 1. The flow of study population (Korea & Japan & UK)

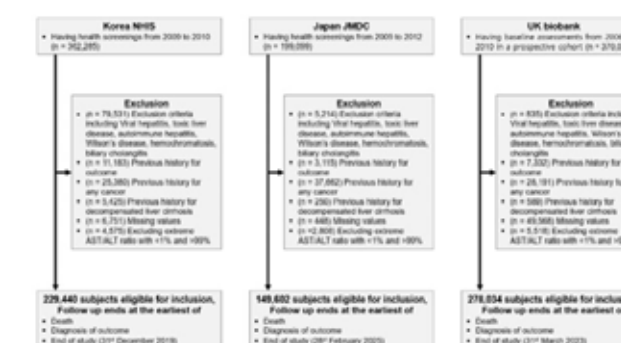


Figure 2. Kaplan-Meier curve for the association between steatotic liver disease and gout

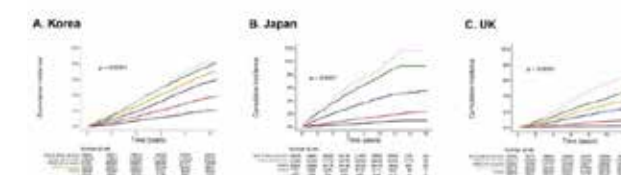
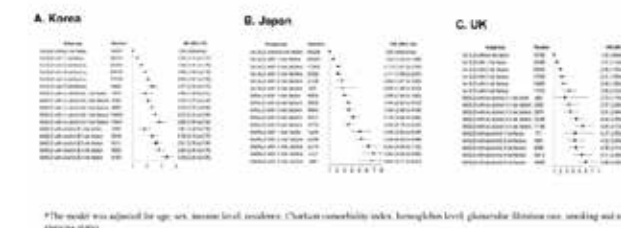


Figure 3. Subgroup analysis according to steatotic liver disease, cardiometabolic risk factors, and alcohol consumption (Korea).



*The model was adjusted for age, sex, income level, smoking, Charlson comorbidity index, hemoglobin level, glucose level, blood pressure, and regular exercise status.

FP-60

Liver-Related Outcomes in Diabetes-Associated MASLD with Low Fatty Liver Index: A Nationwide Cohort Study

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Aims: The fatty liver index (FLI) is widely used to identify hepatic steatosis in metabolic dysfunction–associated steatotic liver disease (MASLD). However, conventional FLI cutoffs may fail to capture clinically meaningful MASLD in some populations. We aimed to evaluate the burden of liver-related outcomes (LROs) among MASLD patients classified as having a low likelihood of steatosis according to FLI.

Methods: A retrospective cohort study was conducted using the Korean National Health Insurance Service (NHIS) database. Patients with diabetes who underwent health screening examinations between 2009 and 2013 were included. Patients were stratified according to FLI into control (FLI<20), suboptimal (FLI 20–30), and definite (FLI≥30) MASLD groups, and LROs were evaluated using Fine–Gray competing risk models. Parallel analyses were performed in the UK Biobank (UKB) cohort.

Results: Among 986,436 individuals in the NHIS database, 149,682 (15.2%) were classified as having suboptimal MASLD. During up to 13 years of follow-up, the suboptimal MASLD group had a significantly increased risk of composite LRO (subdistribution hazard ratio [sHR]=1.10, 95% confidence interval [CI]=1.06–1.15, $P<0.001$) compared to the control group, specifically for hepatocellular carcinoma (sHR=1.17, 95% CI=1.09–1.26, $P<0.001$), and liver-related death (sHR=1.22, 95% CI=1.12–1.34, $P<0.001$). The elevated risk persisted in cause-specific models and across subgroups. However, among 391,220 individuals in the UKB database, the suboptimal MASLD group had a comparable risk of LROs relative to the control group (sHR=1.06, 95% CI=0.61–1.81, $P=0.844$).

Conclusions: In this nationwide cohort study, individuals with MASLD classified as having a low likelihood of steatosis by conventional FLI thresholds still exhibited a substantial burden of LROs. Current FLI cutoffs may be insufficiently sensitive to capture clinically relevant MASLD in some populations.

Keywords: Fatty Liver, Lean Nafld, Liver Cancer, Uk Biobank

FP-61

Potential Influence of PNPLA3 Genotype on Semaglutide Response in Metabolic Dysfunction–Associated Steatotic Liver Disease: Real-World Data in Korean Cohort

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Aims: Semaglutide is widely used for obesity and metabol-

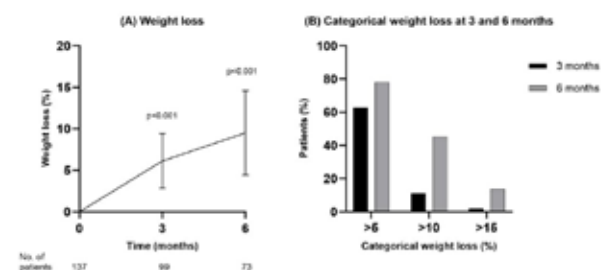
ic-associated steatotic liver disease (MASLD), but real-world data in Korean populations remain limited. Genetic variants in PNPLA3 are known to be associated with MASLD progression. We aimed to evaluate the real-world clinical outcomes of semaglutide and to determine whether the PNPLA3 genotype affects therapeutic response in Korean patients.

Methods: We retrospectively enrolled 137 patients who received once-weekly semaglutide at 2 tertiary hospitals (Seoul St. Mary's Hospital and Eunpyeong St. Mary's Hospital) in Korea between March and December 2025. Clinical outcomes, including weight loss and changes in liver fibrosis and steatosis markers, were assessed. To evaluate the impact of the PNPLA3 genotype on treatment response, outcomes were compared according to genotype, and the association between PNPLA3 variants and therapeutic response was analyzed.

Results: At 3 and 6 months, 99 (72.3%) and 73 (53.3%) patients achieved weight reduction, with mean losses of 5.15 kg (6.13%) and 7.55 kg (9.50%), respectively; at 6 months, 57 (78.1%), 33 (45.2%), and 10 (13.7%) achieved ≥5%, ≥10%, and ≥15% weight loss. Among patients with paired FibroScan data (n=38), mean liver stiffness decreased from 7.65 to 5.74 kPa ($P<0.001$), and mean CAP decreased from 315 to 271 dB/m ($P<0.001$). APRI, AST, and ALT also showed significant reductions at 6 months (all $P<0.001$). The PNPLA3 variant homozygous genotype (GG) showed a tendency toward an attenuated therapeutic response to semaglutide compared with the GC/CC genotype, with fewer responders observed for ALT at 6 months, CAP, and TE. Responder analyses revealed fewer responders among GG carriers, with the 6-month ALT response approaching statistical significance ($P=0.082$).

Conclusions: In this multicenter real-world Korean cohort, once-weekly semaglutide was associated with significant weight loss and improvements in hepatic steatosis and fibrosis-related markers. The PNPLA3 genotype may be served as a potential biomarker for predicting therapeutic response to semaglutide.

Keywords: Semaglutide, PNPLA3, Metabolic Dysfunction-Associated Steatotic Liver Disease, Real-World Data



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Aims: Hepatic fibrosis represents the principal prognostic determinant in metabolic dysfunction–associated steatotic liver disease (MASLD), yet its contribution to future arrhythmic risk remains uncertain. We evaluated whether liver fibrosis burden precedes the development of incident electrocardiogram (ECG)–detected arrhythmia in a population-based cohort with structured rhythm surveillance.

Methods: The study utilized the Lifelines prospective cohort in the Netherlands. MASLD was defined using biochemical steatosis, cardiometabolic risk factors, and strict exclusion of excessive alcohol intake. Liver fibrosis burden was assessed at baseline using the fibrosis-4 (FIB-4) index. Participants with arrhythmia on baseline ECG were excluded. Incident arrhythmia and atrial fibrillation (AF) were identified exclusively through standardized follow-up 12-lead ECG recordings. Cox proportional hazards models were constructed with sequential adjustment for demographic and cardiometabolic variables, with age-stratified analyses.

Results: Among 10,263 participants with MASLD, 1,006 participants had elevated fibrosis burden defined by FIB-4 ≥ 1.45. Importantly, baseline age distributions were comparable across FIB-4 categories, minimizing confounding by chronological age. Despite similar baseline arrhythmic profiles, participants with elevated FIB-4 experienced significantly higher rates of ECG-detected incident arrhythmia during follow-up.

In adjusted models for metabolic insults and alcohol intake, FIB-4 ≥ 1.45 was significantly associated with incident arrhythmia in both the overall cohort and the MASLD subgroup. Especially, among those aged ≥ 50 years, elevated fibrosis burden was associated with significantly higher cumulative incidence and hazard of incident arrhythmia (Figure 1). When analyses were restricted to AF, elevated FIB-4 remained significantly associated with incident AF after multivariable adjustment for metabolic insults and alcohol intake, including within the ≥ 50-year MASLD subgroup (Figure 2).

FP-62

Liver Fibrosis Burden and ECG-Detected Incident Atrial Fibrillation in Metabolic Dysfunction–Associated Steatotic Liver Disease

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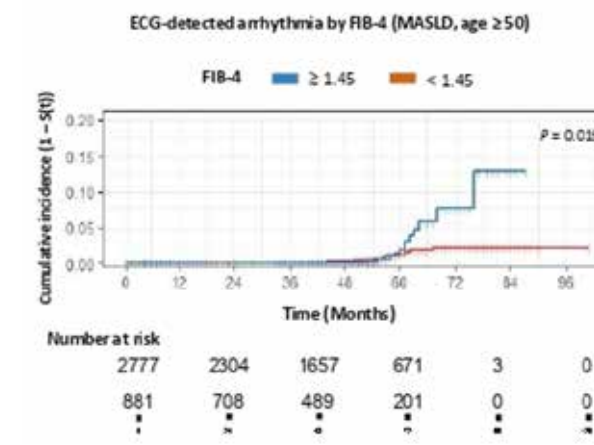


Figure1.

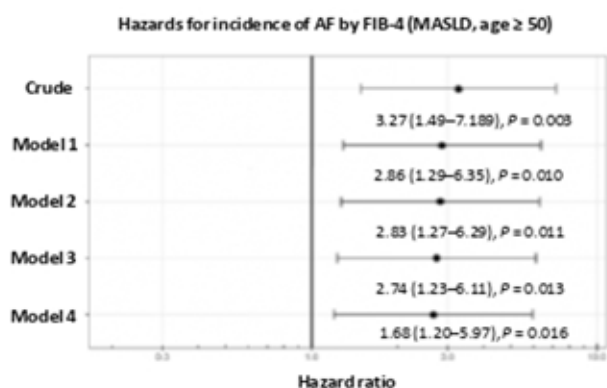


Figure 2.

Conclusions: In a large population-based cohort with objective ECG follow-up, liver fibrosis burden assessed by FIB-4 identified individuals with MASLD at increased risk for future arrhythmic events, particularly AF. The absence of baseline age imbalance and the emergence of risk only during longitudinal follow-up support a fibrosis-driven, rather than age-driven, arrhythmic vulnerability.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease, Liver Fibrosis, Cardiac Arrhythmia, Atrial Fibrillation

Saturday, June 13, 2026, 09:10-10:30

9. HCC, Clinical 2

FP-63

A Mechanism-Informed Six-Gene Prognostic Signature of Hepatocellular Carcinoma Derived from the Multi-Target Anti-Tumor Mechanism of Icaritin

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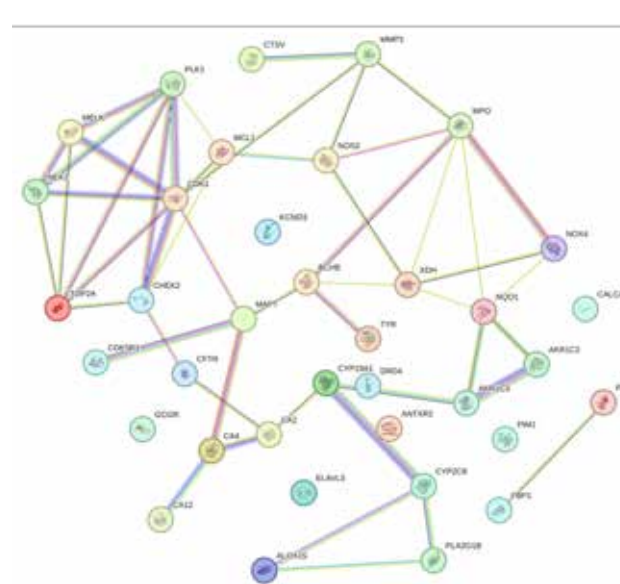
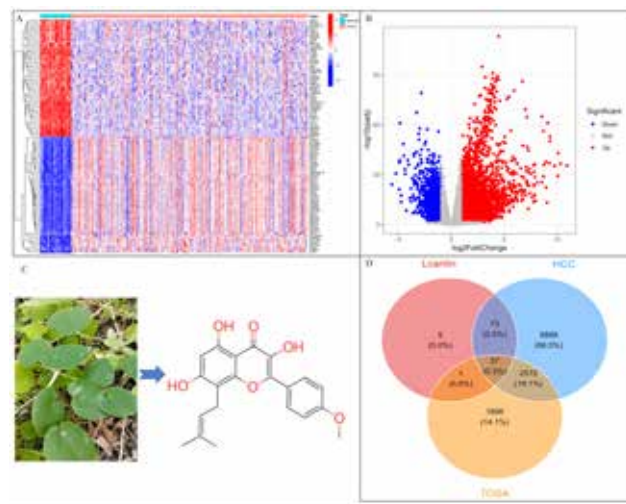
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Aims: To systematically decipher the molecular targets and pathways of Icaritin in anti-HCC therapy, and to construct and validate a prognostic gene model associated with the mechanism of action of Icaritin.

Methods: Transcriptomic data from HCC patients, potential targets of Icaritin, and HCC-related disease genes were integrated from the TCGA – LIHC cohort, specialized drug target databases, and authoritative disease gene knowledgebases,

respectively. Key genes were screened via Venn analysis. Gene Ontology (GO)/Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses and Protein-Protein Interaction (PPI) network construction were performed. Combining survival data, with univariate Cox regression, multivariate Cox regression, and SHapley Additive exPlanations (SHAP) machine learning interpretation model, a risk scoring model was established. The model's efficacy was validated using Kaplan-Meier analysis, time-dependent receiver operating characteristic (ROC) curves, and multivariate Cox regression.

Results: A total of 37 key intersectional genes of Icaritin against HCC were identified. Functional enrichment analysis showed that these key genes were significantly enriched in core pathways involved in HCC development, including cell cycle regulation, p53 signaling pathway, oxidative stress-related chemical carcinogenesis pathway, and arachidonic acid metabolism pathway. Based on clinical survival data of HCC patients, a six-gene prognostic model consisting of *CYP19A1*, *NQO1*, *MMP3*, *PLK1*, *NEK2*, and *CDK5R1* was finally constructed. Patients were divided into high-risk and low-risk groups based on the median risk score (3.58) derived from the model. Kaplan-Meier survival analysis showed that the overall survival of the high-risk group was significantly lower than that of the low-risk group ($P < 0.001$). A clear separation of survival curves was observed early during follow-up, which further diverged as time progressed. Time-dependent ROC curve validation revealed that the area under the curve (AUC) values of the model for predicting 1-, 3- and 5-year overall survival (OS) of HCC patients were 0.826, 0.705, and 0.692, respectively, demonstrating excellent short-term predictive performance and stable long-term predictive performance. Multivariate Cox regression analysis further confirmed that the risk score of this six-gene model was an independent prognostic factor for HCC, independent of age, gender, tumor grade, and stage (HR=2.874, 95% CI: 1.894–4.359, $P < 0.001$).



Conclusions: This study systematically revealed the potential mechanism by which Icaritin exerted anti-HCC effects by intervening in multiple signaling pathways and successfully constructed a robust six-gene prognostic signature. This model not only had clinical potential for predicting the survival risk of HCC patients but also provided a theoretical basis and potential biomarkers for the further development of Icaritin.

Keywords: Icaritin, Hepatocellular Carcinoma, Prognostic Model, Bioinformatics, Machine Learning

FP-64

Comparative Effectiveness of Atezolizumab–Bevacizumab vs. Durvalumab–Tremelimumab in Unresectable HCC: A Systematic Review and Novel Machine Learning-Based Indirect Meta-Analysis

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Aims: Atezolizumab plus bevacizumab (AB) and durvalumab plus tremelimumab (DT) are standard first-line systemic therapies for unresectable hepatocellular carcinoma (uHCC). However, their comparative effectiveness remains uncertain due to the lack of head-to-head studies. We aimed to compare the clinical outcomes of AB and DT across diverse clinical settings using a machine learning (ML)-based framework.

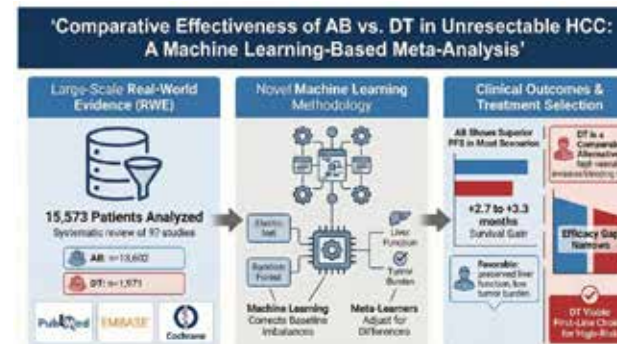
Methods: We performed a systematic review and conducted both conventional random-effects meta-analysis and a ML-based indirect comparison. Optimal predictive algorithms were selected via 5-fold cross-validation (Elastic Net for mPFS;

Random Forest for DCR). Subsequently, causal inference meta-learners (S-learner and T-learner) were developed to estimate the conditional average treatment effect (CATE) across 10 pre-defined clinical scenarios, adjusting for baseline imbalances.

Results: A total of 97 real-world studies (77 AB, 20 DT) involving 15,573 patients were included. Initial pooled analysis showed an mPFS of 7.1 months and DCR of 75.0% for AB, whereas DT showed 3.9 months and 53.1%, respectively. In the ML-adjusted analysis, AB demonstrated superior mPFS compared to DT across most clinical scenarios, including pivotal trial-like populations, first- and later-line settings, diverse geographic cohorts, and Child-Pugh A or B classes. However, this survival benefit was attenuated and lost statistical significance in the advanced disease setting characterized by high tumor burden. Regarding DCR, comparative outcomes were generally similar between the two regimens, except for specific subgroups—such as later-line, Asian, and Child-Pugh B populations—where AB retained superiority.

Conclusions: This novel comparative analysis using machine learning algorithms suggests that AB might be associated with prolonged mPFS compared to DT across most clinical subgroups, although this advantage may diminish in patients with extensive tumor burden. However, given the insufficient relevant studies to draw robust conclusions on clinical outcomes, further accumulation of real-world evidence is warranted to comprehensively evaluate the comparative efficacy of these regimens.

Keywords: Atezolizumab–Bevacizumab, Durvalumab–Tremelimumab, Meta-Analysis, Machine Learning, Hepatocellular Carcinoma



FP-65

Synergistic Efficacy of Radiation Therapy Combined with Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma with Vp4 Portal Vein Tumor Thrombosis: A Multicenter Study

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Aims: Hepatocellular carcinoma (HCC) with Vp4 portal vein tumor thrombosis (PVTT) carries a poor prognosis. While atezolizumab plus bevacizumab (Ate/Bev) is the standard first-line therapy, its efficacy in achieving rapid recanalization of extensive Vp4 thrombi is often limited. Adding radiation therapy (RT) may provide potent local control and synergistic immunomodulatory effects when combined with an immune checkpoint inhibitor (ICI). We evaluated the oncologic benefit of adding planned RT to Ate/Bev in this advanced subgroup.

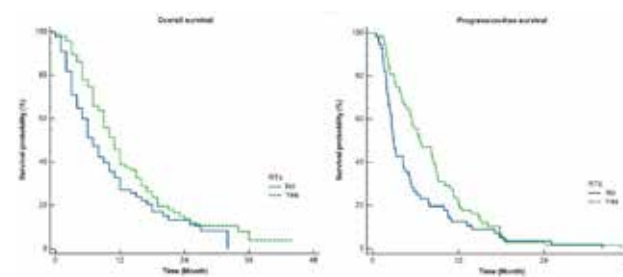
Methods: This multicenter retrospective study analyzed 183 patients with HCC and Vp4 PVTT. Oncologic outcomes were compared between the RT group (n = 95; RT planned before or during systemic therapy) and the no-RT group (n = 88).

Results: Among 183 patients (median 64 years; 82.5% male), 85.2% had Child-Pugh A function. Tumor involvement over 50% and bile duct invasion were noted in 37.7% and 12.0% of cases, respectively. Previous local therapy had been administered to 45.9% of the cohort. In the RT group, 29 (30.5%) and 66 (69.5%) patients received RT before and during systemic therapy, respectively. The RT group demonstrated significantly longer median PFS (6.6 vs. 2.9 months; HR 0.63, $P=0.016$) and median OS (11.0 vs. 7.0 months; HR 0.68, $P=0.030$) than the no-RT group. Regarding response, the during-ICI RT subgroup achieved a superior objective response rate (ORR: during ICI 37.5% vs. before ICI 19.2% vs. No RT 19.4%; $P=0.042$). RT did not increase the risk of over grade 3 adverse events or gastrointestinal bleeding ($P=1.000$).

Conclusions: Integrating planned RT with Ate/Bev significantly improves oncologic outcomes (PFS, OS, and ORR) for Vp4 PVTT without compromising safety. These findings support RT as a potent adjunctive strategy to maximize the efficacy of first-line ICI combination therapy in advanced HCC with extensive macrovascular invasion.

Keywords: Hepatocellular Carcinoma, Portal Vein Tumor Throm-

bosis; Atezolizumab Plus Bevacizumab, Radiation Therapy



FP-66

Development of an Early Prediction Model for Atezolizumab–Bevacizumab Treatment Response in Patients with Advanced Hepatocellular Carcinoma: An Interim Analysis of a Prospective Cohort Study

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Aims: Timely identification of non-responders to atezolizumab–bevacizumab (Atezo–Bev) therapy is critical for optimizing outcomes in advanced hepatocellular carcinoma (HCC). This study aimed to develop and validate an early predictive model based on laboratory and radiologic changes assessed after two cycles of Atezo–Bev therapy (approximately 1.5 months after treatment initiation).

Methods: This prospective study enrolled 136 patients with advanced HCC treated with Atezo–Bev at a single tertiary center between July 2022 and May 2025. Among them, 55 patients with evaluable radiologic data and adequate follow-up were included in the analysis. Clinical, laboratory, and imaging variables assessed at baseline and after two treatment cycles were analyzed. Multivariable Cox proportional hazards regression was used to identify predictors of disease progression including the Model for tumor Recurrence After living donor Liver transplantation (MoRAL = $11 \times \sqrt{[\text{protein induced by vitamin K absence or antagonist-II (PIVKA-II)}]} + 2 \times \sqrt{[\text{alpha-fetoprotein (AFP)}]}$) score. Significant variables were integrated to develop a composite predictive model. Model performance was evaluated using the area under the receiver operating characteristic curve (AUROC) and concordance index (C-index).

Results: Three variables were independently associated with disease progression: baseline MoRAL ($11 \times \sqrt{[\text{protein induced by vitamin K absence or antagonist-II (PIVKA-II)}]} + 2 \times$

$\sqrt{[\text{alpha-fetoprotein (AFP)}]}$) score (hazard ratio [HR]=1.0003, $P=0.05$), rate of change in MoRAL ($\Delta \text{MoRAL} [\%]$; HR=1.0042, $P<0.001$), and rate of change in arterial-phase enhancement ($\Delta \text{Enhancement} [\%]$; HR=1.0133, $P=0.04$). These variables were integrated into a composite model, the MoRAL-ART score, defined as follows: MoRAL-ART = $1 \times \text{MoRAL}_{\text{baseline}} + 12 \times \Delta \text{MoRAL} (\%) + 19 \times \Delta \text{Enhancement} (\%)$. A higher MoRAL-ART score was associated with an increased risk of non-response (HR=1.0004, 95% confidence interval=1.0002–1.0005, $P<0.0001$). MoRAL-ART showed favorable discriminatory performance (area under the receiver operating characteristic curve=0.777, C-index=0.692). When the high-risk group was defined as patients with a MoRAL-ART score ≥ -226 , this group exhibited a 3.6-fold greater risk of disease progression than the low-risk group (MoRAL-ART score < -226) ($P<0.001$). At the same cutoff, the model demonstrated high sensitivity (0.86) and a high negative predictive value (0.96) for identifying early non-responders who experienced disease progression within 3 months.

Conclusions: MoRAL-ART score serves as an objective, non-invasive tool for the early clinical prediction of therapeutic response to Atezo–Bev in advanced HCC. By facilitating the early stratification of non-responders, this model supports clinical decision-making and guides timely treatment modifications. Multicenter external validation is warranted to confirm its generalizability and establish its potential for clinical implementation.

Keywords: Liver Cancer, Immunotherapy, Response Prediction, MoRAL Score

FP-67

PNPLA3, but Not a Five-Variant Polygenic Risk Score, Predicts Hepatocellular Carcinoma in Korean MASLD

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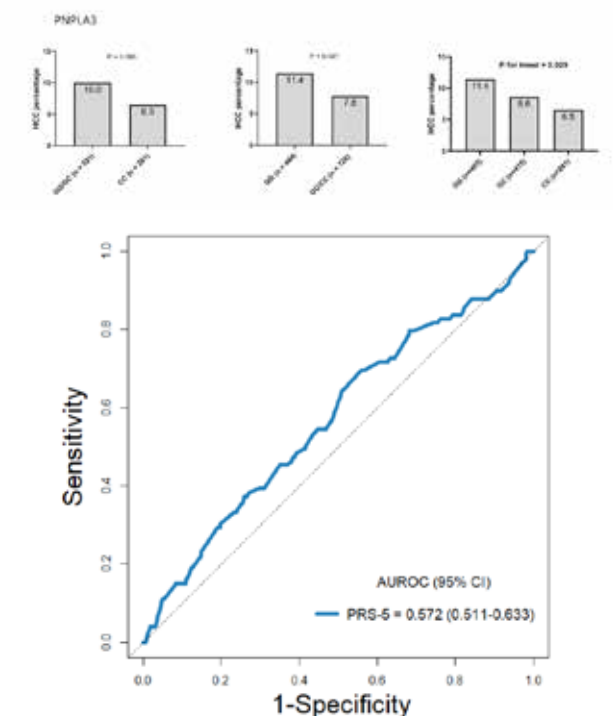
¹Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; ²The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; ³Xenohelix Research Institute, Incheon, Republic of Korea; ⁴Department of Systems Biology, Institute of Life Science and Biotechnology, Yonsei University, Seoul, Republic of Korea; ⁵Division of Hepatology, Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea; ⁶Division of Hepatology, Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

Aims: Genetic variants in *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, and *HSD17B13* have been implicated in MASLD progression, with emerging evidence suggesting a potential role in HCC risk. A five-variant polygenic risk score (PRS-5) has been proposed for HCC risk stratification in Western populations. We aimed to evaluate the association between these variants and HCC and

to assess the performance of PRS-5 in a multicenter Korean MASLD cohort.

Methods: A total of 1,081 patients with MASLD from five tertiary hospitals were enrolled, including 99 patients with HCC. Genotyping was performed for *PNPLA3* (rs738409), *TM6SF2* (rs58542926), *MBOAT7* (rs641738), *GCKR* (rs1260326), and *HSD17B13* (rs72613567). Associations between genotypes and HCC were analyzed under additive and dominant models. The PRS-5 was calculated using previously reported weighted coefficients (Bianco et al., J Hepatol 2021).

Results: The *PNPLA3* rs738409 G allele showed a significant dose-dependent association with HCC. HCC prevalence increased progressively across genotypes (GG 11.4%, GC 8.6%, CC 6.5%; P for trend = 0.029). Under a recessive model, GG homozygotes had a significantly higher HCC prevalence compared with GC/CC carriers (11.4% vs. 7.8%, $P=0.047$), whereas the dominant model did not reach statistical significance ($P=0.090$). In contrast, no significant associations were observed for *TM6SF2*, *MBOAT7*, *GCKR*, or *HSD17B13* genotypes under additive or dominant models. When applying the PRS-5 model to this Korean cohort, the discriminative ability for HCC was modest, with an AUROC of 0.572 (95% CI, 0.511–0.633), substantially lower than that reported in Western populations.



Conclusions: In this multicenter Korean MASLD cohort, *PNPLA3* was the only genetic variant significantly associated with HCC. The PRS-5 model demonstrated limited predictive performance, suggesting that ethnicity-specific genetic architecture

may influence PRS utility. These findings highlight the need for population-specific genetic risk models for HCC stratification in MASLD.

Keywords: Hepatocellular Carcinoma, PNPLA3, Polygenic Risk Score, Metabolic Dysfunction-Associated Steatotic Liver Disease

FP-68

Overcoming the Limitations of GALAD: SeeLiver Enables Superior Early and AFP-Negative HCC Detection

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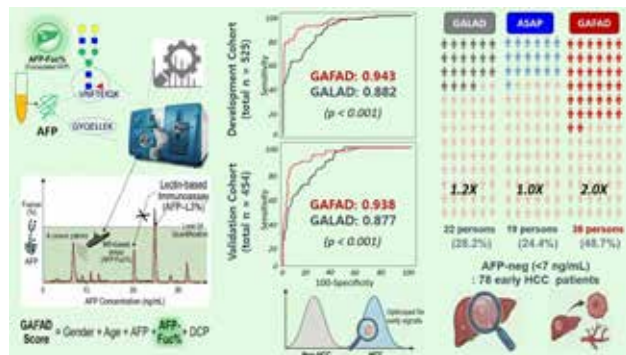
Aims: The GALAD score is widely used for hepatocellular carcinoma (HCC) detection but was largely derived from cohorts with advanced tumors and elevated biomarkers, potentially overestimating performance in early-stage disease. In addition, lectin-based AFP-L3 assays show limited sensitivity at low AFP concentrations, reducing detection of small or AFP-negative tumors. We developed SeeLiver, a diagnostic algorithm (GA-FAD) that replaces AFP-L3 with fucosylated AFP percentage (AFP-Fuc%) quantified using liquid chromatography–tandem mass spectrometry (LC-MS/MS).

Methods: The model was trained in an HBV-related development cohort (HCC n=235; non-HCC n=290) characterized by substantial biomarker overlap, and subsequently validated in two independent cohorts (HCC n=210; non-HCC n=245) including HBV-, HCV-, and non-viral etiologies.

Results: In the development cohort, GAFAD outperformed GALAD (AUC 0.938 vs. 0.887; $P<0.0001$), with higher sensitivity (82% vs. 66%) and accuracy (86% vs. 79%) at 90% specificity. In external validation, GAFAD maintained superior performance (AUC 0.874 vs. 0.841; $P<0.05$), with improved sensitivity (72% vs. 57%) and accuracy (82% vs. 75%). The advantage was particularly evident in early-stage, very-early-stage, and AFP-negative HCC.

Conclusions: SeeLiver provides a robust LC-MS/MS–based approach that overcomes key limitations of GALAD and improves detection of early and AFP-negative HCC across diverse etiologies.

Keywords: Hepatocellular Carcinoma, Early Detection, Alpha-Fetoprotein, Galad



FP-69

In-Context Learning-Based Prediction of 5-Year Hepatocellular Carcinoma Risk in Chronic Hepatitis B

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Aims: Chronic hepatitis B (CHB) remains a leading cause of hepatocellular carcinoma (HCC), and accurate risk stratification is essential for surveillance and treatment. Although existing clinical scoring systems, including PAGE-B, CU-HCC, and mPAGE-B, estimate HCC risk, their performance varies across heterogeneous populations beyond their original development settings, with some low- or intermediate-risk patients still developing HCC in real-world practice. This observation supports the development of more adaptable and context-aware prediction frameworks. TabICL performs context-conditioned inference through a small support set without parameter updates and suits heterogeneous CHB populations with complex clinical variable interactions. This study evaluates TabICL for 5-year HCC risk prediction in Korean patients with CHB.

Methods: TabICL employs a two-stage architecture with column-then-row attention and distribution-aware feature embedding. Predictions for each query patient use a support set of labeled training patients for contextual conditioning. Electronic medical records of 2,142 CHB patients from a tertiary hospital (2010–2021) are used. Model inputs include seven clinical variables from conventional scoring systems (age, sex, platelet count, albumin, bilirubin, HBV-DNA level, and cirrhosis status), with additional analyses including AST and ALP. Five-fold cross-validation evaluates TabICL against logistic regression, feed-forward neural network, random forest, XGBoost, and clinical scoring systems.

Results: PAGE-B, CU-HCC, and mPAGE-B achieve AUROC of 0.7287, 0.7387, and 0.7872, respectively. TabICL achieves AUROC of 0.8503 and AUPRC of 0.7129 with clinical variables from

existing scores. With the inclusion of AST and ALP, AUROC and AUPRC increase to 0.8826 and 0.7724, respectively. This superior performance reflects the ability of TabICL to capture complex nonlinear interactions.

Conclusions: TabICL demonstrates superior discrimination for 5-year HCC risk prediction in Korean patients with CHB. TabICL performs context-conditioned inference through support set examples, enabling adaptable risk stratification for heterogeneous cohorts without model updates. These findings highlight the clinical utility of TabICL for more precise HCC surveillance in patients with CHB.

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Keywords: In-Context Learning, Hepatocellular Carcinoma, Chronic Hepatitis B, Tabicl

Table 1: HCC prediction performance in CHB patients: average (± standard deviation). Boldface denotes statistically superior performance in each column, determined by paired t-tests with a significance level of $\alpha = 0.05$.

	AUROC (↑)	AUPRC (↑)	Precision (↑)	Recall (↑)	Specificity (↑)	F1-score (↑)
PAGE-B	0.7287±0.0305	0.5081±0.0486	0.4971±0.0795	0.5848±0.1003	0.7433±0.1559	0.5204±0.0265
CU-HCC	0.7387±0.0125	0.5068±0.0113	0.4856±0.0151	0.5812±0.0249	0.7081±0.0290	0.5287±0.0111
mPAGE-B	0.7872±0.0229	0.5873±0.0547	0.5280±0.0891	0.6008±0.1154	0.7356±0.1211	0.5855±0.0365
with AST, ALP						
LR	0.8144±0.0130	0.6525±0.0383	0.6087±0.0411	0.6033±0.0375	0.5055±0.0089	0.5564±0.0528
RF	0.8304±0.0138	0.6655±0.0322	0.6829±0.0467	0.5094±0.0688	0.5107±0.0187	0.5816±0.0533
RF	0.8374±0.0186	0.6909±0.0267	0.7339±0.0547	0.5129±0.0449	0.5094±0.0176	0.6026±0.0391
XGB	0.8394±0.0126	0.6967±0.0377	0.7443±0.0597	0.5289±0.0486	0.5454±0.0126	0.6406±0.0527
TabICL	0.8503±0.0092	0.7129±0.0221	0.7174±0.0668	0.5231±0.0363	0.5023±0.0035	0.6043±0.0587
with AST, ALP						
LR	0.8566±0.0168	0.7285±0.0402	0.7407±0.0497	0.5143±0.0468	0.5925±0.0121	0.6071±0.0484
RF	0.8615±0.0181	0.7176±0.0439	0.6508±0.0320	0.6120±0.0918	0.5866±0.0233	0.6458±0.0562
RF	0.8630±0.0180	0.7367±0.0316	0.7453±0.0409	0.5641±0.0321	0.5974±0.0164	0.6112±0.0408
XGB	0.8677±0.0128	0.7423±0.0324	0.7072±0.0321	0.5761±0.0308	0.5929±0.0182	0.6601±0.0388
TabICL	0.8826±0.0139	0.7724±0.0285	0.7623±0.0334	0.6129±0.0359	0.5281±0.0139	0.6778±0.0398

FP-70

The Obesity Paradox in Hepatocellular Carcinoma: Insights from Continuous and Interaction-Based Analyses of Body Mass Index after Hepatic Resection

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Aims: The prognostic significance of body mass index (BMI) in hepatocellular carcinoma (HCC) remains controversial, and whether the obesity paradox reflects tumor biology or host-related factors is unclear. This study evaluated the association between BMI and survival after curative hepatic resection using continuous and interaction-based analyses.

Methods: We retrospectively analyzed 1,349 patients who underwent curative hepatic resection for HCC between 2004

and 2021. BMI was assessed both categorically (low (<18.5 kg/m²), normal (18.5–24.9 kg/m²), and high (≥25 kg/m²)) and as a continuous variable. Overall survival (OS) and recurrence-free survival (RFS) were analyzed using Kaplan–Meier methods and multivariable Cox proportional hazards models. Interaction terms were incorporated to examine whether the prognostic effect of BMI varied across clinically relevant subgroups defined by tumor differentiation, tumor size, tumor number, and alpha-fetoprotein level.

Results: OS differed significantly across BMI categories (log-rank $P<0.001$), whereas differences in RFS were modest. At 3 years, estimated OS rates were 88%, 82%, and 62% in the high, normal, and low BMI groups, respectively. In multivariable analysis, higher BMI as a continuous variable was independently associated with improved OS (hazard ratio per 1-unit increase, 0.87; 95% confidence interval, 0.79–0.95; $P=0.005$), but not with RFS. Subgroup analyses demonstrated a consistent protective association between BMI and OS without significant interactions across tumor-related factors.

Conclusions: Higher BMI is independently associated with improved overall survival after hepatic resection for HCC, irrespective of tumor biology. These findings support a host-related explanation for the obesity paradox in surgically treated HCC.

Keywords: Hepatocellular Carcinoma, Obesity Paradox, Survival

Saturday, June 13, 2026, 09:10–10:30

10. HBV & HCV

FP-71

RE-LIVE Study (Re-Linkage to Pan-Viral Hepatitis): Interim Results from a Multicenter Observational Study on Care Engagement in Chronic Viral Hepatitis

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Aims: Despite the availability of highly effective antiviral therapies, linkage to care remains a key barrier to the global elimination of viral hepatitis. A considerable proportion of individuals with chronic hepatitis B, C, and D remain undiagnosed, untreated, or lost to follow-up, sustaining the burden of disease and transmission. In Korea, reimbursement criteria for

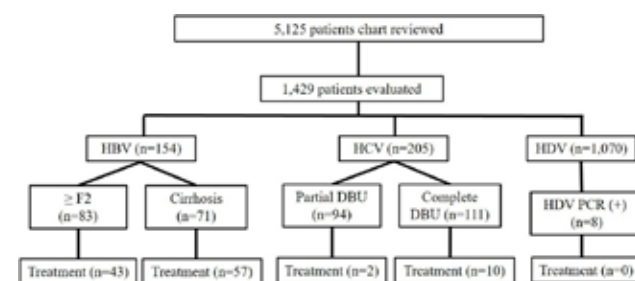
HBV treatment were expanded in 2023; however, a substantial number of eligible patients remain untreated. This study aimed to evaluate systematic re-linkage strategies to re-engage these individuals in the continuum of care, with the goal of improving clinical outcomes and contributing to public health objectives.

Methods: A retrospective chart review was conducted at four tertiary academic hospitals in Korea to identify candidates for antiviral treatment. HBV eligibility included (i) non-cirrhotic patients with HBV DNA >2,000 IU/mL and fibrosis stage ≥ 2 , and (ii) cirrhotic patients with any detectable HBV DNA. For HCV, partially diagnosed-but-untreated (DBU) cases were defined as anti-HCV antibody positive with missing HCV RNA data; completely DBU cases were HCV RNA positive without prior antiviral therapy. HBV patients eligible for HDV screening underwent HDV PCR. All identified patients were re-contacted via text or phone for re-evaluation and potential treatment linkage.

Results: Among 5,125 patient charts reviewed, 154 HBV and 309 HCV patients were enrolled in the re-linkage to treatment program. Among HBV patients, 64.9% (154) initiated antiviral therapy, while 35.1% (54) did not respond to re-linkage program. Of 94 partial HCV DBU cases, 13.0% (12) agreed to evaluation, 3.3% (3) had prior treatment, 3.3% (3) sought care elsewhere, 2.2% (2) refused, and 78.7% (74) did not respond. Among them, 2.1% (2) initiated treatment. Among 111 complete DBU cases, 18.9% (21) agreed to evaluation, and 77.5% (86) did not respond; eventually 9.0% (10) initiated treatment. HDV RT-PCR was performed in 1,070 chronic HBV patients; 0.7% (8) tested positive but declined further management. In total, 30.5% (112) of 367 patients identified through the call-back program initiated antiviral therapy.

Conclusions: Although effective antiviral treatments and expanded eligibility criteria are now available, many patients with viral hepatitis remain disconnected from care. Our re-linkage efforts showed promising success in bringing patients back into the treatment pathway. These findings emphasize the need for continued, practical strategies to improve access to care and support national and global goals for viral hepatitis elimination.

Keywords: Linkage, Treatment, Viral Hepatitis, HCV



FP-72

Association between Chronic Hepatitis C and Extrahepatic Malignancies: A Nationwide Cohort Study Short Title: HCV and Extrahepatic Malignancies

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Aims: Several studies suggest an association between chronic hepatitis C (CHC) and higher risk of extrahepatic malignancies (EHMs), but the impact of direct-acting antiviral (DAA) therapy remains uncertain. This study evaluated the association between CHC, DAA treatment, and the risk of developing EHMs.

Methods: This nationwide, population-based study utilized administrative data from the South Korean NHIS, which represents a real-world, multicenter environment encompassing primary and tertiary care settings across the country. We performed an 18-month landmark analysis and applied inverse probability of treatment weighting and time-varying Cox proportional hazards models. E-values were calculated to assess the robustness of the results to potential unmeasured confounders.

Results: Individuals newly diagnosed with CHC between 2016 and 2018 (n=85,860) and matched controls (n=692,803) were included. Patients with CHC were classified into the DAA-treated (CHC/DAA, n=12,372) and the untreated group (CHC/naïve, n=73,488). During a median follow-up of 69 (66–72) months, 66,662 patients (8.6%) developed EHMs. The overall EHM risk was significantly higher in the CHC/naïve group than in the control group (adjusted subdistribution hazard ratio [aSHR]=1.42, 95% CI=1.38–1.46, $P<0.001$; E-value=2.19). The CHC/DAA group also had a higher risk compared with controls (aSHR=1.20, 95% CI=1.11–1.28, $P<0.001$; E-value=1.69), but a significantly lower risk than the CHC/naïve group (aSHR=0.83, 95% CI=0.77–0.90, $P<0.001$; E-value=1.70). In time-varying Cox analysis, DAA therapy remained associated with a reduced risk of EHM (aSHR=0.83, 95% CI=0.77–0.90, $P<0.001$).

Conclusions: Patients with CHC have an increased risk of developing EHMs, whereas treatment with DAAs is associated with a reduced risk.

Keywords: Hepatitis C Virus, Antiviral Treatment, Non-Liver Cancer

FP-73

Impact of Hepatitis C Virus Treatment on the Risk of Cardiovascular Disease: A Nationwide Population-Based Cohort Study in South Korea

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Aims: Chronic hepatitis C virus (HCV) infection is associated with systemic inflammation. We evaluated the independent association between HCV and the composite cardiovascular disease (CVD) risk and the impact of antiviral treatment completion on this risk.

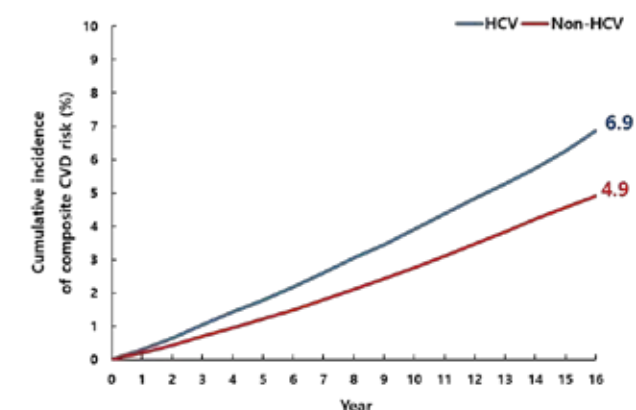
Methods: Using the National Health Insurance Service (NHIS) database of South Korea, we analyzed 40,724 HCV patients and 610,860 age- and sex-matched controls. For each HCV patient, 10 age- and sex-matched non-HCV controls were selected from the general population. Patients with prior liver transplantation, decompensated cirrhosis, or pre-existing CVD were excluded. The composite CVD risk was defined as ischemic heart disease, stroke, or peripheral artery disease. Multivariable Cox models and competing risk regression were used to adjust for socioeconomic status, lifestyle factors, and comorbidities.

Results: The mean age was 46.0 years (± 12.8 standard deviation [SD]) in the HCV group and 46.0 years (± 12.8 SD) in the matched control group. During the follow-up period, 30,348 patients developed composite CVD outcomes (incidence rate: 4.7 per 1,000 person-years).

At baseline, the HCV group had a higher prevalence of diabetes (17.6% vs. 13.1%, $P<0.001$) and hypertension (24.2% vs. 20.1%, $P<0.001$) compared to the non-HCV group. Despite these unfavorable baseline profiles, HCV infection remained independent predictor of CVD. After adjusting for all covariates and accounting for competing risks of death, the HCV group showed a significantly higher composite CVD risk (adjusted hazard ratio [aHR] 1.17, 95% confidence interval [CI]: 1.12–1.22). Within the HCV cohort (treatment completion rate: 33.4%), the risk was markedly lower in those who completed therapy. Compared to the treatment completed group, the composite CVD risk was significantly higher in the untreated group (aHR 1.67, 95% CI: 1.51–1.85).

Conclusions: In this nationwide cohort, HCV infection is independent risk factor for composite CVD. The significant risk reduction associated with HCV treatment underscores that HCV eradication confers systemic benefits extending beyond hepatic outcomes, serving as a critical strategy for cardiovascular prevention.

Keywords: Hepatitis C, Cardiovascular Disease, NHIS, Treatment



FP-74

Outcomes of Direct-Acting Antiviral Agents in Chronic Hepatitis C Patients with Pre-Existing HCC

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Aims: Chronic hepatitis C (CHC) is a significant global health issue and a major risk factor for hepatocellular carcinoma (HCC). While the advent of direct-acting antivirals (DAAs) has revolutionized CHC treatment by achieving high rates of viral clearance and improving liver function, the benefits of DAAs for patients with pre-existing HCC—particularly regarding recurrence, progression, and overall survival—remain controversial. This study aimed to assess the outcomes of various DAA regimens in CHC patients with pre-existing HCC.

Methods: In this real-world observational study, we enrolled CHC patients with pre-existing HCC who received DAA therapy following their HCC diagnosis. Patients were treated with various DAA regimens, including daclatasvir/asunaprevir, sofosbuvir/ribavirin, sofosbuvir/daclatasvir, ledipasvir/sofosbuvir $\pm$ ribavirin, ombitasvir/paritaprevir/ritonavir + dasabuvir $\pm$ ribavirin, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir $\pm$ ribavirin. The primary efficacy endpoint was the sustained virological response at 12 weeks post-treatment (SVR12). Secondary endpoints included adverse events (AEs), overall survival (OS), and HCC recurrence or progression.

Results: A total of 105 patients were included (mean age 67 ± 9.87 years; 67 male; HCV genotypes 1b [n=64] and 2 [n=41]). Eighteen patients (17.1%) had a Child-Pugh score of B. BCLC stages were A (n=68), B (n=28), and C (n=9), and 41 patients (39%) had viable HCC at the initiation of DAA treatment.

Thirty-one patients were treatment-experienced (25 interferon-based, 5 DAA-based). SVR12 rates were 92.4% (97/105) by intention-to-treat (ITT) analysis and 93.1% (94/101) by modified ITT (mITT) analysis. AEs occurred in four patients and were successfully managed with symptomatic treatment. HCC recurred or progressed during or after DAA treatment in 80 patients, with a median time to progression of 10.8 months (95% CI, 3.01–18.59). The OS rate was 66.7%, with a median survival of 81.2 months (95% CI, 62.41–99.99).

Conclusions: This study demonstrates that DAA therapy achieves favorable virological outcomes and is well-tolerated in CHC patients with pre-existing HCC.

Keywords: Hepatocellular Carcinoma, Chronic Hepatitis C, Direct-Acting Antiviral Agents

FP-75

Moderate HBV DNA Levels Are Associated with the Highest Risk of Hepatocellular Carcinoma in Chronic Hepatitis B: A Systematic Review and Meta-Analysis

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Aims: Chronic hepatitis B (CHB) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). While a dose-response relationship between serum HBV DNA levels and HCC risk has been reported, recent evidence suggests a non-linear relationship where patients with moderate viral loads may face a higher risk than previously recognized. This study aimed to quantitatively evaluate HCC risk across different HBV DNA level categories through a systematic review and meta-analysis.

Methods: We conducted a systematic review and meta-analysis of studies evaluating HCC risk according to HBV DNA levels in patients with CHB. Studies were identified from major databases and included prospective and retrospective cohort studies and randomized trials. HBV DNA levels were categorized as low (<3.3 log₁₀ IU/mL), moderate (3.3–7 log₁₀ IU/mL), and high (>7 log₁₀ IU/mL). The primary outcome was HCC incidence.

Results: A total of 46 studies including 130,200 patients were analyzed. The pooled HCC incidence rates per 100 person-years were 0.304 (95% CI 0.248–0.361) in the low HBV DNA

group, 0.859 (95% CI 0.751–0.966) in the moderate group, and 0.409 (95% CI 0.307–0.511) in the high group. Sensitivity analyses using stricter cut-offs (moderate: 3.3–8 log₁₀ IU/mL; high: >8 log₁₀ IU/mL) showed similar patterns, with incidence rates of 0.347 (95% CI 0.280–0.415), 0.805 (95% CI 0.687–0.921), and 0.193 (95% CI 0.153–0.233) per 100 person-years in the low, moderate, and high groups, respectively. Compared with undetectable HBV DNA, the low HBV DNA group had a higher HCC risk (HR 2.25, 95% CI 1.33–3.80). Compared with the low HBV DNA group, the moderate group showed a significantly increased risk (HR 2.95, 95% CI 2.41–3.61), and compared with the high HBV DNA group, the moderate group had an even higher risk (HR 3.56, 95% CI 2.69–4.72). Meta-regression analysis confirmed that moderate HBV DNA levels were significantly associated with increased HCC risk compared with high levels (HR 1.42, 95% CI 1.24–1.63; *P*<0.001). Subgroup analyses according to antiviral therapy, HBeAg status, and ALT level consistently showed the highest HCC incidence in the moderate HBV DNA group.

Conclusions: Moderate HBV DNA levels are associated with the highest risk of HCC in patients with CHB, suggesting a non-linear relationship between viral load and HCC development.

Keywords: Viral Load, Chronic Hepatitis B, Hepatitis B Virus DN, Cancer Risk

FP-76

HBV Core-Related Antigen Levels Correlate with Quantitative HBsAg Levels Regardless of HBeAg Status and Antiviral Therapy

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Aims: Hepatitis B core-related antigen (HBcrAg), which reflects the combined levels of HBcAg, HBeAg, and the p22 core-related protein, has been shown to correlate strongly with serum HBV DNA and intrahepatic covalently closed circular DNA (cccDNA) levels. In this study, we aimed to evaluate HBcrAg levels according to several clinical factors and to assess the correlation between HBcrAg and quantitative HBsAg levels.

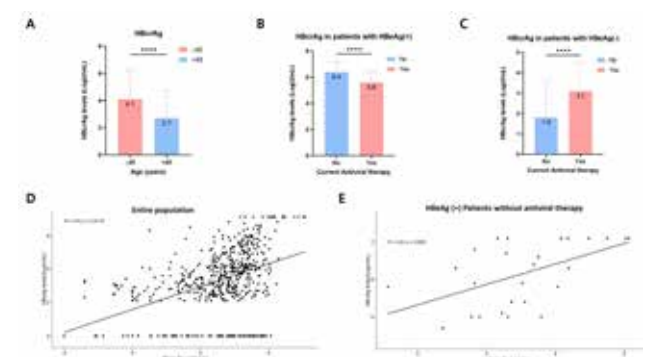
Methods: We prospectively enrolled 876 consecutive patients with chronic HBV infection who underwent HBcrAg testing between March 2025 and February 2026. HBcrAg levels were compared according to age, HBeAg status, and antiviral therapy. In addition, correlation analyses were performed to evaluate the relationship between HBcrAg and quantitative HBsAg levels across HBeAg status and antiviral therapy.

Results: The median age of the study population was 57.9 years, and 56.7% (n=497) were male. Approximately half of

the patients (n=433, 49.4%) were receiving antiviral therapy. The mean HBcrAg level was 2.9 LogU/mL and was significantly higher in younger patients (<45 years) than in older patients (4.1 vs. 2.7 LogU/mL; *P*<0.0001; Figure A) and in HBeAg-positive patients compared with HBeAg-negative patients (5.9 vs. 2.4 LogU/mL; *P*<0.0001). Among HBeAg-positive patients, HBcrAg levels were significantly higher in those not receiving antiviral therapy (*P*<0.0001; Figure B). In contrast, among HBeAg-negative patients, HBcrAg levels were significantly lower in those receiving antiviral therapy (*P*<0.0001; Figure C). HBcrAg levels showed a significant positive correlation with quantitative HBsAg levels (*R*=0.44, *P*<0.0001; Figure D). This correlation was consistently observed across HBeAg status and antiviral therapy, with the strongest correlation found in HBeAg-positive patients not receiving antiviral therapy (*R*=0.53, *P*=0.0053; Figure E). HBcrAg levels were also positively correlated with HBV DNA levels in both HBeAg-positive and HBeAg-negative patients (*P*<0.05). Notably, among 67 patients who achieved HBsAg loss, approximately 25% (17/67) still had detectable HBcrAg levels.

Conclusions: Our findings suggest that HBcrAg levels were lower in older patients and in those with negative HBeAg status. HBcrAg levels were significantly correlated with quantitative HBsAg levels regardless of HBeAg status or antiviral therapy, suggesting that HBcrAg may serve as a useful surrogate marker of viral activity across different clinical settings.

Keywords: HBV DNA, HBsAg, HBeAg, HBcrAg



FP-77

Distinct Virological Features and Quasispecies Dynamics in Advanced Fibrosis by HBeAg Status in Chronic Hepatitis B with Normal or Mildly Elevated ALT

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Aims: Serum alanine aminotransferase (ALT) is widely used to guide antiviral treatment in chronic hepatitis B (CHB), yet many patients with ALT ≤80 IU/L harbor advanced fibrosis. The relative value of conventional and newer HBV viral markers for detecting advanced fibrosis, and how these relationships differ by HBeAg status, remains incompletely understood.

Methods: A total of 312 treatment-naïve CHB patients (162 HBeAg-positive and 150 HBeAg-negative) were enrolled. Circulating (HBVDNA, HBsAg, HBcrAg, and HBVRNA) and intrahepatic HBV markers (cccDNA, total HBV DNA, and pgRNA) were quantified using commercial assay and qPCR. HBV integration was analyzed using NGS-based HBV capture assays. Viral quasispecies was evaluated by Shannon entropy, nucleotide diversity, and the dN/dS ratio. Liver histology was assessed using the Knodell and METAVIR scoring systems.

Results: On histological assessment, advanced fibrosis was not uncommon among patients with ALT ≤80 IU/L. With fibrosis progression, both serum and intrahepatic virological markers declined in HBeAg-positive patients. In contrast, HBeAg-negative patients showed increased HBcrAg and HBVRNA levels, despite relatively stable intrahepatic viral pool. HBV integration burden decreased with advanced fibrosis in HBeAg-positive patients but remained stable in HBeAg-negative patients, with preferential enrichment of genic integrations, including recurrent integration into fibrosis-associated genes such as *FN1*. Viral quasispecies increased globally with fibrosis progression in HBeAg-positive patients, whereas reductions in HBeAg-negative patients were observed only in the C-region. Incorporation of HBV markers—especially HBsAg in HBeAg-positive and HBcrAg in HBeAg-negative patients—into APRI and FIB-4 significantly improved the discrimination of advanced fibrosis, with further improvement achieved by incorporating intrahepatic viral quasispecies.

Conclusions: Liver fibrosis progression in CHB follows distinct virological and evolutionary dynamics according to HBeAg status. Circulating HBsAg and HBcrAg emerged as clinically useful indicators of advanced fibrosis in HBeAg-positive and -negative patients, respectively, with further refinement achieved by incorporating quasispecies diversity, thereby enhancing risk stratification and antiviral treatment decision-making.

Keywords: Chronic Hepatitis B, Fibrosis, Vral Quasispecies, Serum HBV Markers

FP-78

Incidence and Risk Stratification of Hepatitis B Reactivation in Patients Receiving Anti-CD38 Monoclonal Antibody Therapy

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Aims: The human anti-CD38 monoclonal antibody daratumumab, used for multiple myeloma, induces substantial immunosuppression and may increase susceptibility to hepatitis B virus reactivation (HBVr). While reactivation has been documented in anti-HBc-positive individuals, real-world data evaluating the efficacy of prophylactic antiviral therapy and risk-stratification models are limited.

Methods: We retrospectively analyzed a cohort of 180 anti-HBc-positive, HBsAg-negative patients among 709 multiple myeloma patients treated with daratumumab between 2015 and 2025. Clinical outcomes were compared between patients receiving prophylactic nucleos(t)ide analogue (NA) therapy (n=14) and those who did not (n=166). Independent predictors of HBVr were identified using multivariate Cox regression analysis to develop a risk-stratification model.

Results: The overall incidence of HBVr in the untreated cohort was 7.8% (13/166), categorizing daratumumab as a moderate-risk agent (1–10%) according to the EASL framework. Baseline anti-HBs titers < 100 IU/L and the use of daratumumab as later-line (relapsed/refractory) therapy were identified as independent risk factors. In the high-risk subgroup (possessing both factors), the crude incidence of HBVr was 19.6% (11/56), while the estimated 24-month cumulative incidence approached 40%. No reactivation events were observed in the prophylactic NA group. Severe hepatitis (n=7) and liver-related mortality (n=3) occurred exclusively in the untreated group, predominantly among high-risk patients.

Conclusions: Anti-CD38 therapy is associated with a significant and preventable risk of HBVr, particularly in a high-risk phenotype characterized by low baseline anti-HBs and later-line treatment. Routine NA prophylaxis should be prioritized for this high-risk group to prevent life-threatening liver complications, while intensified monitoring may be considered for intermediate-risk patients.

Keywords: HBV Reactivation, Chronic Hepatitis B, Anti-CD38 Therapy, Nucleos(t)ide Analogue

Saturday, June 13, 2026, 09:10-10:20

11. Liver Transplantation 1

FP-79

Graft Weight, Not GRWR, Predicts Recipient Survival in Living Donor Liver Transplantation: Implications for Donor Pool Expansion from a Stratified Analysis of 2,506 Cases

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CLBS, Max Healthcare Institute, India

Aims: The graft-to-recipient weight ratio (GRWR) of 0.8% or higher has traditionally guided graft selection in living donor liver transplantation (LDLT). While these guidelines prioritize GRWR to support graft survival and recipient safety, recent evidence suggests that recipient safety is more closely linked to the graft's absolute metabolic capacity than to recipient-adjusted ratios.

Methods: We analyzed 2,506 consecutive LDLT cases, including 1,868 modified right lobes, 308 extended right lobes, 71 standard right lobes, 111 left lobes, and 114 left lateral segment grafts. Of the 2,247 right lobe grafts, 1,618 had complete data for primary analysis, and 225 left-sided grafts were used for secondary validation.

Results: MRL showed a clear association between graft weight and survival: ≤648g (68.7%), 648–745g (78.0%), 745–836g (85.8%), and >836g (84.5%), a 17.1 percentage point improvement. This corresponds to one additional survivor for every six recipients between the lowest and highest weight categories. ERL grafts had survival rates of 71.8% for ≤616g and 88.3% for >808g, a 16.5 percentage-point increase ($P=0.030$), resulting in one additional life saved per six recipients. Left lobe (n=111) and LL segment (n=114) grafts showed similar weight-dependent survival: left lobe ≤310g (67.9%) versus >460g (67.9%), and LL ≤202g (65.5%) versus >303g (75.9%). Stratified analysis showed that GRWR did not predict survival within any weight category, while GW predicted survival within the GRWR 0.8–1.0% category (75.8% vs 84.3%, $P=0.023$).

Conclusions: Adopting weight-based selection criteria (modified right ≥648g, extended right ≥616g, left lobe ≥310g, left lateral ≥202g) improves recipient protection and increases the donor pool by 23%.

Keywords: GRWR, GRAFT Weight, Liver Transplantation

FP-80

Single-Cell and Bulk RNA Sequencing Reveal MCL1 as a Key Regulator of Mitochondrial Function in Liver Ischemia-Reperfusion Injury

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Aims: Liver ischemia-reperfusion injury (LIRI) may occur after liver transplantation or surgery, and few treatments are available to overcome this problem. The pathogenesis of LIRI is closely related to maladaptive immune responses and mitochondrial dysfunction; however, key regulators that link the above processes are still not known.

Methods: Several microarray datasets (GSE12720, GSE112713, GSE23649, and GSE151648) were used in combination with single-cell RNA sequencing data (GSE171539). Additionally, hub genes were identified through differential analysis (WGCNA) and using four machine learning algorithms (SVM, LASSO, RF, and XGBoost). The results were validated with additional datasets using the murine LIRI model by in silico perturbation.

Results: Our findings revealed that MCL1 is a hub gene related to mitochondria, whose expression is considerably increased in LIRI, and it has satisfactory diagnostic accuracy. Additionally, single-cell analysis revealed that MCL1 was specifically enriched in endothelial cells and macrophages. Moreover, the new macrophage subset CSF1R⁺IL-1B⁺MCL1⁺, which has a dual pro-inflammatory and pro-survival phenotype, was detected in LIRI patients. This process results in increased intercellular crosstalk and is related to important pathways such as the NF- κ B, apoptosis, and cytokine signaling pathways. Moreover, knocking out MCL1 in silico dramatically altered immune-related gene networks. MCL1 was experimentally confirmed to be upregulated, and the macrophage subset was validated to exist in the LIRI mouse model.

Conclusions: Through bulk and single-cell RNA sequencing analysis, we identified that MCL1 is the key factor for LIRI, which links immune inflammation and mitochondrial function through a new subset of macrophages. MCL1 is a candidate diagnostic biomarker and therapeutic target for treating LIRI.

Keywords: Liver Ischemia-Reperfusion Injury, Mitochondrial Dysfunction, Single-Cell RNA Sequencing, Macrophage Polarization

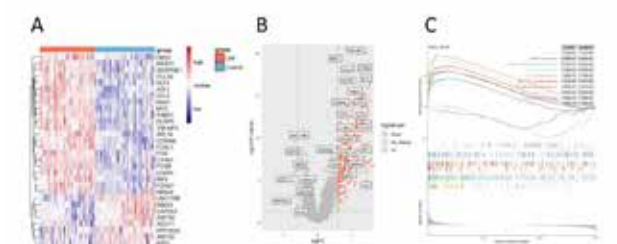


Fig. 1. Differential genes of LIRI and GSEA enrichment analysis. (A) Differential gene heatmap. (B) Differential gene volcano plot. (C) GSEA enrichment analysis based on the LogFC values of all genes.

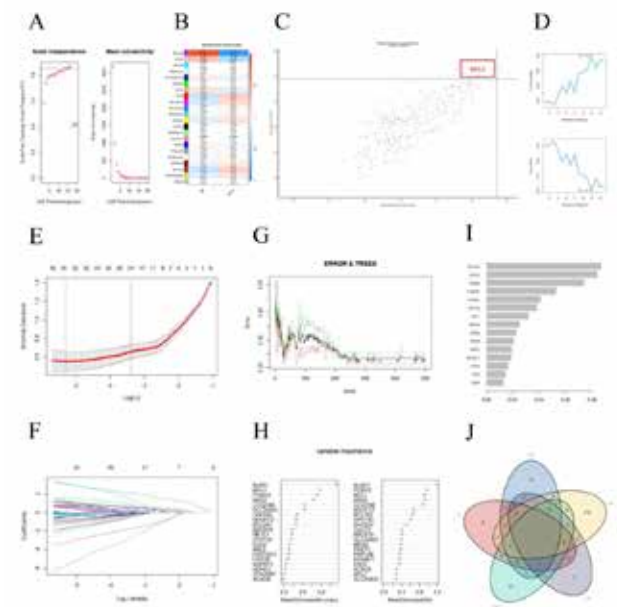


Fig. 2. Screening of critical mitochondria-related genes. (A) WGCNA algorithm - optimal soft threshold selection. (B) Gene module correlation heatmap. (C) Scatter plot of purple module genes. (D) SVM algorithm, accuracy (upper), and error rate (lower). (E-F) LASSO algorithm. (G-H) RF algorithm. (I) XGBoost algorithm. (J) Venn diagram of the hub genes identified by the five machine learning algorithms.

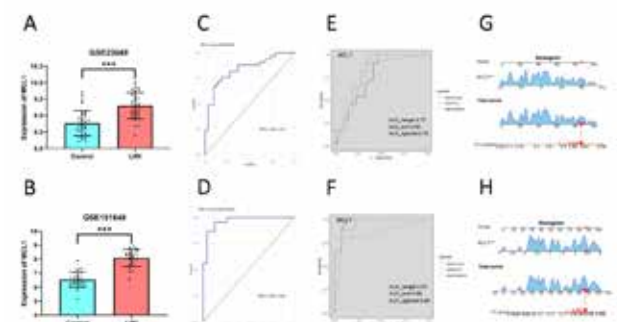


Fig. 3. Validation of the diagnostic value of MCL1 in independent datasets. (A-B) The level of expression of MCL1 in the GSE23649 (A) and GSE151648 (B) datasets. (C-D) The ROC curves used to analyze the diagnostic efficacy of MCL1 in the GSE23649 (C) and GSE151648 (D) datasets. (E-F) Area under the curve (AUC) values of MCL1 calculated by the RF, SVM, and XGBoost algorithms in the GSE23649 (E) and GSE151648 (F) datasets. (G-H) Nomogram models for predicting the risk of LIRI based on MCL1 expression in the GSE23649 (G) and GSE151648 (H) datasets.

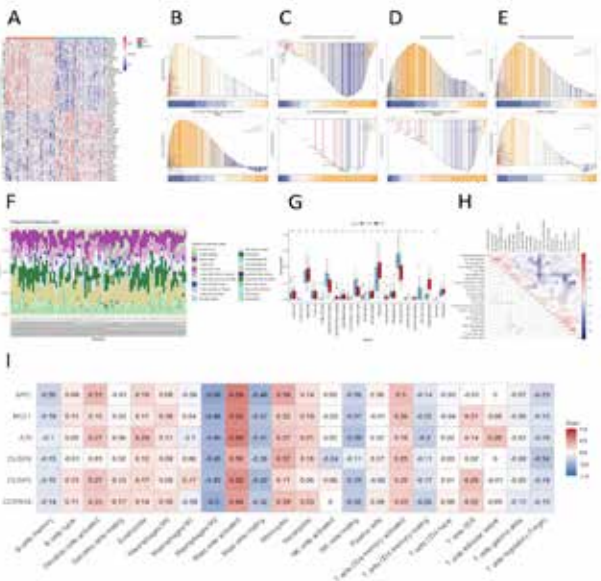


Fig. 4. Transcriptomic profiling and the immune landscape associated with MCL1 in LIRI. (A) Heatmap of the top 25 genes most positively and negatively related to MCL1. (B-E) GSEA of MCL1: enrichment plots for biological process (BP), cellular component (CC), molecular function (MF), and KEGG pathways (E). (F) Stacked bar plot showing the relative proportions of 22 immune cell types across all samples. (G) Bar plot comparing the infiltration levels of immune cells between the LIRI and control groups. (H) Correlation heatmap showing the interrelationships among the 22 immune cell types. (I) Correlation heatmap of MCL1 and mitochondria-related genes co-expressed with MCL1 during immune cell infiltration.

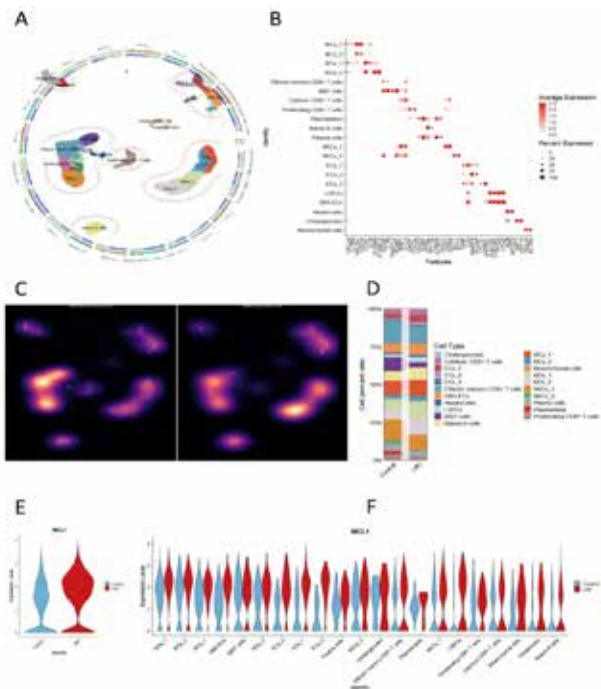


Fig. 5. Expression of MCL1 in the single-cell RNA sequencing dataset. (A) UMAP visualization of 21 distinct cell clusters identified in the dataset (GSE171539; n = 8,790 cells). (B) Dot plot displaying the expression of canonical marker genes used for the annotation of cell types. (C) Density plot comparing the cellular distribution between the control and LIRI groups. (D) Proportional abundance of each cell cluster in the control and LIRI groups. (E) The level of expression of MCL1 in all cells in the control and LIRI groups. (F) MCL1 expression across the 21 identified cell clusters.

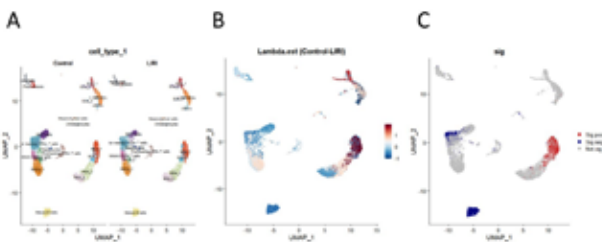


Fig. 6. Identification of LIRI-associated cell clusters by integrating bulk and single-cell transcriptomic data using SCIPAC. (A) UMAP plots of 21 cell types in the control and LIRI groups. (B) The strength of association between each cell type and the LIRI phenotype (positive values = positive correlation, negative values = negative correlation). (C) Statistical significance classification (Not.sig: not significant; Sig.pos: significantly positive correlation; Sig.neg: significantly negative correlation).

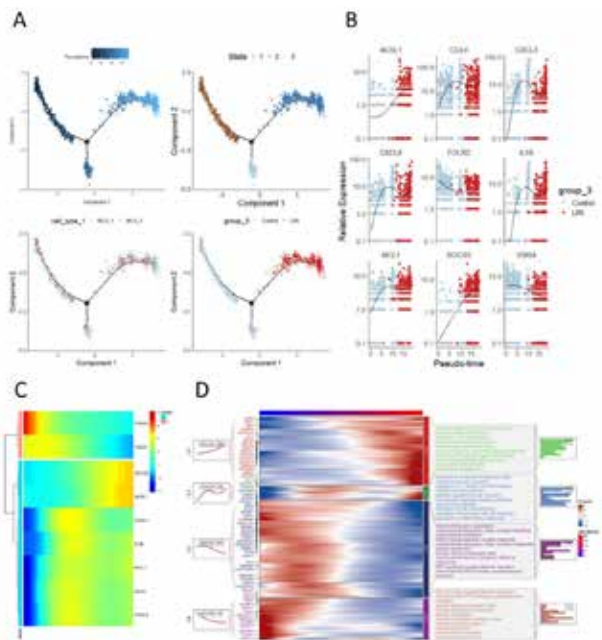


Fig. 7. Pseudotime analysis of macrophages in LIRI. (A) Macrophage pseudotime trajectory: cells are ordered by developmental pseudotime (darker colors suggest earlier developmental states, and lighter colors represent later developmental stages). The state represents the pseudotime-based developmental stages (divided into three stages); cell_type_1 denotes macrophage subclusters, and group_3 indicates sample grouping. (B-C) Dynamic expression patterns of key genes along the pseudotime trajectory from Control to LIRI: MCL1 and IL-1B were progressively upregulated (B), whereas FOLR2 and VSIG4 were downregulated (C). (D) Pathway enrichment analysis along the pseudotime trajectory revealed upregulation of inflammatory signaling pathways and downregulation of mitochondrial-related pathways during the transition from control to LIRI.

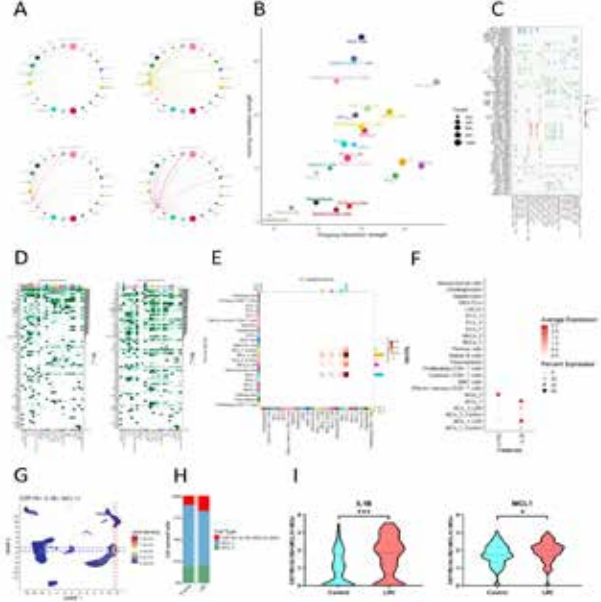


Fig. 8. scRNA-seq cell-cell communication analysis and identification of CSF1R+IL-1B+MCL1+ macrophages. (A) Communication strength between four macrophage subsets (MCs1_Control, MCs1_LIRI, MCs2_Control, and MCs2_LIRI) and other cell types. (B) Dot plot summarizing the outgoing and incoming signaling patterns for all cell populations. (C) Specific communication patterns between the MCs1_LIRI subset and all other cells. (D) Outgoing and incoming signaling pathways for all cells. (E) Bar plot displaying the outgoing and incoming interaction strengths of the IL-1 signaling pathway across cell populations. (F) Dot plot showing IL-1B and IL-1R2 expression across all cells in the IL-1 signaling pathway. (G) UMAP visualization showing the co-localization of CSF1R+IL-1B+MCL1+ triple-positive macrophages in the MC1 cluster. (H) The infiltration level of the CSF1R+IL-1B+MCL1+ macrophage subpopulation was significantly greater in the LIRI group than in the control group. (I) Expression of IL-1B and MCL1 in the identified CSF1R+IL-1B+MCL1+ macrophage subpopulation.

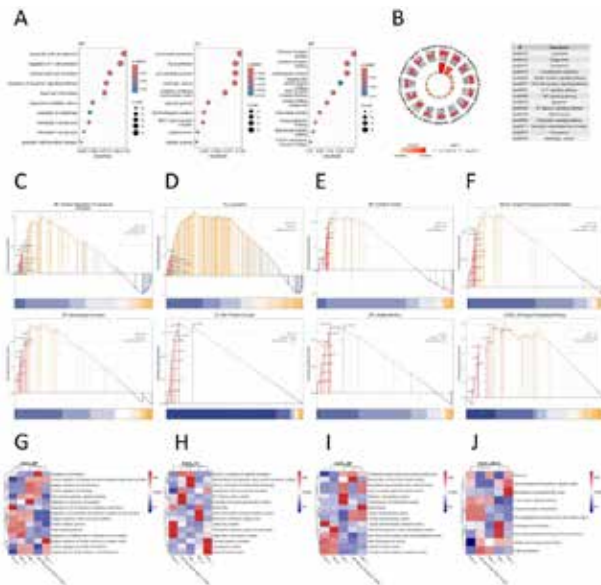


Fig. 9. Functional enrichment profiling of CSF1R+IL-1B+MCL1+ macrophages. (A-B) Functional enrichment analysis of the CSF1R+IL-1B+MCL1+ macrophage subpopulation: GO terms (A) and KEGG pathways (B). (C-F) GSEA of the CSF1R+IL-1B+MCL1+ macrophage subpopulation: BP (C), CC (D), MF (E), and KEGG pathways (F). (G-J) GSEA of the CSF1R+IL-1B+MCL1+ macrophage subpopulation: BP (G), CC (H), MF (I), and KEGG pathways (J).

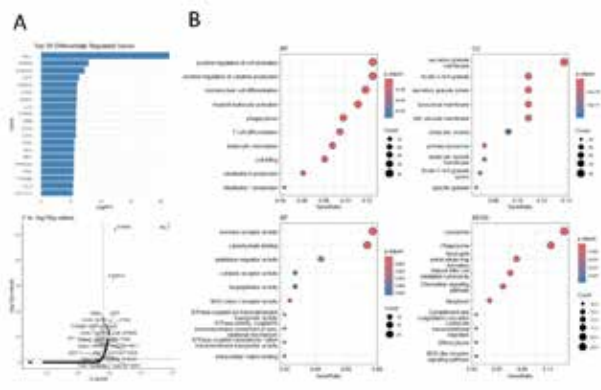


Fig. 10. Single-cell MCL1 virtual knockout via scRNA-seq data. (A) Virtual knockout of MCL1 was performed in 3,645 LIRI-group cells, resulting in 320 significantly regulated genes; the top 20 genes are shown. (B) Functional enrichment analysis (BP, CC, MF, and KEGG) of the 320 differentially regulated genes after virtual knockout of MCL1.

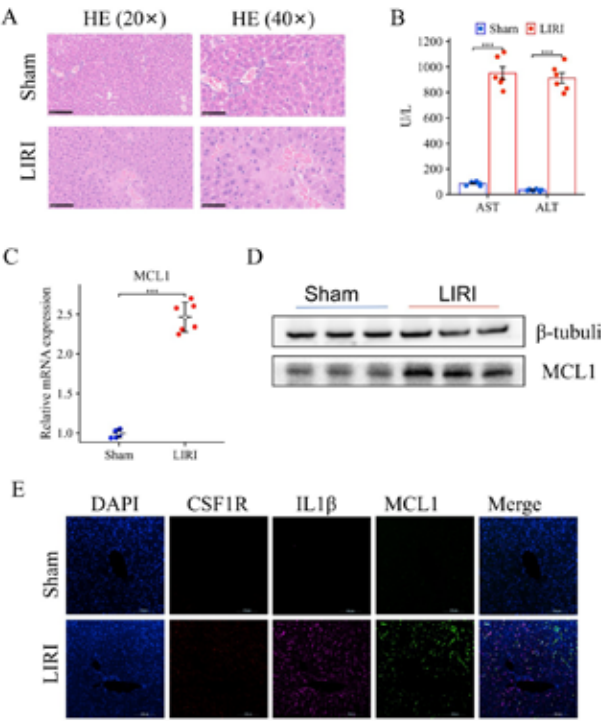


Fig. 11. Experimental validation of the upregulation of MCL1 and identification of CSF1R+IL-1B+MCL1+ macrophages in a murine LIRI model. (A) Representative H&E-stained liver sections from sham and LIRI mice. (B) Serum levels of ALT and AST in sham and LIRI mice. (C) qRT-PCR analysis of MCL1 mRNA expression in liver tissues from sham and LIRI mice. (D) Western blotting analysis of MCL1 protein expression in liver tissues from sham and LIRI mice. (E) Multiplex immunofluorescence staining of liver sections demonstrating the co-expression of CSF1R (red), IL-1β (purple), and MCL1 (green) in macrophages.

FP-81

Integration of a Pre-Transplant 15-Protein Serum Proteomic Signature Predicts Recurrence after Liver Transplantation for HCC: A Multicenter KOTRY Registry Study

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Aims: Morphological criteria and conventional biomarkers (alpha fetoprotein [AFP], protein induced by vitamin K-II [PIVKA-II]) incompletely capture the biological risk of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT). We developed a pre-transplant serum proteomic signature using multiple reaction monitoring–mass spectrometry (MRM-MS) and evaluated whether its integration with the MoRAL score could provide superior risk stratification.

Methods: In this multicenter study, pre-transplant serum from 168 HCC patients at three tertiary centers was analyzed alongside clinical data from the Korean Organ Transplantation Registry (KOTRY). A 15-protein MRM signature was developed and integrated with the MoRAL score to create a combined model. The incremental value of the MoRAL score to the MRM signature was assessed using Harrell's C-index and 2-year area under the curve (AUC) with 1,000 bootstrap resamples.

Results: During the follow-up period, 80 patients (47.6%) developed recurrence. The MRM signature and MoRAL score provided distinct biological information, with no significant correlation between the two metrics ($P=0.89$) and a low risk-stratification agreement (50.9%). Reflecting this complementarity, the integrated MRM+MoRAL model demonstrated a substantial leap in discriminative power for TTR, achieving a C-index of 0.790 (95% CI, 0.715–0.859) and a 2-year AUC of 0.904 (95% CI, 0.849–0.950). Notably, the combined model significantly improved predictive performance compared to the MRM signature alone (Δ C-index +0.048, $P=0.005$; Δ AUC +0.047, $P=0.009$) and the MoRAL score alone (C-index 0.664, $P=0.008$; AUC 0.691, $P<0.001$). The signature was particularly robust in predicting early recurrence (<1 year, $n=47$), effectively capturing pre-existing biological risk independent of tumor-secreted markers.

Conclusions: The integration of a 15-protein MRM signature with the MoRAL score yields a powerful synergistic model that overcomes the limitations of conventional biomarkers. This combined proteomic-biological approach offers superior risk stratification for HCC patients undergoing liver transplantation, potentially guiding more precise candidate selection and per-

sonalized post-operative management.

Keywords: Liver Transplantation, Hepatocellular Carcinoma, Proteomics, Time To Recurrence

FP-82

Donor Complications in Modern LDLT

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Aims: Donor safety remains the highest priority in living donor liver transplantation (LDLT). This study provides an updated and comprehensive assessment of postoperative donor complications at a high-volume LDLT center over a 13-year period.

Methods: All liver donors who underwent right or extended right donor hepatectomy between 2013 and 2025 were retrospectively analyzed. Donor demographics, operative variables, and postoperative outcomes were evaluated. Complications were graded according to the Clavien–Dindo classification.

Results: Among 1,199 donors, 333 (27.8%) underwent open donor hepatectomy (ODH) and 865 (72.2%) pure laparoscopic donor hepatectomy (PLDH). The mean age was 35 years, and 57% were male. The overall complication rate was 7.3% ($n=87$), with annual incidence ranging from 0.9% to 8.0% and no significant temporal variation ($P=0.447$). Biliary morbidity was the most common complication ($n=33$), predominantly bile leaks ($n=26$), followed by infection requiring antibiotics ($n=17$), ileus ($n=5$), and postoperative bleeding ($n=4$). Clavien–Dindo grade 3a complications occurred in 35 donors (2.9%), mainly bile leaks requiring percutaneous drainage ($n=24$). Eight donors (0.7%) required reoperation for bleeding, biliary stricture revision, or removal of retained foreign material. Overall complication rates were comparable between PLDH and ODH (4.3% vs. 4.8%, $P=0.810$), and no association was found with surgical approach, donor warm ischemic time, or biliary, portal vein, or hepatic artery anatomy.

Conclusions: Donor morbidity remained low, stable over time, and largely independent of surgical approach. These updated findings reinforce the safety of modern donor hepatectomy and support ongoing refinement of minimally invasive donor surgery.

Keywords: Living Donor Liver Transplantation, Donor, Complications

FP-83

Optimal Duration of Endoscopic Biliary Stenting after Living Donor Liver Transplantation: A Machine Learning Risk Stratification Analysis

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Aims: Anastomotic biliary strictures (ABSs) are among the most frequent complications after living-donor liver transplantation (LDLT). Endoscopic retrograde biliary drainage (ERBD) is the primary treatment, but the optimal stent duration remains unclear. This study aimed to identify risk factors for ABS recurrence and to develop a machine learning (ML) model to personalize stent removal.

Methods: Among 1,267 LDLT recipients, 173 patients who underwent ERBD stent removal for ABS were analyzed across three tertiary centers (internal $n=131$; validation $n=42$). Clinical and biochemical variables were examined using both logistic and Cox regressions. An ML-logit classifier that integrates stent duration, number of endoscopic retrograde cholangiopancreatography (ERCP) procedures, and laboratory values at removal was developed and compared with fixed-duration cutoffs.

Results: The overall recurrence rate was 25.4% (44/173), with a median recurrence time of 297 days. Independent predictors included shorter stent duration (hazard ratio [HR] 3.45, 95% confidence interval [CI] 1.52–7.83, $P=0.003$), higher ERCP number (HR 2.12, $P=0.036$), elevated bilirubin (HR 2.58, $P=0.011$), and elevated alkaline phosphatase (HR 2.21, $P=0.030$). The recurrence rate was significantly lower when the stenting duration exceeded 12 months (9.9% vs. 47.1%, HR 4.76, $P<0.001$). The ML-logit classifier achieved an area under the receiver operating curve (AUROC) of 0.901, significantly outperforming thresholds at 12 months (AUROC 0.688, $P=0.008$) and 396 days (AUROC 0.730, $P=0.012$). Model stratification separated patients experiencing 5-year recurrence-free survival into low- and high-risk groups (83.4% and 11.4%, respectively), with a HR of 9.06 ($P<0.001$) between groups. These results are consistent in both the internal and external validation cohorts.

Conclusions: While maintaining stents for at least 12 months is essential, individualized ML-based risk assessment provides superior stratification, allowing for earlier removal in low-risk patients and prolonged therapy in high-risk patients.

Keywords: Living-Donor Liver Transplantation, Anastomotic Biliary Stricture, Endoscopic Retrograde Biliary Drainage, Machine Learning

FP-84

Development and Validation of a LI-RADS-Based Competing Risk Survival Models for Liver Transplant Recipients with HCC

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Aims: While various eligibility criteria for liver transplantation (LT) have been proposed for hepatocellular carcinoma (HCC) patients, the optimal cutoff remains controversial due to the significant heterogeneity among recipients. We aimed to develop and validate a prognosis model based on the LI-RADS using a competing risks framework and compare its performance with the random survival forest (RSF) model and conventional criteria.

Methods: We analyzed 1,059 HCC patients who underwent LT from Asan Medical Center. LR-5 of LI-RADS v2018 was categorized as HCC on preoperative CT/MRI. A Fine-Gray (FG) model was developed to predict HCC-specific survival, treating non-HCC-related death as a competing risk. The model's performance (Wolbers' C-index) was compared with the RSF model, and Milan and Up-to-7 criteria. External validation was performed using an independent cohort ($n=398$) from Seoul National University Hospital.

Results: The Fine and Grey model (FG) achieved the highest external validation performance (Wolbers' C index: 0.786), followed by random survival forest model (RSF) (0.765), while conventional scores demonstrated considerably lower discrimination: Milan criteria (0.604), Up-to-Seven criteria (0.567), and Metroticket 2.0 (0.651). In the time-dependent Area under receiver operating curve (AUROC) and integrated Brier score (IBS) analyses, both the FG and RSF models demonstrated higher performance, with AUROC values of 0.802 and 0.790, respectively (compared with 0.612 and 0.575 for the Milan criteria and UTS, respectively; P -values <0.001), and IBS values of 0.065 for the FG and RSF models (compared with 0.093 and 0.082 for the Milan criteria and UTS, respectively).

Conclusions: The FG and RSF model based on pre-transplant clinical variables showed superior prognostic performance

compared with conventional LT criteria. Clinical decision based on this model enables to select the more optimal LT candidates with HCC.

Keywords: Liver Transplantation, Hepatocellular Carcinoma, Fine-Gray Model, Random-Survival Forest Model

FP-85

Artificial Intelligence–Driven Preoperative Risk Stratification for Early Allograft Failure in Living Donor Liver Transplantation

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Aims: Early allograft failure (EAF) following liver transplantation remains a catastrophic complication associated with substantial early mortality and the need for retransplantation. In living donor liver transplantation (LDLT), founded on the sacrifice and risk assumed by a healthy donor, the occurrence of EAF carries greater clinical and ethical implications, representing a particularly grave event.

Methods: We retrospectively analyzed adult LDLT recipients to develop an explainable artificial intelligence model for preoperative prediction of EAF. Among 4,973 recipients, EAF occurred in 148 patients (3.0%). Preoperative donor- and recipient-related variables, including graft-to-recipient weight ratio (GRWR), were used to train a machine learning model. An XGBoost algorithm was served as the primary prediction algorithm, supplemented by an anomaly score derived from an Isolation Forest to enhance detection of rare, high-risk patterns. Model interpretability was assessed using SHapley Additive exPlanations.

Results: On the independent test set, the model achieved an area under the receiver operating characteristic curve of 0.805, demonstrating discriminative performance. Higher C-MELD score, extreme GRWR values (<0.85 or >1.35), advanced donor age, and preoperative ventilator support emerged as the most influential predictors of EAF risk.

Conclusions: By integrating explainable machine learning with comprehensive preoperative evaluation, this model provides a practical and clinically applicable approach for early identification of high-risk recipients. These findings highlight the potential of explainable AI to transform preoperative assessment in LDLT by enabling earlier recognition of high-risk recipients and supporting critical decisions in donor selection and surgical planning. Ultimately, such tools may contribute to preventing EAF events and safeguarding donor sacrifice and recipient survival.

Keywords: Liver Transplantation, Early Allograft Failure, Artificial Intelligence

Saturday, June 13, 2026, 13:50-15:10

12. HBV 2

FP-86

Combination Therapy with Toll-Like Receptor 7 Agonist and Programmed Death Ligand 1 Antibody Restores HBV-Specific CD8⁺T Cells in Virally Suppressed Chronic Hepatitis B

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Aims: In a randomized, controlled phase II trial (OCEANcure05, NCT 04202653), combination therapy with the TLR7 agonist TQ-A3334 and the anti-PD-L1 antibody TQ-B2450 effectively reduced hepatitis B surface antigen (HBsAg) in nucleos(t)ide analogue (NAs)-experienced chronic hepatitis B (CHB) patients, with favorable safety and tolerability. This study aimed to delineate the immunologic features induced by the combination regimen and their relationships with clinical efficacy.

Methods: 24 NAs-experienced CHB patients were randomized into NAs monotherapy, dual therapy with NAs plus TLR7 agonist, or triple therapy with NAs, TLR7 agonist and PD-L1 antibody. After 24 weeks of treatment, patients were followed-up until Week 48. The dynamics of serum cytokine levels from baseline to end of treatment (EOT) were measured by Meso Scale Discovery electrochemiluminescence assay (MSD). The immune status of CD4⁺T cells, CD8⁺T cells, and HBV-specific CD8⁺T cells from PBMC were evaluated by flow cytometry. Single-cell RNA sequencing was performed on PBMC from representative patients. *In vitro* PBMC–HepAD38 co-culture system was employed for validation.

Results: In the triple therapy group, serum IFN- γ , IP-10, and sPD-1 levels were significantly elevated, while sPD-L1 levels were markedly decreased at Week 12. Serum IL-21 levels were profoundly increased and were higher than those in the dual therapy group at EOT. The triple therapy group demonstrated enriched effector phenotypes of CD4⁺T and CD8⁺T cells. Transcriptomic analysis revealed an enrichment of IL-21-related gene sets in CD4⁺T cells from triple therapy patients at EOT. *In vitro*, TLR7 agonist plus PD-L1 antibody increased IL-21⁺CD4⁺T frequency and supernatant IL-21 level compared to TLR7 alone. The triple therapy group exhibited superior HBV-specific CD8⁺T cell responses at EOT. The frequencies of core-IFN- γ ⁺, CD107a⁺, and polymerase-IFN- γ ⁺CD8⁺T cells increased from baseline and higher than those in dual therapy group. *In vitro*, PD-L1 antibody plus TLR7 agonist enhanced core-specific CD8⁺T responses, whereas the addition of IL-21/IL-21R blockade abolished these

effects. Triple therapy triggered STAT3 phosphorylation in CD4⁺T cells and enriched the JAK-STAT signaling pathway. Targeted inhibition of STAT3 in CD4⁺T cells blocked the triple therapy-induced augmentation of core-specific CD8⁺T cell response, HepAD38 lysis, and suppression of HBV DNA and HBeAg levels.

Conclusions: The combination of TLR7 agonist and PD-L1 antibody drives STAT3-dependent IL-21 secretion from CD4⁺T cells, thereby enhancing HBV-specific CD8⁺T cell responses and suppressing viral replication via the IL-21/IL-21 receptor pathway. This mechanism may contribute to the enhanced efficacy of triple therapy in NAs-experienced CHB patients.

Keywords: HBV, Combination Therapy, HBV Specific CD8, Functional Cure

FP-87

High Viral Suppression in Chronic HBV Infection Subjects With Pevifoscorvir Sodium Monotherapy

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Aims: Study ALG-000184-201 (NCT04536337) is a multi-part Phase 1 study that evaluated safety, tolerability, pharmacokinetics of pevifoscorvir sodium (PEVY) in healthy volunteers and additionally antiviral activity of PEVY in untreated participants with chronic Hepatitis B Virus (HBV) infection.

Methods: In Part 4 Cohort B of the study, eligible HBeAg+ and HBeAg- participants received daily oral 300 mg PEVY for 96 weeks followed by an 8-week follow up period with nucleos(t)ide analogues (NA) alone.

Results: A total of 10 HBeAg+ and 11 HBeAg- participants were enrolled. Mean baseline level in HBeAg+ and HBeAg- participants was HBV DNA 8.0 and 4.3 log₁₀ IU/mL, HBV RNA 5.3 and 2.0 log₁₀ copies/mL, HBsAg 4.3 and 3.5 log₁₀ IU/mL, HBcrAg 8.3 and 3.1 log₁₀ U/mL, respectively; and HBeAg level 2.6 log₁₀ PEI U/mL in HBeAg+ participant. During the 96-week PEVY monotherapy: HBV DNA <10 IU/mL (LLOQ, target detected, TD) was achieved in 60% and 100% HBeAg+ participants by Week 48 and Week 96, respectively and in all (100%) HBeAg- participants by Week 20. Fifty percent (5/10) HBeAg+ and 89% (8/9) HBeAg- participants achieved HBV DNA <4.92 IU/mL (target not detected, TND) at Week 96 (Figure). HBV RNA was undetectable (< 10 copies/mL) in all HBeAg+ and HBeAg- participants by Week 52 and Week 8, respectively. No viral breakthrough was observed. In HBeAg+ participants maxi-

mum mean reduction of 0.9 log₁₀ IU/mL in HBsAg, 1.9 log₁₀ PEI U/mL in HBeAg, and 2.2 log₁₀ U/mL in HBcrAg was noted. In HBeAg- participants, HBcrAg declined by a mean of 0.4 log₁₀ U/mL with no notable change in HBsAg. These HBV antigen reductions were sustained in participants during the 8-week NA only follow up period. Safety profile was favorable with no serious adverse events (AEs) and no discontinuations due to treatment-emergent AEs (TEAEs). Grade 3 TEAEs included asymptomatic ALT elevations (HBeAg+: n=3; HBeAg-: n=1) and cholesterol/triglycerides increase (n=1), all of which resolved while dosing continued. All Grade 3 TEAEs of ALT increase was concurrent with significant decline in HBV DNA, with no clinically meaningful change in synthetic/excretory liver function.

Conclusions: 300 mg oral, once daily PEVY for 96 weeks was well-tolerated and led to rapid, profound and durable suppression of HBV DNA and HBV RNA in untreated chronic HBV infection participants. In addition, clinically meaningful declines were noted in viral antigens, including HBcrAg, indicating a potential reduction in cccDNA levels.

Keywords: HBV, CAM, Antiviral, Monotherapy



FP-88

Reduction of HBV Antigens Observed after 96 Weeks of 300 mg Pevifoscorvir Sodium Monotherapy is Sustained During Long-term Follow-up

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Aims: Pevifoscorvir sodium (pevy, ALG-000184) is a novel Type E Capsid Assembly Modulator (CAM-E). In Part 4 Cohort B of the Phase 1 study ALG-000184-201 (NCT04536337), pevy has demonstrated potent on-treatment suppression of HBV DNA, RNA, and viral antigens in participants with chronic HBV infection who received oral, once-daily 300 mg pevy for 96 weeks. Here,

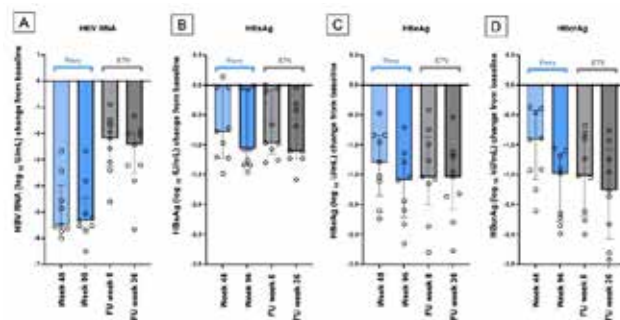
we investigated whether these declines can be sustained during long-term follow-up (LFU) of 24-48 weeks on entecavir (ETV).

Methods: 9 of 10 HBeAg-positive participants of Part 4 Cohort B were evaluated for HBV DNA, RNA and changes in HBsAg, HBeAg, HBcAg, P-HBcAg and HBsAg isoforms during pevy treatment and ETV LFU.

Results: HBV DNA, RNA and P-HBcAg demonstrated significant reductions during pevy treatment, indicating that the CAM primary mechanism of action (MoA, prevention of pgRNA encapsidation), is fully engaged. HBV RNA (Figure A) and P-HBcAg partially rebounded during ETV LFU, as expected by the MoA of ETV. HBV DNA remained suppressed in 5/9 participants during LFU; minor increases in the remaining 4 participants might be due to reduced viral suppression during the ETV treatment phase. Substantial reductions of HBsAg, HBeAg and HBcrAg were observed at the end of pevy treatment (Figures B-D), which were sustained during LFU suggesting a reduction in the cccDNA pool as proposed by the CAM secondary MoA. A decrease of cccDNA during pevy therapy is further supported by larger reductions of the large and medium isoform of HBs, which are predominately cccDNA-derived, compared to the small isoform, which can come from cccDNA and integrated DNA.

Conclusions: Potent on-treatment effects on viral antigens were observed after 96 weeks of 300 mg monotherapy with pevy, indicating a reduction of the cccDNA pool. These effects were sustained during ≥ 24 weeks of ETV FU in HBeAg-positive participants with chronic HBV infection.

Keywords: Capsid Assembly Modulator, Functional Cure, Hepatitis B Infection, Hepatitis B Surface Antigen



FP-89

Exposure to Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate and the Risk of Hepatocellular Carcinoma

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Aims: Nucleos(t)ide analogs (NA) have been associated with reduced risk of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) infection. Many studies suggested that tenofovir-based therapies are more effective than entecavir in reducing HCC risk. Here, we examine HCC risk based on exposure to tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF) in patients with chronic hepatitis B.

Methods: Data from four pivotal phase 3 trials were pooled to examine HCC occurrence. These included Studies 102 and 103, in which patients received TDF or adefovir dipivoxil (ADV) and Studies 108 and 110, in which patients were randomized to TAF or TDF, with follow-up of up to 8 years. HCC occurrence was classified as an adverse event and assessed as part of routine care. Cox proportional hazards models were used to examine the association between tenofovir exposure and time to HCC development. Exposure to TAF vs TDF was defined as the proportion of total TAF exposure time relative to total tenofovir exposure (0 = TDF only; 1 = TAF only). To minimize immortal time bias, HCCs occurring within the first 48 weeks after treatment initiation or switching were excluded.

Results: A total of 2,273 patients (Studies 102/103: n=641; Studies 108/110: n=1,632) were included. By Year 8, 46 (2.0%) patients developed HCC, of whom 9 cases occurred within the first 48 weeks were excluded. In multivariate Cox regression analysis, greater exposure to TAF vs TDF was associated with significantly reduced risk of HCC, corresponding to a 70.0% risk reduction (hazard ratio=0.30). Independently, ALT normalization at Week 24 was also significantly associated with decreased HCC risk.

Conclusions: Long-term TAF treatment was associated with a greater reduction in HCC risk than TDF treatment. Differences

in study design, population, and timing should be considered, and real-world data may help to confirm these findings.

Keywords: Tenofovir Alafenamide (TAF), Hepatocellular Carcinoma, Chronic Hepatitis B, Tenofovir Disoproxil Fumarate (TDF)

Table 1. Factors associated with HCC development (Cox regression analysis)

Parameter	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Sex, male vs female	4.38 (1.14-7.51)	0.025	1.97 (1.97-16.8)	0.004
Age, years	1.08 (1.05-1.13)	<0.001	1.09 (1.09-1.11)	<0.001
Asian, yes vs no	1.52 (0.79-3.77)	0.177	1.59 (1.52-9.72)	0.002
Ceribudo, yes vs no	4.52 (2.24-8.21)	<0.001	-	-
Baseline HBsAg, positive vs negative	9.59 (0.31-1.14)	0.116	-	-
Baseline HIV DNA level:				
0-6 log ₁₀ IU/mL vs >6 log ₁₀ IU/mL	1.31 (0.63-2.69)	0.470	-	-
>6 log ₁₀ IU/mL vs <6 log ₁₀ IU/mL	6.51 (0.39-1.36)	0.175	-	-
ALT normalization at Week 24; yes vs no	0.329 (0.12-0.87)	0.003	0.29 (0.12-0.68)	0.004
Exposure, time on TAF vs TDF	0.41 (0.20-0.83)	0.010	0.30 (0.13-0.71)	0.006

parameters were determined using C25-quantifier tests. An initial multivariate analysis was conducted using all parameters; then, we re-ran using only parameters found to be significant predictors of HCC. On the multivariate model, therefore, parameters without data were not found to be significant. (ii) AAGLD criteria were used for defining (U) 25–50% for females and 50–100% for males. (iii) American Association for the Study of Liver Diseases, (iv) 10% abnormal aminotransferases, (v) 10% desirability, (vi) 10% fibrosis, (vii) 4–6 antigens, (viii) hepatitis B virus, (ix) 10% raised ratio, (x) International Unit, (xi) baseline aminotransferase, (xii) baseline aminotransferase, (xiii) baseline aminotransferase, (xiv) upper limit of normal.

FP-90

Early Antiviral Therapy and the Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Patients with Normal Alanine Aminotransferase Levels: A Prospective Phase II Study

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Aims: There is limited evidence regarding whether antiviral therapy reduces the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) who have normal alanine aminotransferase (ALT) levels. We investigated whether immediate antiviral therapy decreases HCC risk in CHB patients with normal or mildly elevated ALT levels.

Methods: This open-label, prospective phase II study enrolled CHB patients with HBV DNA $\geq 2,000$ IU/mL, ALT $< 2 \times$ upper limit of normal, and D²AS score ≥ 2.0 across seven Korean tertiary centers from July 2015 to June 2017. The D²AS score is a validated risk prediction model for identifying high-risk CHB patients with normal or mildly elevated ALT levels. All participants received entecavir 0.5 mg daily and were followed for 5 years. The primary endpoint was HCC development. Secondary endpoints included virological response (HBV DNA < 20 IU/

mL) and changes in serum ALT levels. Given the exploratory design, the target sample size was set at 126 patients, allowing for a 10% dropout rate.

Results: Of 126 enrolled patients, 115 were included in the intention-to-treat analysis. Virological response rates were 79.4%, 89.9%, and 92.4% at 1, 2, and 5 years, respectively. Median ALT decreased from 37 U/L at baseline to 23, 21, and 19 U/L at 1, 2, and 5 years, respectively. Six patients developed HCC, with cumulative incidence rates of 2.0%, 4.0%, and 6.1% at 1, 2, and 5 years, respectively. Compared with D²AS score predicted rates, the observed HCC incidence did not differ significantly until year 4, but a significant divergence became evident at year 5.

Conclusions: Immediate antiviral therapy in CHB patients with normal or mildly elevated ALT levels resulted in sustained viral suppression, reduced serum ALT levels, and a lower-than-predicted HCC incidence at 5 years, supporting consideration of early antiviral therapy in these patients.

Keywords: Hepatitis B, Antiviral Therapy, Hepatocellular Carcinoma, Normal Alanine Aminotransferase Levels

FP-91

Association between Metabolic Dysfunction-Associated Steatotic Liver Disease and Hepatocellular Carcinoma Risk in Adults with Chronic Hepatitis B: A Nationwide Population-Based Cohort Study

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Aims: The impact of coexisting metabolic dysfunction-associated steatotic liver disease (MASLD) on the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) remains controversial. Existing research is largely limited to hospital-based cohorts with little data from population-based studies. We aimed to investigate the association between MASLD and HCC risk at a population level using a national health service registry.

Methods: We analyzed the Taiwan adult preventive health care service database to identify individuals serologically positive for hepatitis B surface antigen (HBsAg), excluding those with a history of any malignancy including HCC. A total of 129,270 eligible adults (49.9% male; median age, 49 years) were classified by the hepatic steatosis index (HSI) into Non-MASLD (HSI<30), Indeterminate (30≤HSI<36), and MASLD (HSI≥36) groups. HCC incidence rate ratios (IRRs) were estimated using Poisson regression. The association of MASLD with incident HCC was assessed using Fine-Gray competing-risk models and adjusted for demo-

graphic characteristics, metabolic comorbidities, lifestyle factors, and laboratory measurements, with antiviral therapy use and cirrhosis status included as time-varying covariates.

Results: The MASLD, Indeterminate, and Non-MASLD groups comprised 35.8%, 42.9%, and 21.3% of the study population, respectively. At baseline, cardiometabolic burdens were more prevalent in the MASLD group as compared to the Non-MASLD counterpart, including adiposity (BMI ≥ 23 kg/m²: 96.19% vs 8.71%), glucose dysregulation (diabetes: 20.50% vs 3.28%), and elevated blood pressure (hypertension: 47.37% vs 20.67%). Over a median 3.95 years of follow-up, crude HCC incidence rates were 1.45, 1.44, and 1.80 per 1,000 person-years in the MASLD, Indeterminate, and Non-MASLD groups, respectively ($P=0.009$). Compared to the Non-MASLD group, HCC incidence was significantly lower in the Indeterminate (IRR, 0.80, 95% CI: 0.68-0.95) and MASLD (IRR, 0.64; 95% CI, 0.46-0.90) groups. After adjusting for demographic characteristics, metabolic comorbidities including diabetes, lifestyle factors, and laboratory measurements, use of antiviral therapy, and cirrhosis status, MASLD remained inversely associated with incident HCC (adjusted subdistribution HR, 0.22; 95% CI 0.10-0.49; $P=0.0002$).

Table. Multivariable time-dependent subdistribution hazard model for the association between MASLD and hepatocellular carcinoma

Covariate	sHR (95% CI)*
MASLD category	
Non-MASLD (reference)	1.000
Indeterminate	0.709 (0.577–0.872)
MASLD	0.577 (0.427–0.781)
Antiviral therapy use (time-varying)	3.196 (2.550–4.006)
Cirrhosis status (time-varying)	4.948 (3.860–6.343)
gender (reference–female)	3.354 (2.701–4.164)
Age, per year	1.055 (1.048–1.063)
Impaired fasting glucose (yes)	1.050 (0.873–1.263)
Hypertriglyceridemia	0.621 (0.457–0.843)
HypoHDL-cholesterolemia	1.402 (1.134–1.735)
Diabetes mellitus	1.262 (0.976–1.631)
Hypertension	0.938 (0.765–1.151)
Hyperlipidaemia	1.034 (0.724–1.476)
Urbanization	
Metropolitan	1.000
Satellite	1.060 (0.898–1.252)
Rural	0.983 (0.822–1.175)
Smoking status	
None	1.000
Occasional	1.474 (1.057–2.057)
< 1 pack per day	1.766 (1.425–2.188)
≥ 1 pack per day	2.032 (1.497–2.758)
Body mass index, kg/m ²	0.980 (0.946–1.015)
Alcohol consumption	
None	1.000
Occasional	1.019 (0.845–1.229)
Physical activity	
None	1.000
< 150 minutes per week	0.901 (0.774–1.049)
≥ 150 minutes per week	0.661 (0.505–0.864)
AST, U/L	1.003 (1.002–1.004)
ALT, U/L	0.999 (0.998–1.000)
Fasting glucose, mg/dL	1.003 (1.001–1.004)
Diastolic blood pressure, mmHg	1.004 (0.996–1.013)
Systolic blood pressure, mmHg	1.002 (0.996–1.008)
Waist circumference, cm	1.025 (1.014–1.037)
High-density lipoprotein, mg/dL	1.008 (0.998–1.019)
Low-density lipoprotein, mg/dL	1.004 (0.998–1.011)
Total cholesterol, mg/dL	0.994 (0.987–1.001)
Triglycerides, mg/dL	1.000 (0.997–1.002)
Creatinine, mg/dL	0.876 (0.613–1.253)

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; HCC, hepatocellular carcinoma; sHR, subdistribution hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Conclusions: In adults with CHB, coexisting MASLD is associated with a significantly lower risk of incident HCC after adjusting for potential confounding factors including metabolic burden. Our finding may not only inform HCC risk stratification but also underscore the need to investigate the mechanisms underlying this inverse association.

Keywords: Chronic Hepatitis B, Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD), Hepatic Steatosis Index (HSI), Hepatocellular Carcinoma

FP-92

Kinetic Breakpoints and Immune Remodeling during Quantitative HBsAg Decline in Chronic Hepatitis B

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Aims: HBsAg seroclearance is the ultimate goal of chronic hepatitis B (CHB) treatment, yet the immune dynamics during active quantitative HBsAg (qHBsAg) decline remain poorly elucidated. Most studies compare HBsAg-positive vs. resolved states — a binary framing that obscures the dynamic biology of transition. We hypothesized that qHBsAg decline is not a gradual continuum, but a structured process punctuated by discrete kinetic breakpoints, marking a distinct immunological state. We aimed to identify these inflection points and map the longitudinal immune remodeling that accompanies them.

Methods: The prospective cohort in this study included 80 CHB patients with undetectable or low viral load (<1,000 IU/mL) who had serial qHBsAg measurements. Patient-specific qHBsAg kinetic breakpoints (significant inflection points in the decline slope) were identified for subjects who had decreasing qHBsAg level using change-point detection algorithms. Three complementary grouping strategies captured varying granularities of decline: (Grouping 1) maintained vs decreasing qHBsAg levels (n=35 vs 45); (Grouping 2) four trajectory classes – maintained (<0.5 log IU/mL decline over 3 years), slow (0.5–3 log IU/mL over 3 years), fast (≥ 3 log IU/mL over 3 years), and abrupt decline (steady followed by ≥ 3 log IU/mL decline over 3 years); and (Grouping 3) a strict phenotype approach by excluding the slow-declining subgroup to enrich

for definite decrease. Immune cell profiling included flow cytometry and peripheral blood mononuclear cell single-cell RNA sequencing (scRNA-seq) with V(D)J integration (n=12).

Results: Segmented mixed-effects modeling identified a significant acceleration in qHBsAg decline following the breakpoint (additional slope: -2937.1 IU/mL/year, $P<0.001$). Based on these trajectory patterns, three distinct patient grouping strategies were defined. Flow cytometric analysis revealed that, under Grouping 1, patients exhibiting declining qHBsAg levels demonstrated significantly higher TIM-3 expression on both CD4⁺ memory (53.8% vs. 21.0%, $P=0.004$) and CD8⁺ memory T cells (38.8% vs. 16.4%, $P=0.004$), accompanied by a reduced frequency of PLZF⁺ CD4⁺CD8⁺ double-negative (DN) T cells (26.1% vs. 38.4%, $P=0.02$). In Grouping 2, a stepwise reduction in perforin-producing DN T cells was observed across trajectory subgroups (38.3% to 7.1%, maintained vs. abrupt decline; $P=0.002$). Grouping 3 further confirmed a marked decrease in perforin⁺ DN T cells (13.3% vs. 38.3%, $P=0.0009$), alongside increased frequencies of CD4⁺Foxp3⁺ regulatory T cells (6.5% vs. 4.9%, $P=0.02$) and IL-4–producing DN T cells (1.1% vs. 0.3%, $P=0.02$) in patients with definitive qHBsAg decline. Furthermore, single-cell RNA sequencing demonstrated enrichment of NK cell populations and selective clonal expansion of CD8⁺ effector memory T cells, without evidence of global cytotoxic activation. Longitudinal analysis following the breakpoint revealed a decline in T-bet and IL-10–producing DN T cells, accompanied by an increase in PD-1⁺ CD4⁺ memory T cells.

Conclusions: The decline of qHBsAg decline in CHB is punctuated by a patient-specific kinetic breakpoint coinciding with a fundamental immunological transition — from broad innate-like inflammation to highly coordinated adaptive immune cell reactions, characterized by selective clonal expansion and formation of durable CD8⁺ memory T cells. These findings reframe how we interpret the path to HBsAg clearance, with direct implications for immunotherapy timing and functional cure benchmarks.

Keywords: Hepatitis B Virus, Seroconversion

FP-93

Comparative Risk of Hepatocellular Carcinoma among Oral Antiviral Agents in Patients with Chronic Hepatitis B: A Systematic Review and Network Meta-Analysis

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Aims: The comparative effectiveness of various oral nucleos(t)ide analogues (NAs) in preventing hepatocellular carcinoma (HCC) remains a subject of debate. We performed a systematic review and network meta-analysis (NMA) to comprehensively compare the risk of HCC among treatment-naïve patients with chronic hepatitis B (CHB) receiving different NAs, including entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), and besifovir (BSV).

Methods: A systematic literature search was conducted across major electronic databases to identify studies reporting HCC incidence in CHB patients treated with NAs. The primary outcome was the risk of HCC, measured by hazard ratios (HRs) with 95% confidence intervals (CIs). A frequentist NMA was performed, and the statistical consistency of the network model was rigorously validated using both global and local inconsistency tests (node-splitting method).

Results: A total of 36 studies comprising 240,458 adjusted patients and 8,254 HCC events were included in the final analysis. The consistency model was applied as no significant inconsistency was found across the network (all $P>0.05$). In the overall NMA, tenofovir-based regimens showed a significantly lower risk of HCC compared to ETV. The HR for TAF versus ETV was 0.688 (95% CI: 0.516–0.916), and for TDF versus ETV was 0.801 (95% CI: 0.705–0.910). There was no statistically significant difference in HCC risk between TAF and TDF (HR 0.859, 95% CI 0.652–1.131), nor between BSV and ETV (HR 0.668, 95% CI 0.367–1.217). Notably, the superiority of TAF over ETV in reducing HCC risk was consistently maintained in key subgroups, including large-scale studies with ≥ 500 patients per arm (HR = 0.633, 95% CI: 0.454–0.883) and in patients with cirrhosis (HR = 0.717, 95% CI: 0.607–0.847).

Conclusions: In patients with CHB, tenofovir-based therapies (TAF and TDF) are associated with a significantly lower risk of developing HCC compared to ETV. These findings provide a reliable, evidence-based rationale for optimal NA selection to maximize HCC prevention, although the inherent limitations of observational data and the potential for residual confounding should be carefully considered in clinical practice.

Keywords: Chronic Hepatitis B, Hepatocellular Carcinoma, Network Meta-Analysis

Saturday, June 13, 2026, 13:50-15:10

13. LC, Liver Failure & Autoimmune Diseases 2

FP-94

How Hepatitis C Screening Entered South Korea's National Health Screening Program: A Policy Analysis Using Kingdon's Multiple Streams Framework

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Aims: In 2025, South Korea integrated the Hepatitis C Virus (HCV) antibody test into the National Health Screening Program (NHSP) for individuals aged 56 years. However, the policy processes underlying this adoption have not been systematically analyzed. This study examines how HCV screening was incorporated into the NHSP and assesses the broader policy implications for the design of elimination-oriented screening programs.

Methods: We conducted a qualitative policy analysis of policy developments from 2015 to 2024 through a review of policy reports, strategic plans, epidemiologic studies, pilot screening data, and economic evaluations. Kingdon's Multiple Streams Framework was applied to analyze the problem, policy, and politics streams and to identify the policy window that enabled adoption.

Results: In the problem stream, healthcare-associated outbreaks in 2015–2016 and subsequent surveillance exposed persistent underdiagnosis despite curative antiviral therapy; treatment uptake among newly diagnosed patients was 58.1% in 2019. Modeling projected that, without national screening, HCV-related mortality would rise from 3.10 to 9.09 per 100,000 over 20 years, and elimination would be delayed beyond the WHO's 2030 target. In the policy stream, the existing NHSP provided implementation readiness, with a 75.9% participation rate in 2023; a 2020 pilot in 104,918 individuals aged 56 years showed an anti-HCV positivity rate of 0.75%, and favorable economic evaluations further supported adoption. In the pol-

itics stream, the 2023–2027 national viral hepatitis strategic plan, 75.1% public support for NHSP integration, and collaborative policy entrepreneurship by academic experts and senior government actors aligned. These streams converged in 2024, leading to the introduction of one-time anti-HCV screening for 56-year-olds beginning in 2025.

Conclusions: HCV screening was adopted when epidemiologic urgency, implementable delivery infrastructure, and political commitment aligned. This case suggests that evidence is most persuasive when translated into a feasible, phased policy design, offering practical lessons for comparable settings.

Keywords: Hepatitis C, Chronic, Mass Screening, Early Diagnosis, Health Policy



FP-95

Heterogeneous Associations of Clonal Hematopoiesis with Liver Disease Outcomes: A Two-Cohort Study

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Aims: Clonal hematopoiesis of indeterminate potential (CHIP) has emerged as a systemic disease modifier linked to inflammatory and fibrotic disorders, but its impact on liver disease remains unclear. We evaluated the association between CHIP and liver-related outcomes across two complementary Western population-based cohort and Korean clinical cohort.

Methods: We analyzed 502,366 UK Biobank (UKBB) participants with whole-exome sequencing and no prior liver disease, and 549 patients with chronic liver disease from multicenter cohort of Korea. CHIP was defined as somatic mutations in canonical driver genes with a variant allele frequency $\geq 1.5\%$. Outcomes included hepatic decompensation, hepatocellular carcinoma (HCC) incidence or progression, and overall survival. Multivariable Cox models adjusted for demographic, metabolic,

liver-related, and tumor-related covariates.

Results: In UKBB, 20,080 participants (4.0%) carried CHIP. Over 12.8 years of median follow-up, CHIP was associated with an increased risk of hepatic decompensation (adjusted hazard ratio [aHR]=1.22, 95% CI=1.09–1.37, $P<0.001$), largely driven by DNMT3A mutations. No significant associations were observed for incident HCC or overall mortality. In the Korean cohort, CHIP was present in 7.0% of patients. Among HCC patients, CHIP was not associated with tumor progression after multivariable Cox regression (aHR=1.18, 95% CI=0.83–1.68, $P=0.36$). In addition, among all patients with chronic liver disease, CHIP was not associated with liver-related outcomes (aHR=0.97, 95% CI=0.51–1.85, $P=0.92$). However, CHIP was not associated with HCC development, hepatic decompensation, or survival in non-HCC chronic liver disease. Viral etiology did not modify these associations in either cohort.

Conclusions: Across two independent cohorts, CHIP was linked to an increased risk of hepatic decompensation in the UKBB and not associated with HCC progression or liver-related outcomes in Korean cohort. These findings highlight the heterogeneous and context-dependent effects of CHIP on liver disease outcomes and underscore the need for mechanistic studies integrating genomic and immunologic profiling.

Keywords: Clonal Hematopoiesis, Liver-Related Outcomes, TET2, UK Biobank

FP-96

xCT-Dependent Cysteine Metabolism Sustains Pro-Resolving TREM2⁺ MDMs in Liver Fibrosis

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Aims: Hepatic macrophages orchestrate both progression and resolution of liver fibrosis, emerging as therapeutic targets. Although recent studies have reported that TREM2⁺ monocyte-derived macrophages (MDMs) expand to replenish resident macrophages following liver injury, the mechanisms regulating their properties during fibrosis remain unclear. Here, to address this uncertainty, we define the metabolic mechanisms within TREM2⁺ MDMs that regulate liver fibrosis resolution.

Methods: Liver fibrosis was induced in mice by intraperitoneal injection of carbon tetrachloride (CCl₄), followed by single-cell RNA sequencing (scRNA-Seq) on isolated hepatic macro-

phages using 10X Genomics and Python-based-computational analysis. Mouse and human monocyte-derived macrophages were induced *in vitro* (iMDMs) and subjected to functional and metabolic analyses. Macrophage frequency, cellular ROS level, and efferocytosis capacity were analyzed by flow cytometry. Myeloid-specific xCT-deficient mice and iMDMs (*Slc7a11* Δ *LysM*) were utilized to verify the findings.

Results: Kinetic analysis demonstrated a negative correlation between TREM2⁺ MDM abundance and fibrosis severity. At pre-fibrotic stages, single-cell RNA sequencing of mouse liver macrophages showed that TREM2⁺ MDMs exhibited enriched tissue-resolving and wound-healing gene signatures and were highly associated with efferocytosis pathways. Functionally, TREM2⁺ MDMs cleared apoptotic cells more efficiently than resident Kupffer cells. *In vitro*, Efferocytosis rapidly triggered ROS production and inflammatory cytokine expression in iMDMs. Integrated transcriptomic and metabolite analyses identified enhanced cysteine metabolism, which is crucial for glutathione synthesis and redox system maintenance, as a prominent adaptive response. Notably, metabolite tracing analyses revealed that increased intracellular cysteine predominantly originated from xCT-mediated cystine import rather than methionine-derived transsulfuration pathway. Loss of xCT in iMDMs reduced intracellular cysteine and glutathione levels, resulting in increased ROS levels and inflammatory responses with impaired efferocytosis. *In vivo*, *Slc7a11* Δ *LysM* mice exhibited a reduced TREM2⁺ MDM frequency and aggravated liver fibrosis. Furthermore, adoptive transfer of *Slc7a11* Δ *LysM* iMDMs delayed fibrosis resolution.

Conclusions: Our findings identify xCT-dependent cysteine metabolism as a crucial metabolic pathway that supports restorative properties of TREM2⁺ MDMs in liver fibrosis, suggesting a potential target to promote fibrosis resolution.

Keywords: Liver Fibrosis, Monocyte-Derived Macrophage, xCT

FP-97

Cortisol Metabolic Reprogramming in Liver Cirrhosis with Diagnostic and Prognostic Implications

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Aims: Liver cirrhosis (LC) is frequently complicated by adrenal dysfunction; however, whether cirrhosis drives coordinated, pathway-specific reprogramming of cortisol metabolism remains unclear. We aimed to characterize axis-specific alterations in cortisol metabolism across patients with LC, adrenal insufficiency (AI), and controls, and to evaluate their diagnostic and prognostic utility.

Methods: This prospective study included adults with LC (n = 33) and non-cirrhotic referent participants who underwent cosyntropin stimulation testing following transsphenoidal surgery for clinically non-functioning pituitary adenoma (controls, n = 27; adrenal insufficiency [AI], n = 10). Serum and saliva samples were collected at baseline and at 30 and 60 minutes post-stimulation and profiled for 26 serum and 12 salivary steroids using liquid chromatography–tandem mass spectrometry. Multivariate models with internal validation were constructed to identify cirrhosis-associated steroid features and associations with disease severity and decompensation-free survival were assessed.

Results: LC was characterized by coordinated, axis-specific steroid remodeling, including suppressed 11 β -hydroxysteroid dehydrogenase and A-ring reduction activity coupled with activation of the 20 α -reduction pathway. This pattern was distinct from that observed in AI. Iterative model refinement identified a parsimonious seven-steroid signature that discriminated LC from controls with a mean area under the receiver operating characteristic curve of 0.992 (95% confidence interval, 0.970–1.000). Within the LC cohort, the steroid signature correlated with Child–Pugh score and independently associated with hepatic decompensation after adjustment for age, sex, and MELD-Na (hazard ratio 4.06; 95% CI 1.01–16.30; $P=0.048$).

Conclusions: LC induces coordinated cortisol metabolic reprogramming that is mechanistically distinct from adrenal insufficiency. A seven-steroid signature reflects hepatic functional reserve and may enhance risk stratification beyond conventional scoring systems.

Keywords: Liver Cirrhosis, Steroid Profiling, Adrenal Insufficiency

FP-98

Targeting DNA Stress Response as a Synthetic Lethal Strategy for Activated Hepatic Stellate Cells

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Aims: During liver fibrosis, hepatic stellate cells (HSCs) undergo myofibroblastic transdifferentiation driven by YAP/TAZ activation. This process is accompanied by hyper-proliferation, which intrinsically triggers constitutive DNA damage. While highly proliferative cells typically rely on DNA damage response

mechanisms to maintain genomic stability, the specific dependencies in activated HSCs (aHSCs) are poorly understood. We aimed to uncover the essential survival mechanisms of aHSCs and exploit them to develop a selective synthetic lethal strategy for anti-fibrotic therapy.

Methods: A kinase inhibitor library screen was conducted to identify novel targets capable of suppressing YAP/TAZ signaling. We evaluated the hit candidates by assessing DNA damage accumulation using primary mouse HSCs and the human HSC line LX-2 to verify the specificity and mechanism of action. Furthermore, the *in vivo* therapeutic efficacy was evaluated using a CCl₄-induced mouse model of liver fibrosis.

Results: Our screening identified Checkpoint kinase 1 (CHK1) as a crucial master regulator for activated HSC survival. We found that both fibrotic livers and isolated aHSCs spontaneously exhibit elevated baseline DNA damage. Pharmacological blockade of CHK1 selectively triggered catastrophic DNA damage and subsequent depletion of activated HSCs, effectively suppressing their proliferation and fibrogenic activation. Intriguingly, quiescent HSCs were spared from this synthetic lethality. Systemic administration of a CHK1 inhibitor in the CCl₄ mouse model significantly reduced extracellular matrix deposition and restored liver function.

Conclusions: Activated HSCs exhibit an absolute dependence on CHK1 to tolerate the DNA stress induced by their hyper-proliferative state. Exploiting this dependency through CHK1 inhibition induces selective depletion, presenting a potent and targeted therapeutic approach for ameliorating liver fibrosis.

Keywords: Liver Fibrosis, Hepatic Stellate Cell, CHK1, DNA Damage Response

FP-99

Impact of Cardiometabolic Risk Factors and Alcohol Consumptions in Decompensated Liver Cirrhosis

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Aims: Cardiometabolic risk factors (CMRFs) and alcohol consumption are well-established determinants of disease progression in metabolic dysfunction–associated steatotic liver disease (MASLD). However, their relative prognostic impact after transition to decompensated cirrhosis remains unclear. This study aimed to delineate the influence of CMRFs and alcohol exposure on clinical outcomes in patients with decompensated cirrhosis.

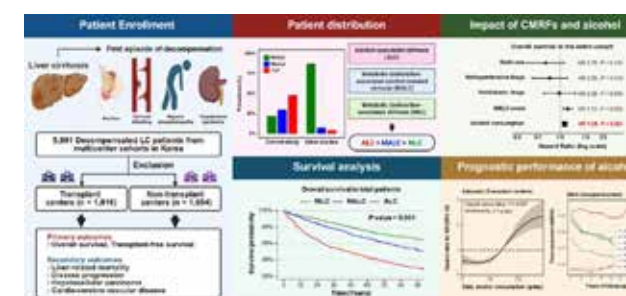
Methods: In this multicenter cohort study, 5,991 adults diag-

nosed with first decompensation between 2002 and 2024 were screened, and 2,670 were finally enrolled. Patients were categorized as metabolic dysfunction–associated liver cirrhosis (MLC), metabolic dysfunction–associated alcohol-related liver cirrhosis (MALC), and alcohol–associated liver cirrhosis (ALC). Overall survival (OS) and transplant-free survival (TFS) were evaluated using multivariable Cox models. Discriminative performance was assessed using time-dependent area under the receiver operating characteristic curve.

Results: Survival and liver-related outcomes declined progressively from MLC to MALC to ALC ($P<0.001$). The incidences of hepatocellular carcinoma and cardio-cerebrovascular disease did not differ significantly across the subgroups. Daily alcohol consumption was independently associated with mortality in both OS ($P<0.001$) and TFS ($P<0.001$). Alcohol intake consistently emerged as a stronger prognostic determinant than CMRFs or related medications. Alcohol consumption showed superior short-term prognostic discrimination and, when integrated into liver function–based models, significantly improved predictive performance and clinical net benefit, confirming its dominant role in survival.

Conclusions: In decompensated cirrhosis, alcohol exposure—rather than CMRFs—remains the principal determinant of survival, with risk increasing across higher levels of intake. These findings highlight the need for refined risk stratification in decompensated cirrhosis, where alcohol burden represents a key determinant of prognosis.

Keywords: Decompensated Liver Cirrhosis, Alcohol Consumption, Cardiometabolic Risk Factors, Survival Analysis



FP-100

Efficacy of Albumin Therapy in Patients with Decompensated Cirrhosis: A Systematic Review and Meta-Analysis

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Aims: Recent evidence suggests that albumin provides multi-faceted physiological benefits, beyond oncotic pressure maintenance. This study aimed to evaluate the long-term efficacy of albumin therapy in patients with decompensated cirrhosis, specifically focusing on its impact on all-cause mortality and other clinical complications.

Methods: A systematic search was conducted across PubMed, EMBASE, and the Cochrane Library to identify studies published up to August 31, 2025. Eligible studies were those evaluating the efficacy of albumin in reducing mortality and clinical complications of cirrhosis. We analyzed the overall prevalence rates of clinical events and compared these rates based on albumin therapy to assess its therapeutic efficacy.

Results: A total of 61 studies involving 7,692 patients were included, including both randomized controlled trials (RCTs) and observational studies. The meta-analysis revealed that the albumin-treated group had a significantly lower pooled prevalence ratio (PR) for overall mortality at 0.79 (95% CI 0.69–0.90; $I^2=26.3\%$) compared to the placebo group. Analysis restricted to RCTs confirmed this benefit with a consistent PR of 0.86 (95% CI 0.75–0.92; $I^2=7.9\%$). In age-based subgroup analysis, patients aged 57 and older showed a significant mortality reduction (PR=0.72; 95% CI 0.55–0.94; $I^2=48.7\%$), whereas no significant difference was observed in younger patients. Regarding etiology, albumin significantly improved survival in non-alcohol-related liver diseases (PR=0.78; 95% CI 0.65–0.95; $I^2=45.4\%$), but not in alcohol-related cases. Severity-based analysis showed a significant mortality benefit in studies with a median MELD score below 20 (PR=0.67; 95% CI 0.52–0.86; $I^2=26.5\%$). Conversely, no significant survival advantage was found in patients with a median MELD score of 20 or higher (PR 0.92; 95% CI 0.79–1.06; $I^2=50.7\%$).

Conclusions: Albumin administration significantly reduces mortality in patients with cirrhosis, particularly in those with lower MELD scores and non-alcoholic etiology, highlighting the need for risk-stratified treatment strategies.

Keywords: Albumin, Liver Cirrhosis, Mortality, Ascites

FP-101

Comparative Effectiveness of Antibiotic Prophylaxis for Spontaneous Bacterial Peritonitis in Patients with Cirrhosis: A Network Meta-Analysis of Randomized Trials

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Aims: Spontaneous bacterial peritonitis (SBP) is a major complication in patients with cirrhosis and ascites. Although several prophylactic antibiotics are recommended, their relative effectiveness remains uncertain. We performed a network meta-analysis of randomized controlled trials (RCTs) to compare the efficacy of antibiotic prophylaxis for preventing SBP.

Methods: We systematically searched PubMed, Embase, Cochrane Library, and Web of Science for RCTs evaluating antibiotic prophylaxis in cirrhotic patients at risk of SBP. Interventions included norfloxacin, ciprofloxacin, rifaximin, trimethoprim-sulfamethoxazole (TMP/SMX), and placebo. The primary outcomes were the incidence of SBP and all-cause mortality.

Results: A total of 27 RCTs were included. Rifaximin (prevalence ratio [PR], 0.32; 95% confidence interval [CI], 0.19–0.54), ciprofloxacin (PR, 0.40; 95% CI, 0.18–0.88), and norfloxacin (PR, 0.55; 95% CI, 0.33–0.91) were associated with a significantly lower risk of SBP compared with placebo, whereas TMP/SMX did not show a significant benefit. For all-cause mortality, rifaximin (PR, 0.49; 95% CI, 0.32–0.76) and norfloxacin (PR, 0.68; 95% CI, 0.50–0.93) were associated with a reduced risk compared with placebo, while ciprofloxacin showed a borderline effect. In studies evaluating primary prophylaxis (high-risk patients without prior SBP), rifaximin (PR, 0.43; 95% CI, 0.24–0.76) and norfloxacin (PR, 0.46; 95% CI, 0.26–0.84) were associated with a lower risk of SBP. Among studies evaluating secondary prophylaxis (patients with a prior history of SBP), rifaximin (PR, 0.08; 95% CI, 0.02–0.29) and norfloxacin (PR, 0.36; 95% CI, 0.14–0.90) were also associated with a lower risk of SBP. Reductions in all-cause mortality were not consistently observed across sub-

group analyses.

Conclusions: In this network meta-analysis, antibiotic prophylaxis was associated with a reduced risk of SBP in patients with cirrhosis. Among several antibiotics, rifaximin and norfloxacin showed the most consistent preventive effects.

Keywords: Decompensation, SBP, Prophylaxis, Antibiotics

Saturday, June 13, 2026, 13:50-14:50

14. Liver Transplantation 2

FP-102

Correlation of Early Post-Operative Outcomes on Graft Weight Variations in Right Lobe Recipient Living-Donor Liver Transplantation: A Single Center Retrospective Study

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Aims: Graft-recipient weight ratio (GRWR) has been identified as a critical determinant influencing post-transplant outcomes, where both undersized and oversized grafts can precipitate a cascade of complications. We therefore retrospectively analyzed the correlation of GRWR variations on early patient outcomes.

Methods: 2151 patients receiving a Right lobe graft who underwent LDLT from January 2017 to May 2025. They were categorized on Six groups based on Actual GRWR to Expected GRWR difference (< -10%, -5% to -10%, 0 to -5%, 0 to +5%, +5 to +10% and > +10%). One-way ANOVA is used to determine the statistically significant difference among the six groups based on: total days of hospitalization, total days to drain removal, total drain output volume, total days to normalization of bilirubin and Patient Mortality.

Results: None of the measured early post-operative recipient outcomes showed a statistically significant difference across the six GRWR deviation groups. Sex, Diagnosis, Comorbidities, overall Complications, MELD Na, Cold Ischemia Time (CIT), Blood Loss, and Operative Duration showed no statistically significant differences across the deviation groups. Actual GRWR was lower by approximately 5.14 percentage (or ~6.67% in absolute size) showing highly significant differences across the deviation groups (p-value < 0.001).

Conclusions: Preoperative CT volumetry systematically overestimated graft size, with Actual GRWR consistently and significantly lower than Expected GRWR. The six GRWR deviation groups revealed no significant association with early post operative outcomes. Ensuring a sufficient AGRWR, maintaining high quality peri operative management and functional graft adequacy is more important in right lobe LDLT.

Keywords: Early Postoperative Outcomes, Living Donor Liver Transplant, LDLT, LRLT, GRWR, Actual GRWR, Expected GRWR

FP-103

Randomized Trial Comparing Postoperative Outcomes of PTFE vs. Polyethylene Terephthalate Grafts in Neo-Middle Hepatic Vein Reconstruction for Right Lobe Living Donor Liver Transplantation

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Aims: Adequate venous outflow is critical for graft function in living donor liver transplantation (LDLT). Reconstruction of the middle hepatic vein (MHV) with synthetic conduits such as polytetrafluoroethylene (PTFE) and polyethylene terephthalate (Dacron) is commonly practiced, but comparative data are limited. This randomized trial evaluated early postoperative outcomes and patency of PTFE versus Dacron grafts in neo-MHV reconstruction for right lobe LDLT.

Methods: In this single-centre prospective trial conducted from February 2024 to July 2025, 84 adult LDLT recipients were randomised, prior to bench work into two groups: Dacron (n=42) and PTFE (n=42). Donor right hepatectomy was performed with standardised reconstruction of the anterior sector venous tributaries using the allocated graft. The primary endpoint was neo-MHV patency at postoperative day (POD) 14, assessed by Doppler and cross-sectional imaging. Secondary outcomes included neo MHV patency at 90 days, major post liver transplant-complications (bile leak, stricture, sepsis, Rejection), highest Clavien-Dindo grade, early graft dysfunction (Olthoff criteria), ICU and hospital stay and 90-day mortality.

Results: Neo-MHV patency at POD 14 was 80.5% with Dacron and 82.9% with PTFE (P=1.000). At POD 90, patency was 64.1% and 65.0%, respectively (P=0.59). Amongst the occluded Neo-MHV (n=27) 55% occluded within 14 days (n=15). Mortality in the group that occluded within 14 days was 13.3% (2/15) compared to 0% (0/12) in the group that occluded between 14 and 90 days, and 3.9% (3/51) in the patent group. This dif-

ference was statistically non-significant. Complication rates (Clavien-Dindo ≥3: 50% vs. 40.5%, P=0.54), bile leak (23.8% vs. 21.4%, P=0.794), sepsis (7.1% vs. 4.8%, P=1.000) and ninety-day mortality (9.5% vs 7.1%, P=0.693) were comparable between Dacron and PTFE graft.

Conclusions: Both PTFE and Dacron grafts demonstrated comparable short-term outcomes in terms of patency, complication rates, and mortality following MHV reconstruction in LDLT. Neo-MHV thrombosis within 14 days may have a detrimental impact on mortality.

Keywords: MHV, Patency, Graft Outcomes

FP-104

Sequential NRP and Hypothermic versus Normothermic Ex-Situ Perfusion in Extended Criteria DCD Liver Transplantation: A Randomized Prospective Trial

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Aims: Despite the prolonged warm ischemia required in donation after circulatory death (DCD), the Italian experience has demonstrated favorable outcomes using normothermic regional perfusion (NRP) combined with end-ischemic machine perfusion (MP). However, consensus is lacking on whether hypothermic oxygenated MP (HMP) or normothermic MP (NMP) provides superior outcomes in this setting.

Methods: From December 2020 to August 2024, all DCD liver grafts undergoing NRP and meeting Milan viability criteria were prospectively included and randomized 1:1 to HMP or NMP. The primary endpoint was the incidence of serious adverse events (SAE), defined as vascular or biliary complications, and investigate predictive factors for graft loss and SAE.

Results: Fifty DCD liver transplantations were performed, equally allocated to HMP and NMP (n=25 each). Mean recipient age was 62 years, whereas HCC was the leading indication (62%), and mean MELD-Na was 11. At a mean follow-up of 24 months, SAE rates did not differ significantly between HMP and NMP (16% vs 20%, P=0.713). Overall biliary complications occurred in 12% versus 24%, respectively (P=0.269). Biliary leak was observed exclusively after NMP (0% vs 16%, P=0.037), while anastomotic strictures (8% vs 12%, P=0.687) and ischemic cholangiopathy (0% vs 8%, P=0.149) were comparable. One-year graft and patient survival were 88% and 100% for HMP and NMP, respectively (P=0.074).

Conclusions: Sequential NRP followed by ex-situ MP was safe regardless of perfusion technique, with no clear superiority of HMP over NMP. Nonetheless, HMP and NMP demonstrated different onset and profile of complications. Perfusion parameters, inflammatory cytokines, lactate clearance, and portal flow dynamics may serve as additional viability criteria to refine graft assessment.

Keywords: Liver Transplantation, Perfusion Machines, Extended Criteria Donors

FP-105

Translational Application of Acellular Dermal Matrix for Hepatic Vein Reconstruction in LDLT: From Bench Validation to Clinical Efficacy

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Aims: Venous reconstruction in living donor liver transplantation (LDLT) typically relies on synthetic grafts, which are prone to infection and thrombosis. This study aimed to translate pre-clinical findings of a novel biological conduit, Human Acellular Dermal Matrix (ADM), into clinical practice to overcome these limitations.

Methods: Following validation in rabbit and porcine models which demonstrated rapid endothelialization, we conducted a prospective clinical study (2022–2025). Forty adult LDLT recipients underwent middle hepatic vein (MHV) reconstruction using ADM. Clinical outcomes were compared with matched historical controls using Hemashield (n=40) or PTFE (n=20). The primary endpoints were graft patency and biologic safety.

Results: Preclinical histology confirmed that ADM rapidly transforms into host-integrated neotissue. Clinically, ADM achieved excellent patency during the critical regeneration window (95.0% at 3 months; 85.0% at 6 months). While mid-term patency at 18 months (62.5%) was comparable to synthetics ($P=0.785$), the safety profile was superior. The ADM group had zero graft-related infections or erosions, whereas the synthetic group experienced a 3.3% rate of major structural complications. Notably, all ADM occlusions were clinically silent without congestion.

Conclusions: This study successfully bridges bench-to-bedside, validating ADM as a viable “temporary biological scaffold.” ADM ensures venous outflow during the critical regeneration phase and eliminates the catastrophic complications associated with permanent synthetic foreign bodies. It represents a paradigm shift from permanent patency to biological integration and safety.

Keywords: Liver Transplantation, Acellular Dermal Matrix, Translational Research

FP-106

Initial Extreme High Titer Does Not Worsen Outcomes When Adequate Desensitization Is Performed in ABO-Incompatible Living Donor Liver Transplantation

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Aims: ABO-incompatible (ABOi) living donor liver transplantation (LDLT) has become feasible with standardized desensitization protocols. However, whether recipients presenting with an initial extreme high isoagglutinin titer ($\geq 1:1024$) are at increased risk of antibody-mediated rejection (AMR), biliary complications, or poor survival remains uncertain. We evaluated the impact of an initial extreme high antibody titer on immunologic and biliary complications, graft survival, and patient survival after ABOi LDLT.

Methods: We retrospectively analyzed 981 adult recipients who underwent ABOi LDLT at Asan Medical Center between December 2012 and December 2023. Patients were classified into a high-titer group ($\geq 1:1024$, n=42) and a non-high-titer group ($< 1:1024$, n=939). All recipients received rituximab-based desensitization followed by preoperative plasma exchange (PE) according to institutional protocol. Postoperative complications and survival outcomes were compared.

Results: The high-titer group had higher MELD scores (median 13 vs. 11, $P=0.045$), required more preoperative PE sessions (6 [6–8] vs. 3 [2–4], $P<0.001$), and showed a greater incidence of antibody rebound $> 1:16$ (38.1% vs. 23.1%, $P=0.026$). However, postoperative complications—including AMR (7.1% vs. 5.6%, $P=0.728$), acute cellular rejection (7.1% vs. 4.8%, $P=0.455$), biliary stricture (28.6% vs. 23.4%, $P=0.443$), and diffuse intrahepatic biliary stricture (7.1% vs. 4.8%, $P=0.455$)—were comparable between the two groups. In-hospital mortality (0% vs. 2.7%, $P=0.621$) also showed no significant difference. Patient and graft survival were comparable (log-rank $P=0.807$ and $P=0.998$, respectively), with similar 5-year survival rates.

Conclusions: In ABOi LDLT, an initial extreme high antibody titer does not adversely affect postoperative complications or long-term survival when adequate desensitization is performed, despite the need for more intensive preoperative management.

Keywords: Liver Transplantation, ABO Incompatible, Rejection

FP-107

Sex Disparities in Liver Transplant Prioritization across Scoring Systems: A Korean Multicenter Cohort Study

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Aims: Given the scarcity of donor organs, equitable allocation in deceased donor liver transplantation (DDLT) is crucial. The Model for End-Stage Liver Disease (MELD) score was developed to prioritize patients with the highest mortality risk. Although it has significantly improved organ allocation, the MELD score has been associated with sex disparities, leading to the introduction of MELD 3.0. However, validation of these revised models in Asian populations remains limited. Thus, using a Korean multicenter cohort, this study aims to validate whether these improved scoring systems mitigate sex disparities in liver transplant allocation within an Asian population.

Methods: We retrospectively analyzed consecutive patients aged ≥ 19 years listed for DDLT between 2010 and 2024 using multicenter cohorts from Seoul National University Hospital (SNUH) and the Catholic Medical Center (CMC). To account for the transition in South Korea's organ allocation system from the Child-Pugh Score (CPS) to the MELD score during the study period, analyses were stratified into the CPS era and the MELD era. The primary outcome was DDLT within 90 days. Death without transplantation was treated as a competing event, and the outcomes were assessed using cumulative incidence functions and Fine-Gray subdistribution hazard models. The secondary outcomes were transplantation-free survival (TFS) and 90-day waitlist mortality.

Results: A total of 1,390 patients were included (1,034 from SNUH and 356 from CMC). During the CPS era, the cumulative incidence of DDLT within 90 days was significantly higher in females (subdistribution hazard ratio 1.37, 95% CI 1.06–1.78, $P=0.02$, Figure 1). However, this sex disparity was resolved in the MELD era ($P=0.36$). Waitlist mortality showed no significant sex differences in either the CPS ($P=0.95$) or MELD ($P=0.38$) eras. Transplantation-free survival (TFS) was significantly reduced in females during the CPS era (hazard ratio 1.32, 95% CI 1.07–1.63, $P=0.01$), likely driven by their higher transplantation

rate, whereas no significant difference was observed in the MELD era ($P=0.85$) (Figure 2). Furthermore, in the CPS era, the sex-based difference in 90-day waitlist mortality risk increased sharply within the high-risk group. In the MELD era, the Gender-Equity Model for Liver Allocation corrected by serum sodium (GEMA-Na) model demonstrated the lowest and most stable sex disparity (Figure 3).

Conclusions: While the transition of DDLT allocation criteria from CPS to the MELD score has partially alleviated sex disparities, our findings suggest that GEMA-Na could serve as a more optimal scoring system for the Asian population.

Keywords: Transplantation, Waitlist Mortality, Sex Inequity

Figure 1

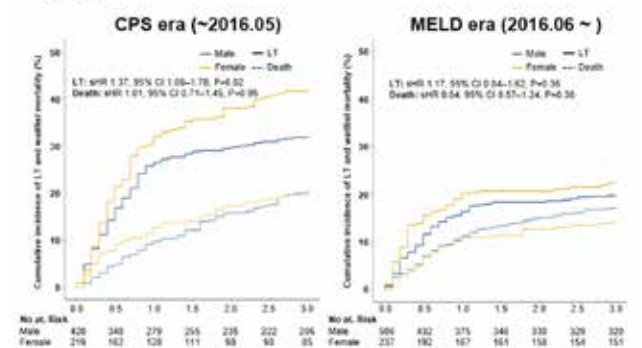


Figure 2

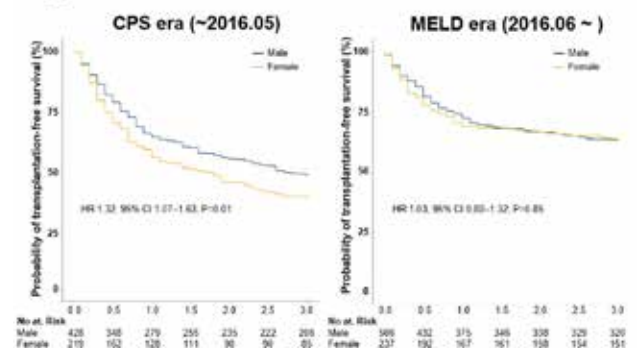
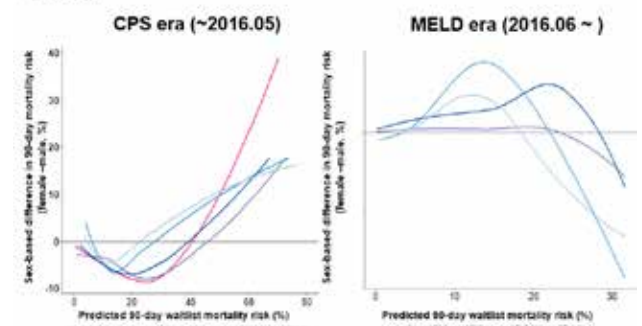


Figure 3



THE LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
in conjunction with EALA

June 11-13, 2026 | Conrad Seoul, Korea

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ORAL POSTER PRESENTATION 1

OP-1~OP-6	HBV & MASLD 1
OP-7~OP-11	MASLD & ALD, Basic
OP-12~OP-16	MASLD & ALD, Clinical
OP-17~OP-22	LC, Liver Failure & Autoimmune Diseases 1
OP-23~OP-28	Liver Transplantation
OP-29~OP-34	HCC, Basic 1
OP-35~OP-40	HCC, Clinical
OP-41~OP-46	HCC & LC
OP-47~OP-50	Surgery, Technical Issues
OP-51~OP-56	Others



Friday, June 12, 2026, 16:20-17:20

1. HBV & MASLD 1

OP-1

Direct Effects of the Glucagon/GLP-1 Receptor Dual Agonist Survodutide on Liver Endpoints Beyond Weight Loss: Insights from a Phase 2 Trial in People with Metabolic Dysfunction-Associated Steatohepatitis and Fibrosis

Mazen Noureddin¹, Arun J. Sanyal², Pierre Bedossa³, Mandy Fraessdorf⁴, Corinna Schoelch⁵, Elena Startseva⁶, Guy W. Neff⁷, Eric J. Lawitz⁸, Elisabetta Bugianesi⁹, Quentin M. Anstee¹⁰, Philip N. Newsome¹¹, Vlad Ratziu¹², Azadeh Hosseini-Tabatabaei¹³, Jörn M. Schattenberg¹⁴, Naim Alkhouri^{8,15}, Ramy Younes⁶, **Jinhong Cho**¹⁶

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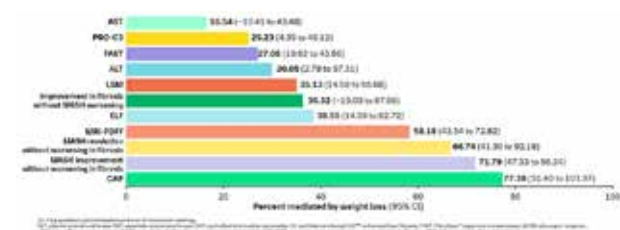
Aims: We evaluated weight-loss direct and indirect effects of survodutide, a glucagon receptor/glucagon-like peptide-1 receptor dual agonist, on liver endpoints in a phase 2 trial in people with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and F1 – F3 liver fibrosis.

Methods: In a randomized trial (NCT04771273), 295 patients received weekly injections of survodutide (2.4, 4.8, or 6.0 mg) or placebo. Among them, 170 patients with F2/F3 fibrosis and paired biopsies were analyzed; survodutide groups were pooled. A mediation analysis assessed how much of survodutide's effect on liver outcomes was directly due to treatment versus indirectly through weight loss (WL). Liver endpoints at Week 48 included MASH resolution, fibrosis improvement, ELF score, PRO-C3, FAST score, LSM, and MRI-PDFF. The model adjusted for baseline weight, diabetes status, and fibrosis stage. Results are presented as total effect (TE), odds ratios (OR), and percentage mediated by WL (% med), with 95% confidence intervals.

Results: Survodutide's effects on liver outcomes were partly

mediated by WL. Resolution of MASH without worsening fibrosis showed the highest mediation (66.7%; OR: 14.70; response: 62.9% vs 13.0% for placebo). MRI-PDFF changes were also highly mediated (58.2%; TE: -50.3). Fibrosis improvement without MASH worsening had lower mediation (36.3%; OR: 3.68). Other endpoints showed modest mediation: ELF (38.6%; TE: -0.64), PRO-C3 (25.2%; -28.63), FAST (27.1%; -65.16), and LSM (35.1%; -38.78). These findings suggest both direct and indirect (via WL) effects of survodutide on liver health.

Figure 1. Improvements in fibrosis, PRO-C3, and ELF score due to a direct effect of survodutide on the liver



Conclusions: The results suggest that MASH resolution induced by survodutide was broadly mediated by WL. However, liver endpoints related to improvement in inflammation and fibrosis were less so, suggesting the reduction in these endpoints can be attributed to a direct effect of survodutide on the liver, likely via direct glucagon effect beyond WL.

Keywords: Survodutide, Mash, Mash Resolution

OP-2

Iron-Driven Hepatokine Dysregulation Promotes Systemic Metabolic Dysfunction in MASLD

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern, with hepatic iron overload implicated as a contributing factor. However, how hepatic iron dysregulation leads to systemic metabolic dysfunction remains unclear. We aimed to investigate whether hepatocyte-derived factors mediate this link.

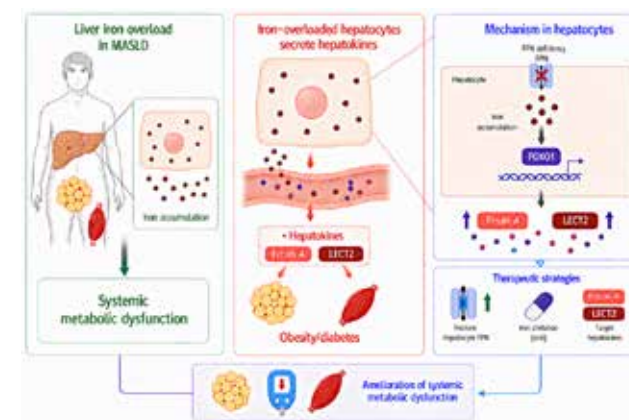
Methods: Hepatic iron regulation was assessed in human MASLD samples and mouse models. Hepatocyte-specific ferroportin (FPN; SLC40A1) loss- and gain-of-function approaches were used to evaluate metabolic outcomes and underlying mechanisms.

Results: FPN expression was significantly reduced in hepatocytes from both human MASLD samples and experimental

models, accompanied by hepatic iron accumulation. Hepatocyte-specific deletion of FPN markedly aggravated diet-induced obesity and insulin resistance, along with decreased energy expenditure and impaired thermogenic function. Mechanistically, iron accumulation driven by FPN deficiency promoted the upregulation of the hepatokines Fetuin-A and LECT2 via activation of the transcription factor FoxO1. Importantly, targeting this axis through hepatokine knockdown, hepatocyte-specific FPN restoration, or oral iron chelation effectively ameliorated systemic metabolic abnormalities.

Conclusions: These findings support a model in which hepatocyte iron overload drives systemic metabolic dysfunction through hepatokine-mediated signaling. Modulation of hepatic iron homeostasis and its downstream endocrine outputs may represent a promising strategy for the treatment of MASLD and associated metabolic disorders.

Keywords: MASLD, Ferroportin, Iron Overload, Hepatokine, Metabolic Dysfunction



OP-3

Assessment of Liver Function Test in Vegetarian and Non-Vegetarian

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Aims: The aim of the study was to examine whether vegetarians had a lower risk of fatty liver disease and less severe liver fibrosis compared to non-vegetarians. This study will be carried out to evaluate different parameters of Liver Function Test in vegetarians and non-vegetarians.

Methods: In this study, 174 vegetarian and non-vegetarian healthy people were included from Frontline Hospital, Old Baneshwor, Kathmandu, Nepal. In a vegetarian diet, the food intake of a person is confined to a large variety of foods derived from plants along with milk and dairy. And, any form of meat and products derived from animals are completely avoided. A

non-vegetarian diet includes all forms of plant foods as well as foods and by-products that are derived from animals, such as poultry, fish, meat, etc. The results of Liver Function Test were performed using Fully automated analyzer (i.e.; Mindray BS-360E) during the year 2022.

Results: In total of 174 vegetarian and non-vegetarian people, the mean $\pm$ SD of total bilirubin in vegetarian was 0.42 ± 0.18 and 0.83 ± 0.32 in non-vegetarian which was significant at $P < 0.05$. Similarly, direct bilirubin was also significant at $P < 0.05$ where its mean $\pm$ SD was calculated as 0.27 ± 0.17 . Also, SGOT, Total protein were significant in non-vegetarian at $P < 0.05$. but there was no significant change in SGPT, ALP and albumin in vegetarian and non-vegetarian

Conclusions: From this study, it can be concluded that dietary pattern is significantly associated with liver function test. And liver enzymes show a positive correlation with respect to the finding, it is necessary to follow vegetarian diet rather than non-vegetarian diet.

Keywords: Vegetarian, Non-Vegetarian, Diet, LFT

OP-4

Statin Prescription and Major Adverse Cardiovascular Events by Antiviral Therapy in Chronic Hepatitis B: A Nationwide Real-World Study

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Aims: As antiviral therapy has reduced liver-related complications in chronic hepatitis B (CHB), cardiovascular disease has emerged as an increasingly important cause of mortality in this population. Although previous studies have consistently reported a higher incidence of dyslipidemia with tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate (TDF) or entecavir (ETV), whether this lipid change confers increased cardiovascular risk remains unclear. We compared the risk of major adverse cardiovascular events (MACE) among patients treated with TAF, TDF, or ETV, with analyses stratified by hyperlipidemia status and statin use.

Methods: Using nationwide claims data from the Health Insurance Review and Assessment Service (HIRA) of Korea (2018–2022), we conducted a retrospective cohort study of 57,775 patients with CHB who received TAF (n=15,829), TDF (n=23,945), or ETV (n=18,001) for at least 3 months. The primary outcome was MACE, defined as hospitalization for ischemic heart disease, myocardial infarction, or ischemic stroke.

Results: The incidence of newly diagnosed hyperlipidemia was highest in the TAF group (26.4%), followed by TDF (17.0%) and ETV (16.1%). Statin initiation was also most frequent with TAF (10.4%), compared with ETV (7.8%) and TDF (5.7%) ($P<0.001$). Despite higher rates of dyslipidemia and statin use, TAF was not associated with an increased risk of MACE compared with TDF (HR 0.99, 95% CI 0.79–1.25, $P=0.94$), and this finding remained consistent across subgroups defined by hyperlipidemia and statin use.

Conclusions: Although TAF was associated with higher rates of dyslipidemia and statin initiation, it was not associated with an increased risk of MACE compared with TDF. This finding was consistent across subgroups defined by hyperlipidemia status and statin use. Longer follow-up is needed to clarify long-term cardiovascular outcomes.

Keywords: Chronic Hepatitis B, Tenofovir Alafenamide, Statin, Major Adverse Cardiovascular Events

OP-5

Tenofovir Alafenamide Improves ALT and HCC Risk Stratification in Chronic Hepatitis B with Normal or Mildly Elevated ALT

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Aims: Guidelines for antiviral treatment initiation in non-cirrhotic chronic hepatitis B (CHB) patients with HBV DNA level $> 2,000$ IU/mL, but with normal or mildly elevated alanine aminotransferase (ALT) remain controversial. We evaluated whether tenofovir alafenamide (TAF) improves ALT normalization and attenuates hepatocellular carcinoma (HCC) risk scores in this population.

Methods: This retrospective single-center study analyzed non-cirrhotic CHB patients with HBV DNA level $> 2,000$ IU/mL, but with normal or mildly elevated ALT. Patients were classified into those who initiated TAF (antiviral treatment [AVT] group, $n=96$) and those under untreated observation (control group, $n=28$). At 1-year of follow-up, we assessed longitudinal ALT changes, ALT normalization rates by EASL, AASLD, and KASL criteria, and HCC risk score transitions using HCC risk models including REACH-B and CU-HCC.

Results: Over 1 year, AVT group showed significant ALT reduction (median 24.5 $\rightarrow$ 21.0 U/L, $P<0.001$), whereas controls remained unchanged (25.0 $\rightarrow$ 26.5 U/L, $P=0.385$). ALT normalization rates improved significantly in the treatment

group by AASLD (63.5% $\rightarrow$ 80.2%, $P=0.003$) and KASL criteria (70.8% $\rightarrow$ 85.4%, $P=0.005$), while it was statistically unchanged across all criteria (all $P>0.05$). For HCC risk stratification over 1 year, the proportion of patients in the low-risk category significantly increased in the AVT group according to REACH-B (2.1% $\rightarrow$ 45.8%, intragroup $P<0.001$) and CU-HCC criteria (76.3% $\rightarrow$ 94.6%, intragroup $P<0.001$). Furthermore, these shifts in risk distribution were significantly different from the control group (intergroup $P=0.015$ and $P=0.036$ for REACH-B and CU-HCC, respectively). Conversely, risk distributions by PAGE-B and aMAP showed no significant changes over time or between-group differences (all $P>0.05$).

Conclusions: TAF initiation in grey-zone non-cirrhotic CHB patients significantly improved ALT levels and achieved greater attenuation in HCC risk stratification compared to untreated controls, supporting the beneficial efficacy of early initiation of AVT in this population.

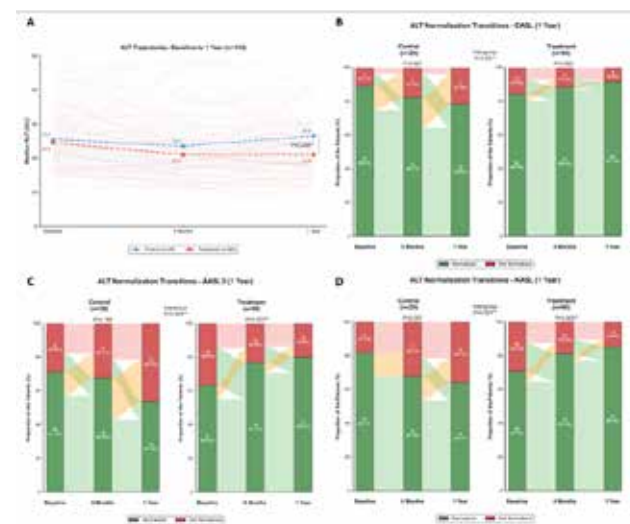


Table 1. Changes in HCC risk stratification during 1-year antiviral treatment						
Score	Group	Risk	Baseline	6-month	1-year	Inter-group p-value ²
PAGE-B	Control (n=22)	Low	13 (59.1)	13 (59.1)	13 (59.1)	0.999
		Intermediate	6 (27.3)	6 (27.3)	6 (27.3)	
		High	3 (13.6)	3 (13.6)	3 (13.6)	
	Treatment (n=45)	Low	17 (37.8)	18 (40.0)	18 (40.0)	0.607
		Intermediate	26 (57.8)	28 (62.2)	27 (60.0)	
		High	2 (4.4)	1 (2.2)	2 (4.4)	
REACH-B	Control (n=28)	Low	3 (10.7)	3 (10.7)	6 (21.4)	0.050
		Intermediate	20 (71.4)	21 (75.0)	19 (67.9)	
		High	5 (17.9)	4 (14.3)	3 (10.7)	
	Treatment (n=96)	Low	2 (2.1)	45 (46.9)	44 (45.8)	<0.001**
		Intermediate	71 (74.0)	42 (43.8)	48 (50.0)	
		High	23 (24.0)	9 (9.4)	4 (4.2)	
aMAP	Control (n=22)	Low	21 (95.5)	22 (100.0)	21 (95.5)	0.368
		Intermediate	1 (4.5)	0 (0.0)	1 (4.5)	
		High	0 (0.0)	0 (0.0)	0 (0.0)	
	Treatment (n=45)	Low	44 (97.8)	44 (97.8)	45 (100.0)	0.616
		Intermediate	1 (2.2)	1 (2.2)	0 (0.0)	
		High	0 (0.0)	0 (0.0)	0 (0.0)	
CU-HCC	Control (n=27)	Low	21 (77.8)	21 (77.8)	21 (77.8)	0.368
		Intermediate	6 (22.2)	6 (22.2)	4 (14.8)	
		High	0 (0.0)	0 (0.0)	0 (0.0)	
	Treatment (n=90)	Low	71 (78.3)	85 (94.4)	80 (94.6)	<0.001**
		Intermediate	22 (23.7)	8 (8.6)	5 (5.4)	
		High	0 (0.0)	0 (0.0)	0 (0.0)	

Values are presented as number (percentage) for categorical variables.
¹P-values for intragroup overall trend across 2 or 3 timepoints were calculated using the McNemar test or Cochran's Q test.
²P-values for group-by-time interaction were calculated using generalized estimating equations. * $P<0.05$, ** $P<0.01$.
aMAP, aspartate aminotransferase; CU-HCC, Chinese University HCC; HCC, hepatocellular carcinoma; PAGE-B, score based on platelets, age, and gender; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; NA, not applicable.

Keywords: Hepatitis B, Chronic, Tenofovir, Carcinoma, Hepatocellular, Risk Assessment

OP-6

Cas9-gRNA Circular Templates Reduce Hepatitis B Virus Replication via cccDNA Degradation

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Aims: Chronic hepatitis B virus (HBV) infection persists due to covalently closed circular DNA (cccDNA), which serves as a stable nuclear template for viral transcription. Although nucleos(t)ide analogues effectively suppress viral replication, they fail to eliminate cccDNA. Here, we aimed to develop an RNA nanoparticle platform derived from circular templates encoding CRISPR-associated protein 9 (Cas9) and guide RNA (gRNA) to induce cccDNA degradation and suppress HBV replication.

Methods: Circular DNA templates encoding Cas9 and HBV-targeting gRNA were transcribed via rolling circle transcription (RCT) to generate RNA nanoparticles. These nanoparticles were subsequently conjugated with poly-L-lysine and N-acetylgalactosamine (GalNAc) to enable hepatocyte targeting. Antiviral efficacy was evaluated in HepAD38 replication and HepG2-NTCP infection. Intracellular cccDNA levels were quantified by quantitative PCR, and secreted hepatitis B surface antigen (HBsAg) was measured by ELISA. Particle size and zeta potential were characterized using dynamic light scattering.

Results: Unmodified nanoparticles exhibited an average size of ~60 nm, which increased to ~80 nm following poly-L-lysine conjugation and ~100 nm after GalNAc modification. Zeta potential shifted from negative to near-neutral or partially positive values. Cas9-gRNA circular template-derived nanoparticles reduced intracellular cccDNA by 24% ($P=0.018$) and decreased HBsAg secretion by 41% ($P=0.006$) compared with controls, with consistent effects observed across both models.

Conclusions: Cas9-gRNA circular template-derived RNA nanoparticles effectively reduce HBV cccDNA and suppress viral antigen production *in vitro*. This modular platform provides a promising strategy for the development of direct cccDNA-targeting therapeutics for chronic hepatitis B.

Keywords: HBV, cccDNA, Cas9-gRNA Circular Template

Friday, June 12, 2026, 16:20-17:10

2. MASLD & ALD, Basic

OP-7

A Study to Evaluate the Impact of Zinc Deficiency on Liver Fibrosis in Lean vs. Obese Metabolic Dysfunction-Associated Steatotic Liver Disease Patients

Archana Chaudhari, Aashal Bhavesh Shah

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) one of the most common chronic liver disorders, with distinct phenotypes, lean MASLD and obese MASLD. Lean MASLD patients are at increased risk of cardiovascular mortality. Zinc deficiency usually occurs in advance cirrhosis patients. Data regarding its role in the progression of early-stage fibrosis in various MASLD phenotypes is limited. Hence, this study was planned to evaluate the predictive impact of zinc deficiency on disease progression in lean and obese MASLD patients.

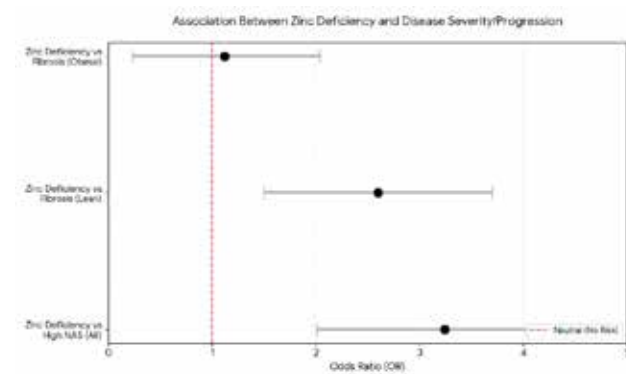
Methods: This was prospective observational study, conducted at a tertiary care hospital over a duration of two years. Treatment-naïve patients with biopsy-proven MASLD were included in the study. Patients were divided into three groups based on body mass index (BMI): lean (BMI <23 kg/m²), overweight (23-24.9 kg/m²) and obese (>25 kg/m²). Follow up was conducted every six months for two years. Serum zinc levels were measured at all follow-ups. Serum zinc levels <70 µg/dL were considered deficient. Liver stiffness measurement (LSM) was also done every six months. Primary endpoint was considered as progression of fibrosis, defined by ≥ 2 kPa increase in LSM or advanced stage in METAVIR scores. Relevant statistical analysis was conducted to identify the independent predictors of advanced hepatic fibrosis. $P<0.05$ was considered significant.

Results: Total 368 patients were included. 34.24% ($n=126$) patients had zinc deficiency. At the end of two years, 19.57% ($n=72$) patients had significant progression of fibrosis. There was significantly higher prevalence of zinc deficiency in lean MASLD patients as compared to obese MASLD patients (42.51% vs. 28.89%, $P<0.01$). Zinc deficiency significantly correlated with higher NAFLD activity scores (Odds ratio: 3.24, 95% CI: 2.01-4.27). The consistently low levels of zinc in lean MASLD were associated with 2.6 times higher advance fibrosis risk. On the other hand, correlation between zinc and fibrosis in obese MASLD patients was negligible (OR: 1.12, 95% CI: 0.23-2.04).

Conclusions: Serum zinc deficiency serves as an independent predictor of fibrosis progression in patients with lean MASLD phenotype. Thus, monitoring zinc status in such patients may

help in preventing disease progression in such patients.

Keywords: Lean Masld, Obese MASLD, Zinc Deficiency



OP-8

Differential Activation of Complement System Drives Immune Cell Differentiation to Promote Nonalcoholic Fatty Liver Disease Progression

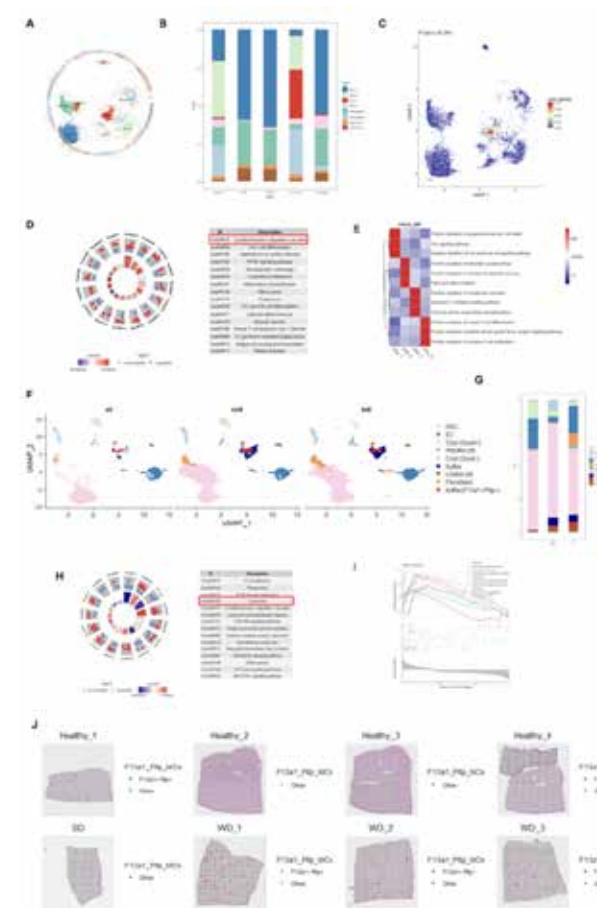
Mingjiang Liu^{1,2,3}, **Hao Xing**^{1,3,4}, Wei Gao^{1,3,4}, Guangtao Ma^{1,3,4}, Yuntao Bao^{1,3,4}, Zhiyong Lin^{1,3,4}, Shilian Chen^{1,3,4}, Yulan Li^{1,3,4}, Chenyi Zhuo^{1,3,4}, Huizhao Su^{1,3,4}, Zhenya Guo^{1,3,4}, Zaiwei Wei^{1,3,4}, Rensheng Wang^{4,5}, Guandou Yuan^{1,3,4}, Yonglian Zeng^{1,3,4}, Songqing He^{1,3,4}

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Aims: Non-alcoholic steatohepatitis (NASH)-related liver fibrosis has become the leading cause of chronic liver disease with limited therapeutic options. This study aims to investigate the mechanism by which intracellular complement activation in macrophages drives the differentiation of a specific macrophage subset (F13A1+PLTP+MCs, referred to as complement C3-dependent macrophages) and promotes liver fibrosis progression. We hypothesize that intracellular complement C3 activation drives the formation of the F13A1+PLTP+MCs subset, which subsequently activates hepatic stellate cells (HSCs) through cytokine or protein secretion, leading to excessive extracellular matrix (ECM) deposition and irreversible hepatic fibrosis.

Methods: Clinical samples including blood and liver biopsy specimens were collected from NASH and NASH-related liver fibrosis patients. *In vitro* studies utilized macrophage cell lines (RAW264.7 and THP-1) and primary bone marrow-derived macrophages from wild-type (WT) and C3-deficient (C3-/-

) mice to induce F13A1+PLTP+MCs formation using oleic acid (OA), palmitic acid (PA), and carbon tetrachloride (CCl₄). Two mouse models were established: methionine-choline deficient (MCD) diet and high-fat diet (HFD) combined with CCl₄ injection. Various techniques were employed, including immunohistochemistry (IHC), multiplex immunofluorescence, flow cytometry, single-cell RNA sequencing (scRNA-seq), transcriptomics, and proteomics. The therapeutic potential of the dual-targeting complement inhibitor CR2-Crry was evaluated in fibrotic mouse models.



Results: Single-nucleus RNA sequencing analysis of 170,000 cells from healthy and NAFLD progression samples revealed that F13A1+PLTP+MCs were significantly enriched in cirrhosis stage, with strong complement-related pathway activation. *In vitro* induction of primary macrophages with OA+PA+CCl₄ resulted in elevated expression of F13A1+PLTP+MCs markers (CSF1R, F13A1, and PLTP) along with increased intracellular C3b, indicating intracellular complement activation. Notably, C3 deficiency markedly reduced the formation of this macrophage subset. In HFD+CCl₄-induced fibrotic mouse models, prominent C3d deposition and increased F13A1+PLTP+MCs infiltration were observed in lipid-accumulated and fibrotic regions. C3 knockout significantly attenuated liver fibrosis,

reduced C3d deposition, and decreased F13A1+PLTP+MCs subset formation. Furthermore, treatment with CR2-Crry effectively improved hepatic steatosis and fibrosis while reducing F4/80 expression and F13A1+PLTP+MCs infiltration.

Fig 2

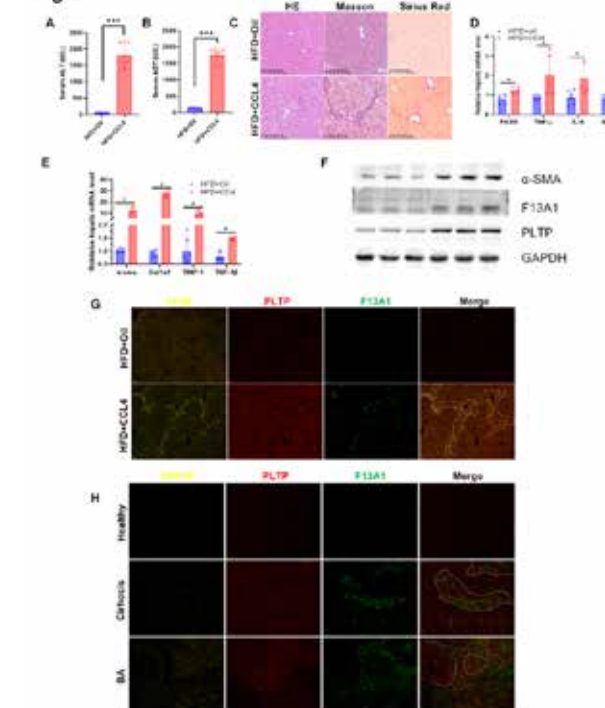
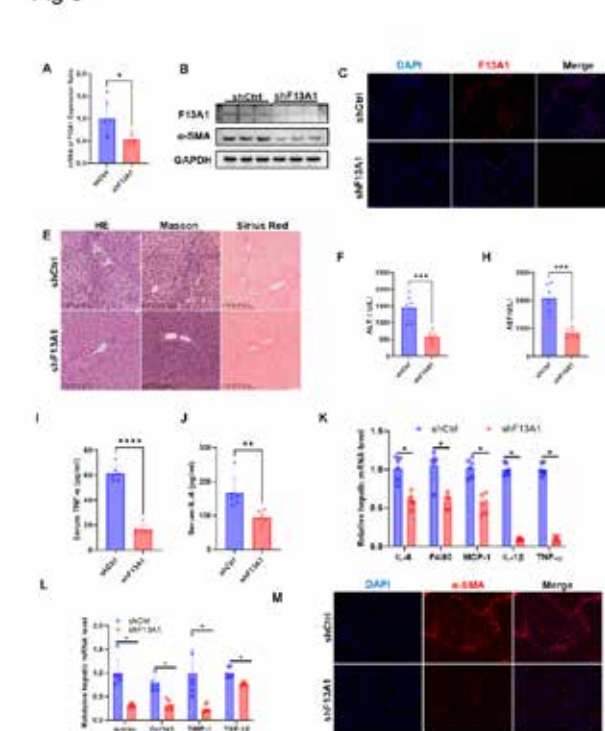


Fig 3



Conclusions: This study demonstrates that intracellular complement C3 activation drives the differentiation of F13A1+PLTP+MCs, a specific macrophage subset that plays a crucial role in promoting NASH-related liver fibrosis. The C3-dependent nature of this macrophage subset highlights the importance of intracellular complement system in regulating immune cell differentiation and fibrogenesis. Targeting intracellular complement activation using the dual-targeting inhibitor CR2-Crry represents a promising therapeutic strategy for liver fibrosis treatment. These findings provide novel insights into the pathogenesis of NASH-related liver fibrosis and identify F13A1+PLTP+MCs as a potential therapeutic target for clinical intervention.

Keywords: NASH, Intracellular Complement, Macrophage, Hepatic Fibrosis

OP-9

Fibroblast- and Macrophage-Derived Thrombospondin-1 Orchestrates the Fibroinflammatory Niche in Metabolic Dysfunction-Associated Steatohepatitis-Induced Fibrosis

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Aims: Thrombospondin-1 (THBS1) activates latent TGF- β 1 and contributes to stromal-immune communication. However, how THBS1 derived from fibroblasts and macrophages collectively contributes to fibroinflammatory remodeling in MASH has not been clearly defined.

Methods: THBS1 expression was examined in liver tissue and serum from patients with MASLD and in two dietary murine MASH models. We integrated single-cell RNA sequencing, immunohistochemistry, confocal microscopy, and flow cytometry with targeted perturbation of fibroblasts and macrophages using nintedanib, the THBS1-blocking peptide LSKL, and siRNA-mediated THBS1 silencing.

Results: THBS1 and the fibroblast activation marker FAP increased in association with fibrosis severity and IL-6 levels.

scRNA-seq and spatial imaging demonstrated THBS1 expression in both FAP⁺ fibroblasts and monocyte-derived macrophages, indicating a coordinated fibroinflammatory niche. Nintedanib reduced THBS1 expression in both compartments, decreased CD11b⁺MERTK⁺ macrophages and FAP⁺PD-L1⁺ fibroblasts, and improved histologic fibrosis. Direct THBS1 inhibition produced similar antifibrotic effects. *In vitro*, THBS1 knockdown or blockade suppressed TGF- β 1-induced fibroblast activation and reduced LPS-stimulated IL-1 β and IL-6 production in macrophages, supporting reciprocal THBS1-dependent stromal-immune signaling.

Conclusions: THBS1 functions as a shared signaling mediator between fibroblasts and macrophages in MASH. Therapeutic suppression of THBS1, either through nintedanib or direct inhibition, disrupts this fibroinflammatory circuit and may represent a viable strategy to limit fibrosis progression in MASLD/MASH.

Keywords: Thrombospondin-1, Nintedanib, Fibroblast Activation, Metabolic Dysfunction-Associated Steatohepatitis

OP-10

Zonation-Dependent Enrichment and Spatial Remodeling of Intrahepatic CD3⁺ T Cells in MASLD Fibrosis

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Aims: Increased intrahepatic T-cell infiltration is reported in metabolic dysfunction-associated steatotic liver disease (MASLD), yet stage-dependent redistribution across hepatic microdomains remains unclear. We quantified portal versus central CD3⁺ T-cell density across fibrosis stages and performed stage-spanning spatial transcriptomic profiling to assess zonation-related transcriptional changes in T cell-enriched regions.

Methods: Human MASLD liver biopsies spanning fibrosis stages F0–F4 were analyzed by CD3 immunohistochemistry (F0 n=5; F1 n=17; F2 n=9; F3 n=4; F4 n=4). CD3⁺ cell density was quantified per 20,000 μ m² using predefined regional criteria. Portal density was calculated as the mean of 3–5 anatomically defined portal regions per biopsy. Central density was assessed only when identifiable (0–2 regions per biopsy) and summarized from available regions. Spatial transcriptomics was performed on biopsies spanning F1–F4 (one specimen per stage; n=4). Analyses compared early (F1–F2) and advanced fibrosis (F3–F4), including pseudo-bulk differential expression in T cell-enriched regions.

Results: Portal CD3⁺ cell density increased across fibrosis stages, whereas central density, where evaluable, showed a modest rise. In the spatial cohort (n=4), advanced fibrosis was associated with architectural distortion and reduced he-

patocyte metabolic zonation features. T cell-enriched regions in advanced-stage samples showed transcriptional patterns consistent with reduced hepatocyte metabolic programs and increased immune- and extracellular matrix-related signatures, with deconvolution suggesting greater immune and fibroblast-associated signals in specific zones. Portal enrichment by quantitative IHC aligned with spatial remodeling of zonation-associated programs in advanced fibrosis.

Conclusions: Integrating quantitative histology with stage-spanning spatial profiling, MASLD fibrosis progression is associated with portal CD3⁺ T-cell enrichment and zonation-related transcriptional remodeling in advanced disease. These findings support spatial reorganization of immune-fibrotic microenvironments and warrant validation in larger cohorts.

Keywords: MASLD, Spatial Transcriptomics, Intrahepatic T Cells, Microenvironment

OP-11

Establishment of a CO₂-Independent Platform for iPSC-Derived Hepatocyte Differentiation to Enable 3D Bioprinting in Space

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Aims: Chronic liver diseases remain a major cause of global morbidity and mortality, while the limited availability of donor organs continues to restrict liver transplantation as a definitive treatment. Engineered liver tissues via 3D bioprinting offer a promising alternative, but gravity-induced scaffold collapse and cell sedimentation hinder application on Earth. Although microgravity environments can mitigate these challenges, conventional CO₂-dependent culture systems are incompatible with enclosed spaceflight environments.

Methods: We established a CO₂-independent differentiation protocol for generating hepatocyte-like cells (HLCs) from human iPSCs using L-15 medium with optimized cytokines and supplements. Hepatic differentiation was evaluated by hepatic marker expression (ALB, HNF4A), metabolic function assays including ICG uptake and PAS staining. In parallel, iPSC-derived HLC spheroid generation protocol was established to enhance cell viability within bio-inks, and functionality and stability were evaluated under launch-simulated conditions.

Results: HLCs generated under CO₂-independent conditions exhibited differentiation efficiency and hepatic marker expression comparable to those produced under CO₂-dependent conditions. Hepatocyte-specific metabolic functions were preserved, as demonstrated by ICG uptake and PAS staining. Notably, iPSC-derived HLC spheroid encapsulated in the optimized bio-ink maintained high cell viability and structural

integrity under simulated launch conditions, outperforming conventional bio-ink formulations.

Conclusions: Our findings demonstrate that functional HLCs can be generated under CO₂-independent conditions and that an iPSC-derived HLC spheroid platform enhances bio-ink viability and stability under launch-simulated conditions. This platform establishes a practical foundation for microgravity-adapted 3D bioprinting and expands the feasibility of engineering transplantable liver tissues in CO₂-limited environments, including space.

Keywords: iPSC-Derived Hepatocyte, CO₂ Independent Culture, BIO-INK

Friday, June 12, 2026, 16:20-17:10

3. MASLD & ALD, Clinical

OP-12

Patterns of Alcohol Consumption and Clinical Spectrum of Alcohol-Related Liver Disease in a Rural Setting in Nepal: A Hospital-Based Study

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Aims: Alcohol consumption is common in Nepal, where alcoholic beverages are widely available and alcohol use is culturally integrated into many community and festival practices. Regular alcohol intake, particularly among farmers and small business workers who frequently consume alcohol after work, contributes to the burden of alcohol-related liver disease (ALD). However, data describing alcohol consumption patterns and the clinical spectrum of ALD in rural Nepal remain limited. This study aimed to evaluate patterns of alcohol use and the clinical spectrum of ALD in a resource-limited rural healthcare setting.

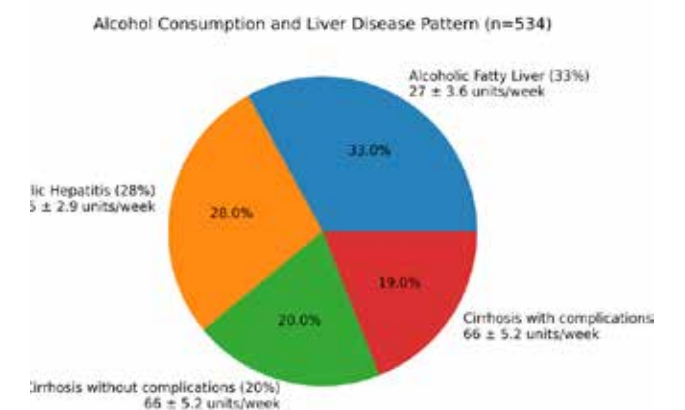
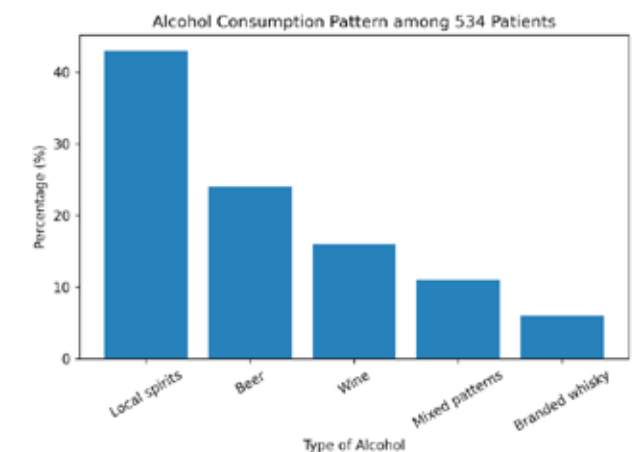
Methods: A hospital-based observational study was conducted at Mediplus Hospital, Nepal, from May 1, 2025 to October 30, 2025. Patients with a history of significant alcohol consumption (>40 g/day in men and >20 g/day in women for at least 5 years) meeting inclusion criteria were enrolled. Data regarding demographic characteristics, type of alcohol consumed, and weekly alcohol intake (in alcohol units) were recorded. Patients were categorized into alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis with or without complications. A total of 534 patients with alcohol-related liver disease were included in the final analysis. Statistical analysis was performed using SPSS version 25.0.

Results: A total of 553 patients were initially enrolled, of whom

534 met the inclusion criteria and were analyzed. The mean age of patients was 49 $\pm$ 3.5 years, and the majority were male (66%). Alcoholic fatty liver was observed in 33% of patients, alcoholic hepatitis in 28%, alcoholic cirrhosis without complications in 20%, and cirrhosis with complications in 19%. Local spirits were the most commonly consumed beverage (43%), followed by beer (24%), wine (16%), mixed patterns of alcohol consumption (11%), and branded whisky (6%). Mean weekly alcohol consumption increased with disease severity: fatty liver 27 $\pm$ 3.6 units/week, alcoholic hepatitis 42.5 $\pm$ 2.9 units/week, and cirrhosis 66 $\pm$ 5.2 units/week. A significant association was observed between higher alcohol intake and increasing severity of liver disease ($P < 0.001$).

Conclusions: Alcohol-related liver disease represents a major health burden in rural Nepal. Increasing alcohol intake is significantly associated with more advanced liver disease. These findings highlight the need for alcohol control strategies and early screening programs in rural communities.

Keywords: Alcoholic Beverages, Alcohol-Related Liver Disease, Cirrhosis, Significant Consumption



OP-13

Clonal Hematopoiesis of Indeterminate Potential and Metabolic Dysfunction-Associated Steatotic Liver Disease: Comprehensive Analysis of Biopsy-Proven Cohorts

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Aims: Clonal hematopoiesis of indeterminate potential (CHIP) has emerged as a potential contributor to the pathogenesis of complex age-related diseases; however, its clinical relevance to metabolic liver disease remains to be established. This study investigated the association between CHIP and metabolic dysfunction-associated steatotic liver disease (MASLD) severity in a well-characterized, biopsy-proven cohort.

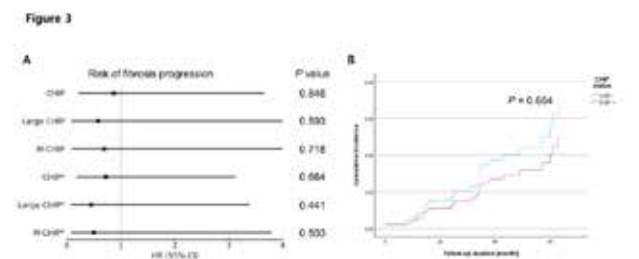
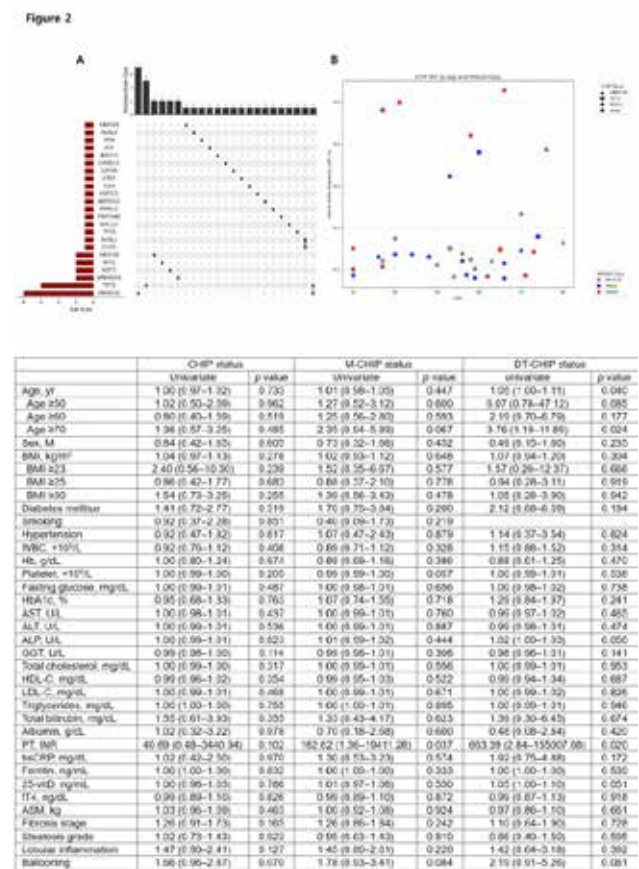
Methods: We conducted a prospective analysis of 486 patients with clinically suspected MASLD who underwent liver biopsy and whole genome sequencing at Seoul Metropolitan Government Boramae Medical Center between 2014 and 2023. CHIP variants were identified using stringent bioinformatics pipelines with a threshold of variant allele frequency $\geq 2\%$. Histological assessment was performed using the NASH-CRN scoring system. Logistic regression was used for cross-sectional associations, and Cox proportional hazards models were applied for fibrosis progression outcomes.

Results: Among 427 eligible participants (median age 56 years), 37 (8.7%) harbored pathogenic CHIP variants, predominantly in *DNMT3A* ($n=8$) and *TET2* ($n=6$). CHIP prevalence did not differ significantly across histological categories: no steatotic liver disease (10.9%), metabolic dysfunction-associated steatotic liver (6.5%), and metabolic dysfunction-associated steatohepatitis (10.9%; $P=0.269$). No clinical or histological variable was consistently associated with CHIP status in univariate or sensitivity analyses. Over a median follow-up of 28 months, fibrosis progression occurred in 28 of 287 patients with serial assessments; no significant association with CHIP status was observed (HR 0.72, 95% CI 0.17–3.12; $P=0.664$).

Conclusions: In this Korean biopsy-proven MASLD cohort, CHIP was not associated with hepatic histological severity or fibrosis progression. These findings contrast with established CHIP–cardiovascular disease relationships and underscore the con-

text-dependent nature of CHIP’s clinical impact. Longer-term longitudinal studies with larger sample sizes are warranted to fully elucidate CHIP’s role in metabolic liver disease.

Keywords: Clonal Hematopoiesis of Indeterminate Potential, Liver Fibrosis, Metabolic Dysfunction-Associated Steatotic Liver Disease



OP-14

Trends in the Prevalence of Steatotic Liver Disease and Its Subtypes in Korea: A Nationwide Population-Based Study (2007–2023)

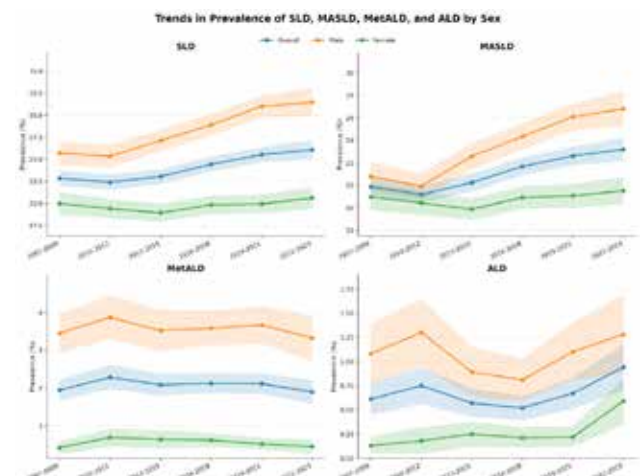
Sang Hun Park^{1,3}, Min Na Kim², Jun Sik Yoon³, Sung Jae Park³, Youn Jae Lee³

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Aims: The concept of steatotic liver disease (SLD) has recently been proposed as a new classification encompassing metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD). However, population-based epidemiologic data using this new definition remain limited. We aimed to evaluate the prevalence and temporal trends of SLD and its subtypes in Korea using nationally representative data.

Methods: We analyzed data from the Korea National Health and Nutrition Examination Survey (KNHANES) from 2007 to 2023. Adults aged ≥ 18 years were included. Participants with a history of malignancy, those without sufficient data to calculate the hepatic steatosis index (HSI), and those without alcohol consumption history were excluded. SLD was defined as hepatic steatosis with an HSI ≥ 36 . Participants were classified into MASLD, MetALD, or ALD according to the new SLD criteria. Sampling weights were applied to obtain nationally representative estimates.

Results: A total of 20,987 participants were included (49.4% male; median age 51 years [IQR 38–63]). The prevalence of SLD increased from 22.84% (95% CI, 21.97–23.71) in 2007–2009 to 26.07% (95% CI, 24.99–27.15) in 2022–2023 (Figure 1). Similarly, the prevalence of MASLD increased from 19.89% (95% CI, 19.10–20.68) to 23.18% (95% CI, 22.14–24.22) over the same period. In contrast, the prevalence of MetALD (1.94% to 1.89%) and ALD (0.61% to 0.94%) remained relatively stable throughout the study period. Male participants consistently showed a higher prevalence of all SLD subtypes than females, with the increase in MASLD being particularly prominent among men.



Conclusions: In this nationwide population-based study, the prevalence of SLD and MASLD in Korea has steadily increased over the past 15 years, whereas the prevalence of MetALD and ALD has remained relatively stable. These findings suggest that the rising burden of SLD in Korea is largely driven by metabolic dysfunction-associated liver disease.

Keywords: Steatotic Liver Disease, Prevalence, Metabolic Dysfunction-Associated Steatotic Liver Disease

OP-15

Multiparametric Ultrasound for the Evaluation of MASLD: An Individual Patient Data Meta-Analysis and External Validation of Prediction Models for MASH and At-Risk MASH

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Aims: Non-invasive assessment of metabolic dysfunction-associated steatotic liver disease (MASLD) is crucial for clinical management. We conducted an individual patient data (IPD) analysis to evaluate the diagnostic performance of multiparametric ultrasound combining attenuation imaging (ATI) and 2D shear-wave elastography (2D-SWE) for liver stiffness (LS) and shear wave dispersion slope (SWDS) and to develop prediction models for MASH and at-risk MASH.

Methods: Published studies using multiparametric ultrasound incorporating ATI (attenuation coefficient, dB/cm/MHz) and 2D-SWE including SWDS ([m/s]/kHz) and LS (kPa) with histopathology as reference were systematically identified. IPD from 13 centers ($n=485$) were analyzed using one-stage mixed-effects modeling. Optimal cut-offs were determined by maximizing the Matthews correlation coefficient. Prediction models for MASH and at-risk MASH were derived from the IPD analysis and validated internally via leave-one-study-out cross-validation. External validation was performed in an independent prospective cohort ($n=119$).

Results: Optimal cut-offs were 0.62, 0.70, and 0.78 dB/cm/MHz for $\geq S1$, $\geq S2$ and $\geq S3$ steatosis; 10.6, 11.6, and 11.8 [m/s]/kHz for $\geq I1$, $\geq I2$, and $\geq I3$ inflammation; and 5.6, 7.3, 7.9, and 10.3 kPa for $\geq F1$, $\geq F2$, $\geq F3$ and $\geq F4$ fibrosis. Pooled AUCs ranged from 0.78–0.93 across histologic grades. The prediction model for MASH incorporated attenuation coefficient >0.62 dB/cm/MHz and SWDS >10.6 [m/s]/kHz. The at-risk MASH prediction model additionally required LS >7.3 kPa indicating the presence of $\geq F2$. For MASH detection, AUCs were 0.707 (internal) and 0.801 (external). For at-risk MASH, AUCs were 0.791 and 0.982, respectively.

Conclusions: Multiparametric ultrasound enables a comprehensive and non-invasive assessment of MASLD. The IPD-derived prediction models demonstrate robust performance in identi-

fying MASH and at-risk MASH, providing a validated framework to assist in selecting candidates for confirmatory liver biopsy.

Keywords: MASLD, Mutliparametric Ultrasound, Attenuation Imaging, Shear Wave Elastography

OP-16

Referral Burden and Second-Tier Testing in Two-Step Algorithms for Detecting Significant Hepatic Fibrosis among Asian Community-Based Type 2 Diabetes Mellitus

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Aims: Current guidelines recommend a FIB-4 based two-step screening algorithm for hepatic fibrosis in type 2 diabetes mellitus (T2DM). We evaluated the social burden (need 2nd tier testing (%), referral rate, missing rate, and false-positive rate of 1st tier test) of two-step algorithm for significant hepatic fibrosis in community-based T2DM cohorts.

Methods: We analyzed data from three Asian community-based health check-up cohorts comprising 3,152 individuals with T2DM assessed using vibration-controlled transient elastography or magnetic resonance elastography.

Results: The prevalence of significant hepatic fibrosis (≥F2) among individuals with T2DM ranged from 4.3% to 18.3%, and advanced fibrosis (≥F3) from 0.9% to 7.4%. Using the two-step algorithm based on age-adjusted FIB-4, 22.3–29.0% required 2nd tier testing, and 11.2–12.7% required hepatology referral. However, the FIB-4 model showed low sensitivity (54.9–58.1%), with a high negative rate of 2nd tier testing in the intermediate-risk group (72.6–100%). Lowering the FIB-4 threshold increased 2nd tier testing and referrals without improving sensitivity. In contrast, strategies based on NFS and MAF-5 tended to overclassify risk, resulting in higher rates of 2nd tier testing and referrals, whereas the LiverRisk score tended to underclas-

sify risk, showing low sensitivity.

Conclusions: In Asian community-based cohorts, the FIB-4-based two-step algorithm demonstrated acceptable 2nd tier testing and referral rates but low sensitivity and a high negative rate of 2nd tier testing in individuals with T2DM for detecting significant hepatic fibrosis.

Keywords: T2DM, Referral, Two Step Algorithm

Friday, June 12, 2026, 16:20-17:20

4. LC, Liver Failure & Autoimmune Diseases 1

OP-17

Impact of Glycemic Control on Liver-Related Events in Patients with Hepatitis B Virus-Related Cirrhosis and Type 2 Diabetes Mellitus

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Aims: Diabetes mellitus (DM) is highly prevalent among patients with cirrhosis and is associated with adverse outcomes. However, the specific impact of glycemic control on liver-related events (LREs) in patients with hepatitis B virus (HBV)-related cirrhosis remains unclear.

Methods: This retrospective cohort study included 2,130 patients with HBV-related cirrhosis receiving antiviral therapy at a tertiary care center in Korea. Patients were classified into three groups based on their follow-up HbA1c levels: non-DM (n=1,706), well-controlled DM (<7.0%; n=281), and poorly-controlled DM (≥7.0%; n=143). The primary outcome was LRE, defined as hepatic decompensation or liver transplantation. Secondary outcomes included hepatocellular carcinoma (HCC) and a composite of HCC or LRE.

Results: During a median follow-up period of 69.9 months, 256 patients (12.0%) developed LRE. Among diabetic patients, the poorly-controlled group showed a significantly higher incidence of LRE compared to the well-controlled group (25.2% vs. 15.7%; $P=0.013$), whereas the incidence of HCC did not differ significantly between the two diabetic groups ($P=0.404$). In multivariable Cox regression, poorly-controlled DM was independently associated with a 74% increased risk of LRE (HR 1.74; 95% CI 1.12–2.70; $P=0.013$). A significant interaction was observed for sex (P -interaction=0.028), with the risk being particularly pronounced in male patients (hazard ratio [HR] 4.40; 95% confidence interval [CI] 1.57–12.39; $P=0.005$). Among LRE subtypes, the incidence of hepatorenal syndrome was signifi-

cantly higher in the poorly-controlled group (3.5% vs. 0.4%, $P=0.031$).

Conclusions: In patients with HBV-related cirrhosis and DM, poor glycemic control is independently associated with an increased risk of LRE, particularly in males. Optimizing glycemic control is a vital strategy to reduce severe decompensation events, such as hepatorenal syndrome, in this population.

Keywords: Hepatitis B, Chronic, Liver Cirrhosis, Diabetes Mellitus, Type 2

OP-18

Hepatic Safety and Clinical Outcomes of Fexuprazan Compared with Proton Pump Inhibitors in Patients with Liver Cirrhosis

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Aims: Acid suppressants are frequently prescribed in patients with liver cirrhosis, but concerns remain regarding their hepatic safety and clinical outcomes. Fexuprazan, a novel potassium-competitive acid blocker, has limited safety data in cirrhotic patients. We aimed to compare hepatic safety and liver-related clinical outcomes between fexuprazan and conventional proton pump inhibitors (PPIs) in patients with liver cirrhosis.

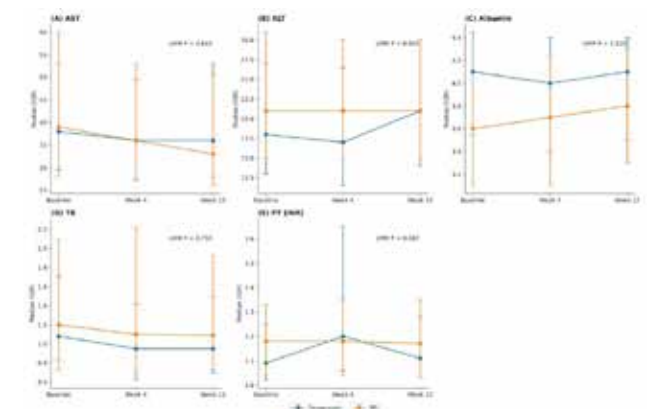
Methods: This comparative cohort study included a prospectively enrolled fexuprazan group and a conventional PPI group prescribed during a comparable period. A total of 287 patients with liver cirrhosis were included, comprising 99 patients treated with fexuprazan and 188 treated with conventional PPIs. Serial liver function parameters were assessed at baseline, week 4, and week 12 using linear mixed-effects models. Liver-related outcomes during the 12-week follow-up were analyzed using multivariable logistic regression, and propensity score matching was performed as a sensitivity analysis.

Results: The mean age was 61.5 years, and 64.1% of patients were male. At baseline, the fexuprazan group had higher albumin levels and lower ALT levels than the PPI group. Linear mixed-effects model analyses revealed no significant group-by-time interactions for AST, ALT, albumin, total bilirubin, or PT (all $P>0.05$; Figure 1). In multivariable analyses, there were no significant differences between the groups in the risks of ascites (adjusted OR, 0.91; 95% CI, 0.37-2.27), hepatic encephalopathy (adjusted OR, 0.39; 95% CI, 0.08-1.94), composite liver-related outcomes (adjusted OR, 1.20; 95% CI, 0.34-4.22),

or death (adjusted OR, 3.22; 95% CI, 0.57-18.23). After PSM (81 pairs), outcomes remained comparable between groups.

Conclusions: Fexuprazan showed hepatic safety and liver-related clinical outcomes comparable to those of PPIs in patients with liver cirrhosis.

Keywords: Fexuprazan, Proton Pump Inhibitor, Liver Cirrhosis, Complication



OP-19

The Paradigm Shift toward DOACs in Liver Cirrhosis: A Longitudinal Analysis of Prescription Dynamics and Clinical Outcomes

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Aims: Since the mid-2010s, the introduction of direct oral anticoagulants (DOACs) has fundamentally transformed the landscape of anticoagulation. This study aimed to analyze 10-year trends in anticoagulant prescription patterns among patients with liver cirrhosis and to compare the risks of major bleeding and liver-related complications between warfarin and DOACs, particularly in high-risk clinical settings.

Methods: Using the Korean National Health Insurance database (2015–2022), we conducted a retrospective cohort study including 15,197 patients with liver cirrhosis who received oral anticoagulants (warfarin, n=2,661; DOACs, n=12,536). Patients were categorized into two indication groups: Indication 1 (cardioembolic) and Indication 2 (liver- or cancer-related thrombosis). Prescription patterns were analyzed according to clinical characteristics, including portal vein thrombosis (PVT), hepatocellular carcinoma (HCC), and hepatic decompensation. Hazard ratios (HRs) for major bleeding and liver-related complications were estimated.

Results: DOAC prescriptions increased markedly after 2015 and progressively surpassed warfarin prescriptions over time. Despite this shift, warfarin remained more frequently prescribed in patients with advanced disease features, including PVT, HCC, and decompensated cirrhosis, suggesting the presence of a severity-related prescribing bias. Overall, DOAC use was associated with a significantly lower risk of major bleeding compared with warfarin. Among DOAC agents, edoxaban consistently demonstrated the lowest bleeding risk across both indication groups. In Indication 2, edoxaban reduced the risk of major bleeding by 48% compared with warfarin (HR 0.52, 95% CI 0.41–0.65; $P < 0.001$). In addition, DOAC therapy was associated with significantly lower risks of liver-related complications, including hepatic encephalopathy, ascites-related complications, and variceal bleeding. Notably, edoxaban reduced liver-related complications by nearly 45% in Indication 2 (HR 0.55, 95% CI 0.46–0.65; $P < 0.001$).

Conclusions: Our findings indicate that DOACs—particularly edoxaban—offer significantly lower bleeding risks and superior prevention of liver-related complications. These results suggest that DOACs are a safe and effective alternative even in high-risk cirrhosis, warranting further validation through randomized controlled trials (RCTs).

Keywords: Anticoagulants, Direct Oral Anticoagulants, Liver Cirrhosis, Hemorrhage

OP-20

Integrative Signed Network and Literature Mining Framework Identifies Novel Molecular Regulators of Liver Fibrosis

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Aims: Liver fibrosis is a complex chronic disease driven by multi-layered molecular interactions, yet many genes functionally involved in the progression of liver fibrosis remain insufficiently characterized. Conventional gene discovery approaches often focus on genes that have already been extensively studied, which can cause less-studied but biologically important regulators to receive comparatively less attention.

Methods: To address this limitation, we developed a signed network-based analytical framework integrating large-scale literature mining with network topology-aware gene prioritization. Gene-gene interactions related to liver cirrhosis were systematically extracted from PubMed using automated text-mining and classified into positive (activating) and negative (suppressive) regulatory associations. Direction-specific interaction networks were constructed, and hidden gene candidates were prioritized using a composite scoring scheme

incorporating network proximity to fibrosis-associated seed genes, exclusion of hub and seed nodes, and a literature-informed novelty penalty. The stability of candidate prioritization was examined by applying literature subsampling strategies, perturbation of seed inputs, and null modeling adjusted for network degree distribution.

Results: The prioritization framework consistently identified candidate genes that were functionally embedded within cirrhosis-related interaction networks yet lacked extensive prior characterization. Intensive analyses demonstrated stable candidate rankings across multiple perturbation scenarios. The resulting hidden gene signatures effectively discriminated fibrotic from control samples in independent mouse bulk and single-cell transcriptomic datasets. Importantly, these signatures were further validated in independent human liver cirrhosis cohorts, showing reproducible discriminatory performance across species.

Conclusions: Collectively, our results demonstrate that signed network-based prioritization enables systematic identification of under-characterized molecular regulators of liver cirrhosis. This framework provides a complementary strategy to conventional gene discovery approaches and may be broadly applicable to other complex chronic diseases characterized by regulatory heterogeneity.

Keywords: Liver Fibrosis, Large Language Model, Genetic Association, Reasoning Model

OP-21

SE-1 Antibody-Mediated Surface Engineering of MSC-Derived Exosomes Enables Selective Targeting of Liver Sinusoidal Endothelial Cells

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Aims: Liver sinusoidal endothelial cells (LSECs) play a central role in hepatic fibrosis and represent a promising target for liver-directed nanotherapeutics. This study aimed to develop and validate an antibody-mediated surface engineering strategy to selectively direct mesenchymal stem cell (MSC)-derived exosomes to LSECs using SE-1 antibody conjugation.

Methods: MSC-derived exosomes were purified and characterized by nanoparticle tracking analysis (NTA). Surface modification was performed via PEG(2000)-maleimide post-insertion chemistry to conjugate either SE-1 antibody or control IgG to exosome membranes. Particle concentration and size distribution were assessed by NTA, and surface charge changes were evaluated by zeta potential analysis to confirm successful engi-

neering.

For targeting assessment, DiD-labeled naïve exosomes, IgG-conjugated exosomes, and SE-1-conjugated exosomes were incubated with freshly isolated primary mouse LSECs at a defined particle-to-cell ratio. Cellular uptake was quantified by flow cytometry after 4 hours of incubation.

Results: Purified naïve exosomes exhibited a concentration of 1.89×10^{12} particles/mL. Following surface engineering, particle concentrations were 8.4×10^{10} particles/mL for IgG-PEG-exosomes and 8.77×10^{11} particles/mL for SE-1-PEG-exosomes. Zeta potential analysis demonstrated a shift toward a less negative surface charge (-9.6 mV), consistent with successful antibody incorporation.

Flow cytometric analysis revealed significantly enhanced uptake of SE-1-conjugated exosomes by primary LSECs compared to naïve and IgG-conjugated controls. SE-1-treated cells showed a marked rightward shift in fluorescence intensity and increased mean fluorescence intensity, indicating selective and antibody-dependent targeting.

Conclusions: SE-1 antibody-mediated surface engineering enables selective targeting of MSC-derived exosomes to primary LSECs. This platform provides a robust and reproducible strategy for LSEC-directed delivery and highlights the therapeutic potential of antibody-guided exosome systems for anti-fibrotic applications.

Keywords: Liver Sinusoidal Endothelial Cells, MSC-Derived Exosome, Selective Targeting

OP-22

An Investigation into the Effects of Microplastic Exposure on Hepatic Function through Hydro-Dynamic Injection

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Aims: The widespread environmental presence of microplastics has raised significant concerns regarding their potential impact on human health. This study aims to investigate the pathophysiological effects of microplastic exposure on hepatic function, specifically examining how systemic delivery via hydro-dynamic tail vein injection (HTVI) influences liver homeostasis and cellular integrity.

Methods: In this study, mouse models were subjected to GFP-labeled microplastics (GFP-MPs) delivered through HTVI. The intrahepatic localization of GFP-MPs was visualized using immunofluorescence (IF) microscopy on liver sections. Hepatic function was assessed through plasma biochemical markers.

To evaluate structural changes, H&E staining was performed. Furthermore, cytokine array analysis was conducted to identify systemic inflammatory responses affected by microplastic exposure.

Results: Immunofluorescence imaging clearly visualized the presence and distribution of GFP-MPs within the liver parenchyma, confirming successful systemic delivery and accumulation. Microplastic exposure led to a significant elevation in both plasma Bilirubin and ALT levels. H&E staining revealed signs of localized inflammatory infiltration in the microplastic-exposed group. Cytokine array analysis surprisingly identified a global downregulation of pro-inflammatory markers and chemokines.

Conclusions: These results demonstrate that acute exposure to microplastics through HTVI adversely affects hepatic function and induces inflammatory damage. The integration of histopathological data underscores the potential hepatotoxicity of microplastics, emphasizing the need for further research into the long-term consequences of plastic particle accumulation.

Keywords: Microplastic, Hyrdodynamic Tail-Vein Injection, Liver

Friday, June 12, 2026, 16:20-17:20

5. Liver Transplantation

OP-23

Pink1/Parkin Signaling Regulates Liver Regeneration by Modulating Sigma-1 Ubiquitination and Hepatocyte Succinate Production

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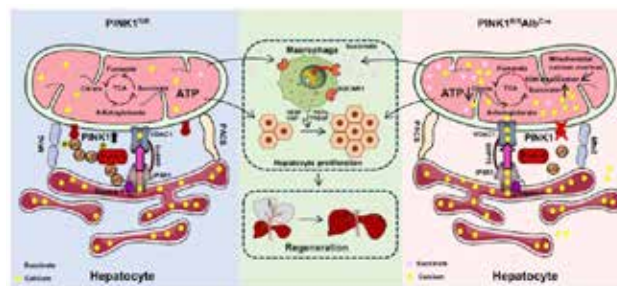
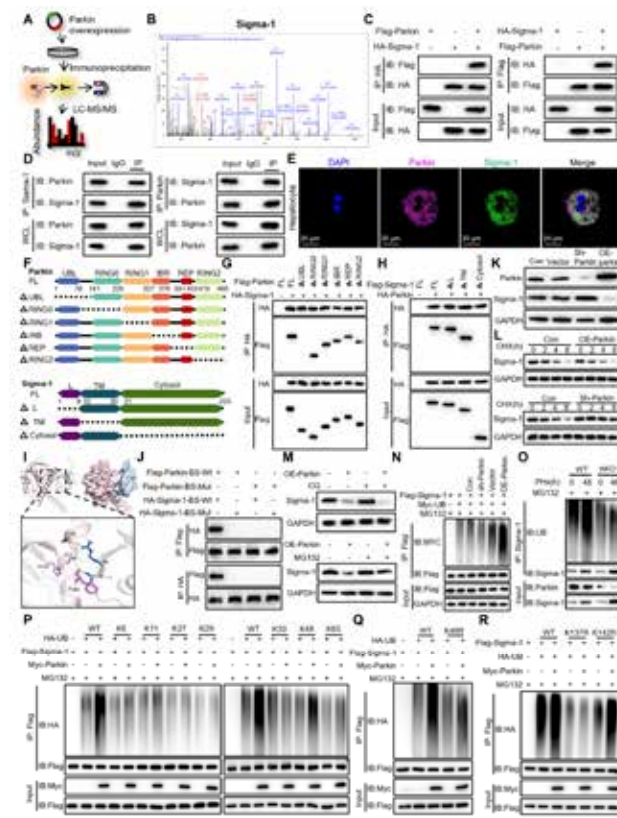
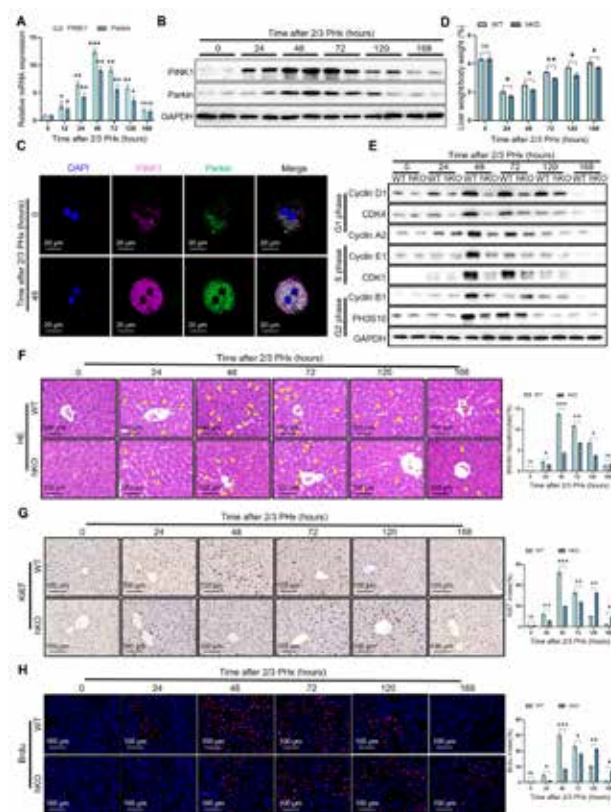
Aims: Liver regeneration is regulated by both metabolic processes and immune responses. Nonetheless, there is limited comprehension of the mechanisms involved. PINK1/Parkin-mediated mitophagy has been well documented, the role and underlying alternative mechanism of PINK1/Parkin in regulating mitochondrial metabolism during liver regeneration remains unclear.

Methods: Liver tissues from mice undergoing hepatectomy were utilized to evaluate the expression levels of PINK1/Parkin. Hepatocyte-specific PINK1 knockout and transgenic mouse models were generated to investigate the impact of PINK1 on regeneration. Mass spectrometry, co-immunoprecipitation, and ubiquitination assays were performed to explore the underlying molecular mechanisms.

Results: We observed PINK1/Parkin expression was markedly

upregulated in hepatic tissue following liver resection. PINK1 depletion in hepatocytes caused impaired liver regeneration. Moreover, mitochondrial calcium overload was found be responsible for restricted TCA by inhibiting succinate dehydrogenase activity in PINK1 deficient hepatocytes. Interestingly, PINK1 deficiency leads to succinate accumulation and release from hepatocytes, which impairs liver regeneration by restricting macrophage pro-repair phenotypes. This effect was further confirmed by enhanced regeneration in myeloid SUCNR1 knock-out mice. Mechanistically, Sigma-1 is a molecular chaperone of the endoplasmic reticulum calcium channel IP3R, which helps maintain its normal functional conformation. Parkin was able to bind Sigma-1 through its UBL domain, facilitating its k48-linked ubiquitination, which promotes Sigma-1 degradation and subsequently suppressing calcium transfer from the ER to mitochondria at the mitochondrial-associated ER membrane.

Conclusions: Our findings unveil a non-canonical role for PINK1/Parkin in linking organelle communication to metabolic-immune crosstalk during liver regeneration. Mechanistically, Parkin-mediated ubiquitination and degradation of Sigma-1 modulate ER-mitochondria calcium flux to maintain TCA cycle fidelity. This prevents aberrant succinate accumulation, which otherwise acts as a potent metabo-immune checkpoint via macrophage SUCNR1 to impede regeneration. Thus, the PINK1/Parkin-Sigma-1 axis is a crucial guardian of mitochondrial-metabolic fitness, offering new therapeutic avenues.



Keywords: Liver Regeneration, Hepatocytes, Macrophages, Metabolism

OP-24

Aspartate Aminotransferase (AST) Level on Day 4 as a Predictor of Steroid Response in Biopsy Proven Rejection after Liver Transplantation

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Aims: To identify biochemical predictors of response to corticosteroids used in the treatment of acute rejection with particular focus on the Aspartate aminotransferase (AST) as a dynamic

marker of early treatment response.

Methods: A retrospective analysis of biopsy-proven rejections between January 2021 to Oct 2025 was conducted and we included all types of T cell Mediated Rejection (Mild to moderate TCMR, moderate to severe TCMR, severe TCMR, late TCMR, Early chronic and Chronic rejection). Each recipient had received injection methyl prednisolone 500 mg to 1gm as pulse every day for 3 to 5 days. Biochemical parameters (LFT) were collected from Day 0 to Day 5, at 1 week, 1 month, 3 months, 12 months and last follow up. Biochemical response was assessed at thresholds of >25%, >50%, and >75% AST reduction from baseline. ROC analysis was done to evaluate the level of AST values and the corresponding post pulse day which shows maximum predictive accuracy for treatment response. Baseline clinical characteristics, liver biochemistry, and rejection category were compared between responders and non-responders. Survival at last follow-up was documented.

Results: We analysed 21 post liver transplant patients who developed biopsy proven rejection. Mean age was 43.4 ± 16.2 years. M:F ratio of 16:5 with 76% being male. LDLT constituted 95% of transplants. Mild - moderate TCMR, moderate-severe TCMR, severe TCMR, late TCMR, early chronic rejection and chronic rejection were comprising 9.52%, 47.61%, 9.52%, 9.52%, 19.04% and 4.76, respectively. Biochemical response rates differed across thresholds: 10/21 (47.6%) at >25%, 9/21 (42.9%) at >50%, and 2/21 (9.5%) at >75% AST reduction. Day-4 AST showed the strongest predictive capability, with AUROC 0.882 (SE 0.086, $P < 0.001$; 95% CI 0.714–1.00). Days 0-3 and 5 showed lower discrimination (AUROC 0.595–0.800). Recipients were grouped as responders $n=9$ and non responders $n=12$ based on >50 % reduction in AST values on day 4. AST trends diverged significantly from Day 2 onwards, with responders showing rapid and sustained AST reduction, while non-responders showed persistently elevated values. Responders had higher baseline elevated bilirubin (12.1 ± 5.5 mg/dL vs 7.1 ± 8.7 mg/dL) and ALT (354.8 ± 295.6 IU/L vs 212.5 ± 127.3 IU/L) compared with non-responders. Non-responders had higher ALP (330.5 ± 458.2 IU/L vs 183.1 ± 160.4 IU/L in responders. Where as GGT was equivocal in both the groups 366.2 ± 712.4 vs 475.5 ± 608.3 . Responders mostly included moderate to severe TCMR while non-responders showed a broader rejection spectrum. Baseline clinical variable, demographics including age, gender, rejection phenotypes or steroid pulsing does not predict therapy response ($P > 0.05$). Survival at last follow-up was 77.8% vs 58.3% with mortality of 22.2% vs 33.3% in responders and non responders respectively.

Conclusions: More than 50 % reduction in AST on day 4 is a strong early biochemical marker of steroid-pulse response and will help in early identification of steroid-refractory rejection which facilitates early use of second-line immunomodulatory strategies. Larger prospective studies are needed to validate these findings.

Keywords: Liver Transplantation, T Cell Mediated Rejection, Aspartate Aminotransferase (AST), Steroid Response

OP-25

Recurrent Autoimmune Hepatitis after Liver Transplantation in a Young Woman: A Case Report with Histological Overlap of Chronic Rejection

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Aims: To report a case of recurrent autoimmune hepatitis after liver transplantation in a young woman and to highlight established risk factors for recurrence, including high pre-transplant IgG levels, early post-transplant mycophenolate mofetil use, reduction of immunosuppression, and postpartum immune modulation.

Methods: A retrospective clinical analysis was conducted of a female patient with autoimmune hepatitis who underwent living-donor liver transplantation. Pre-transplant immunologic profile, post-transplant IgG dynamics, modifications of immunosuppressive therapy, and histopathological findings of graft biopsy were reviewed.

Results: A 37-year-old woman underwent living-donor liver transplantation for autoimmune hepatitis-related cirrhosis. Prior to transplantation, she demonstrated markedly elevated IgG levels, reflecting high immunologic disease activity. Early post-transplant immunosuppression included tacrolimus and mycophenolate mofetil during the first year after transplantation. Mycophenolate mofetil was later discontinued due to severe leukopenia associated with hypersplenism, resulting in reduced immunosuppressive intensity.

During the postpartum period and following further reduction of immunosuppression, the patient developed biochemical evidence of hepatocellular injury along with a significant increase in IgG levels (up to 50 g/L), raising suspicion for disease recurrence. Liver graft biopsy revealed severe interface hepatitis with dense lymphoplasmacytic infiltration, focal ductopenia involving approximately 40% of portal tracts, and obliterative arteriopathy with fibrointimal thickening, consistent with recurrent autoimmune hepatitis with overlapping features of chronic rejection. Intensification of immunosuppressive therapy led to biochemical improvement.

Conclusions: Recurrent autoimmune hepatitis after liver transplantation remains a clinically significant complication, particularly in young female patients with high pre-transplant IgG levels. Early post-transplant mycophenolate mofetil exposure, reduction of immunosuppression, and postpartum immune modulation may contribute to disease recurrence. Careful

immunologic monitoring and timely histological assessment are essential to prevent graft dysfunction and progression to chronic injury.

Keywords: Recurrent autoimmune hepatitis, Liver transplantation, High pre-transplant IgG, Postpartum immune modulation

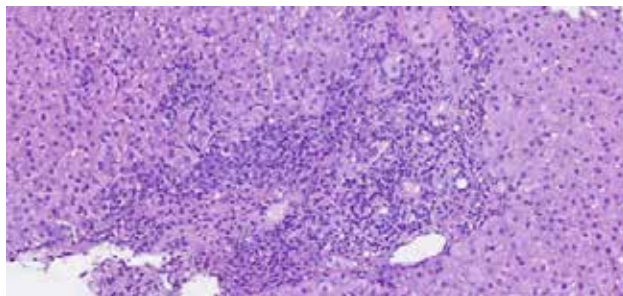


Figure1_Interface_Hepatitis_HEx2

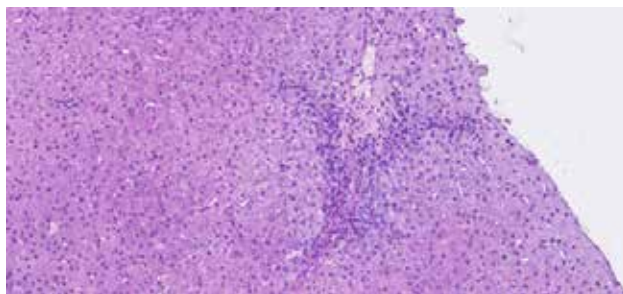


Figure2_Ductopenia_HEx20

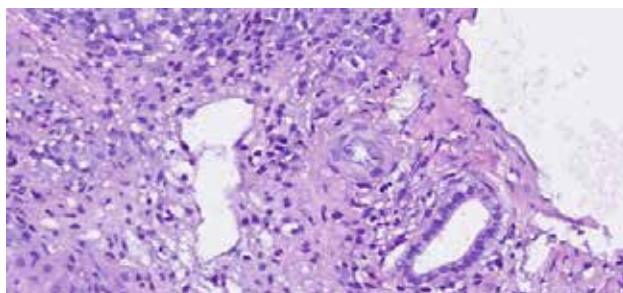


Figure3_Obliterative_Arteriopathy_HEx40

OP-26

Extra-Anatomical Portal Inflow Reconstruction Using Splanchnic and Collateral Veins in Living Donor Liver Transplantation for Portal Vein Thrombosis

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Aims: Extensive portal vein thrombosis (PVT) remains a major obstacle to living donor liver transplantation (LDLT), frequently requiring alternative portal inflow reconstruction. However, outcomes according to reconstruction strategy remain poorly defined.

Methods: We retrospectively analyzed 50 patients who underwent liver transplantation with alternative portal inflow reconstruction for extensive PVT. Patients were stratified into renoportal anastomosis, splanchnic vein-based, and collateral vein-based reconstruction groups. Operative characteristics, portal vein-related complications, and patient survival were evaluated.

Results: Among 50 patients, 43 (86.0%) underwent LDLT. Operative time exceeded 1,000 minutes in the renoportal and splanchnic vein-based groups. Interposition grafts were used in all renoportal cases and 88.9% of splanchnic vein-based cases but only 15.8% of collateral vein-based cases. Portal vein-related complications occurred in 40.0%, 44.4%, and 47.4% of patients in the renoportal, splanchnic vein-based, and collateral vein-based groups, respectively, with earlier onset after renoportal reconstruction and delayed presentation after splanchnic vein-based reconstruction. Overall mortality rates were 26.7%, 44.4%, and 15.8%, respectively. Patient survival at 1, 5, and 10 years was 80.0%, 73.3%, and 73.3% in the renoportal group, 88.9%, 61.0%, and 61.0% in the splanchnic vein-based group, and 94.7%, 88.0%, and 88.0% in the collateral vein-based group.

Conclusions: Physiological portal inflow reconstruction is essential for successful LDLT in extensive PVT. Alternative reconstruction using splanchnic and collateral veins can achieve durable outcomes with meticulous preoperative evaluation and advanced surgical expertise.

Keywords: PVT, LDLT, Portal Vein

OP-27

Safety and Feasibility of Left Lobe Graft in Living Donor Liver Transplantation: A Comparative Study with Right Lobe Graft

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Aims: Living donor liver transplantation (LDLT) primarily utilizes right lobe (Rt) grafts to ensure sufficient graft volume for recipients. However, donor safety remains the highest priority. This study aimed to evaluate the clinical efficacy and donor safety of left lobe (Lt) grafts compared to Rt grafts.

Methods: We retrospectively analyzed 418 living donors (Rt: n=372, Lt: n=46) who underwent LDLT between 2023 and 2025. Perioperative outcomes, donor recovery, and graft-to-recipient weight ratio (GRWR) were compared using the Mann-Whitney U test and Fisher's exact test.

Results: Between 2023 and 2025, a total of 418 living donors (Rt: n=372, Lt: n=46) were analyzed. Regarding donor safety, the Lt

group demonstrated superior recovery profiles, characterized by significantly lower peak total bilirubin (2.00 [1.65–2.60] vs. 3.00 [2.30–4.10] mg/dL, $P<0.001$) and peak INR (1.28 [1.22–1.36] vs. 1.58 [1.47–1.71], $P<0.001$) compared to the Rt group. Although the operative time was slightly longer in the Lt group (198 vs. 182 min, $P=0.042$), the incidence of major complications (Clavien-Dindo grade $> 3b$) did not differ significantly (4.3% vs. 5.9%, $P=1.000$), and the hospital stay was shorter for Lt donors (6 vs. 7 days, $P=0.016$). Notably, the Lt group maintained a substantially larger remnant liver volume (70.20% vs. 39.27%, $P<0.001$). From a recipient perspective, the Lt grafts provided a median field GRWR of 0.95 [0.74–1.15], which effectively met the clinical safety threshold of 0.8 in the majority of cases, confirming the functional feasibility of left lobe donation.

Conclusions: Left lobe donation is a safer alternative to right lobe donation, providing a significantly larger remnant liver volume and faster postoperative functional recovery for donors. Furthermore, Lt grafts provide an adequate graft volume (GRWR > 0.8) for recipients, suggesting that the use of Lt grafts should be more actively considered to maximize donor safety without compromising transplant outcomes.

Keywords: Liver Transplantation, Living Donor, Left Graft

OP-28

Engineering Immune-Evasive Vascularized Liver Modules Using CRISPR-Edited Hypoimmune Stem Cells

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Aims: Allogeneic graft rejection and donor organ scarcity remain major obstacles in transplantation medicine. To overcome these limitations, we generated genetically engineered immune-evasive meta-stem cells capable of circumventing host immune surveillance.

Methods: The ALC3-3 line was derived from TnRhipsc-4F cells through CRISPR-Cas9 editing to eliminate HLA expression and introduce immune-checkpoint regulators, thereby conferring robust immunotolerant properties.

Results: Using a 16-day protocol, the engineered cells were efficiently differentiated into hepatocyte-like cells, with lineage specification validated by RT-PCR and immunocytochemistry. Flow cytometry confirmed $> 90\%$ differentiation efficiency based on albumin positivity. For functional evaluation, the resulting hepatocytes were combined with endothelial cells to

construct vascularized 3D liver organ modules and transplanted into a rabbit model. Post-transplant assessments revealed progressive decreases in ALT, AST, and TBIL levels, indicating amelioration of liver injury. Histological analyses further verified structural integrity and stable engraftment of the transplanted modules.

Conclusions: Collectively, these findings demonstrate that ALC3-3-derived immune-evasive hepatic modules represent a promising strategy for next-generation regenerative liver therapy. This study supported by Korea Evaluation Institute of Industrial Technology(20012378), This research was supported by a grant of the Korea-US Collaborative Research Fund(KU-CRF), funded by the Ministry of Science and ICT and Ministry of Health & Welfare, Republic of Korea (grant number: RS-2025-16063805).

Keywords: Hypoimmune Stem Cells, Crispr-CAS9, Immune-Evasive

Friday, June 12, 2026, 16:20-17:20

6. HCC, Basic 1

OP-29

A Novel Copper Ionophore A3 Combined with PX-478 Induces Cuproptosis and Enhances Immunogenic Cell Death in Hepatocellular Carcinoma

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Aims: To develop a novel copper ionophore (A3/Cu) and determine whether combining A3/Cu with the HIF-1 α inhibitor PX-478 enhances antitumor activity and immunogenic cell death (ICD)-associated DAMP signaling in hepatocellular carcinoma (HCC), thereby promoting a more immune-permissive tumor microenvironment.

Methods: Antiproliferative activity of A3/Cu (with Es/Cu as a comparator) was assessed in Huh-7 and additional tumor cell lines using MTT assays. Intracellular copper accumulation was quantified, and copper dependence was evaluated using tetra-thiomolybdate (TTM) rescue. Mitochondrial injury was examined by transmission electron microscopy, while redox status and stress responses were assessed by intracellular glutathione (GSH) measurement and autophagy marker analysis (p62, LC3B). Cuproptosis-related molecular events were evaluated by immunoblotting for Fe-S cluster-related proteins (POLD1, LIAS, FDX1), DLAT alterations, and DLAT oligomerization. ICD-associated DAMPs were measured by extracellular ATP

assays, flow cytometric analysis of calreticulin (CRT) exposure, and immunofluorescence detection of HMGB1 translocation. *In vivo* efficacy was tested in a C57BL/6J H22 subcutaneous tumor model treated with PBS, A3/Cu, A3/Cu+PX-478, Es/Cu, or Es/Cu+PX-478. Tumor volume, endpoint tumor weight, and tumor growth inhibition (TGI) were recorded; tumor H&E and Ki-67 staining were performed. Tolerability was evaluated by body weight monitoring and H&E of major organs. Tumor DLAT/FDX1 signals were examined by immunofluorescence, and intratumoral CD8⁺ T cells were assessed by immunofluorescence and flow cytometry (CD3⁺CD8⁺)

Results: A3/Cu inhibited tumor cell growth and significantly increased intracellular copper levels. A3/Cu induced mitochondrial damage, GSH depletion, and enhanced autophagy, while PX-478 co-treatment further aggravated mitochondrial stress. A3/Cu reduced Fe-S cluster-related proteins and induced DLAT abnormalities, including DLAT oligomerization; these changes were amplified by PX-478. A3/Cu promoted ICD-related DAMP signaling, including increased extracellular ATP release, enhanced CRT exposure, and HMGB1 nuclear-to-cytoplasmic translocation, all of which were further strengthened by PX-478. *In vivo*, A3/Cu markedly suppressed H22 tumor growth, and combination therapy improved TGI from 73.51% to 93.95%, accompanied by reduced Ki-67 staining and more pronounced tumor tissue damage. Treatment was well tolerated, with stable body weight and no overt histopathological abnormalities in heart, liver, spleen, lung, or kidney. Tumor DLAT/FDX1 signals were altered following treatment, and intratumoral CD8⁺ T-cell infiltration increased (CD3⁺CD8⁺: 1.06% in controls, 5.24% with A3/Cu, 6.04% with A3/Cu+PX-478).

Conclusions: A3/Cu triggers copper-dependent mitochondrial stress and cuproptosis-associated molecular alterations in HCC and induces a robust ICD-like DAMP program. PX-478 further amplifies DAMP signaling and delivers superior anti-tumor efficacy *in vivo* with increased CD8⁺ T-cell infiltration. These findings support a promising cuproptosis-ICD-oriented combination strategy to potentially improve immunotherapy responsiveness in HCC

Keywords: Hepatocellular Carcinoma, Cuproptosis, Immunogenic Cell Death, Damps

OP-30

Nidogen 1 mRNA Vaccine Facilitates T Cell Homing and Induces Anti-Tumor Immunity against Hepatocellular Carcinoma

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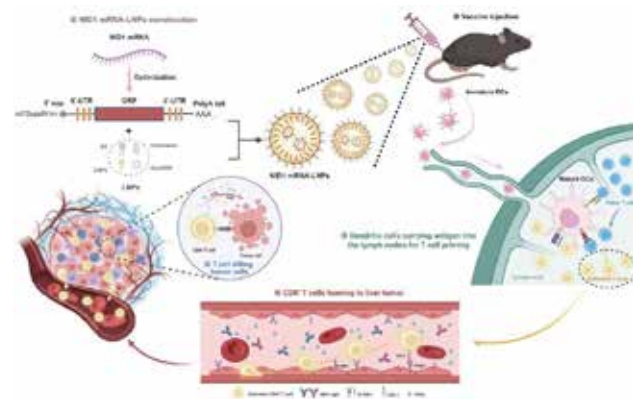
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Aims: Hepatocellular carcinoma (HCC) is a highly prevalent malignancy with limited therapeutic options. Nidogen 1 (NID1) is highly overexpressed in HCC and plays a critical role in the development and metastasis of HCC. Targeted intervention against NID1 can effectively suppress HCC progression with a satisfactory safety profile, making it a promising candidate antigen for cancer vaccine development.

Methods: A lipid nanoparticle (LNP)-encapsulated murine NID1 mRNA vaccine was constructed. The immunogenicity of the vaccine was evaluated both *in vitro* and *in vivo*. The therapeutic and prophylactic efficacy, along with the safety profile, of the vaccine were systematically assessed using an orthotopic implantation model of HCC. Direct and indirect endothelial adhesion assays and transendothelial migration assay were adopted to investigate the vaccine-induced T cell homing ability.

Results: The NID1-mRNA vaccine effectively induced antigen presentation and promoted the bone marrow dendritic cell maturation with minimal apoptosis. *In vivo*, it efficiently elicited NID1-specific IgG production and increased the population of cytotoxic T cells. Both therapeutic and prophylactic effects of NID1-mRNA vaccine were demonstrated with excellent tolerability. Moreover, the NID1-mRNA vaccine significantly improved the survival rate of tumor-bearing mice and prevented lung metastasis of HCC. Mechanistically, the NID1-mRNA vaccine enhanced dendritic cell motility and maturation, up-regulated the expression of liver tumor-homing receptor LFA-1 on activated T cells, and promoted the adhesion of T cells to inflamed endothelial cells in the liver tumor.



Conclusions: An experimental mRNA vaccine for HCC immunotherapy in murine models was developed, which exhibited favorable prophylactic efficacy, therapeutic effects, and a safety profile. NID1-mRNA vaccine elicited both cellular and humoral immunity and imprinted activated T cells with liver tumor tro-

pism to exert its anti-tumor effect. These findings highlight the potential of NID1-based vaccines in the better management of HCC, providing a promising strategy to enhance anti-tumor immunity and improve clinical outcomes for HCC patients.

Keywords: Nidogen 1, Mrna Vaccine, Hepatocellular Carcinoma, T Cell Homing

OP-31

High Ammonia Promotes EHHADH-Dependent Pyrimidine Degradation to Induce Cell Death in HCC

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Aims: Metabolic reprogramming is a hallmark of Hepatocellular Carcinoma (HCC), often manifesting as urea cycle disruption and subsequent ammonia accumulation in the liver. The impact of ammonia on tumor cells is concentration-dependent: while sub-toxic levels promote proliferation, elevated concentrations induce proteotoxicity and cell death. Since hyperammonemia is clinically associated with poor prognosis, this study aims to identify the molecular drivers of ammonia-induced HCC cell death to uncover novel therapeutic vulnerabilities.

Methods: To investigate these mechanisms, we established a novel transgenic HCC mouse model subjected to a high-ammonia diet. Integrating multi-omics—including metabolomics, transcriptomics, proteomics, and modification-omics—alongside metabolic flux analysis, we characterized the role of the ammonia-induced gene *EHHADH* in mediating cell death. Cytotoxicity was quantified by LDH and HMGB1 release, while the ultrastructural features of inflammatory cell death were visualized via electron microscopy. Biochemical assays, including protein purification and enzymatic analysis, were employed to evaluate Dihydropyrimidine Dehydrogenase (DPYD) activity. Furthermore, single-cell RNA sequencing (scRNA-seq) was used to resolve the impact of *EHHADH* overexpression on the HCC immune microenvironment. Finally, we assessed the translational potential of this pathway by evaluating the synergistic efficacy of an *EHHADH* agonist combined with anti-CTLA4 therapy *in vivo*.

Results: High ammonia therapy inhibits HCC growth by triggering GSDME dependent pyroptosis and apoptosis. We found that ammonia induced oxidative stress activates the PPAR α - EHHADH axis, driving peroxisome β oxidation and cytoplasmic acetyl CoA accumulation. This metabolic transformation induces acetylation and overactivation of DPYD, leading to pyrimidine depletion and replication stress. In addition, the

resulting levels of β - alanine inhibited the expression of PD-L1. By inducing cell death, we successfully modified the TME, increased the infiltration of phagocytes and CD8⁺ T cells, and demonstrated that targeting the EHHADH pathway can significantly enhance the sensitivity of HCC to CTLA-4 blockade.

Conclusions: Our study identifies a novel metabolic-immune axis defined by ammonia-induced PPAR α -EHHADH signaling. This pathway drives pyrimidine catabolism and replication stress, triggering cell death and PD-L1 downregulation. These results highlight EHHADH as a viable therapeutic target to inhibit tumor growth and synergistically improve the efficacy of immune checkpoint blockade in HCC.

Keywords: Hepatocellular Carcinoma, High Ammonia, Pyrimidine Metabolism, Inflammatory Cell Death

OP-32

Exosomal miR-30a-5p Serves as a Predictive Biomarker and Therapeutic Target for Atezolizumab/Bevacizumab Therapy in Advanced HCC

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Aims: A reliable biomarker for predicting the therapeutic response of atezolizumab and bevacizumab combination therapy — the standard treatment for advanced hepatocellular carcinoma — has not yet been established. This study focused on identifying exosomal miRNA biomarkers that could predict a positive response to this treatment, and further investigated their potential as therapeutic targets.

Methods: Exosomal miRNA from the sera of patients with advanced hepatocellular carcinoma, collected before atezolizumab-bevacizumab therapy, was analyzed using small RNA sequencing. Decision tree and t-test analyses identified miRNAs that distinguished the two groups. To evaluate the functional role of candidate miRNAs, HepG2 cells were transfected with miR-30a-5p and subjected to cell migration assays. Furthermore, extracellular vesicles (EVs) loaded with miR-30a-5p were engineered and administered in a murine xenograft model of HCC to assess their therapeutic efficacy *in vivo*.

Results: A total of 1,076 miRNAs were identified by next-generation sequencing (NGS) in patients receiving atezolizumab-bevacizumab therapy. Among them, 12 miRNAs showed significant differences between responders and non-responders; notably, 3 miRNAs — let-7c-5p, miR-30a-5p, and miR-192-5p — were significantly upregulated in responders. Decision tree analysis further identified miR-30a-5p as a key predictive factor

capable of distinguishing responders from non-responders. The elevated expression of miR-30a-5p in responders was further corroborated by external validation using quantitative PCR, confirming its consistent upregulation in an independent cohort. *In vitro* functional validation demonstrated that transfection of miR-30a-5p into HepG2 cells significantly suppressed cell migration relative to controls. Importantly, EVs engineered to carry miR-30a-5p were successfully produced, and their administration in a xenograft mouse model resulted in marked suppression of HCC tumor growth *in vivo*, suggesting that miR-30a-5p exerts direct antitumor activity.

Conclusions: Exosomal miR-30a-5p demonstrate great potential not only as predictive biomarkers for response to atezolizumab and bevacizumab therapy, but also as promising therapeutic targets. The development of miR-30a-5p-loaded EVs and the demonstration of their tumor-suppressive effects in a xenograft HCC model collectively highlight a dual role for this miRNA as both a liquid biopsy-based predictor and an EV-mediated therapeutic agent.

Keywords: HCC, Mirna, Biomarker, EV

OP-33

Baseline Peripheral Blood Frequency of CD69⁺ TRM-Like T Cells Predicts Response to Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma

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Aims: Atezolizumab plus bevacizumab (ATE/BEV) is the standard first-line therapy for advanced hepatocellular carcinoma (HCC); however, the objective response rate remains approximately 30–35%. Identifying predictive immune biomarkers is therefore critical. Although CD69 is traditionally considered an early T-cell activation marker, under chronic antigen exposure it may reflect T-cell differentiation state and functional plasticity. We investigated whether baseline peripheral CD69⁺ T cells are associated with clinical response to ATE/BEV in patients with advanced HCC.

Methods: Peripheral blood mononuclear cells (PBMCs) were collected from patients with advanced HCC prior to ATE/BEV treatment (n=36; responders [R] n=13, non-responders [NR] n=23). Single-cell RNA sequencing was performed to characterize baseline immune transcriptional profiles (n=6; R=3, NR=3). Multiparametric flow cytometry quantified CD69⁺ T-cell subsets and co-expression of CD39, chemokine receptors

(CXCR3, CXCR4, CXCR6, CX3CR1), and immune checkpoint molecules (PD-1, TIGIT, CTLA-4) (n=30; R=10, NR=20). Treatment response was assessed at week 3 according to mRECIST criteria.

Results: Single-cell RNA sequencing revealed increased CD69 expression in both CD8 and CD4 T cells in responders compared with non-responders. These cells were enriched for transcription factors associated with memory maintenance and suppression of terminal differentiation, including BACH2, ETS1, and FOXO4. Moreover, CD69⁺ CD8 T cells showed increased expression of the tissue-homing chemokine receptors CXCR4 and CXCR6, suggesting potential for hepatic tissue re-entry.

Flow cytometry confirmed a significantly higher frequency of CD69⁺ CD8 T cells in responders. Notably, CD69⁺CD39⁺ CD8 T cells were enriched in responders, consistent with a tumor-antigen-experienced circulating TRM-like phenotype. Tissue-homing receptor analysis further demonstrated increased CXCR3⁺, CXCR4⁺, and CXCR6⁺ CD69⁺ CD8 T cells in responders (P<0.001), whereas CX3CR1⁺ CD69⁺ CD8 T cells, a marker of terminally differentiated cytotoxic effector cells, were relatively reduced (P<0.03). Checkpoint analysis demonstrated increased PD-1⁺, TIGIT⁺, CTLA-4⁺, and CD39⁺ CD69⁺ CD8 T cells in responders (P<0.01), indicating a progenitor-like exhausted state potentially responsive to immune checkpoint blockade.

CD69⁺ CD4 T cells in responders exhibited significantly higher CXCR3 expression compared with non-responders (P<0.001), suggesting enrichment of Th1-polarized helper T cells with migration potential toward IFN- γ -driven inflammatory environments.

Conclusions: Baseline peripheral CD69⁺ T cells in responders exhibit transcriptional and phenotypic features consistent with circulating TRM-like cells with tissue-homing capacity and progenitor-like exhaustion. CD69-based immunophenotyping of PBMCs may therefore serve as a predictive circulating immune biomarker for response to ATE/BEV therapy in advanced HCC.

Keywords: Atezolizumab Plus Bevacizumab, Baseline Peripheral Blood, Memory-Biased CD69⁺ CD8 T Cells, Hepatocellular Carcinoma

OP-34

PLD1 Knockdown Suppresses Hepatocellular Carcinoma Growth and Progression through Upregulation of IGFALS

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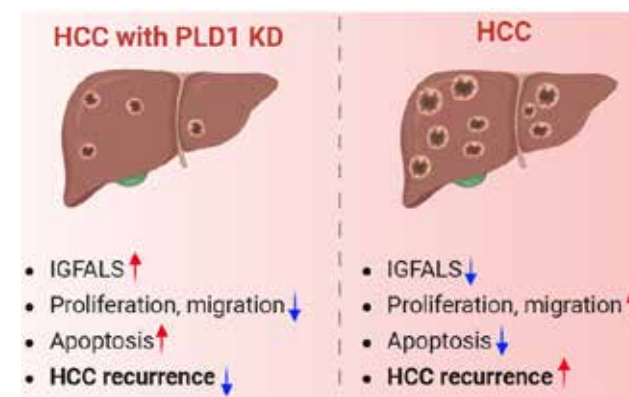
Aims: Phospholipase D1 (PLD1) has been reported to be up-regulated in hepatocellular carcinoma (HCC). Because activation of insulin-like growth factor (IGF) signaling in HCC cells is associated with enhanced tumor cell survival and increased epithelial-mesenchymal transition, we investigated whether PLD1 knockdown (KD) modulates insulin-like growth factor acid-labile subunit (IGFALS) expression and influences tumor cell behavior in HCC.

Methods: PLD1 was genetically ablated in the mouse liver using the Sleeping Beauty transposon system, and tumor tissues were subsequently subjected to RNA sequencing (RNA-seq). In human HCC cell lines, PLD1 expression was silenced using siRNA-mediated KD. Furthermore, PLD1 expression levels and their clinical association with postoperative outcomes were evaluated in human HCC tissue samples.

Results: PLD1-deficient mice exhibited a significant reduction in both tumor size and tumor number compared with control mice. RNA-seq analysis of murine HCC tissues demonstrated a significant up-regulation of IGFALS expression in PLD1-deficient tumors. Consistently, siRNA-mediated suppression of PLD1 in HCC cell lines increased IGFALS expression and significantly inhibited tumor cell proliferation and migration. In human HCC specimens, PLD1 expression was significantly associated with postoperative recurrence.

Conclusions: Our findings indicate that PLD1 negatively regulates IGFALS expression in the liver. Loss of PLD1 leads to the upregulation of IGFALS, which subsequently attenuates IGF signaling, reduces tumor cell survival, and inhibits HCC progression. These results suggest that targeting PLD1 may serve as a potential therapeutic strategy for HCC.

Keywords: HCC, PLD1, IGFALS



Friday, June 12, 2026, 16:20-17:20

7. HCC, Clinical

OP-35

GAAD Score as a Diagnostic and Prognostic Marker from Cirrhosis to Hepatocellular Carcinoma

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Aims: This study evaluated the diagnostic and prognostic performance of GAAD across the clinical spectrum of liver cirrhosis (LC) and HCC.

Methods: A retrospective analysis was conducted on 234 subjects, including non-evolutive LC (NELC, n = 107), evolutive LC developing HCC (ELC, n = 32), and HCC (n = 95). AFP and PIVKA-II were measured and GAAD scores calculated. GAAD scores and clinical parameters were compared across groups and within HCC subcategories (lesion type, BCLC stage, etiology). Diagnostic accuracy was assessed by ROC analysis, including solitary nodules < 2 cm, and correlations were evaluated with Spearman's rho. GAAD-based stratification was used for competing-risk and survival analyses.

Results: ROC analysis demonstrated excellent diagnostic accuracy for HCC (AUC = 0.88; sensitivity 83%; specificity 82.9%) and good performance for solitary nodules < 2 cm (AUC = 0.76), outperforming standard biomarkers including the GALAD score. GAAD increased progressively across disease stages: median [IQR] 1.81 [0.35–2.94] in NELC, 1.96 [0.62–2.84] in ELC, and 6.69 [3.44–9.17] in HCC (P<0.0001). Within HCC, GAAD correlated with tumor burden (P=0.04) and BCLC stage (P=0.01), but not with etiology (P=0.58). GAAD and PIVKA-II levels correlated significantly with maximum tumor diameter ($\rho = 0.457$ and $\rho = 0.503$; P<0.001). Higher GAAD at HCC diagnosis was associated with poorer overall survival (P=0.007). Among cirrhotic patients without HCC, GAAD positivity predicted higher HCC risk within 24 months (P=0.044) and shorter HCC-free survival (P=0.003).

Conclusions: The GAAD score provides robust diagnostic and prognostic information across cirrhosis and HCC, outperforming existing biomarkers and correlating with tumor stage

and outcomes. Its integration into personalized surveillance strategies could enhance early detection and risk stratification. Further validation in larger, prospective cohorts is warranted.

Keywords: GAAD, HCC, Diagnosis

OP-36

Stereotactic Body Radiation Therapy as an Add-on to Targeted Agents in Patients with Locally Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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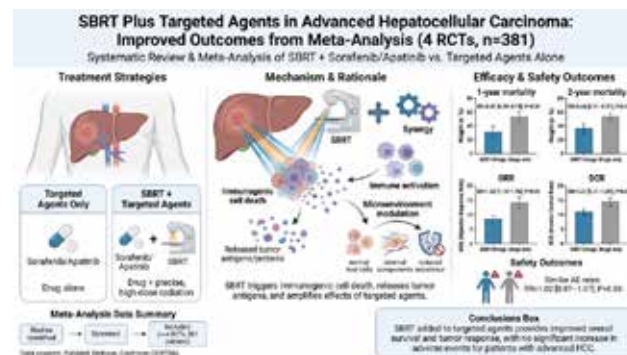
Aims: Stereotactic body radiation therapy (SBRT) is a highly precise radiation technique that delivers ultra-high doses to tumors in one or a few fractions while sparing surrounding normal tissues. In inoperable hepatocellular carcinoma (HCC), SBRT achieves local control rates comparable to radiofrequency ablation and is not restricted by tumor location or adjacent vessels. In locally advanced or oligometastatic disease, SBRT may relieve symptoms, promote rapid regression of localized lesions, and delay resistance to systemic therapy. Emerging evidence also suggests that SBRT can enhance antitumor immunity and synergize with targeted agents or immunotherapies. However, existing data are limited by small sample sizes, retrospective designs, and insufficient long-term follow-up. This systematic review and meta-analysis evaluated the efficacy and safety of SBRT combined with targeted agents and/or immunotherapies versus pharmacological treatment alone in locally advanced HCC.

Methods: PubMed, Embase, and Cochrane CENTRAL were searched through March 2025. Randomized controlled trials involving adults with locally advanced HCC treated with SBRT plus targeted agents versus targeted agents alone were included. Risk ratios (RRs) were pooled using a random-effects model, and heterogeneity was assessed with the I^2 statistic.

Results: Four RCTs involving 381 patients were included. SBRT significantly reduced mortality at 1 year (RR = 0.47, 95% CI: 0.28–0.78, $P < 0.01$) and 2 years (RR = 0.68, 95% CI: 0.51–0.91, $P < 0.01$). It also improved objective response rate (ORR) (RR = 1.31, 95% CI: 1.11–1.54, $P < 0.01$) and disease control rate (DCR) (RR = 1.53, 95% CI: 1.19–1.96, $P < 0.01$). Adverse events were comparable between groups (RR = 1.02, 95% CI: 0.97–1.07, $P = 0.88$).

Conclusions: Adding SBRT to sorafenib or apatinib improved survival and tumor response without increasing toxicity in patients with locally advanced HCC.

Keywords: Locally Advanced Hcc, SBRT, Targeted Therapy



OP-37

Identifying the Novel Target and Immunotherapy Strategies for the Precision Treatment of Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide. Tyrosine kinase-based targeted therapies and immunotherapy represent the main treatment options for advanced HCC. However, therapeutic resistance substantially limits their efficacy and durability. Therefore, it is urgent to identify novel molecular targets and develop more effective immunotherapeutic strategies for the precision treatment of HCC.

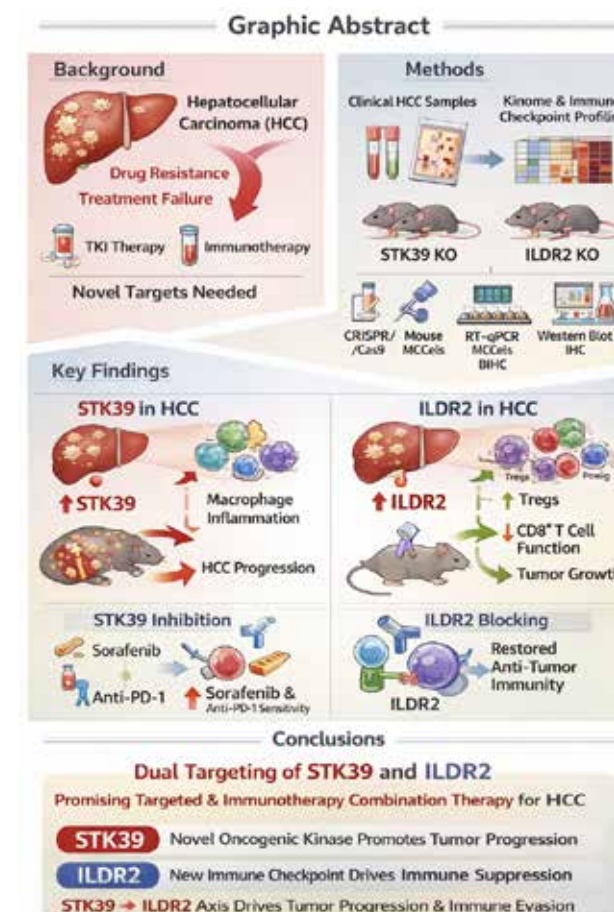
Methods: We profiled the whole kinome and immune checkpoint expression in hundreds of paired clinical HCC samples and identified significant overexpression of STK39 and ILDR2. STK39- or ILDR2-knockout mice were generated using CRISPR/Cas9 technology, and their roles were investigated in multiple murine HCC models. The expression levels of STK39 and ILDR2 were examined by RT-qPCR, Western blotting, and immunohistochemistry. Cell proliferation and apoptosis were assessed using CCK-8 and TUNEL assays. Various carcinogen-induced HCC models were established in wild-type and STK39- or ILDR2-deficient mice. Multiple *in vitro* and *in vivo* HCC models were further utilized to evaluate the therapeutic potential of ILDR2 as an immunotherapy target.

Results: We report for the first time that STK39 is a novel kinase highly overexpressed in HCC and significantly correlates with poor patient survival. Pharmacological inhibition of STK39 markedly attenuated HCC progression (Patent No. ZL 2020 1 0857353.9). STK39 overexpression further promoted HCC development by enhancing macrophage-mediated inflammatory responses in carcinogen-induced liver injury, fibrosis, and HCC models. Moreover, inhibition of STK39 improved the

therapeutic efficacy of sorafenib and anti-PD-1 treatment. Through comprehensive profiling of immune checkpoint molecules, we identified ILDR2 as a novel immune checkpoint in HCC (Patent application No.202510619490.1). Tumor-derived ILDR2 interacts with CD4⁺ T cells, leading to increased regulatory T cell (Treg) expansion, suppression of T helper 1 (Th1) polarization, impaired CD8⁺ T cell cytotoxicity, and induction of CD8⁺ T cell exhaustion. In murine HCC models, ILDR2 suppressed tumor-infiltrating T cell function and promoted tumor progression.

Conclusions: Our study identifies STK39 as a novel oncogenic kinase and ILDR2 as a previously unrecognized immune checkpoint in HCC. Targeting STK39 and ILDR2 may represent promising combination therapeutic strategies for improving targeted therapy and immunotherapy in HCC.

Keywords: Hepatocellular Carcinoma, STK39, ILDR2, Immunotherapy



OP-38

An Anchored Matching-Adjusted Indirect Comparison of First-Line Systemic Therapies in Advanced HCC

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Aims: First-line systemic regimens for advanced hepatocellular carcinoma (HCC)—atezolizumab plus bevacizumab (Atezo+Bev), tremelimumab plus durvalumab (Trem+Durv), nivolumab plus ipilimumab (Nivo+Ipi) have demonstrated efficacy versus sorafenib, but head-to-head comparisons remain unavailable. We performed a population-adjusted indirect comparison of these first-line therapies using a Korean real-world (RW) sorafenib cohort as a common anchor.

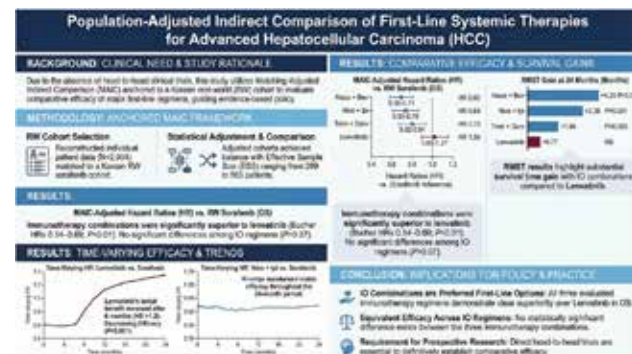
Methods: Individual patient data (N=2,904) were reconstructed from the Kaplan-Meier curves of the IMbrave150, HIMALAYA, CheckMate 9DW, and REFLECT trials. A Korean RW cohort of treatment-naïve advanced HCC patients (sorafenib N=858) served as the anchor. Matching-adjusted indirect comparison (MAIC) was conducted by reweighting the RW cohort to balance baseline characteristics across trials. The primary endpoint was overall survival (OS).

Results: After weighting, all covariates achieved adequate balance (standardized mean differences <0.08). Effective sample sizes ranged from 269 (31.4%, HIMALAYA) to 563 (65.7%, IMbrave150). MAIC-adjusted HRs versus weighted RW sorafenib were: Atezo+Bev 0.60 (95% CI 0.50–0.71; $P < 0.001$), Nivo+Ipi 0.64 (0.53–0.78; $P < 0.001$), Trem+Durv 0.75 (0.62–0.91; $P = 0.003$), and lenvatinib 1.09 (0.95–1.27; $P = 0.203$). All three immunotherapy combinations were significantly superior to lenvatinib (Bucher HRs 0.54–0.69; all $P < 0.01$), whereas no statistically significant differences were observed among the three regimens (pairwise HRs 0.79–0.93; all $P > 0.07$). RMST gains at 24 months were +4.25, +3.28, +1.84, and +0.77 months (NS), respectively. Time-varying HR analysis revealed that lenvatinib violated the proportional hazards assumption (trend $P < 0.001$): an initial benefit (HR=0.60, 0–6 months) reversed after 6 months (HR>1.2), while Nivo+Ipi maintained stable efficacy (HR 0.50–0.65) through 24 months. MVI and AFP≥400 were the only significant treatment effect modifiers across all four trials (interaction HRs 0.36–0.55; all $P < 0.001$), explaining 70–80% and 40–50% of treatment effect heterogeneity, respectively. CATE analysis demonstrated dramatic benefit in high-burden patients (MVI+/AFP≥400: HR 0.25–0.37) but no benefit in low-burden patients (MVI–/AFP<400: HR>1.0) of immunotherapeutic regimens.

Conclusions: In this population-adjusted analysis, all three first-line immunotherapy combinations demonstrated significant OS benefits over sorafenib and outperformed lenvatinib. How-

ever, no single immunotherapy regimen showed statistical superiority over the others, indicating comparable efficacy among them. These findings highlight the need for prospective head-to-head trials.

Keywords: Hepatocellular Carcinoma, Matching-Adjusted Indirect Comparison, Systemic Therapy



OP-39

Thioredoxin as a Novel Sensitive Marker of Early Diagnosis in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is one of the most common cancer in the world. Currently, the detection of HCC relies on diagnostic imaging techniques and the measurement of serum biomarkers, most notably α -fetoprotein (AFP). However, with respect to the early diagnosis of HCC, AFP and other blood laboratory tests have shown limitations in both sensitivity and specificity. We investigated the promising novel diagnostic serum protein biomarkers, such as thioredoxin 1 (TRX1), AFP, AST, and etc.

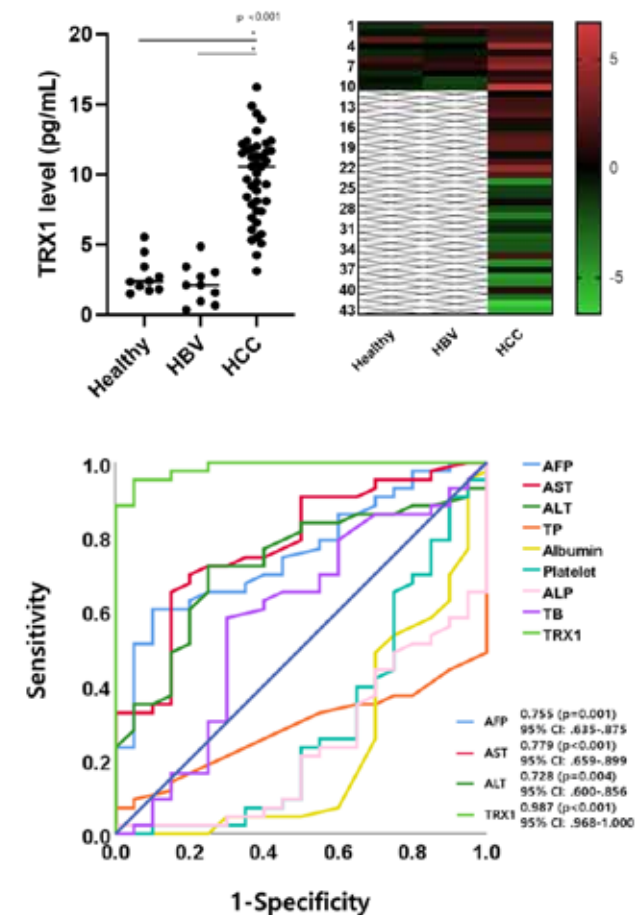
Methods: A total of 63 human blood samples, including 43 HCC volunteers, 10 patients with HBV infection, and 10 healthy donors, were obtained from the biobank of Chungnam National University Hospital. Furthermore, blood samples from diagnosed with HCC were collected and clinicopathological information. An indirect ELISA (enzyme-linked immunosorbent assay) was performed to quantify the serum levels of Trx1 protein. This research was approved by the Institutional Review Board of Chungnam National University Hospital (approval no. CNUH IRB 2020-08-049-003). The levels of peripheral blood biomarkers were compared based on Mann-Whitney *U* test and clinical capabilities of blood biomarkers were further as-

sessed by constructing a receiver operating characteristic (ROC) curve.

Results: TRX1 concentrations demonstrated early diagnostic value in distinguishing HCC patients from healthy donors and patients with HBV infection. TRX1 serum levels of HCC patients showed a significant increase, with a mean serum TRX1 concentration on HCC patients of 7.5 ± 4.3 pg/mL (mean $\pm$ SD), compared to healthy donors and HBV infection patients of 2.8 ± 1.3 pg/mL, and 2.2 ± 1.4 pg/mL ($P < 0.001$ and 0.001 , respectively). The area under the ROC curve (AUROC) of TRX1 levels (0.987, 0.968-1.000; $p < 0.001$), AFP (0.755, 0.635-0.875, $p = 0.001$), AST (0.779, 0.659-0.899, $p < 0.001$), and ALT (0.728, 0.600-0.856, $p = 0.004$), were higher than those measure from HCC vs. non-HCC (AUROC, 95%CI; p value).

Conclusions: Our study suggests TRX1 levels were significantly increased in HCC, although the sample size of our patients was not enough. Therefore, TRX1 has a potential use as a diagnostic marker and companion marker to AFP, AST, and ALT for the early detection of HCC.

Keywords: Hepatocellular Carcinoma (HCC), Thioredoxin



OP-40

Multicenter Propensity-Weighted Comparison of Hepatic Arterial Infusion Chemotherapy and Tyrosine Kinase Inhibitors in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Atezolizumab-Bevacizumab

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Aims: Following the failure of first-line atezolizumab-bevacizumab (AB), the optimal second-line strategy for advanced hepatocellular carcinoma (HCC) remains undefined. The 2025 BCLC recommendations emphasize individualized decision-making under the CUSE framework. This study aimed to compare the clinical outcomes of hepatic arterial infusion chemotherapy (HAIC) and tyrosine kinase inhibitors (TKIs) in this setting.

Methods: This multicenter retrospective study included 90 patients (HAIC, n=51; TKIs, n=39) from four tertiary centers who experienced disease progression after AB. Baseline characteristics, including higher tumor burden and portal vein tumor thrombosis (PVTT) in the HAIC group, were adjusted using inverse probability of treatment weighting (IPTW). Tumor response was assessed via mRECIST by blinded radiologists. Primary endpoints were progression-free survival (PFS) and overall survival (OS).

Results: HAIC yielded significantly higher objective response rates (35.3% vs. 5.1%, $P = .0025$) and disease control rates (66.7% vs. 25.6%, $P < .0015$) compared to TKIs. In the IPTW-weighted analysis, HAIC was associated with significantly longer PFS (7.1 vs. 3.4 months; $P < .0015$), although OS did not differ significantly between the groups (10.5 vs. 6.3 months; $P = .315$). Notably, the TKI group had a substantially higher rate of treatment discontinuation due to toxicity compared to the HAIC group (53.8% vs. 15.7%).

Conclusions: As a second-line treatment after AB failure, HAIC provides superior radiologic response and longer PFS compared to TKIs. While no definitive OS benefit was observed, these findings support HAIC as an effective investigational salvage option, particularly for patients with liver-dominant disease requiring robust intrahepatic control.

Keywords: Hepatocellular Carcinoma, Atezolizumab Plus Bevacizumab, Hepatic Artery Infusion Chemotherapy, Tyrosine Kinase Inhibitor

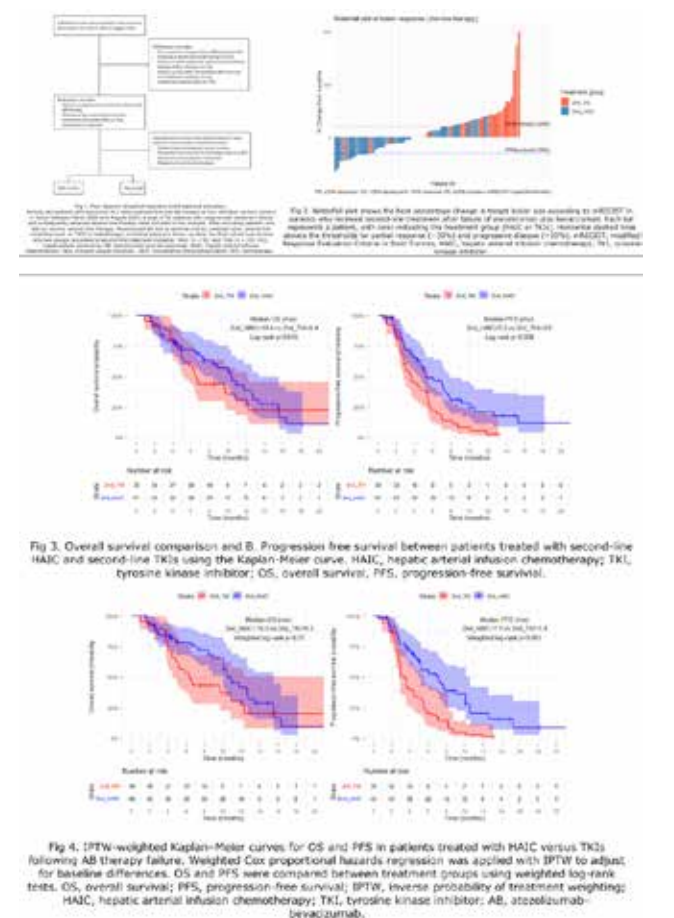


Table 3. Treatment Response by Receipt on Therapy of Hepatocellular Carcinoma			
Response	HAIC (n=51)	TKI (n=39)	p-value
CR	18 (35.3%)	2 (5.1%)	<.0015
PR	14 (27.6%)	2 (5.1%)	<.0015
SD	19 (37.3%)	35 (89.5%)	<.0015
PD	0 (0%)	0 (0%)	
DC	17 (33.3%)	21 (53.8%)	<.0015
NA	1 (2%)	4 (10.3%)	
ORR	32 (62.7%)	4 (10.3%)	<.0015
DCR	32 (62.7%)	27 (69.2%)	

Table 4. Weighted Cox regression analysis of overall survival			
Variable	HR (95% CI)	p-value	HR (95% CI)
Tumor size	1.02 (1.01-1.03)	<.001	1.02 (1.01-1.03)
Age	0.98 (0.97-0.99)	<.001	0.98 (0.97-0.99)
Sex	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)
ECOG PS	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)
HAIC vs TKI	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)

Table 5. Weighted Cox regression analysis of progression-free survival			
Variable	HR (95% CI)	p-value	HR (95% CI)
Tumor size	1.02 (1.01-1.03)	<.001	1.02 (1.01-1.03)
Age	0.98 (0.97-0.99)	<.001	0.98 (0.97-0.99)
Sex	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)
ECOG PS	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)
HAIC vs TKI	1.01 (0.99-1.03)	.85	1.01 (0.99-1.03)

Friday, June 12, 2026, 16:20-17:20

8. HCC & LC

OP-41

Low Tumor Burden Predicts Benefit from Transarterial Treatment in Hepatocellular Carcinoma with Extrahepatic Metastasis: A Nationwide Cohort Study**Jaejun Lee**^{1,2}, Hyun Yang^{1,2}, Keungmo Yang^{1,3}, Ji Won Han^{1,4}, Pil Soo Sung^{1,4}, Jeong Won Jang^{1,4}, Si Hyun Bae^{1,2}

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Aims: In patients with hepatocellular carcinoma (HCC) and extrahepatic metastasis (EHM), intrahepatic disease control may remain clinically relevant in selected cases. This study aimed to compare survival outcomes between transarterial treatment (TAT) and systemic therapy (ST) as initial treatment.

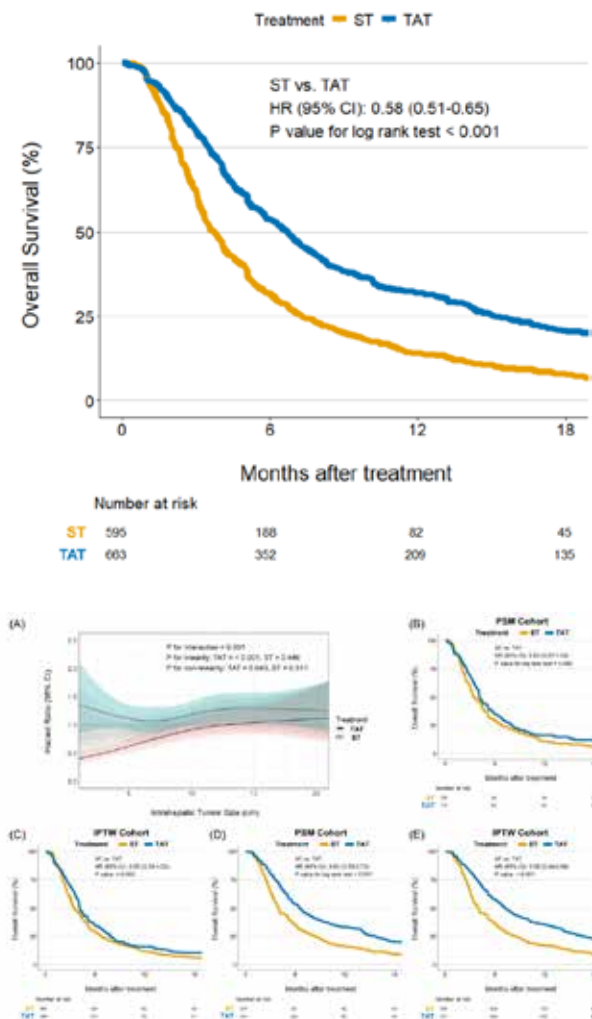
Methods: Data from the Korean Central Cancer Registry (2008–2020) were analyzed. TAT included chemoembolization, radioembolization, and hepatic arterial infusion chemotherapy. Systemic therapy consisted predominantly of tyrosine kinase inhibitors (>98%). Overall survival (OS) was the primary endpoint. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) adjusted for confounding.

Results: Among 19,753 treatment-naïve HCC patients, 2,517 had EHM. Of these, 663 received TAT and 595 received ST as initial therapy. In the overall cohort, TAT was associated with significantly longer OS than ST (median OS: 6.7 vs. 3.7 months, $P<0.001$), and this benefit remained in both PSM and IPTW analyses ($P<0.001$ for both). The advantage of TAT persisted across subgroups defined by metastatic site, number of metastatic organs, portal vein tumor thrombosis (PVTT), and tumor size, although the difference narrowed in tumors >10 cm. Multivariable analysis identified TAT, single-organ metastasis, AFP <400 ng/mL, and absence of PVTT as independent predictors of improved survival. TAT showed better survival in patients with low tumor burden, defined as intrahepatic tumor size <10 cm or metastasis confined to lymph nodes. In contrast, no significant difference was seen in those with high tumor burden, including large tumors and extrahepatic metastasis beyond lymph nodes.

Conclusions: These findings suggest that TAT may be a viable initial treatment option for selected HCC patients with EHM, particularly those with lower tumor burden. Further compar-

ative studies, especially with immunotherapy, are needed to define its optimal role in clinical practice.

Keywords: HCC, Transarterial Chemoembolization, Systemic Treatment, Extrahepatic Metastasis



OP-42

Sequential Transarterial Radioembolization and Atezolizumab plus Bevacizumab Improves Survival in Advanced Hepatocellular Carcinoma: A Propensity Score-Matched Analysis**Yunmi Ko**, Hyunjae Shin, Moon Haeng Hur, Jeayeon Park, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

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Aims: Yttrium-90 transarterial radioembolization (TARE) combined with immune checkpoint inhibitors has been investi-

gated as a potential therapeutic strategy for advanced hepatocellular carcinoma (HCC); however, evidence supporting its addition to current standard systemic therapy remains limited. We aimed to compare clinical outcomes in patients with advanced HCC treated with TARE followed by atezolizumab plus bevacizumab (TARE–Atezo/Bev) and Atezo/Bev alone.

Methods: This retrospective cohort study included systemic therapy-naïve patients with advanced HCC treated with Atezo/Bev alone or TARE–Atezo/Bev at a single tertiary hospital between 2018 and 2025. Baseline characteristics were adjusted using propensity score matching (PSM) and inverse probability of treatment weighting (IPTW). The primary outcome was overall survival (OS), and the secondary outcome was progression-free survival (PFS).

Results: A total of 156 eligible patients were enrolled, including 93 in the Atezo/Bev group and 63 in the TARE–Atezo/Bev group. In the unmatched cohort, median OS was significantly longer in the TARE–Atezo/Bev group than in the Atezo/Bev group (14.1 vs. 6.4 months; hazard ratio=0.43, 95% confidence interval=0.29–0.63; $P<0.001$), with consistent results after PSM ($P=0.01$) and IPTW ($P<0.001$). Although PFS was comparable between groups in the overall cohort, patients with Child-Pugh class A (OS: 14.6 vs. 7.1 months; PFS: 7.7 vs. 6.3 months) or ALBI grade 1 (OS: 21.4 vs. 8.3 months; PFS: 8.1 vs. 5.7 months) had significantly longer OS and PFS in the TARE–Atezo/Bev group, with similar results after adjustment.

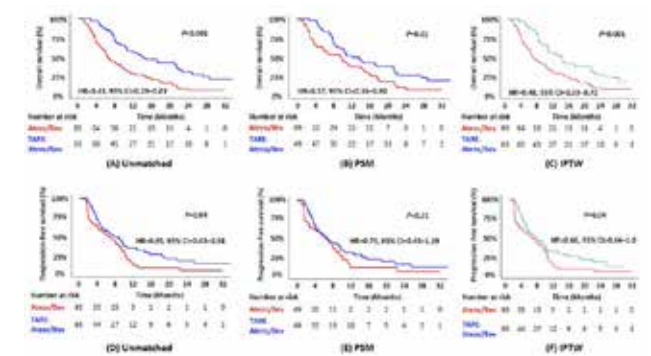


Figure 1.

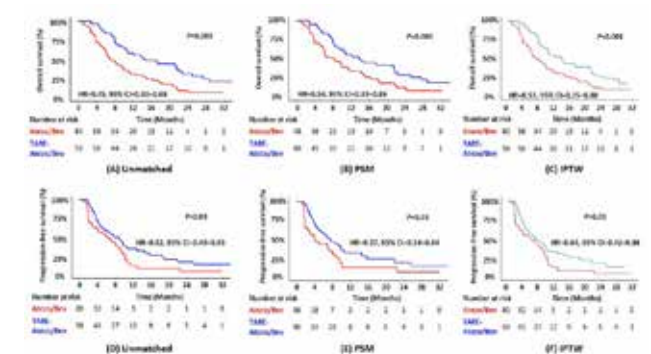


Figure 2.

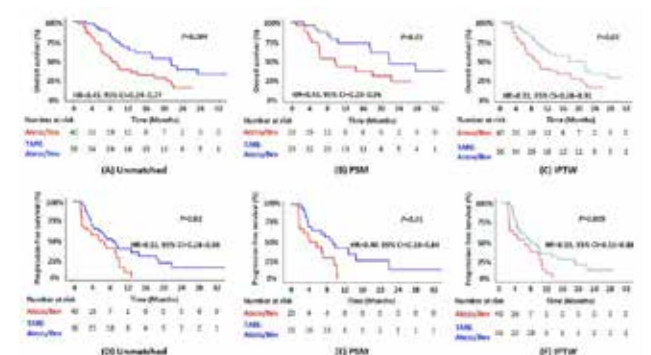


Figure 3.

Conclusions: Sequential TARE–Atezo/Bev may improve survival compared with Atezo/Bev alone in patients with advanced HCC and well-preserved liver function.

Keywords: Hepatocellular Carcinoma, Transarterial Radioembolization, Immunotherapy, Atezolizumab Plus Bevacizumab

OP-43

Surgical Resection versus Non-Surgical Treatment for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis**Seok-Hwan Kim**¹, Sang-Hoon Kim², Hae-Won Lee³, Dong-Sik Kim⁴

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Aims: The role of surgical resection (SR) as a primary treatment for hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) remains uncertain.

Methods: A comprehensive search of electronic databases from January 2000 to April 2024 identified relevant studies, and meta-analysis was performed when at least two eligible studies were available for a specific treatment comparison, including comparisons of SR with transarterial chemoembolization (TACE), combined TACE and radiation therapy (TACE-RT), or sorafenib. Hazard ratios (HRs) with 95 percent confidence intervals (CIs) for overall survival (OS) were extracted or reconstructed from Kaplan–Meier curves.

Results: Twelve retrospective cohort studies involving 4,498 patients were included. SR demonstrated superior long-term OS compared with TACE in Vp1–2 (5-year OS: HR 0.53, 95% CI 0.35–0.79) and Vp3 (5-year OS: HR 0.68, 95% CI 0.61–0.75), with comparable outcomes in Vp4. SR and TACE-RT showed similar 1- and 3-year OS, although SR demonstrated a clear 5-year OS advantage in Vp1–3 PVTT (HR 0.48, 95% CI 0.31–0.74). Compared with sorafenib, SR provided superior OS in Vp1–2 (3-year OS: HR 0.26, 95% CI 0.18–0.38) and comparable OS in Vp3.

Sensitivity analyses demonstrated the consistency of these findings, and no significant publication bias was identified.

Conclusions: Based on current evidence, SR is not inferior to non-surgical treatments including TACE, TACE-RT, and sorafenib in patients with HCC and PVTT and provides meaningful long-term survival benefits, particularly in those with segmental PVTT (Vp1–2). Further comparative studies incorporating immunotherapy are needed in future research.

Keywords: Hepatocellular Carcinoma, Portal Vein Tumor Thrombosis, Surgical Resection, Meta-Analysis

Figure 1. PRISMA flow diagram of study inclusion

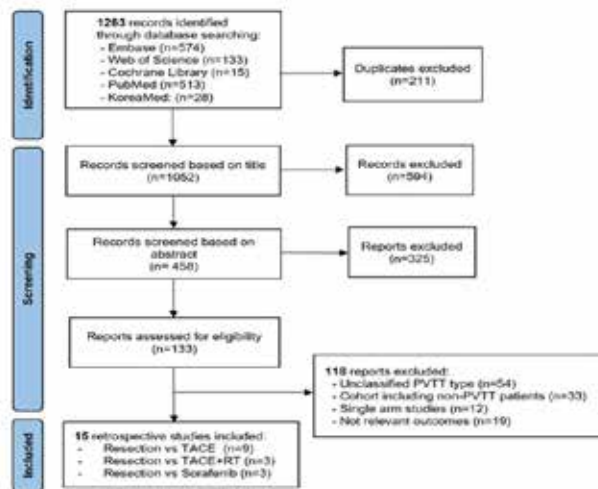


Figure 2. Summary of meta-analysis outcomes (A) surgical resection vs TACE, (B) surgical resection vs combined TACE and RT, and (C) surgical resection vs sorafenib.

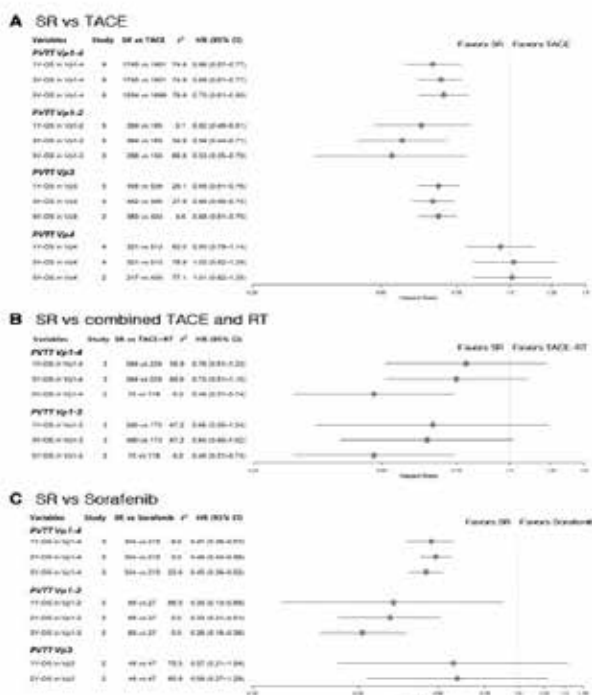
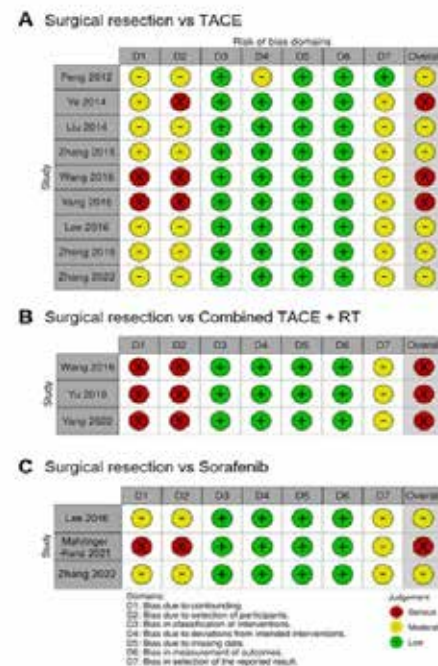


Figure 3. Risk of bias assessment of included studies using the ROBINS-I tool for (A) surgical resection vs TACE, (B) surgical resection vs combined TACE and RT, and (C) surgical resection vs Sorafenib.



OP-44

Evaluating the Clinical Utility of Large Language Models for Hepatocellular Carcinoma Treatment Recommendations: A Nationwide Registry Study

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Aims: Hepatocellular carcinoma (HCC) management requires complex decision-making considering tumor burden, liver function, and patient's functional performance status. Large language models (LLMs) show promise in clinical applications, but their utility in HCC treatment recommendations remains unexplored. We evaluated the clinical relevance of LLM-generated treatment recommendations by comparing concordance with real-world physician decisions and survival outcomes.

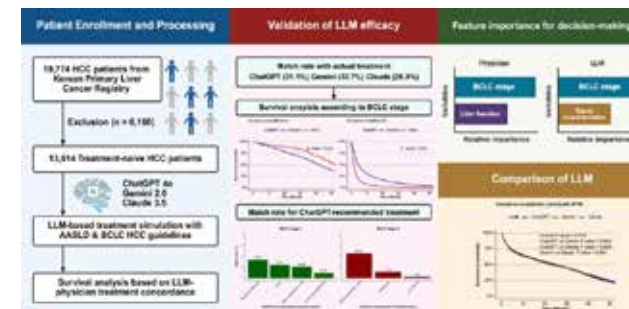
Methods: We analyzed 13,614 treatment-naïve HCC patients diagnosed between 2008 and 2020 in the Korean Primary Liver Cancer Registry. Treatment recommendations were generated using ChatGPT 4o, Gemini 2.0, and Claude 3.5 with standardized prompts referencing the American Association for the Study of Liver Diseases and the European Association

for the Study of the Liver guidelines. Patients were classified as “matched” when LLM recommendations corresponded to actual treatments received. Overall survival (OS) was compared between matched and mismatched groups, stratified by the Barcelona Clinic Liver Cancer (BCLC) stage. Decision tree analysis identified factors influencing treatment selection patterns.

Results: Concordance rates between LLM recommendations and physician decisions were 31.1% (ChatGPT), 32.7% (Gemini), and 26.8% (Claude). In BCLC-A patients, treatment concordance with LLM recommendations was associated with significantly improved survival (ChatGPT HR: 0.743, 95% CI [0.665, 0.831], $P < 0.001$). Conversely, in BCLC-C patients, concordance was associated with worse survival outcomes (ChatGPT HR: 1.650, 95% CI [1.523, 1.787], $P < 0.001$; Gemini HR: 1.586, 95% CI [1.470, 1.711], $P < 0.001$; Claude HR 1.483, 95% CI [1.366, 1.610], $P < 0.001$). In BCLC-B, concordance showed only modest or nonsignificant associations with survival across models. Decision tree analysis revealed that physicians prioritized liver function parameters, while LLMs emphasized tumor characteristics. In early-stage HCC, physicians avoided curative treatments when hepatic reserve was limited, whereas in advanced-stage HCC, physicians preferred locoregional therapies in patients with preserved liver function despite guideline recommendations for systemic therapy.

Conclusions: Concordance between LLM-generated and physician treatment decisions was associated with improved survival in early-stage HCC, whereas this association was not observed in advanced-stage disease. While LLMs may serve as adjunctive tools for guideline-concordant decisions in straightforward scenarios, their recommendations may reflect limited contextual awareness in complex clinical situations requiring individualized care.

Keywords: Hepatocellular Carcinoma, Large Language Model, Clinical Decision-Making, Survival Analysis



OP-45

PAK4–YAP Axis Controls Hepatic Stellate Cell Activation and Liver Fibrogenesis

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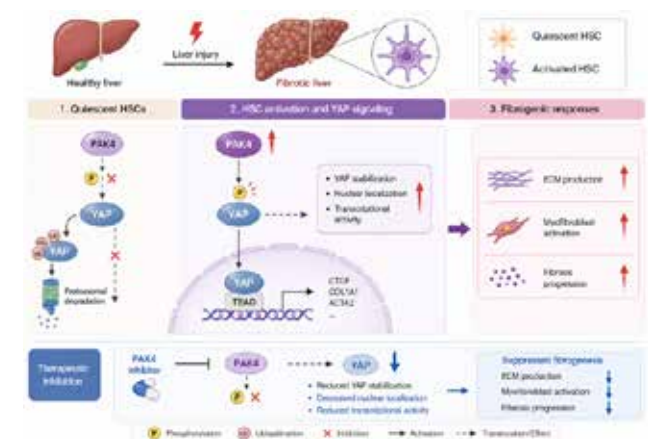
Aims: Elucidating the molecular mechanisms that regulate hepatic stellate cell (HSC) fate is critical for the development of effective anti-fibrotic therapies. We aimed to investigate the role of p21-activated kinase 4 (PAK4) in HSC activation and to explore its downstream signaling mechanisms in liver fibrosis.

Methods: PAK4 expression was examined in human and murine fibrotic liver tissues. Functional studies were conducted in primary HSCs using genetic silencing and pharmacological inhibition of PAK4. PAK4-mediated phosphorylation of Yes-associated protein (YAP) was analyzed using LC–MS/MS and an *in vitro* kinase assay. *In vivo*, HSC-specific Pak4 deletion and pharmacological inhibition were evaluated in mouse models of liver fibrosis.

Results: PAK4 expression was markedly increased in activated HSCs and fibrotic liver tissues. Inhibition of PAK4 significantly reduced HSC activation, as evidenced by decreased proliferation, migration, and fibrogenic responses. Mechanistically, PAK4 phosphorylated YAP at threonine 428, identifying a novel phosphorylation site. This phosphorylation promoted YAP stabilization and nuclear accumulation, leading to increased transcriptional activity. *In vivo*, both genetic deletion and pharmacological inhibition of PAK4 attenuated liver fibrosis.

Conclusions: These findings demonstrate that PAK4 is a key regulator of YAP signaling and HSC activation, contributing to the progression of liver fibrosis. Targeting the PAK4–YAP axis may offer a promising therapeutic strategy for anti-fibrotic treatment.

Keywords: Liver Fibrosis, Hepatic Stellate Cell, PAK4, YAP Phosphorylation



OP-46

Periportal Arginine Deficiency Drives Macrophage Senescence to Blunt Aged Liver Regeneration

Haoran Hu, Yuan Liang, Hao Wang, Feng Cheng, Haoming Zhou

Hepatobiliary Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

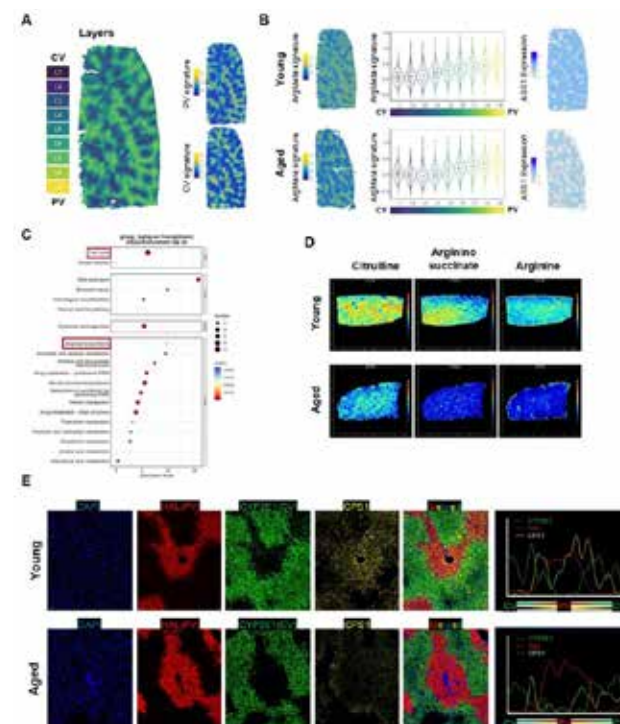
Aims: Liver regeneration is a vital reparative process following injury. While it is well-established that aging significantly compromises liver regeneration, yet the specific metabolic-immune crosstalk driving this impairment remains elusive. Macrophages are crucial non-parenchymal cells within the liver that play a pivotal role in regulating regeneration. This study aims to investigate the metabolic alterations in the aged liver during regeneration and determine how these changes impede the regenerative process via macrophages.

Methods: We established a model of regeneration after 70% partial hepatectomy (PHx) using aged (100-week-old) and young (8-week-old) mice. Single-cell transcriptomics were employed to analyze alterations in hepatocytes and macrophages during regeneration. Spatial transcriptomics and spatial metabolomics were utilized to further characterize zonal variations in arginine metabolism within the aged liver. *In vivo* and *in vitro* experiments were conducted to assess the impact of arginine deficiency on macrophages senescence and liver regeneration.

Results: Our analysis revealed significant abnormalities in hepatic arginine metabolism in aged mice during the regenerative phase. Spatial multi-omics data confirmed that key enzymes in the arginine metabolism, specifically CPS1 and ASS1, were significantly downregulated in hepatocytes within the periportal (PV) zone of aged mice. Consequently, the abundance of multiple metabolites involved in arginine metabolism—such as citrulline and argininosuccinate—was markedly reduced in the PV zone of the aged group compared to young controls. This metabolic deficiency significantly induced the migration and senescence of CD274+ monocyte-derived macrophages, creating a microenvironment unfavorable for regeneration. Supplementation with arginine or its precursors reversed these alterations and improved liver regeneration in aged mice.

Conclusions: Aberrant arginine metabolism in the PV zone of the regenerating aged liver induces the migration and senescence of CD274+ macrophages, leading to impaired liver regeneration. Strategies involving the exogenous supplementation of arginine and its precursors can alleviate macrophage senescence and restore regeneration in the aged liver.

Keywords: Liver Regeneration, Aging, Macrophage, Multi-Omics



Friday, June 12, 2026, 16:20-17:00

9. Surgery, Technical Issues

OP-47

Comparison of Surgical Outcomes between Robotic and Laparoscopic Liver Resection

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Aims: Robotic liver resection (RLR) has been increasingly adopted in minimally invasive liver surgery as an alternative to laparoscopic liver resection (LLR). Despite potential technical advantages, concerns persist regarding longer operative time and higher costs associated with robotic platforms. This systematic review aimed to evaluate recent comparative evidence on robotic versus laparoscopic liver resection.

Methods: A systematic search was conducted in PubMed, Ovid Embase, and Cochrane using the keywords *robotic liver resection*, *robot-assisted hepatectomy*, *laparoscopic liver resection*, *minimally invasive liver surgery*, and *hepatectomy*. Studies published between 2021 and 2025 comparing RLR and LLR were included in accordance with PRISMA guidelines.

Results: Four comparative studies met the inclusion criteria, comprising a total of 5,225 patients, including 974 patients un-

dergoing robotic liver resection and 4,251 patients undergoing laparoscopic liver resection. Overall perioperative outcomes such as blood loss, postoperative morbidity, and length of hospital stay were comparable between the two approaches. However, robotic liver resection was consistently associated with longer operative time and higher procedural costs compared with laparoscopic liver resection, while offering potential technical advantages in selected complex cases.

Conclusions: Recent evidence indicates that robotic and laparoscopic liver resections have comparable perioperative safety profiles. Although robotic liver resection may provide technical benefits in complex procedures, its increased operative duration and higher cost remain important limitations. Further high-quality studies are required to define its cost-effectiveness and optimal indications in hepatobiliary surgery.

Keywords: Robotic Liver Resection, Laparoscopic Liver Resection, Minimally Invasive Liver Surgery

OP-48

Laparoscopic Surgery for Liver Echinococcus

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Aims: The only way to treat liver echinococcosis is surgery. New perspectives in the treatment of echinococcosis using the possibilities of video endoscopic surgical interventions - laparoscopic echinococcectomies.

The goal is to improve the results of surgical treatment of patients with liver echinococcosis by reducing the traumatism of operations, the frequency of postoperative complications, relapses and the duration of rehabilitation of patients after surgical treatment.

Methods: In the surgical department of the Aktobe Medical Center, 35 laparoscopic liver echinococcectomy (LLE) were performed on patients with liver echinococcosis between 2017 and 2025. The duration of surgery and postoperative stay, as well as the frequency of complications, were evaluated.

Results: LLE was performed on 23 men and 12 women aged 15 to 58 years. The surgeries were performed under endotracheal anesthesia. Totally 3 trocar were used: 10 mm - in the umbilical area; 10 mm trocar - in the right subcostal area, at the point directly above the cyst; 5 mm trocar - along the anterior axillary line. Gauze moistened with a povidone solution were introduced into the abdominal cavity to cover the area around the cyst. The cyst was punctured with a thick needle and the contents were completely aspirated using a vacuum pump. A 1% povidone solution was injected into the residual cavity twice through the same needle, with an exposure of 5-7 minutes each time. The cyst wall was opened using electrocautery scissors, and excess fibrous capsule was excised. The chitinous

capsules were removed from the cyst cavity using an endo-container or a wide vacuum aspirator. If perforating bile ducts were detected, argon plasma coagulation or sutured were performed. The residual cavity was drained. LLE was successful in all 35 patients. All surgeries were performed without conversion to laparotomy. The average duration of surgery was 43.5 ± 3.4 minutes (30 to 55 minutes). Drainage from the residual cavity was removed on 4.2 ± 1.6 days after surgery with prior ultrasound control. There were no conversions to laparotomy. The average hospital stay was 6.0 ± 1.8 days. There were no deaths. A complication was observed in one patient (2.8%) - after 6 months, a residual cavity cyst formed. A puncture and drainage under ultrasound control were performed.

Conclusions: Laparoscopic echinococcectomy can be used in the surgical treatment of liver echinococcosis. The absence of a laparotomic incision significantly reduces the rehabilitation period for patients after surgical treatment.

Keywords: Liver Cyst, Liver Echinococcosis, Laparoscopic Echinococcectomy

OP-49

Surgery for Hepatocellular Carcinoma Patients with Portal Vein Main Trunk Thrombosis (Vp4): Initial Experience of a Single Center

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Vietnam National Hospital of Tropical Diseases, Vietnam

Aims: Hepatocellular carcinoma with main portal vein trunk thrombosis is a very poor prognostic factor, with an overall survival time ranging from 2.7 – 4 months. Treatment methods are not uniform and include: surgery, radiotherapy, HAIC (Hepatic Arterial Infusion Chemotherapy), and systemic therapy. Surgery may restore portal vein patency, potentially improving the patient's overall survival. Hepatocellular carcinoma with main portal vein trunk thrombosis is a very poor prognostic factor, with an overall survival time ranging from 2.7 – 4 months.

Methods: From February 2023 to July 2025, we performed surgery on 12 cases of HCC with Vp4 Portal Vein Tumor Thrombosis (PVTT), including 2 cases with accompanying Biliary Duct Tumor Thrombosis (BDTT), and 1 case with Inferior Vena Cava (IVC) thrombosis.

Results: We performed: 1 case of isolated portal vein thrombectomy; 11 cases of major hepatectomy and thrombectomy, including 1 case combined with splenectomy, 2 cases of extrahepatic bile duct resection, and 1 case of IVC segment replacement. Postoperative mortality occurred in 1 case. Acute postoperative portal vein thrombosis was observed in 4 cases. The mean follow-up period was 8.6 months (3 months – 24 months) for 10 patients (1 case lost to follow-up). There were 3 deaths at 4 months and 23 months post-surgery due to advanced cancer.

Conclusions: Surgery may be a beneficial measure in multimodal

treatment coordination, potentially improving the overall survival of HCC patients with main portal vein trunk thrombosis.

Keywords: HCC, Portal Vein Tumor Thrombus, Vp4, Surgery

OP-50

Overcoming the Lack of Dedicated Vascular Clamps in Laparoscopic Anatomical Liver Resection: The “Double Foley Loop” Technique as a Cost-Effective Alternative

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Aims: Laparoscopic anatomical liver resection (LALR) demands precise Glissonian pedicle control for both malignant and complex benign lesions, typically requiring expensive vascular clamps often unavailable in developing centers. We introduce the “Double Foley Loop” as a novel, cost-effective solution for this challenge.

Methods: From Jan-Dec 2025, 16 consecutive patients underwent LALR. Due to resource constraints, a modified double-loop tourniquet made from a standard Foley catheter was used for inflow occlusion. Indocyanine Green (ICG) fluorescence confirmed the ischemic boundaries.

Results: The cohort (11 males, 5 females; mean age 53.8 ± 13.2) included 12 HCC, 1 cholangiocarcinoma, and 3 benign lesions. The device achieved 100% successful pedicle occlusion. Mean operative time was 179.2 ± 69.9 minutes, and blood loss was 309.4 ± 150.8 ml. Pure laparoscopy was completed in 12 cases (75%). Conversion occurred in 4 cases (25%) due to bleeding or tumor location, unrelated to tourniquet failure. The technique provided a dry surgical field comparable to dedicated instruments but at negligible cost.

Conclusions: The “Double Foley Loop” is a safe, feasible, and accessible innovation. It effectively overcomes equipment shortages, offering a strategic alternative to popularize LALR in resource-limited settings.

Keywords: Laparoscopic Anatomical Liver Resection, Double Foley Loop, Cost-Effective

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Aims: This study aimed to characterise the clinical presentation, underlying risk factors, and visual outcomes of patients diagnosed with endogenous endophthalmitis complicating pyogenic liver abscess in Northern Vietnam.

Methods: We conducted a retrospective case series based on hospital records from March 2021 to 2023. Patients with confirmed pyogenic liver abscess who subsequently developed endogenous endophthalmitis were identified. Demographic data, comorbidities, abscess characteristics, ophthalmologic findings, and treatment outcomes were systematically analyzed.

Results: Out of 588 patients diagnosed with pyogenic liver abscess, 12 cases of endogenous endophthalmitis were identified, corresponding to an incidence of 2.0%. The mean age was 61.5 ± 12.0 years (range: 41–78), and diabetes mellitus was present in 7 of 12 patients. Most abscesses were located in the right hepatic lobe (7/12) and were solitary lesions (9/12), with an average maximum diameter of 5.8 ± 1.7 cm (range: 3.3–9). All patients developed ocular manifestations, most commonly eye pain (9/12), followed by purulent discharge (3/12), hypopyon (1/12), eyelid swelling (2/12), and corneal edema (2/12). In the majority of cases, the liver abscess was diagnosed prior to the onset of endophthalmitis (10/12). The mean interval between the diagnosis of liver abscess and ocular involvement was 6.1 ± 1.9 days, while the duration from onset of ocular symptoms to confirmation of endophthalmitis was 4.4 ± 2.3 days. All affected eyes received intravitreal injections with ceftazidime, amikacin, and vancomycin. Despite treatment, two patients ultimately required evisceration.

Conclusions: Endogenous endophthalmitis remains a rare but serious complication of pyogenic liver abscess, associated with significant and often irreversible visual impairment. Given its subtle early presentation and rapid progression, heightened clinical awareness and early ophthalmologic referral are crucial to improve outcomes.

Keywords: Pyogenic Liver Abscess, Endophthalmitis, Klebsiella Pneumoniae

OP-52

Mobile Self-Management Coaching Program for Chronic Liver Disease with Metabolic Risk Factors in Middle-Aged Men: A Pilot Randomized Controlled Trial

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cine, Seoul, South Korea; ⁵Yonsei Liver Center, Severance Hospital, Seoul, South Korea; ⁶Mo-Im Kim Nursing Research Institute, Yonsei University, Seoul, South Korea

Aims: Chronic liver disease (CLD) combined with metabolic risk factors requires sustained self-management, yet structured support for middle-aged men remains limited. This pilot randomized controlled trial (RCT) aimed to evaluate the feasibility and preliminary effectiveness of a family-engaged mobile self-management coaching program.

Methods: A parallel pilot RCT was conducted at a university hospital in South Korea. Participants were assigned to an intervention group (IG, n = 18) or control group (CG, n = 17) using block randomization. The IG received a 12-week intervention based on the Information–Motivation–Behavioral Skills model, which included app-based self-monitoring, educational content, feedback support, and family-involved online coaching sessions every four weeks. The CG received usual care. Data were collected at baseline and 12 weeks and analyzed using Wilcoxon signed-rank and Mann–Whitney U tests. Coaching session transcripts were analyzed using a large language model (ChatGPT-5.2) to identify facilitators and barriers to conduct self-management.

Results: At 12 weeks, the IG showed significant improvement in self-management (U=66, P=.004), and clinical indicators, including serum albumin, body fat percentage, and AST levels (all P<.05) compared with the CG. Spousal support, including dietary assistance and lifestyle behavior recording, was identified as a facilitator of self-management adherence. In contrast, work demands, family or household events, environmental factors related to weather, fatigue, and non-hepatic health problems were associated with reduced app engagement and lower adherence.

Conclusions: This study suggests that a family-engaged mobile self-management coaching program is feasible and shows preliminary effectiveness in self-management and clinical indicators among middle-aged men with CLD and metabolic risk factors. Identified facilitators and barriers to adherence underscore the need for individually tailored strategies in future trials. Larger trials with adequate power are warranted to confirm these findings.

Keywords: Chronic Liver Disease, Mobile Application, Health Coaching, Self-Management

OP-53

Chirality-Dependent Nanoparticle Activation of Dendritic Cells Induces Inflammasome-Associated Inflammatory Responses to Drive Liver Inflammation

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mensional Genomics Research Center, Kangwon National University, Korea; ³ Core-Facility for Innovative Cancer Drug Discovery (CFICDD), Kangwon National University, Korea; ⁴ College of Chemistry, Kangwon National University, Korea

Aims: Inflammatory signaling mediated by inflammasomes plays a critical role in liver immune responses and contributes to the pathogenesis of hepatic inflammatory diseases. Activation of inflammasome pathways in myeloid cells promotes the secretion of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), which are key regulators of hepatic inflammation. This study aimed to determine whether nanoparticle chirality influences monocyte-derived dendritic cell (DC) activation and inflammasome-associated inflammatory responses.

Methods: Two chiral nanoparticles—particle A (left-handed) and particle B (right-handed)—were evaluated using bone marrow-derived dendritic cells (BMDCs) *in vitro*. DC activation was assessed by measuring the expression of the co-stimulatory molecule CD40 and the secretion of inflammatory cytokines including tumor necrosis factor- α (TNF α), IL-1 β , and IL-12. Cytotoxicity was evaluated using lactate dehydrogenase (LDH) release assays.

Results: Both particle A and particle B increased CD40 expression in BMDCs, with no significant difference observed between the two particles. Notably, particle B induced substantially higher IL-1 β secretion compared with particle A, suggesting enhanced activation of inflammasome-associated inflammatory signaling. LDH release assays showed comparable cytotoxicity between the two particles across the tested concentrations.

Conclusions: These findings demonstrate that nanoparticle chirality influences dendritic cell activation and inflammatory cytokine production. In particular, particle B strongly promotes IL-1 β -associated inflammatory responses, suggesting that chiral nanomaterials may serve as tools for modulating inflammasome-mediated inflammatory processes relevant to liver immune environments.

Keywords: Inflammasome, Liver Inflammation, Nanoparticle Chirality, IL-1 B

OP-54

Deacetylated α -Tubulin in Biliary Epithelial Cells Drives Hepatic Ductular Reaction

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Aims: Ductular reaction is characterized by the hyperplasia of cholangiocytes which leads to poor prognosis of patients since it is accompanied by the secretion of inflammatory cytokines

and the recruitment of neutrophils. However, little is known about the mechanistic basis of how cholangiocytes abnormally proliferate. Given that ciliary deformations in biliary epithelial cells are frequently observed during ductular reaction, we hypothesized that aberrant deacetylation of α -tubulin is involved.

Methods: We induced hepatic cholestasis in mice by feeding diets containing 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) or alpha-naphthyl isothiocyanate (ANIT). Using the CRISPRi system, we knocked down α -tubulin acetyltransferase 1 (ATAT1), the major tubulin acetylator, in the H69 cholangiocyte cell line. To evaluate clinical relevance, we analyzed a publicly available mRNA-seq dataset from human patients with cholelithiasis.

Results: We found that α -tubulin is robustly deacetylated during bile duct injury in mice induced by diets containing DDC or ANIT. Consistent with our experimental models, analysis of a human cholelithiasis liver transcriptomics dataset (GSE183754) revealed a significant downregulation of ATAT1 expression. Furthermore, we confirmed that CRISPR-mediated silencing of ATAT1 in cholangiocyte cell line H69 promotes the secretion of inflammatory cytokines and chemokines. In mice, stabilization of acetylated α -tubulin by a histone deacetylase 6 inhibitor alleviated the severity of ductular reaction triggered by DDC or ANIT diet.

Conclusions: Our findings highlight α -tubulin deacetylation as a core mechanism underlying cholangiocyte-derived inflammation. Consequently, evaluating the acetylation status of α -tubulin emerges as a potential diagnostic tool for disease progression, and targeting this balance with HDAC6 inhibitors represents a translational therapeutic approach for cholestatic liver diseases.

Keywords: Cholestatic Liver Disease, Ductular Reaction, Alpha Tubulin Acetylation

OP-55

Quantum-Informed Molecular Representation Learning for Preclinical Drug-Induced Liver Injury Prediction

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Aims: Drug-induced liver injury (DILI) remains a major cause of clinical trial termination and post-market withdrawal. Early identification of hepatotoxic risk during preclinical development is critical to minimizing costly late-stage failures. Existing DILI prediction models rely primarily on molecular topology, which does not explicitly capture electronic structure properties associated with toxicity. This study evaluates whether quantum-in-

formed molecular representations improve DILI prediction.

Methods: We propose a quantum-informed molecular encoder for DILI prediction, termed Q-DILI, that complements structural drug embeddings with features derived from electronic-structure-based molecular maps. Molecular maps of the Interaction Region Indicator (IRI), a real-space electronic descriptor that reveals chemical bonding and non-covalent interaction regions from electron density, were extracted from density functional theory calculations. These electronic interaction patterns may influence molecular reactivity and binding behavior relevant to drug-induced hepatotoxicity. The maps were encoded using a Video Vision Transformer to capture global electronic interaction features across spatial dimensions. Molecular topology was modeled using a graph isomorphism network (GIN) to distinguish subtle structural differences, including isomeric variations. The two encoders capture complementary aspects of molecular properties relevant to hepatotoxicity. Model performance was evaluated on a benchmark DILI dataset using stratified five-fold cross-validation. Performance metrics included AUROC, F1-score, MCC, accuracy, precision, and recall.

Results: Q-DILI achieved an AUROC of 0.6260, F1-score of 0.6789, and MCC of 0.1507, compared to a graph-based DILI prediction baseline, DILIGeNN, which yielded AUROC of 0.5911, F1-score of 0.6156, and MCC of 0.1373. Q-DILI consistently surpassed DILIGeNN across all three metrics, suggesting that augmenting molecular graph representations with quantum chemical descriptors provides complementary information for DILI risk discrimination.

Conclusions: Quantum-informed molecular representations introduce complementary electronic information not captured by graph-based models, and their integration may enhance hepatotoxic risk discrimination in preclinical DILI prediction. These results support further investigation into quantum-level molecular features as a generalizable strategy for computational toxicology.

* This research was supported by the Ministry of Science and ICT (MSIT), Korea, under (1) the Global Research Support Program in the Digital Field (RS-2024-00431394), (2) the National Program for Excellence in SW (2023-0-00055), both supervised by the Institute for Information & Communications Technology Planning & Evaluation (IITP), and under (3) the Development of AI Precision Medical Solution (Doctor Answer 2.0, S0252-21-1001), supervised by the National IT Industry Promotion Agency (NIPA).

Keywords: DILI, Quantum Chemical Descriptor, Multi-Modality, Machine Learning

Table 1: Performance comparison between Q-DILI and DILIGeNN [Lee et al., 2025]

Model	Accuracy	Precision	Recall	F1-score	MCC	AUROC
DILIGeNN	0.5678 ± 0.0081	0.5901 ± 0.0018	0.5681 ± 0.1109	0.5126 ± 0.0929	0.1373 ± 0.0007	0.5911 ± 0.0023
Q-DILI	0.6054 ± 0.0018	0.6903 ± 0.0045	0.7127 ± 0.3266	0.6789 ± 0.1100	0.1507 ± 0.0036	0.6260 ± 0.0487

OP-56

Complacency, Knowledge, and Awareness across the Hepatitis Care Cascade: A Population-Based Survey

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Aims: Improving screening and treatment uptake remains a major challenge for viral hepatitis elimination. Previous Liver Index studies have described public awareness of liver diseases but have rarely examined behavioral determinants across the hepatitis care cascade. This study aimed to identify determinants of screening, treatment intention, and treatment initiation related to viral hepatitis.

Methods: A population-based face-to-face survey of 1,000 adults was conducted using stratified multistage sampling by region, sex, and age to ensure representativeness. Knowledge and awareness of liver diseases were assessed using standardized Liver Index questionnaires. Multivariable regression analyses were performed to evaluate determinants of hepatitis-related health-seeking behaviors.

Results: A total of 1,000 participants were included in the analysis, of whom 74 (7.4%) reported prior hepatitis diagnosis. Low perceived necessity was the most frequently reported reason for not undergoing hepatitis screening, reported by 62.1% of respondents who had never been screened. In multivariable analyses among participants without prior hepatitis diagnosis, higher knowledge scores were positively associated with intention to undergo screening if exposed to risk ($\beta=0.013$, 95% confidence interval [CI]: 0.006–0.019; $P<0.001$) and intention to initiate treatment if diagnosed ($\beta=0.019$, 95% CI: 0.014–0.024; $P<0.001$). In contrast, systemic barriers related to cost or provider issues were negatively associated with treatment intention ($\beta=-0.672$, 95% CI: -1.189 to -0.155; $P=0.011$). For participants with prior hepatitis diagnosis, knowledge score remained positively associated with treatment intention ($\beta=0.039$, 95% CI: 0.023–0.056; $P<0.001$). Higher awareness scores were associated with lower odds of delayed treatment initiation (Adjusted Odds Ratio [aOR]: 0.68, 95% CI: 0.49–0.96; $P=0.027$).

Conclusions: Different determinants were observed across stages of the hepatitis care cascade. Screening behavior was associated with perceived necessity, treatment intention was associated with knowledge, and treatment initiation was asso-

ciated with awareness. These findings suggest the importance of stage-specific strategies to improve hepatitis screening and treatment uptake.

Keywords: Hepatitis, Viral, Health Knowledge, Attitudes, Practice, Patient Acceptance Of Health Care, Health Behavior

THE LIVER WEEK 2026

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June 11-13, 2026 | Conrad Seoul, Korea

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ORAL POSTER PRESENTATION 2

OP-57~OP-61	HBV 2
OP-62~OP-67	HBV & HCV
OP-68~OP-73	MASLD, Clinical
OP-74~OP-79	LC, Liver Failure & Autoimmune Diseases 2
OP-80~OP-85	LC, Liver Failure & Autoimmune Diseases 3
OP-86~OP-91	MASLD, Basic & Clinical
OP-92~OP-97	Liver Transplantation & ALD
OP-98~OP-103	HCC, Basic 2
OP-104~OP-109	HCC, Clinical 3
OP-110~OP-115	Biliary and Pancreatic Disease & Others



Saturday, June 13, 2026, 08:00-08:50

11. HBV

OP-57

HBV Infection Accelerates Hepatocyte Senescence and Induces T Cell Exhaustion via SASP Secretion Pathway

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Aims: Background/Hypothesis: Chronic liver disease results in persistent cellular damage and the generation of senescent cells, exacerbating tissue dysfunction. These senescent cells secrete factors known as the senescence-associated secretory phenotype (SASP). Chronic HBV infection often manifests as diminished and absent virus-specific T cell responses, described as an “exhausted” state. This study aims to elucidate the relationship between HBV-induced cellular senescence and T cell exhaustion.

Methods: Materials and Methods: We assessed cellular senescence in mouse models (AAV-HBV1.3 at 2 vs. 15 months) and HepG2-hNTCP cell lines through *in vitro* and *in vivo* experiments. The functional characteristics of liver T cells were evaluated using flow cytometry and transcriptomics. Isolated liver immune cells were tested *in vitro* for the effects of SASP on T cell exhaustion. Mice were treated with IFN α or senolytic agent ABT263 to evaluate the impact on liver SASP and T cell functionality.

Results: Results: HBV infection significantly increased the mRNA levels of CDKN1A in liver tissue, and multiple immunofluorescence staining revealed a marked increase in senescent cells in the liver following HBV infection. In HepG2-hNTCP cells, serum DNA damage and hepatocyte senescence markers (β -gal, γ -H2AX, p21) were notably elevated by day 7 post-infection. Transcriptomic analysis indicated reduced T cell function in 15-month-old HBV-infected mice. Flow cytometry revealed increased markers of T cell exhaustion (LAG-3, CTLA-4, TIM-3). GSVA analysis showed enrichment of SASP-related pathways, and Luminex assays identified elevated levels of CCL11, SCF, IL-1RA, and β -NGF in infected mice, which induced T cell exhaustion. Treatment with ABT263 reduced SASP levels and restored T cell function.

Conclusions: Conclusions: HBV infection induces cellular senescence, which may promote T cell exhaustion through SASP upregulation. Targeting the senescence-associated pathway could be a novel therapeutic strategy against HBV

infection.

Keywords: HBV, Hepatitis, Cell senescence, SASP, T cell exhaustion

Figure1. Mice aged 2 months and 15 months were injected with AAV (control group) and AAV-HBV (experimental group), respectively. One month later, the mice were euthanized, and liver tissues were collected. A. The liver senescence markers CDKN1A and CDKN2A were assessed, revealing that HBV infection promotes hepatic cell senescence. B. An *in vitro* infection experiment was conducted using the human hepatocyte cell line HepG2-hNTCP, which showed that HBV infection led to increased serum DNA damage and decreased antioxidant levels (indicators of senescence) starting from day 7 post-infection. C. The cellular senescence markers in HBV-infected HepG2-hNTCP cells were evaluated, demonstrating a significant increase in senescence by day 7 post-infection.

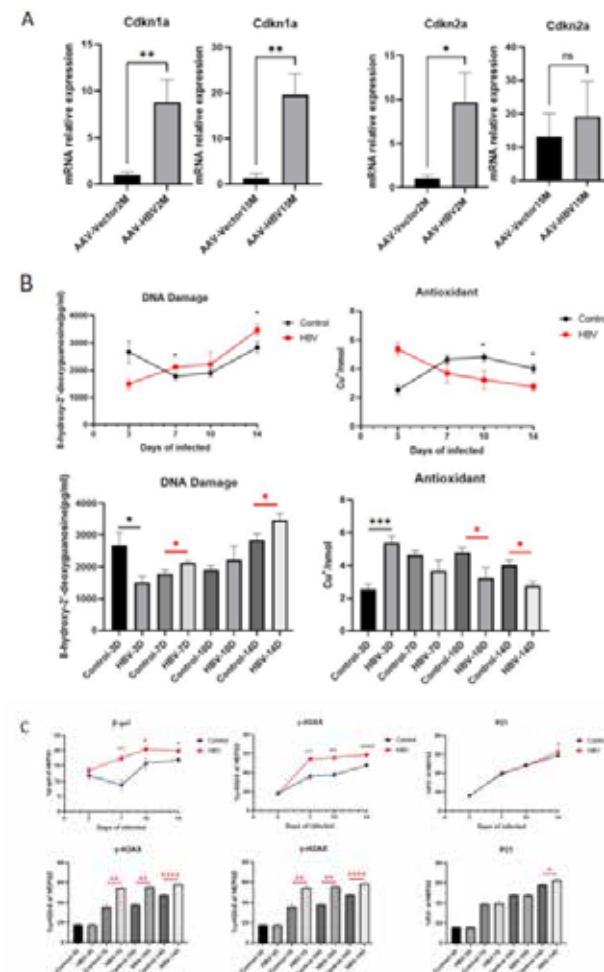


Figure2. A and B. After HBV infection, CD4⁺T cells and CD8⁺T cells in the livers of 15-month-old HBV-infected mice exhibited significant exhaustion. C. Additionally, T cells in the livers of 15-month-old HBV-infected mice demonstrated pronounced senescence. D. Transcriptomic sequencing of liver tissue revealed that, following HBV infection, T cell functionality declined in 15-month-old mice. In contrast, the liver T cells of 15-month-old mice uninfected with HBV showed a decline in immunoregulatory functions compared to 2-month-old mice, without any significant changes in T cell functionality.

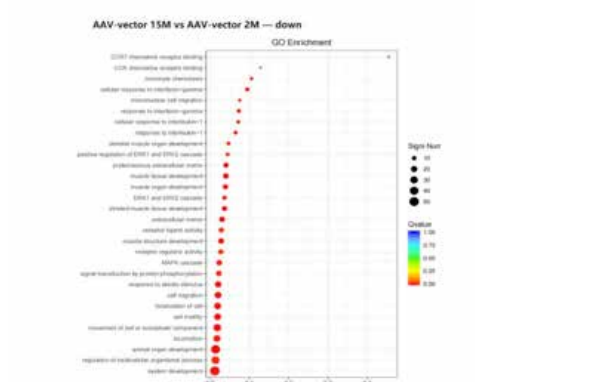
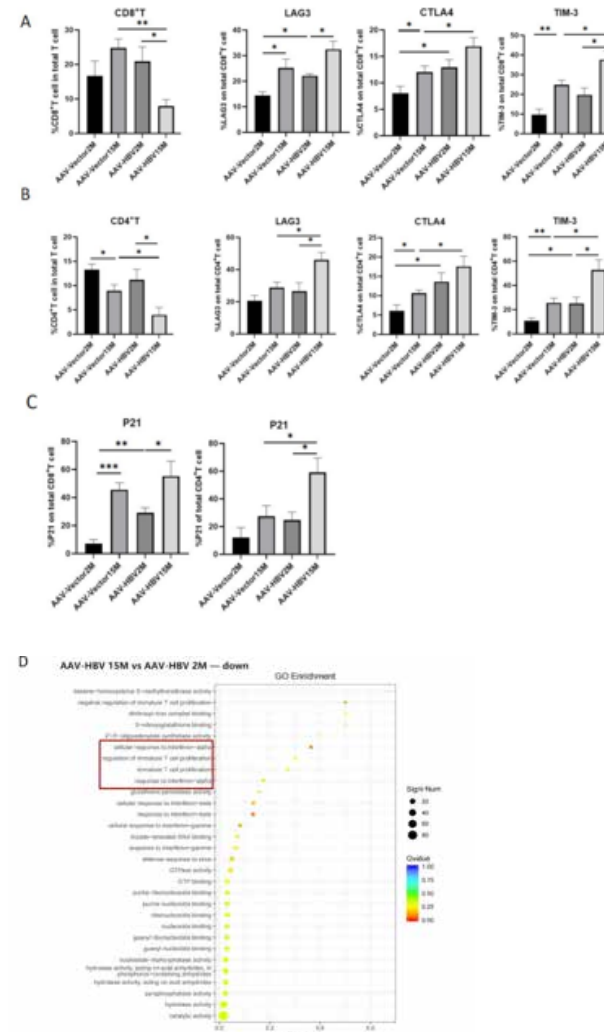
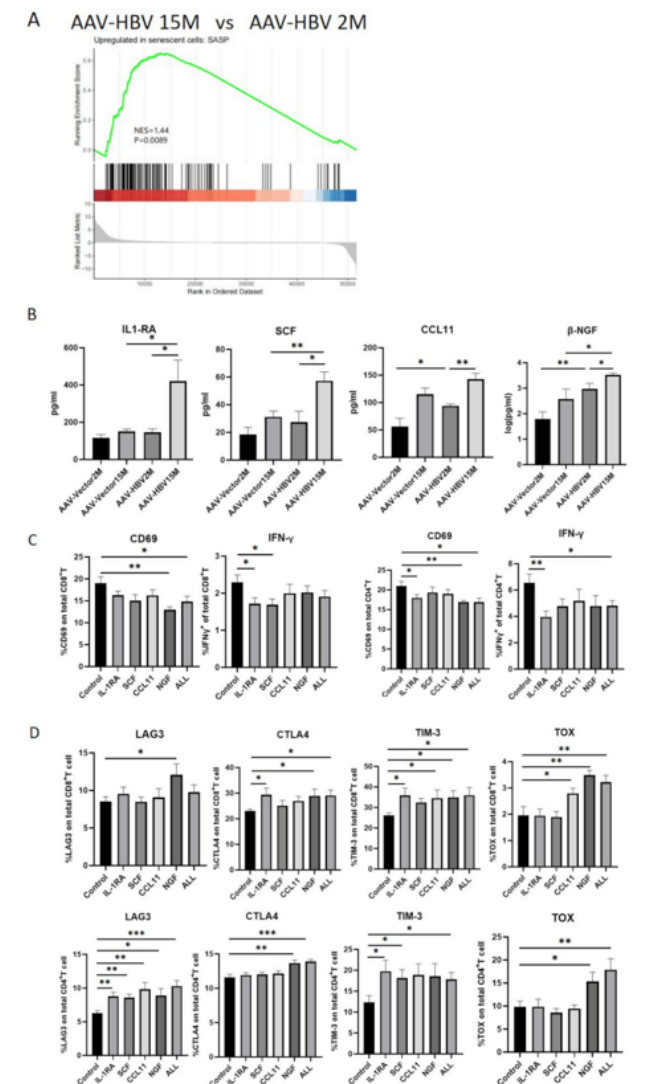


Figure3. A. GSVA analysis of liver transcriptomic sequencing revealed significant enrichment of SASP-related pathways in 15-month-old HBV-infected mice. B. Luminex multiplex assay was performed to detect common SASP factors in mouse liver homogenates, which showed that CCL11, SCF, IL-1RA, and β -NGF were significantly elevated in 15-month-old HBV mice and also increased notably following HBV infection. C. When mouse liver T cells were stimulated *in vitro* with CCL11, SCF, IL-1RA, and β -NGF, it was observed that these four SASP factors weakened the T cell activation marker CD69 and reduced IFN- γ secretion. D. Stimulation of mouse liver T cells with these four SASP factors *in vitro* can promote T cell exhaustion.



OP-58

Age-Standardized Trends in Chronic Viral Hepatitis in Mongolia: Implications for HBV, HCV, and Delta Co-Infection Burden (2022–2024)

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icine Department, Mongolian National University of Medical Science; ³Etugen Medical University; ⁴Mongolian National University Science and Technology, Mongolia

Aims: Viral hepatitis remains a major public health concern in Mongolia, with a substantial burden of chronic infection. Understanding recent epidemiological trends is essential for guiding national prevention and control strategies. To analyze temporal trends and demographic patterns of reported viral hepatitis cases in Mongolia between 2022 and 2024.

Methods: A retrospective descriptive analysis was conducted using national health statistical reports (EMT-301.15). Annual reported cases were extracted for 2022–2024. Diagnoses were classified according to ICD-10 codes, including chronic hepatitis B (B18.1), chronic hepatitis C (B18.2), and hepatitis B with delta agent (B18.0). Descriptive statistics were used to assess trends by year, sex, and age group.

Results: A total of 7,424 cases were reported in 2022, followed by a substantial decline to 5,674 cases in both 2023 and 2024, representing a 23.6% reduction. Chronic hepatitis B (B18.1) remained the predominant diagnosis across all three years, although cases decreased by approximately 26% after 2022. Chronic hepatitis C (B18.2) demonstrated a marked reduction of nearly 47% from 2022 to 2023. In contrast, hepatitis B with delta agent (B18.0) more than doubled in 2023 compared to 2022. Across all years, females slightly outnumbered males (~53%). The highest disease burden was consistently observed among individuals aged 30–54 years, indicating concentration within the economically active population.

Conclusions: Although overall viral hepatitis cases declined after 2022, chronic hepatitis B remains the leading contributor to national disease burden. The marked increase in delta co-infection warrants further epidemiological investigation. Targeted interventions focusing on the working-age population remain essential for effective disease control

Keywords: HBV, HCV, HDV co-infection, Chronic liver disease

OP-59

Clinical and Biochemical Characteristics of Acute Hepatitis B and Viral Coinfections in Hospitalized Patients in Mongolia

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Aims: Although Mongolia introduced universal hepatitis B vaccination in 1992, acute hepatitis B virus (HBV) infection continues to occur among adults. Coinfection with hepatitis D virus (HDV) or hepatitis C virus (HCV) may worsen disease severity

and delay biochemical recovery. This study aimed to compare the clinical and biochemical characteristics of acute HBV mono-infection and viral coinfections.

Methods: A retrospective study was conducted among patients hospitalized at the National Center for Communicable Diseases between October 2024 and October 2025. Patients with clinical features of acute hepatitis were included and categorized into three groups: acute HBV mono-infection (n=20), acute HBV+HDV coinfection (n=8), and acute HBV+HCV coinfection (n=9; anti-HCV and HBsAg positive). Patients with other chronic viral liver diseases were excluded. Demographic data, length of hospital stay, and biochemical parameters (ALT, AST, total and direct bilirubin) at admission and discharge were analyzed.

Results: The mean age was 34 years in the HBV group, 36 years in the HBV+HDV group, and 41 years in the HBV+HCV group. Male predominance was observed in the HBV mono-infection group (65%). The mean hospital stay was similar across groups (23–24 days).

At admission, ALT levels were highest in the HBV mono-infection group (2530.6 U/L) compared to HBV+HDV (1566.07 U/L) and HBV+HCV (1070.76 U/L). Total bilirubin levels were elevated in all groups, with the highest level in HBV+HDV coinfection (172.08 μmol/L). At discharge, biochemical improvement was observed in all groups; however, persistent elevation of transaminases and bilirubin was more pronounced in the HBV+HDV group.

Conclusions: Acute HBV mono-infection presented with higher transaminase levels at admission, whereas HBV+HDV coinfection showed more persistent biochemical abnormalities at discharge. These findings suggest that HBV coinfections may be associated with slower biochemical recovery and warrant closer monitoring.

Keywords: Coinfection with hepatitis D virus, acute HBV mono-infection, viral coinfections

OP-60

Hepatic Biochemical Abnormalities in Chronic Hepatitis B: Evidence from a Tertiary Care Hospital in Nepal

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Aims: Chronic hepatitis B (CHB) is a global public health problem that can causes liver cirrhosis and hepatocellular carcinoma and is commonly associated with abnormal hepatic biochemical markers. Data on hepatic biochemical abnormalities among CHB patients in Nepal are limited. This study aimed to evaluate liver function test abnormalities in CHB patients attending a tertiary care hospital in Nepal.

Methods: A retrospective cross-sectional study was conducted including CHB patients who underwent liver function testing between 2018 and 2025 at a tertiary care hospital in Nepal. . Ethical approval was obtained from the Institutional Review Committee of KIST Medical College and Teaching Hospital. Demographic and laboratory data were retrieved from hospital records. Data were analyzed using SPSS version 17.0. Continuous variables are presented as mean ± SD, categorical variables as n (%), and one-sample t-tests were used to compare mean values with reference ranges. A p value < 0.05 was considered statistically significant.

Results: Among 200 CHB patients, elevated AST, ALT, and ALP were observed in 38.5%, 24.0%, and 23.5% of patients, respectively. Total and direct bilirubin were elevated in 20.5% and 10.5% of patients. Hypoalbuminemia was present in 25.0% of patients, while reduced total protein was found in 6.0%. Mean values of AST (42.28 ± 39.79 U/L), ALT (44.26 ± 31.33 U/L), and ALP (117.14 ± 103.07 U/L) were above reference ranges, whereas mean albumin (3.84 ± 0.65 g/dL) and total protein (7.02 ± 0.69 g/dL) were below normal. All differences were statistically significant (P<0.001).

Conclusions: Hepatic biochemical abnormalities are common among CHB patients in Nepal, especially elevated liver enzymes and reduced markers of liver synthetic function. Routine monitoring of liver function biomarkers is essential for accurate clinical assessment and management, particularly in resource-limited settings.

Keywords: Chronic Hepatitis B, Hepatic, ALT, AST

OP-61

A Nationwide Seroepidemiology Study of Hepatitis D Virus Infection in South Korea

Jeong Eun Song¹, Ju-Yeon Cho², Kwang Il Seo³, Young-Kul Jung⁴, Moon Young Kim⁵, In Hee Kim⁶, Jin Dong Kim⁷, Ji Won Han⁸, Heechul Nam⁹, Jung Hyun Kwon¹⁰, Myeong Jun Song¹¹, Seok-Hwan Kim¹¹, Hee Yeon Kim¹², Sung Won Lee¹², Jeong Won Jang⁸

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Aims: Hepatitis D virus (HDV) infection, which requires the presence of hepatitis B virus (HBV), is associated with a more aggressive clinical course in patients with chronic hepatitis B (CHB). Although the estimated global anti-HDV prevalence among HBsAg-positive individuals is 4.5%, data on HDV prevalence in South Korea remain limited. This study aimed to investigate the seroprevalence of HDV infection in patients with CHB in South Korea.

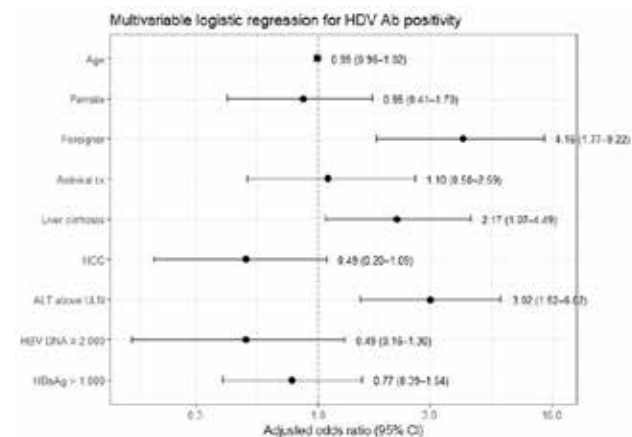
Methods: This prospective, multicenter cohort enrolled 2,115 patients with CHB from 13 tertiary centers in South Korea. Demographic, biochemical, and clinical liver disease data were collected. Anti-HDV antibodies were measured at a central laboratory using competitive enzyme and chemiluminescence immunoassays. Additional exploratory analyses were performed in a matched subset to assess virologic features associated with HDV infection.

Results: The median age of the cohort was 57 years, and 62% were male. Forty-eight patients (2.3%) were anti-HDV positive. Anti-HDV seroprevalence varied by geographic region, and the seroprevalence ranged from 0 to 3.5%. Anti-HDV positivity was significantly more frequent in foreign residents than in Korean nationals (13/140 [9.3%] vs. 35/1,975 [1.8%], P<0.001), in patients with liver cirrhosis than in those without cirrhosis (28/871 [3.2%] vs. 20/1,244 [1.6%], P=0.022), and in patients with ALT above the upper limit of normal (27/732 [3.7%] vs. 21/1,382 [1.5%], P=0.002). In multivariable analysis, foreign nationality (adjusted odds ratio [aOR], 4.16; 95% confidence interval [CI], 1.77-9.22), liver cirrhosis (aOR, 2.17; 95% CI, 1.07-4.49), and ALT above the upper limit of normal (aOR, 3.02; 95% CI, 1.52-6.02) were independent predictors of anti-HDV positivity. Among the 48 anti-HDV-positive patients, 13 (27.1%) had detectable HDV RNA. All had HBV DNA levels below 2,000 IU/mL and HBsAg titers above 100 IU/mL. In additional exploratory analyses, HBsAg and S RNA levels were significantly higher, whereas other serum and intrahepatic HBV markers were lower in the anti-HDV-positive group.

Conclusions: The national anti-HDV seroprevalence in South Korea remains lower than the global estimate; however, clinically

meaningful higher-risk subgroups were identified. Targeted HDV Ab screening should be considered in CHB patients with elevated ALT, liver cirrhosis, or foreign nationality. Further studies are needed to clarify the clinical impact of HDV coinfection in HBV-endemic areas.

Keywords: Hepatitis D Virus, Chronic Hepatitis B, Seroprevalence, Screening



Saturday, June 13, 2026, 08:00-09:00

12. HBV & HCV

OP-62

Current Status of Acute HCV Infection in Mongolia (2024–2025)

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¹National Center for Communicable Diseases, ²Mongolian National University of Medical Sciences, ³Liver Center, Mongolia

Aims: The prevalence of hepatitis C virus (HCV) infection in Mongolia was 9.3% as of 2021. Since the introduction of direct-acting antiviral (DAA) therapy in 2015, the overall prevalence of HCV infection and the burden of chronic HCV disease have shown a declining trend. Under the national “Eleg Büten Mongol” program, launched in 2017, more than 52,000 individuals have received antiviral treatment. However, despite these advances, new cases of acute HCV infection continue to be detected at the National Center for Communicable Diseases (NCCD).

Methods: We included patients who were hospitalized at the NCCD between October 2024 and October 2025 with anti-HCV positivity and clinical features consistent with acute HCV infection. Patients with other viral hepatitis infections (e.g., HBV, HDV) were excluded from the study.

Results: A total of 48 patients were hospitalized with acute

HCV infection. The mean age was 37.75 years, and 28 patients (58.3%) were male.

By marital status, the distribution was as follows:

- Married: 31 patients (64.6%), mean age 44.13 years, 18 males (58.1%)

- Unmarried: 17 patients (35.4%), mean age 25.88 years, 10 males (58.8%)

The mean length of hospital stay was 24.18 days. Baseline laboratory values upon admission were as follows: ALT – 1279.47 U/L, AST – 876.80 U/L, total bilirubin – 176.58 μ mol/L, direct bilirubin – 115.98 μ mol/L. At discharge, these values had decreased to ALT – 103.65 U/L, AST – 72.58 U/L, total bilirubin – 47.00 μ mol/L, and direct bilirubin – 35.69 μ mol/L.

Conclusions: The 48 acute HCV cases recorded at the NCCD during 2024–2025 indicate that acute HCV transmission remains ongoing in Mongolia, highlighting persistent gaps in risk behavior control and infection prevention. The higher incidence among younger, unmarried individuals suggests a need to strengthen targeted education and preventive interventions for high-risk groups.

Keywords: Acute HCV Infection in Mongolia, acute HCV, acute HCV infection

OP-63

Study of the Association between Liver Fibrosis and Renal Impairment in Chronic Hepatitis C

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Aims: Patients with chronic hepatitis C have an increased risk of developing diabetes mellitus, hepatic steatosis, and dyslipidemia, which may be associated with metabolic disturbances. Therefore, we aimed to determine the main causes of renal dysfunction, especially related to metabolic dysfunction, among patients with hepatitis C virus (HCV).

Methods: We included a total of 486 patients with HCV infec-

tion, who did not initiate the treatment of the direct-acting antiviral treatment at Kaohsiung Medical University Hospital between 2004 and 2021. We retrospectively collected patients general information (such as age, gender, and comorbidity), laboratory parameters (liver and kidney function, lipid profile, and glucose), and fibroscan test results. The scores evaluating the liver fibrosis severity (FIB4, APRI, and NAFLD Fibrosis Score (NFS)) and glomerular filtration rate (eGFR) are estimated using the standard approaches stated in the method section.

Results: We categorized the participants into the following three groups according to the NFS score: <-1.455 = F0-F2; $-1.455-0.675$ = indeterminate score, and >0.675 = F3-F4. Participants age and BMI were significantly higher in the F3-F4 group, compared to the other two groups. In addition, serum aspartate aminotransferase and alpha-fetoprotein levels were significantly elevated in the F3-F4 group, compared to the remaining groups. Whereas, in the F3-F4 group, platelet count and albumin level were significantly decreased ($P<0.001$). The incidence of chronic kidney disease ($\text{eGFR}<60\text{ml/min/1.73m}^2$) was significantly higher in the F3-F4 group than in the other two groups. Also, The eGFR was significantly decreased in participants categorized into F3-F4, compared to the remaining groups ($P<0.001$). We performed linear regression analysis, and the FIB4 score increased by 0.28 ($r^2=42.4$, $P<0.001$) units when the NFS score increased by one unit. Moreover, eGFR decreased by $-0.008\text{ ml/min/1.73m}^2$ ($r^2=43.8$, $P<0.001$), as the NFS score increased by one unit.

Table 3. Comparison of study variables by NAFLD Fibrosis Score category

	Total, n=486	FO-F2, n=139	Indeterminate, n=240	F3-F4, n=107	One-Way ANOVA p value
Age (mean $\pm$ SD)	60.32 $\pm$ 11.2	50.08 $\pm$ 10.1	60.62 $\pm$ 9.0	67.68 $\pm$ 9.5	<0.001 **
Gender, n (%)					
Male	200 (41.2)	51 (10.5)	109 (22.4)	40 (8.2)	0.002 *
Female	286 (58.8)	88 (11.5)	131 (27.0)	67 (20.4)	
BMI (mean $\pm$ SD)	25.02 $\pm$ 3.9	23.78 $\pm$ 3.3	24.81 $\pm$ 3.6	26.27 $\pm$ 4.5	<0.001 **
HbA1c (g/L)	13.52 $\pm$ 1.6	14.53 $\pm$ 1.6	13.84 $\pm$ 1.6	12.85 $\pm$ 1.4	<0.001 **
Liver function					
AST (U/L)	70.31 $\pm$ 53.4	54.70 $\pm$ 47.0	66.79 $\pm$ 55.2	83.51 $\pm$ 52.0	<0.001 **
ALT (U/L)	80.02 $\pm$ 66.2	74.96 $\pm$ 69.9	83.25 $\pm$ 67.4	78.66 $\pm$ 61.3	0.509
BLT (mg/dL)	0.94 $\pm$ 0.4	0.85 $\pm$ 0.3	0.92 $\pm$ 0.4	1.08 $\pm$ 0.4	<0.001 **
BLD (mg/dL)	0.13 $\pm$ 0.1	0.15 $\pm$ 0.0	0.17 $\pm$ 0.0	0.23 $\pm$ 0.1	<0.001 **
ALB (g/dL)	4.33 $\pm$ 0.4	4.57 $\pm$ 0.3	4.40 $\pm$ 0.3	4.21 $\pm$ 0.4	<0.001 **
PLT (10 ⁹ /L)	169.99 $\pm$ 66.6	244.27 $\pm$ 62.8	169.48 $\pm$ 62.8	113.69 $\pm$ 45.0	<0.001 **
AFP (g/L)	17.38 $\pm$ 124.5	5.32 $\pm$ 3.4	11.05 $\pm$ 33.7	37.48 $\pm$ 227.7	0.079
Lipid profile					
TCHOL (mg/dL)	173.70 $\pm$ 35.9	170.40 $\pm$ 36.3	175.92 $\pm$ 36.1	166.13 $\pm$ 32.6	0.013 *
TG (mg/dL)	96.42 $\pm$ 52.9	93.67 $\pm$ 45.4	97.21 $\pm$ 58.1	97.22 $\pm$ 49.0	0.833
HDL-C (mg/dL)	50.13 $\pm$ 14.6	50.18 $\pm$ 13.9	50.35 $\pm$ 16.0	49.70 $\pm$ 12.6	0.063
LDL-C (mg/dL)	100.57 $\pm$ 29.8	105.12 $\pm$ 32.3	103.42 $\pm$ 29.9	89.88 $\pm$ 26.6	<0.001 **
Glucose parameters					
AG sugar (mmol/L)	100.71 $\pm$ 15.0	97.44 $\pm$ 11.8	100.80 $\pm$ 14.5	103.15 $\pm$ 17.6	0.013 *
FG sugar (mmol/L)	143.11 $\pm$ 51.6	117.85 $\pm$ 36.3	141.30 $\pm$ 47.3	165.68 $\pm$ 57.9	<0.001 **
Liver fibrosis methods (SD)					
FIB4 (SD)	3.73 $\pm$ 3.4	1.42 $\pm$ 0.9	2.96 $\pm$ 1.9	6.91 $\pm$ 4.4	<0.001 **
APRI (SD)	1.43 $\pm$ 1.6	0.64 $\pm$ 0.6	1.22 $\pm$ 1.5	2.12 $\pm$ 1.9	<0.001 **
FibroScan (kPa)	12.05 $\pm$ 10.1	7.64 $\pm$ 4.4	11.72 $\pm$ 6.4	19.18 $\pm$ 13.6	<0.001 **
Renal function					
Cr (mg/dL)	0.97 $\pm$ 1.1	0.87 $\pm$ 0.9	1.04 $\pm$ 1.3	0.92 $\pm$ 0.9	0.434
BUN (mg/dL)	14.35 $\pm$ 9.4	12.20 $\pm$ 4.5	15.05 $\pm$ 9.9	16.83 $\pm$ 11.1	0.019 *
eGFR (ml/min/1.73m ²)	92.45 $\pm$ 25.7	101.45 $\pm$ 26.4	91.35 $\pm$ 27.9	87.74 $\pm$ 29.1	<0.001 **
eGFR <60, n (%)	216 (44.6)	31 (6.5)	110 (23.2)	75 (15.8)	<0.001 **
eGFR <30, n (%)	46 (9.7)	3 (0.6)	20 (4.2)	23 (4.9)	<0.001 **
Comorbidities (n%)					
DM (%)	453 (93.2)	104 (21.4)	225 (46.3)	124 (25.5)	0.168
HTN (%)	326 (67.1)	85 (17.5)	160 (32.9)	81 (16.7)	0.011 *
Cryoglobulinemia (%)	176 (36.3)	52 (10.7)	86 (17.7)	38 (7.8)	0.018 *
HLD (%)	435 (89.5)	99 (20.4)	206 (42.4)	130 (25.7)	0.095
CKD (%)	464 (95.5)	105 (21.8)	225 (46.3)	133 (27.4)	0.278
HCV RNA (log ¹⁰)	5.67 $\pm$ 0.9	5.66 $\pm$ 1.0	5.78 $\pm$ 0.9	5.49 $\pm$ 0.9	0.017 *

We assessed NAFLD Fibrosis score in 486 participants in the study. Because some participants had missing diagnostic data, it was not possible to assess NAFLD Fibrosis score. Continuous and categorical variables were analyzed using ANOVA test to compare the NAFLD Fibrosis score groups. Descriptive statistics (mean and standard deviation (SD), A probability value <0.05 was considered to indicate statistical significance. * $p<0.05$, ** $p<0.01$. NAFLD = Non-Alcoholic Fatty Liver Disease; BMI = Body Mass Index; HbA1c = Hemoglobin A1c; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; BLT = Total Bilirubin; BLD = Bilirubin; PLT = Platelet; AFP = Alpha-fetoprotein; TCHOL = Total Cholesterol; TG = Triglyceride; HDL-C = High-density lipoprotein; LDL-C = Low-density lipoprotein; AG = Fasting glucose; FG = Fasting glucose; FIB4 = Fibrosis-4; APRI = AST to Platelet Ratio Index; Cr = Creatinine; BUN = Blood Urea Nitrogen; eGFR = estimated Glomerular Filtration Rate; DM = Diabetes Mellitus; HTN = Hypertension; HLD = Hyperlipidemia; CKD = Chronic Kidney Disease; HCV RNA = Hepatitis C Virus Ribonucleic acid.

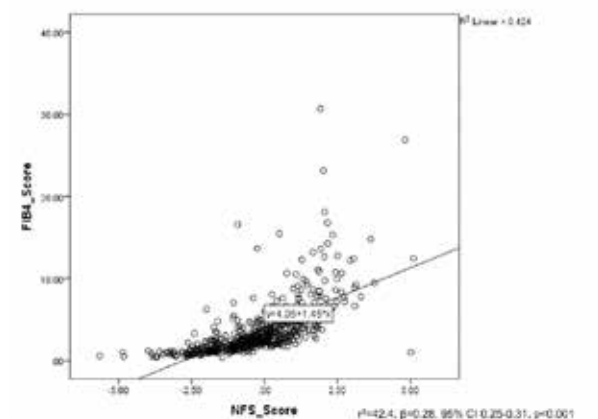


Figure 1. Linear regression NFS score and FIB4 index association

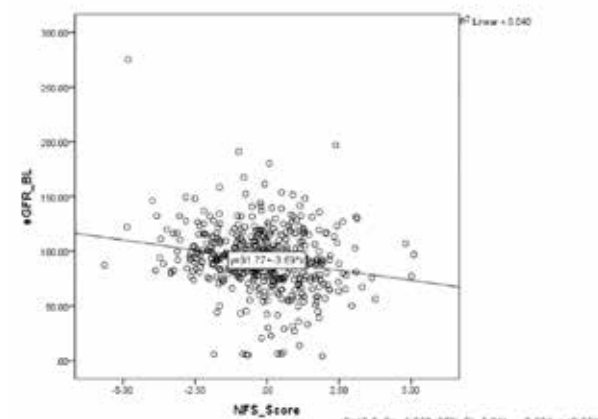


Figure 2. Linear regression NFS score and eGFR association

Conclusions: We found that patients who have a higher probability of developing advanced liver fibrosis have a higher risk of having kidney dysfunction. Therefore, the liver fibrosis and metabolic dysfunction caused by HCV may increase the risk of developing renal impairment.

Keywords: NAFLD Fibrosis Score, FIB4, APRI, Glomerular Filtration Rate, Renal Function

OP-64

Exploring Predictors of Hepatitis C Treatment Uptake among People Who Use Drugs (PWUDs): A Prospective, Multicenter Study

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Aims: Treatment of people who use drugs (PWUD) with hepatitis C virus (HCV) infection is critical for achieving HCV elimination goals. Given that policies for drug, HCV prevalence, and medical environments for PWUD vary across countries, there is a need to analyze factors associated with treatment at an individual level. Therefore, this study aimed to assess the treatment uptake among PWUD with HCV and to explore factors associated with treatment.

Methods: A total of 50 PWUDs (median age 54 years, 88% male, and intravenous drug user 98%) with positive anti-HCV and HCV RNA were prospectively enrolled in 4 hospitals from August 2022 to December 2025. For them, blood tests including complete blood cell count and liver panel, and questionnaires related to socioeconomic, psychiatric and risk factors for HCV infection were conducted.

Results: Among 50 PWUDs with HCV, the overall treatment rate was only 48% (24/50). The treated group (n=24) showed a significantly higher median AST level (35 vs. 28 U/L, $P=0.029$), higher proportion of the Medicaid (73.3% vs. 38.5, $P=0.001$) and point-of-care treatment (91.7% vs. 15.4%, $P<0.001$), and lower proportion of low education (70.8% vs. 96.2%) than the no-treated group (n=26).

Among treated group, sustained virologic response (SVR) was achieved in 58.3%, while the remaining 41.7% received a full course of direct acting antiviral (DAA) therapy but could not be evaluated for SVR due to loss to follow-up. Among no-treated group, the main reasons for not receiving HCV treatment were cost of DAA regimen (57.7%), incarceration (23.1%), and loss to follow-up (19.2%).

In the multivariate logistic regression analysis, the point-of-care (POC) treatment (RR [relative risk] 57.453; 95% CI 8.097 – 407.673) and the no out-of-pocket expense (medicaid; RR 7.036; 95% CI 1.044 – 51.109) were the significant factor for a HCV treatment uptake (RR 62.256, 95% CI 5.811 – 128.654, $P=0.001$).

Conclusions: The HCV treatment rate in the PWUD-HCV patient population is 48% far below the target for HCV elimination. The POC treatment program and financial aid is crucial factors to improve the linkage-of-care for HCV.

Keywords: Hepatitis C, Hepatitis C Treatment Uptake among People Who Use Drugs, Linkage to Care, Policy

OP-65

Associated Factors of HCV Transmission between Couples Using National Health Insurance Data

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Aims: Hepatitis C virus (HCV) is primarily transmitted through blood-borne and sexual routes. Although spousal transmission of HCV represents a significant public health concern within the context of sexual transmission, large-scale, population-based studies on this issue remain scarce. Utilizing a spousal pair cohort, this study aimed to evaluate the incidence of HCV infection among spouses according to the duration of exposure following the diagnosis of the index case, and to assess the risk factors associated with the infection.

Methods: Utilizing the eligibility data of the insured from the National Health Insurance database, a cohort was constructed comprising newly diagnosed HCV patients (index cases) aged 20 years and older and their spouses between 2005 and 2022. A washout period from 2002 to 2004 was applied to identify incident index cases. Spousal pairs diagnosed with HCV on the same day or cases where either spouse was diagnosed outside the duration of their marriage were excluded. Ultimately, 93,644 spousal pairs were included in the final analysis. The cumulative risk of spousal infection according to the duration of exposure following the index case diagnosis was estimated using the Kaplan-Meier method, and Cox proportional hazards models were employed to evaluate the risk factors for transmission.

Results: During an average follow-up of 9.1 years, HCV infection occurred in 3,356 spouses (cumulative infection rate, 3.6%; incidence rate, 3.9 per 1,000 person-years). The risk of spousal infection peaked within the first year following the index case diagnosis (10.6 per 1,000 person-years) and gradually decreased thereafter. Notably, the cumulative infection rate was 28.3% for female spouses of male index cases, compared to 2.5% for male spouses of female index cases. The risk of spousal transmission was significantly higher when the index case was male (aHR=12.97, 95% CI: 12.03-13.99).

Transmission risk significantly decreased for index cases diagnosed after the August 2015 introduction of DAAs compared to earlier cases (aHR=0.50, 95% CI: 0.45-0.55). Risk also increased with older index case age (aged : aHR=1.32, 95% CI: 1.09-1.61). For spouses, older age, a history of HBV, and a Charlson Comorbidity Index(CCI) of (aHR=2.16, 95% CI: 1.91-2.43) were significant factors increasing vulnerability to HCV infection.

Conclusions: Spousal HCV infection risk is highest immediately after the index case diagnosis, especially from male index cases to female spouses. However, antiviral treatment of the index case significantly mitigates this risk. Thus, newly diagnosed HCV cases warrant prompt DAA therapy alongside immediate spousal screening.

Keywords: Hepatitis C Virus, Spousal Infection, Prevention Strategies, Big Data

OP-66

Re-Engagement to Rescue Therapy with Sofosbuvir/Velpatasvir/Voxilaprevir in Hepatitis C after Direct-Acting Antiviral Failure

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Aims: Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) enables rescue therapy for patients with chronic hepatitis C (CHC) who failed previous direct-acting antiviral (DAA) regimens. This study aimed to re-engage patients lost to follow-up (LTFU) after DAA failure and evaluate outcomes of SOF/VEL/VOX re-treatment.

Methods: A prospective observational study was conducted at 10 tertiary centers in South Korea. Investigators identified LTFU patients after DAA failure via electronic medical record screening, assessed eligibility for SOF/VEL/VOX retreatment, and contacted them by telephone to facilitate re-engagement. DAA failure was defined as failure to achieve sustained virologic response at 12 weeks post-treatment (SVR12) or post-SVR12 relapse of HCV RNA. Eligible patients who provided written consent received 12 weeks of SOF/VEL/VOX and checked SVR12.

Results: Among 4,439 patients who had received DAA therapy between 2015 and 2023, 45 LTFU patients (1.0%) were eligible for SOF/VEL/VOX retreatment. Of these (n=45), 19 (42.2%) patients were successfully contacted, but only eight (42.1%) returned for an in-person visit. Of these (n=8), 5 (62.5%) patients agreed to initiate SOF/VEL/VOX treatment, and all achieved SVR12.

Conclusions: SOF/VEL/VOX enabled re-engagement and successful retreatment of patients previously LTFU after DAA failure. However, nationwide frameworks are required to strengthen linkage to care.

Keywords: Hepatitis C, Chronic, Antiviral Agents, Therapeutic Use, Treatment Failure, Sofosbuvir; Velpatasvir; Voxilaprevir

OP-67

Real-World Effectiveness and Safety of Pangenotypic Direct-Acting Antivirals in Patients with Chronic Hepatitis C: A Large-Scale Multicenter Cohort Study

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Aims: The therapeutic paradigm for chronic hepatitis C (CHC) has shifted toward pangenotypic direct-acting antiviral (DAA) regimens, significantly mitigating the diagnostic burden of genotype-specific testing. This study aimed to evaluate the real-world clinical effectiveness, safety, and biochemical outcomes of pangenotypic DAAs (Glecaprevir/Pibrentasvir and Sofosbuvir/Velpatasvir) in a large-scale, representative Korean cohort.

Methods: We conducted a retrospective, multicenter cohort analysis using the Clinical Data Warehouse (CDW) from eight affiliated hospitals of the Catholic Medical Center. A total of 1,220 patients with CHC who initiated pangenotypic DAA therapy between January 2019 and September 2024 were enrolled. The primary endpoint was the achievement of sustained virologic response at 12 weeks post-treatment (SVR12). Secondary endpoints included on-treatment virologic dynamics, ALT normalization rates, and the incidence of adverse clinical events.

Results: Among the 1,220 patients (mean age 60.4 years), 1,080 were treated with Glecaprevir/Pibrentasvir and 140 with Sofosbuvir/Velpatasvir. The cohort represented a broad clinical spectrum, including patients with liver cirrhosis (9.1%) and a history of hepatocellular carcinoma (1.7%). The overall SVR12 rate was 95.9% (95.6% for Glecaprevir/Pibrentasvir and 97.6% for Sofosbuvir/Velpatasvir), demonstrating consistent therapeutic potency across all genotypes with no statistically significant difference between the two treatment regimens ($P>0.05$). Virologic suppression was rapid, with 84.7% achieving undetectable

HCV RNA by week 4 and 96.4% at the end of treatment (EOT). Biochemical response was equally robust, with 96.8% achieving ALT normalization at the SVR12 time point. The treatment completion rate exceeded 97%, indicating excellent tolerability. Virologic breakthrough and post-treatment mortality were observed in only 1.72% and 2.21% of patients, respectively, confirming a manageable safety profile in clinical practice.

Conclusions: In this large-scale real-world analysis, pangenotypic DAA regimens demonstrated robust clinical efficacy and a favorable safety profile across a diverse spectrum of Korean CHC patients, including those with advanced liver disease. The high rates of SVR12 and biochemical recovery, coupled with superior treatment adherence, validate pangenotypic therapy as the optimized standard of care to facilitate simplified treatment algorithms and support global HCV elimination efforts.

Keywords: Chronic Hepatitis C, Direct-Acting Antiviral Agents, Sustained Virologic Response, Pangenotypic

Saturday, June 13, 2026, 08:00-09:00

13. MASLD, Clinical

OP-68

Fat-to-Muscle Ratio and Subtype-Specific Protective Effects of Exercise in Steatotic Liver Disease: A Large-Scale Cohort Study

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Aims: The Steatotic Liver Disease (SLD) nomenclature encompasses various subtypes, including MASLD, MetALD, and ALD. However, the specific impact of body composition and physical activity across these SLD subtypes remains to be elucidated. We aimed to evaluate the association of the fat-to-muscle ratio (FMR) and different exercise modalities with the risk of SLD subtypes.

Methods: A total of 64,923 participants (mean age 52.1 years) from a large-scale Korean cohort were included. Hepatic steatosis was diagnosed by abdominal ultrasonography, and participants were categorized into MASLD, MetALD, and ALD based on metabolic risk factors and alcohol intake. Body composition indices, including the appendicular skeletal muscle index (ASMI) and FMR, were calculated. Multivariable logistic regression

analysis was performed to determine the adjusted odds ratios (aORs) for each SLD subtype according to body composition and exercise patterns (aerobic and strength training).

Results: The prevalence of MASLD, MetALD, and ALD was 24.4%, 5.3%, and 2.9%, respectively. High FMR demonstrated a remarkably strong association with hepatic steatosis (aOR 14.63 [95% CI 11.30–18.94]), exceeding individual measures of fat or muscle mass. Both aerobic and strength exercises were generally protective against all SLD subtypes (aORs: 0.68-0.81). However, subgroup analyses revealed distinct patterns: In older participants (>60 years) and non-obese ALD participants (BMI <25 kg/m²), strength training exhibited a significantly more robust protective effect (aOR 0.51) than aerobic exercise. In the MetALD group, strength training was particularly effective for females (aOR 0.51), whereas aerobic exercise showed no significant benefit in this subgroup.

Conclusions: The FMR is a powerful and independent predictor across the entire spectrum of SLD. The protective effects of physical activity vary significantly by disease subtype and clinical characteristics. Tailored strategies, particularly prioritizing strength training for older or non-obese alcohol-related SLD patients, are warranted for effective disease management.

Keywords: Liver Steatosis, Sarcopenia, Body Composition, Resistance Training

OP-69

Impact of Hyperuricemia on the Mortality in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Hyperuricemia is implicated in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD); however, the association between hyperuricemia and mortality in patients with MASLD remains unclear. We evaluated the associations of hyperuricemia, continuous serum uric acid levels, and hyperuricemia normalization with all-cause mortality in patients with MASLD.

Methods: This study included 32,129 adults aged ≥40 years with MASLD who underwent health examinations. MASLD was diagnosed by ultrasonography, and hyperuricemia was defined as a serum uric acid level >7 mg/dL in men and >6 mg/dL in

women. The outcome of this study was all-cause mortality.

Results: During 263,461 person-years of follow-up (mean duration, 8.4 years), 570 participants died. Compared with participants without hyperuricemia, those with hyperuricemia had a higher risk of all-cause mortality (adjusted hazard ratio [aHR], 1.26; 95% confidence interval [CI], 1.02–1.55), which was consistent across prespecified subgroups and propensity score-matched analyses. When serum uric acid was analyzed as a continuous variable and categorized into quartiles, the aHRs (95% CI) were 0.93 (0.73–1.18), 0.83 (0.64–1.08), and 1.11 (0.85–1.45) for Q2–Q4 versus Q1, which was consistent with a J-shaped association. Hyperuricemia normalization was associated with a reduced risk of all-cause mortality (aHR, 0.68; 95% CI, 0.43–1.09) when analyzed as a time-varying exposure.

Conclusions: In patients with MASLD, hyperuricemia was associated with increased all-cause mortality, whereas continuous serum uric acid levels showed a J-shaped association with mortality. The normalization of hyperuricemia was associated with a reduced mortality risk. These findings suggest that monitoring and managing serum uric acid levels may be clinically relevant, while avoiding excessively low levels.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Hyperuricemia, Mortality

OP-70

Safety and Efficacy of Lactobacillus Delbrueckii Subsp. Lactis CKDB001 in Metabolic-Associated Steatotic Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Trial

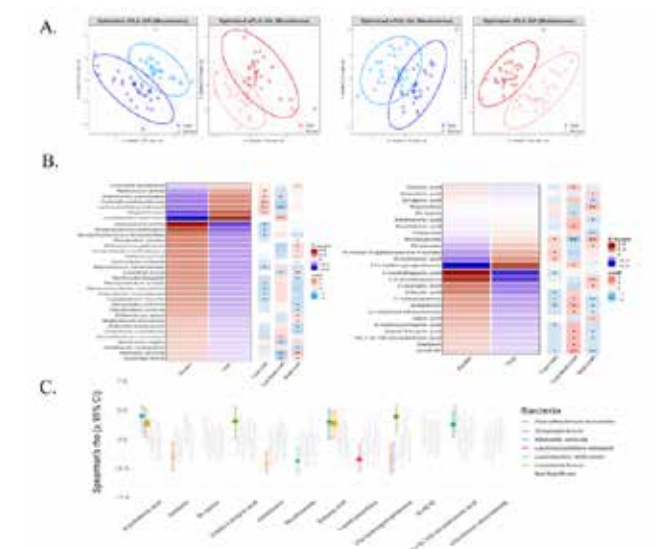
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Aims: Lactobacillus delbrueckii subsp. lactis CKDB001 is a probiotic derived from raw milk fermentation with hepatoprotective and metabolic effects mediated through bile acid metabolism, lipid handling, and gut–liver axis signaling. This study evaluated its safety, clinical efficacy, and gut microbiome–metabolome modulation in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: In this randomized, double-blind, placebo-controlled trial, patients with MASLD received CKDB001 (5.0 × 10⁹ CFU/day, one capsule twice daily; n = 46) or placebo (n = 43) for 12 weeks. Primary outcomes were changes in serum AST and ALT. Secondary outcomes included liver function markers, lipid and glucose metabolism parameters, and fatigue. Exploratory outcomes assessed anthropometry, hepatic steatosis and stiffness by transient elastography, and gut microbiome and metabolome profiles using an integrative multi-omics

Results: Eighty-nine participants (mean age 44.7 years; mean BMI 29.9 kg/m²) were included, with comparable baseline characteristics between groups and no withdrawals. CKDB001 was well tolerated, with no differences in adverse events or aminotransferase levels compared with placebo. Favorable trends were observed in insulin resistance and hepatic steatosis. Significant reductions in waist and hip circumference were observed exclusively in the intervention group (all *P* < 0.005). Multi-omics analyses revealed stable microbial diversity but intervention-specific shifts in microbial taxa and metabolites at Week 12. Treatment-by-time interactions were identified for 8 taxa and 12 metabolites, including increases in *L. delbrueckii* and the butyrate-producing *Faecalibacterium duncaniae* (all *P* < 0.001). Lipid-related and bioactive metabolites involved in inflammation and host signaling were significantly altered. Correlation analyses linked *L. delbrueckii* with indole-3-butyric acid and 17 α -hydroxyprogesterone, and *F. duncaniae* with arachidonic acid–related metabolites, indicating coordinated microbe–metabolite modulation.



Conclusions: CKDB001 supplementation modulated key metabolites and lipid mediators associated with gut–liver axis signaling in patients with MASLD. These findings suggest a mechanistic basis for its metabolic benefits and support further large-scale studies to evaluate its potential as a therapeutic target for MASLD.

Keywords: Lactobacillus Delbrueckii Subsp. Lactis CKDB001, Metabolic-Associated Steatotic Liver Disease, Gut Microbiome, Metabolomics

OP-71

Differential Prognostic Roles of Muscle and Adiposity in MASLD: Insights from MRI-Based Body Composition Analysis

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Aims: MRI-derived body composition parameters may refine risk stratification in steatotic liver disease (SLD), but the relative contributions of hepatic fat, adiposity, and muscle composition remain poorly defined. We aimed to evaluate their independent and interactive effects on long-term clinical outcomes.

Methods: We analyzed 24,976 UK Biobank participants with abdominal MRI, classified as no SLD, metabolic dysfunction-associated SLD (MASLD), or metabolic alcohol-related liver disease (MetALD). MRI-derived metrics included proton density fat fraction (PDFF), visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT), muscle fat infiltration (MFI), and fat-free muscle volume (FFMV). Multivariable Cox models, time-dependent ROC analyses, and interaction analyses were performed for overall survival, cardiovascular disease, and cerebrovascular disease.

Results: Clinical outcomes worsened stepwise from no SLD to MASLD and MetALD ($P<0.001$). In the overall cohort, higher MFI was independently associated with increased mortality, whereas lower FFMV was protective (both $P<0.001$); PDFF and VAT were not significant after full adjustment. In MASLD, muscle parameters were the strongest prognostic markers: higher MFI was associated with increased mortality and cerebrovascular disease, while lower FFMV and higher VAT predicted increased cardiovascular disease risk (all $P<0.001$). In contrast, MRI-derived parameters had limited prognostic value in individuals without SLD. In MASLD, predictive performance analyses showed that a model integrating adiposity and muscle parameters achieved the highest discrimination for mortality (AUC ~0.71), outperforming other models. Interaction analyses demonstrated that the adverse effect of higher MFI and the protective effect of higher FFMV were consistently observed across subgroups, with more pronounced and robust associations in the MASLD population.

Conclusions: MRI-derived body composition provides substantial prognostic value in MASLD beyond hepatic fat alone. MFI and FFMV are key determinants of outcomes, supporting the clinical utility of comprehensive MRI-based phenotyping for risk stratification.

Keywords: MASLD, Magnetic Resonance Imaging, Muscle Fat Infiltration, Body Composition

OP-72

The MASLD Journey in the General Population: Linkage-to-Care and Patient-Reported Uptake of Fibrosis Risk Assessment

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Aims: Despite the growing burden of steatotic liver disease (SLD), real-world evidence on patient-reported post-diagnostic care pathways and fibrosis risk assessment remains limited. We aimed to describe the patient-reported care pathway from initial diagnosis to subsequent follow-up and fibrosis assessment among individuals with self-reported SLD, including those meeting at-risk criteria, in a population-based survey sample.

Methods: A web-based survey was conducted among Korean adults aged ≥ 19 years recruited from an established online research panel, using quota strata to approximate the national distribution of key demographics. Respondents completed a screening questionnaire; those who screened positive for self-reported physician-diagnosed or imaging-detected fatty liver/SLD proceeded to the full survey on post-diagnosis healthcare utilization and follow-up. Of 12,946 respondents with a valid screening questionnaire, 1,000 individuals with self-reported SLD comprised the final analytic sample.

Results: The self-reported prevalence of physician-diagnosed or imaging-detected SLD was 23.7%. Most participants (79.9%) reported an incidental diagnosis during routine medical check-ups. Overall, 57.7% (577/1,000) reported linkage-to-care, and 14.9% (86/577) of those reporting linkage-to-care also reported having undergone fibrosis assessment. Among those reporting no follow-up, the most commonly cited reason was the belief that SLD was not a serious condition. Among those reporting linkage-to-care, 68.8% (397/577) reported follow-up in primary clinics and 31.2% (180/577) in referral centers; patient-reported fibrosis assessment was 10.6% (42/397) and 24.4% (44/180), respectively. The at-risk subgroup comprised 61.9% (619/1,000); 65.6% (406/619) reported linkage-to-care, and 12.1% (75/619) reported fibrosis assessment. Patient-reported linkage-to-care was 55.5% in MASLD, 59.7% in MetALD, and 65.2% in ALD.

Conclusions: In this survey sample, most respondents with self-reported SLD reported an incidental diagnosis during medical check-ups, and patient-reported fibrosis assessment was uncommon, including among those meeting at-risk criteria.

Keywords: MASLD, Linkage to Care, Guideline Implementation

OP-73

Development and Validation of an AI-Based Prediction Model for Cardiovascular Disease Events in Patients with MASLD

Yewon Park¹, Han Ah Lee¹, Sang Gyune Kim², Soo Young Park³, Young Youn Cho¹, Hyung Joon Kim¹, Yeon Seok Seo⁴, Seung Up Kim⁵, Dae Won Jun⁶, On behalf of the VCTE-based Liver Investigation Network (V-LINK) Study group

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Aims: Traditional cardiovascular disease (CVD) risk scores show suboptimal predictive performance in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to develop and validate a MASLD-specific AI-based risk prediction model.

Methods: The analysis was conducted using the V-LINK SLD cohort, which integrates data from seven major tertiary centers in Korea. Various machine-learning algorithms were tested for model development. Model performance was rigorously evaluated using the C-index, AUROC, AUPRC, and F1-score at 3 and 5 years, and compared with previous risk scores using DeLong's test and Net Reclassification Improvement (NRI).

Results: A total of 16,425 patients was divided into a training set (N=11,250) and a test set (N=5,175). A total of 2,302 CVD events occurred during the follow-up. In the multivariable Cox analysis, significant predictors of CVD were older age (HR=1.04), dyslipidemia (HR=1.34), higher HbA1c (HR=1.08), smoking (HR=1.19), and higher liver stiffness measurement (HR=1.02). Among the various models tested, the XGBoost (XGB) model demonstrated the highest accuracy. In the training set, the 3-year performance showed a C-index of 0.944, an AUROC of 0.954, an AUPRC of 0.762, and an F1-score of 0.575. The model also exhibited high stability; the 5-year performance in the training set yielded a C-index of 0.936, an AUROC of 0.951, an AUPRC of 0.861, and an F1-score of 0.727. In the test set, the model maintained robust generalizability with a 3-year AUROC of 0.895 and a 5-year AUROC of 0.891. In comparative analysis, the XGB model significantly outperformed traditional scores;

the AUROCs for PCE_10yr and PREVENT were 0.702 and 0.718, respectively ($P<0.001$ by DeLong's test). Furthermore, the XGB model achieved a Category-free NRI of 0.384 ($P<0.001$) compared to PCE_10yr.

Conclusions: The XGB model, by integrating hepatic fibrosis and steatosis indicators with metabolic factors, provides a highly accurate and validated tool for CVD risk stratification in MASLD.

Keywords: Cardiovascular Disease, Metabolic Dysfunction-Associated Steatotic Liver Disease, Artificial Intelligence, Prediction

Saturday, June 13, 2026, 08:00-09:00

14. LC, Liver Failure & Autoimmune Diseases 2

OP-74

Current Status and Prognosis of Autoimmune Hepatitis Based on the Japanese AIH Registry

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Aims: We established the nationwide Japanese AIH Registry in 2025. This study aimed to clarify the clinical characteristics and prognosis of AIH using the Japanese AIH Registry.

Methods: Among all registered patients, the present study focused on those who were followed for ≥ 1 year with evaluable complete biochemical response (CBR). Patients with ursodeoxycholic acid monotherapy were excluded. Clinical background, treatment, relapse, hepatocellular carcinoma (HCC), and outcomes were assessed.

Results: Overall, 1,156 patients with AIH were analyzed. Median age was 62 years; 83% were women. The prevalence of cirrhosis at diagnosis was 17.4%. Initial treatment was prednisolone alone in 78.0% and prednisolone plus azathioprine in 21.4%. CBR rates were 62.1% at 6 months and 80.4% at 12 months. During a mean follow-up of 5.1 years, relapse occurred in 30.3%, HCC in 1.9%, liver transplantation in 0.3%, and death in 2.9% (liver-related 1.0%). Transplant-free survival at 3, 5, and 10 years was 99.3%, 99.0%, and 97.9%, respectively. After adjusting for covariates, a failure to achieve CBR was strongly associated with poorer survival at both 6 and 12 months ($P<0.001$). Cirrhosis and relapse did not affect overall survival. Cumulative HCC incidence was 0.4%, 0.6%, and 2.1% at 3, 5, and 10 years. Cirrhosis at diagnosis was significantly associated with higher HCC risk ($P<0.005$).

Conclusions: This large-scale registry analysis provides an up-

dated overview of AIH in Japan. A failure to achieve CBR is a strong predictor of poor prognosis, while cirrhosis at diagnosis is associated with increased HCC risk.

Keywords: Autoimmune Hepatitis, Prognosis, Complete Biological Response, Nation-Wide Study

OP-75

Noninvasive Risk Stratification of Advanced Fibrosis in Autoimmune Liver Disease Using Machine Learning

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Aims: Assessing fibrosis without invasive procedures is important in autoimmune liver disease. However, separating advanced from non-advanced fibrosis remains difficult, especially in patients with intermediate stages. We aimed to develop a clinically interpretable machine learning model to identify advanced fibrosis using routinely available noninvasive parameters.

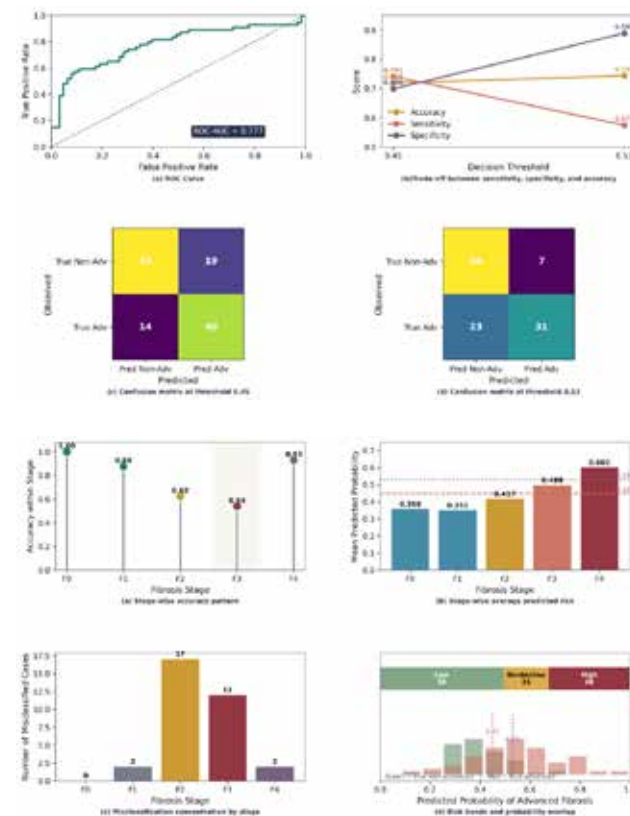
Methods: We retrospectively analyzed 117 patients with biopsy-referenced fibrosis stages F0-F4. The primary endpoint was advanced fibrosis (F3-F4) versus non-advanced fibrosis (F0-F2). Only noninvasive clinical and laboratory variables were considered. After feature selection, a 14-variable model was derived, including immunoglobulin IgA, immunoglobulin IgG, INR, bilirubin, ALT, GGT, sodium, body mass index, systolic and diastolic blood pressure, alcohol history, smoking status, anti-nuclear antibody, and anti-smooth muscle antibody. Stratified 5-fold cross-validation with out-of-fold prediction was used to evaluate performance. Logistic regression was compared with calibrated linear support vector classification, random forest, and extra trees. Risk categories were defined as low-risk (<0.45), borderline (0.45-0.53), and high-risk (>0.53).

Results: Logistic regression achieved an ROC-AUC of 0.777 and provided the best overall performance among tested algorithms. At threshold 0.53, performance was 74.4% accuracy, 73.2% balanced accuracy, 81.6% precision, 88.9% specificity, and 57.4% sensitivity. At threshold 0.45, performance was 71.8% accuracy, 72.0% balanced accuracy, 67.8% precision, 69.8% specificity, and 74.1% sensitivity. Risk stratification identified 58 low-risk, 21 borderline, and 38 high-risk cases. Stage-specific performance was highest at the extremes (F0-F1 and F4, 88–100% accuracy) but lower at the F2-F3 transition (54–62%), where 88% of misclassifications occurred.

Conclusions: A 14-feature logistic regression model provided useful, fully noninvasive discrimination of advanced fibrosis in autoimmune liver disease. A threshold of 0.53 supports high-confidence classification, whereas 0.45 may be preferable

for screening. Cases near the F2-F3 boundary remained the main area of uncertainty and may require confirmatory evaluation with elastography or biopsy.

Keywords: Autoimmune Liver Disease, Liver Fibrosis, Noninvasive Risk Stratification, Machine Learning



OP-76

Hepatocyte ApoJ Accelerates Injury-Induced Liver Fibrosis by Orchestrating Ranbp2-Mediated SUMOylation and Subsequent STAT3 Activation

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Aims: Dysregulation of the signal transducer and activator of transcription 3 (STAT3) pathway is closely linked to redox imbalance and exacerbates liver injury. Apolipoprotein J (ApoJ) is a chaperone that responds to oxidative stress. We aimed to investigate how hepatocyte ApoJ regulates STAT3 signaling

to mediate paracrine activation of hepatic stellate cells (HSCs) in fibrogenesis.

Methods: Hepatocyte-specific ApoJ knockout (ApoJ-HKO) and ApoJ-overexpressing mouse models were generated, and experimental liver fibrosis was induced. Paracrine interactions between hepatocytes and HSCs were assessed by treating HSCs with hepatocyte-conditioned media. Additionally, single-cell RNA sequencing data from patients with liver cirrhosis and healthy controls were analyzed to determine ApoJ expression patterns.

Results: ApoJ expression in hepatocytes was significantly elevated in patients with cirrhosis and in multiple mouse models of liver fibrosis. Single-cell analysis showed that this ApoJ upregulation was predominantly localized to hepatocytes in fibrotic livers. ApoJ-HKO mice exhibited markedly attenuated injury-induced fibrosis, characterized by reduced HSC activation, diminished F4/80 macrophage infiltration, and preserved redox balance. Conversely, hepatocyte-specific ApoJ overexpression exacerbated liver fibrosis. Mechanistically, oxidative stress induced ApoJ expression, which interacted with Ran-binding protein 2 (RanBP2) to enhance SUMOylation of STAT3 at lysine 679. SUMOylated STAT3 exhibited increased nuclear translocation, leading to STAT3 pathway activation and subsequent upregulation of TGF- β and reactive oxygen species production in hepatocytes. Treatment with the STAT3 inhibitor Stattic significantly attenuated fibrosis progression in ApoJ-overexpressing mice.

Conclusions: These findings demonstrate that hepatocyte ApoJ is a key driver of liver fibrosis via RanBP2-mediated SUMOylation and activation of STAT3. Targeting the ApoJ/STAT3/RanBP2 axis may provide a novel therapeutic strategy for preventing and treating fibrotic liver disease.

Keywords: Liver Fibrosis, Apolipoprotein J, STAT3, RANBP2

OP-77

Succinate-SUCNR1 Signaling in Endothelial Contributes to Liver Fibrosis Progression

Jian Xu, Yuechen Wang, Haoming Zhou

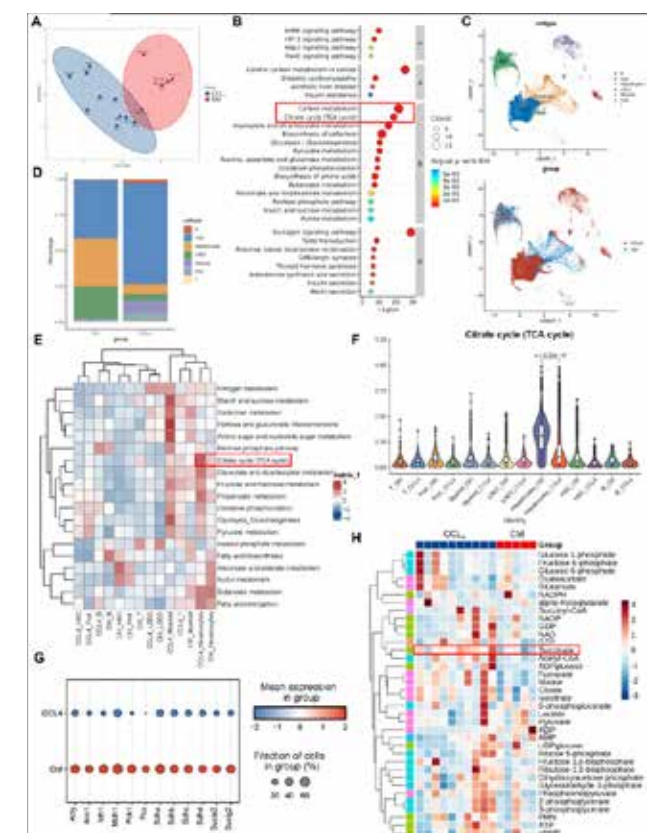
The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

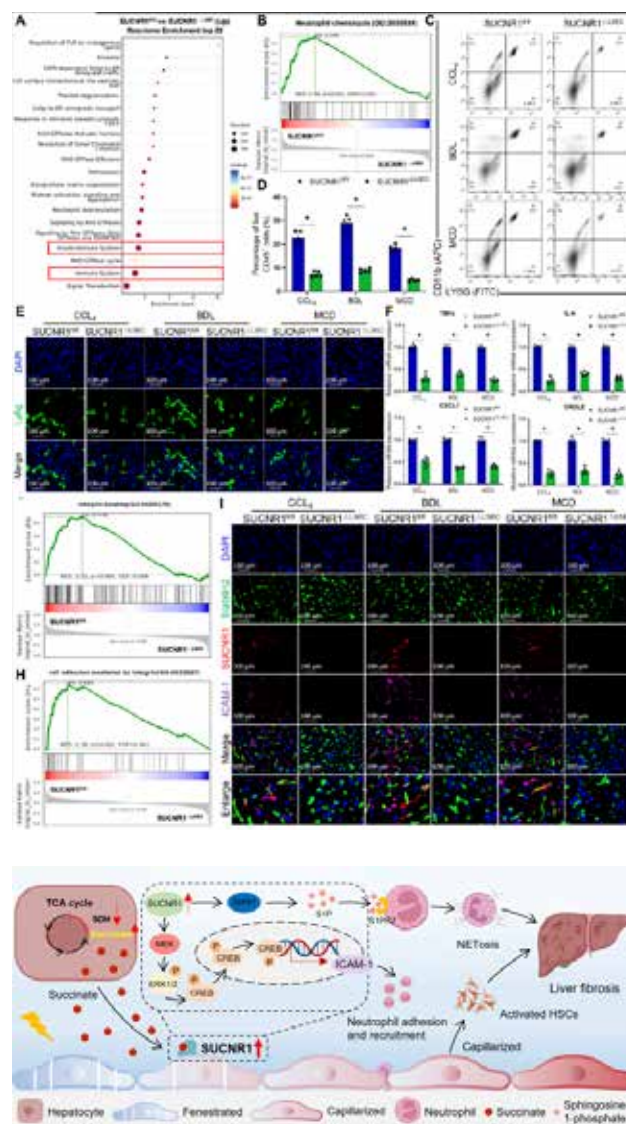
Aims: Succinate receptor 1 (SUCNR1) is an autocrine and paracrine sensor for succinate, a metabolic stress signal. However, the role in modulating liver sinusoidal endothelial cells (LSECs) function and neutrophil-related inflammation during liver fibrosis remains unexplored. Herein, we aim to characterize the function of SUCNR1 in LSECs during the progression of liver fibrosis.

Methods: Succinate levels and SUCNR1 expression were measured in human and mouse fibrotic liver tissues. Endothelial-specific SUCNR1 knockout mice were generated, and

experimental liver fibrosis was induced by chronic carbon tetrachloride administration, bile duct ligation and methionine-choline deficient diet. Liver samples were evaluated using RNA-seq, electron microscopy, and immunostaining. Primary LSECs and neutrophils were isolated for gene expression analysis to explore the function and mechanism of SUCNR1 in LSECs during fibrosis.

Results: Hepatic succinate levels were significantly elevated in fibrotic livers from both mice and humans, and exogenous succinate markedly accelerated fibrosis progression. SUCNR1 expression was upregulated in LSECs from fibrotic human and mouse livers. LSEC-specific knockout of SUCNR1 effectively attenuated liver fibrosis. Furthermore, SUCNR1 promoted injury-induced LSEC capillarization and hepatic stellate cells (HSCs) activation. RNA-seq revealed that SUCNR1 enhanced the expression of ICAM-1 in LSECs, thereby promoting neutrophil adhesion, recruitment, and the formation of neutrophil extracellular traps (NETs), which collectively drove hepatic inflammation and fibrosis progression. Mechanistically, SUCNR1 activated the ERK/CREB signaling pathway to promote ICAM-1 transcription. Additionally, RNA sequencing showed that SUCNR1 deficiency suppressed sphingosine kinase 1 (Sphk1), reducing the production of sphingosine-1-phosphate (S1P). LSEC-derived S1P functioned as a critical signaling molecule that activated S1P receptor 2 (S1PR2) on neutrophils to promote NETs formation.





Conclusions: SUCNR1 of LSECs as a central regulator of inter-cellular communication and neutrophil immune response in liver fibrosis, integrating endothelial dysfunction with sustained neutrophilic inflammation to promote disease. This study uncovers a novel pro-fibrotic axis in liver fibrosis: hepatocyte-derived succinate promotes disease progression by activating SUCNR1 on LSECs. Specific deletion of SUCNR1 in LSECs alleviates fibrosis by inhibiting both the succinate–SUCNR1–ERK–CREB–ICAM1 axis-mediated neutrophil recruitment and the SUCNR1–Sphk1–S1P–S1PR2 axis-induced NETosis. These findings provide a rationale for targeting SUCNR1 as a therapeutic strategy for liver fibrosis.

Keywords: Liver Fibrosis, Hepatocyte, Liver Sinusoidal Endothelial Cell, Neutrophil

OP-78

VCAM Serves as a Potential Biomarker in Paediatric Portal Hypertension

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Aims: Portal hypertension (PHT) is a pivotal stage in cirrhosis that heralds severe complications of liver disease. Currently, no reliable biomarker exists to characterize PHT, particularly in paediatric patients. This study aimed to evaluate the diagnostic utility of vascular cell adhesion molecule-1 (VCAM-1) in paediatric PHT and to explore its association with disease severity.

Methods: Plasma samples were obtained from 55 paediatric patients with PHT (22 females, 33 males) and 15 age-matched controls without liver disease. Plasma levels of multiple immune-related biomarkers were measured using standardized assays. Clinical parameters were collected and analyzed for correlation with biomarker levels.

Results: Plasma concentrations of soluble CD163 (sCD163) (633.5 vs. 414.8 ng/mL, $P=0.0028$) and VCAM-1 (861.0 vs. 397.7 ng/mL, $P<0.0001$) were significantly higher in children with PHT than in controls. VCAM-1 levels positively correlated with sCD163 ($r=0.5267$, $P=0.0002$) and matrix metalloproteinase-7 (MMP-7) ($r=0.3374$, $P=0.014$). Receiver operating characteristic analysis demonstrated excellent diagnostic performance of VCAM-1 for PHT (AUC = 0.957). At a cutoff value of 549.1 ng/mL, VCAM-1 achieved a sensitivity of 93.3% and a specificity of 91.1%, outperforming other biomarkers. VCAM-1 levels did not differ according to portal vein thrombosis status, spleen stiffness, or von Willebrand factor antigen levels. However, patients with a history of variceal bleeding exhibited lower VCAM-1 concentrations (816 vs. 964 ng/mL, $P=0.04$). VCAM-1 also positively correlated with liver stiffness and decreased significantly with non-selective beta-blocker therapy (869.7 vs. 651.9 vs. 397.7 ng/mL, $P<0.0001$).

Conclusions: Plasma VCAM-1 is strongly associated with the presence and progression of paediatric PHT. Its high diagnostic sensitivity and specificity support its potential role as a reliable biomarker for PHT.

Keywords: Paediatric Portal Hypertension, VCAM, Biomarker

OP-79

Anti-STC1 as a Therapeutic Strategy for Liver Fibrosis

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Aims: Liver fibrosis is a crucial component of chronic liver disease, associated with significant morbidity and mortality. Molecular therapies for liver fibrosis at bedside, however, is limited. Our group previously reported the role of stanniocalcin 1 (STC1) as a biomarker for HBV-related liver fibrosis and unraveled its functions on hepatic stellate cells, the pivotal cell type implicated in liver fibrogenesis (*J Pathol.* 2022 Jun;257(2):227-238). Herein, we aim to extend our investigation and explore the therapeutic implications of targeting secreted STC1 with a custom antibody using liver fibrosis models.

Methods: A custom anti-STC1 antibody (anti-STC1-3P8B) was produced. Basic characterization was performed with immunohistochemistry and western blotting. Functional effects of anti-STC1-3P8B on activated hepatic stellate cells (LX2 cell line) was examined with *in vitro* assays. Downstream signaling cascade was elucidated with proteomic profiling using mass spectrometry. *In vivo* effects of anti-STC1-3P8B was evaluated with thioacetamide (TAA)-induced liver fibrosis mouse model.

Results: Anti-STC1-3P8B downregulated expression of fibrogenic markers α -SMA, TIMP1 and collagen I (both intracellular and secreted forms) in activated LX2 cells. The enhanced contractility of LX2 upon activation was partially abrogated upon administration of anti-STC1-3P8B. Profiling results revealed PTTG1 as a downregulated target in antibody-treated activated LX2 cells. Validation experiments demonstrated the regulatory role of PTTG1 on TIMP1 expression upon anti-STC1-3P8B treatment. Pathway enrichment analysis highlighted “metabolic process”, and additional assays showed the suppression of glycolysis and glycolytic enzyme hexokinase 2 by anti-STC1-3P8B in activated LX2 cells. Besides, anti-STC1-3P8B led to cell cycle arrest of activated LX2 cells. *In vivo*, anti-STC1-3P8B attenuated liver fibrosis induced by TAA in mice with minimal toxicity.

Conclusions: Targeting STC1 with anti-STC1-3P8B is a potential therapeutic strategy for liver fibrosis through suppression of multiple activated phenotypes of hepatic stellate cells. Its potential efficacy on cirrhosis regression is yet to be determined with *in vivo* models.

Keywords: Liver Fibrosis, Biomarker, Novel Therapeutics

Saturday, June 13, 2026, 08:00-09:00

15. LC, Liver Failure & Autoimmune Diseases 3

OP-80

Clinically Meaningful Improvements in Moderate to Severe Pruritus Patients with Primary Biliary Cholangitis Treated with Seladelpar: 30 Months of ASSURE

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Aims: Pruritus affects up to 80% of patients with primary biliary cholangitis (PBC), impairing quality of life. Seladelpar, a first-in-class delpar (selective PPAR- δ agonist) approved for second-line treatment of PBC, has shown efficacy improving cholestasis and pruritus in the placebo-controlled RESPONSE study (NCT04620733). We report long-term pruritus outcomes from RESPONSE and interim results from its OLE, ASSURE (NCT03301506), with psychometric validation of the pruritus numeric rating scale (NRS).

Methods: Pruritus NRS was collected daily for 6 months (M), then one week each month through 12M (RESPONSE); in ASSURE: collected daily for 6M then at scheduled clinic visits. Other measures included 5-D Itch and PBC-40. Patients with moderate-to-severe pruritus (NRS ≥ 4) at baseline (MSPN) were analyzed based on randomization to seladelpar 10mg/PBO in RESPONSE and reported as continuous/crossover seladelpar 10mg groups in ASSURE. Regression analysis and Bland-Altman plots assessed single-visit and weekly averaged NRS score agreement. Psychometric validation of NRS included: reliability/convergent validity/meaningful within-patient change analyses. CfB in NRS, 5-D Itch, PBC-40 Itch domain scores were assessed in ASSURE (data cut: 31-Jan-2025).

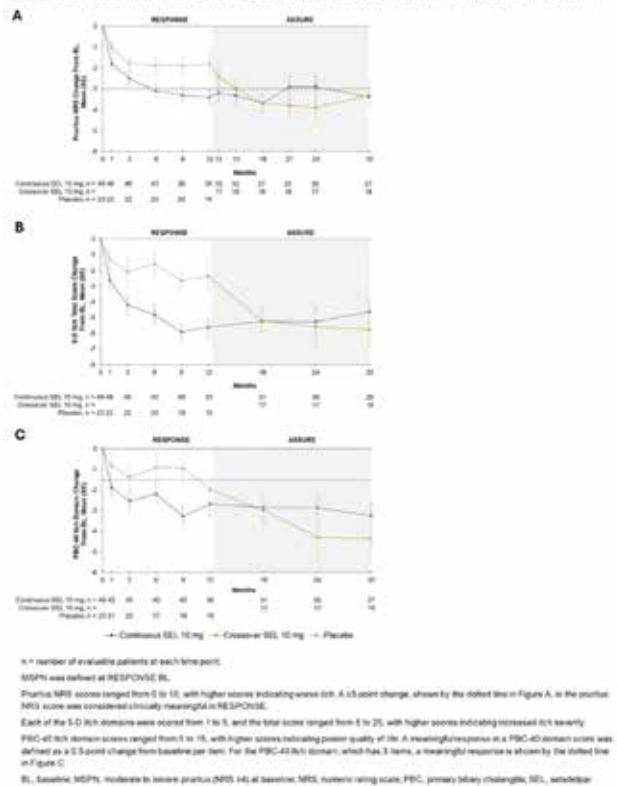
Results: 49 seladelpar/23 placebo MSPN patients, respectively, at baseline in RESPONSE: 33/17 rolled over to ASSURE; 27/16 reached 30M. Daily NRS and weekly NRS were strongly correlated (r [95% CI], 0.93 [0.90, 0.95]), validation showed validity and reliability. Pruritus reduction with seladelpar in RESPONSE maintained in ASSURE to 30M: clinically meaningful NRS improvement observed in $\geq 50\%$ of patients upon seladelpar

initiation for crossover patients in ASSURE from 15M–30M. Mean(SE) 5-D Itch total and PBC-40 Itch domain scores reduced from baseline in continuous (−4.6[0.7]; −3.3[0.7]) and crossover seladelpar (−5.8[1.1]; −4.3[1.0]) patients.

Conclusions: Seladelpar led to sustained, clinically meaningful improvement in pruritus among MSPN patients in RESPONSE up to 30M of treatment. Repeated psychometric validation confirmed reliability and validity of the NRS as an outcome measure of pruritus in PBC.

Keywords: Primary Biliary Cholangitis, Seladelpar, Pruritus, Peroxisome Proliferator-Activated Receptor Delta (PPARΔ)

Figure. Pruritus NRS (A), 5-D Itch Scale Total (B), and PBC-40 Itch Domain (C) Score Change From BL Over 30 Months From RESPONSE to ASSURE in Patients With PBC and MSPN



OP-81

Human Albumin Infusion for Large-Volume Paracentesis in Liver Cirrhosis: A Systematic Review and Meta-Analysis

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Medicine, Seoul, Republic of Korea; ⁵Department of Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea

Aims: While human albumin infusion (HAI) is widely used to prevent complications after large-volume paracentesis (LVP) in liver cirrhosis, its comprehensive clinical impact remains to be fully evaluated. This systematic review and meta-analysis were conducted to assess the effect of albumin administration on clinical outcomes in cirrhotic patients undergoing LVP.

Methods: We searched Web of Science, Embase, MEDLINE, and the Cochrane Library for randomized controlled trials (RCTs) and retrospective studies evaluating the HAI in patients with cirrhosis undergoing LVP. The primary outcome was all-cause mortality after paracentesis. Secondary outcomes included paracentesis-induced circulatory dysfunction (PICD), acute kidney injury (AKI), hyponatremia, hepatic encephalopathy (HE), gastrointestinal hemorrhage, and infection. Random-effects risk ratios (RRs) and their 95% confidence intervals (CIs) were calculated.

Results: A total of 25 studies were included in the systematic review and meta-analysis. HAI did not significantly reduce the all-cause mortality prevalence ratio compared with standard care (0.85; 95% CI, 0.65–1.11). However, HA infusion significantly decreased the risk of PICD (RR 0.45; 95% CI, 0.34–0.59) and hyponatremia (RR 0.50; 95% CI, 0.34–0.75). There was no significant difference in the overall risk of AKI (RR 0.68; 95% CI, 0.41–1.14), hepatic encephalopathy (RR 0.66, 95% CI: 0.42–1.04), gastrointestinal hemorrhage (RR 1.04; 95% CI, 0.38–2.83), or infection (RR 0.98; 95% CI, 0.52–1.85). Notably, in the subgroup analysis based on albumin dose, HAI of ≥6 g/L significantly reduced the risk of AKI (RR 0.55; 95% CI, 0.36–0.85) and hyponatremia (RR 0.45; 95% CI, 0.27–0.74), whereas HAI of <6 g/L did not show significant effects for AKI (1.03, 95% CI: 0.29–3.74) or hyponatremia (0.66, 95% CI: 0.33–1.34).

Conclusions: HAI is highly effective in reducing the risk of PICD and hyponatremia after LVP, although it does not confer a significant survival benefit regarding all-cause mortality. Furthermore, subgroup analysis highlights that a minimum HAI dose of 6 g/L is necessary to significantly reduce the risk of AKI and hyponatremia. Therefore, administering adequate HAI doses (≥6 g/L) should be standard practice to mitigate severe post-paracentesis complications.

Keywords: Albumin, Large Volume Paracentesis, Cirrhosis

OP-82

Serum Albumin Response to Intravenous Albumin and Its Association with Short-Term Prognosis in Patients with Acute Decompensated Cirrhosis

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Aims: Albumin plays multiple roles in cirrhosis beyond maintaining intravascular oncotic pressure and effective circulating volume. Recently, interest in albumin therapy has increased, yet both supportive and critical perspectives coexist regarding its routine use. Nevertheless, the optimal frequency and dosing strategy of albumin administration in decompensated cirrhosis remain subjects of ongoing debate. In this study, we investigated the short-term effects of albumin administration in patients hospitalized with acute decompensation and evaluated its potential benefits in preventing acute-on-chronic liver failure (ACLF) using real-world data.

Methods: Patients hospitalized for acute decompensation of cirrhosis were included, and the amount of albumin administered during hospitalization was analyzed. Clinical outcomes, including mortality, readmission, additional decompensation events, and development of ACLF, were evaluated.

Results: A total of 218 patients with acutely decompensated cirrhosis were analyzed, with a 3-month mortality rate of 22.9%. Higher weekly albumin dosing was associated with greater increases in serum albumin levels; however, dose-based stratification alone did not translate into improved clinical outcomes.

In multivariable Cox proportional hazards analysis adjusting for age, sex, albumin dose group, and CTP score, an increase in serum albumin during hospitalization was independently associated with improved 3-month survival (HR 0.313, 95% CI 0.170–0.576, P<0.001). In contrast, patients receiving ≥80 g/week of albumin demonstrated a significantly higher mortality risk (HR 5.715, 95% CI 2.642–12.363, P<0.001), likely reflecting greater baseline disease severity. CTP score remained an independent predictor of mortality (HR 1.329 per point increase, P<0.001).

The discriminative ability of albumin change for predicting 3-month mortality was modest in the overall cohort (AUC 0.56) but improved in patients with CTP class C cirrhosis (AUC 0.61).

Conclusions: Albumin administration per se did not confer a survival benefit in acutely decompensated cirrhosis. Instead, improvement in serum albumin levels during hospitalization was independently associated with reduced short-term mortality. These results highlight the importance of targeting meaningful biochemical response rather than relying solely on predefined dosing regimens, particularly in patients with advanced liver dysfunction.

Keywords: Albumin, Liver Cirrhosis, Portal Hypertension, Acute On Chronic Liver Failure

OP-83

Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) for the Differential Diagnosis and Prognosis of Acute Kidney Injury in Liver Cirrhosis: A Systematic Review and Meta-Analysis

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Aims: Differentiating hepatorenal syndrome (HRS) from acute tubular necrosis (ATN) is a major clinical challenge in cirrhotic patients with acute kidney injury (AKI). We aimed to evaluate the diagnostic accuracy and prognostic value of urinary neutrophil gelatinase-associated lipocalin (uNGAL) in this population.

Methods: A systematic search was performed across PubMed, EMBASE, Cochrane Library, and local databases through August 31, 2025. We included 22 studies evaluating uNGAL in cirrhotic patients with AKI. Primary outcomes included the diagnostic odds ratio (DOR) for ATN differentiation and hazard ratios (HR) for mortality.

Results: Among 22 included studies, uNGAL demonstrated high diagnostic accuracy for ATN, with a pooled DOR of 23.07 (95% CI: 9.67–55.08) and an AUC of 0.86. Notably, uNGAL effectively differentiated ATN from HRS (pooled OR 25.49; 95% CI: 8.59–75.63) with zero heterogeneity ($I^2 = 0.0\%$). Regarding prognosis, elevated baseline uNGAL was a robust predictor of 28-day mortality (HR 2.49; 95% CI: 1.74–3.57; $I^2 = 0.0\%$) and remained significant for 90-day mortality (HR 1.08 per unit increase). Furthermore, low uNGAL levels were exceptionally predictive of AKI recovery (pooled OR 58.67).

Conclusions: uNGAL is a reliable “liquid biopsy” marker for differentiating ATN from HRS and predicting short-term survival in cirrhotic patients with AKI. Its consistent performance across diverse cohorts supports its integration into clinical triaging protocols.

Keywords: Liver Cirrhosis, Acute Kidney Injury, Hepatorenal Syndrome, Urinary Neutrophil Gelatinase-Associated Lipocalin

OP-84

Ascites Microbiome Alterations Associated with Hepatocellular Carcinoma in Patients with Decompensated Cirrhosis

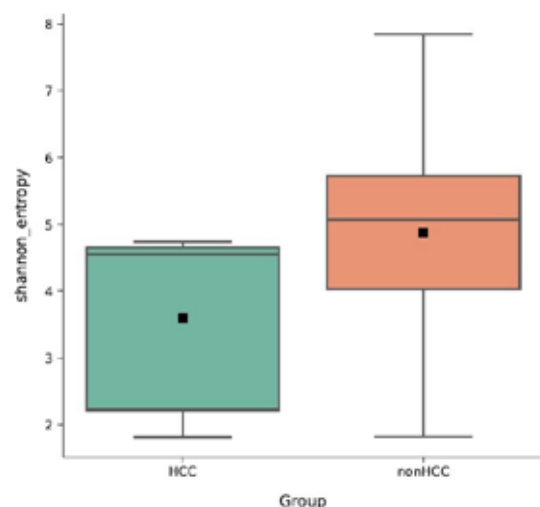
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Aims: Gut dysbiosis and bacterial translocation play an important role in the progression of liver cirrhosis. Although alterations of gut microbiota have been widely studied, microbiome profiles in ascitic fluid remain poorly understood. We aimed to investigate differences in ascites and stool microbiome profiles according to the presence of hepatocellular carcinoma (HCC) in patients with decompensated liver cirrhosis and ascites.

Methods: We prospectively established a cohort of patients with decompensated liver cirrhosis accompanied by ascites. Clinical information including liver function, HCC status, and survival outcomes was collected. Ascitic fluid and stool samples were obtained and analyzed using 16S rRNA gene sequencing. Microbiome diversity and composition were evaluated using alpha diversity analysis, operational taxonomic unit (OTU) comparison, and LEfSe (linear discriminant analysis effect size). Patients were stratified according to the presence of HCC.

Results: A total of 33 patients were enrolled (76.0% male; median age 59 years [IQR 55–65]), including 8 patients with HCC. Ascitic samples were obtained from 22 patients and stool samples from 19 patients. Median survival duration was significantly shorter in the HCC group compared with the non-HCC group (2.2 vs. 9.1 months, $P=0.001$). In ascitic fluid analysis, alpha diversity measured by the Shannon index was significantly lower in patients with HCC ($P=0.042$; Figure 1). The proportion of unique OTUs was also markedly lower in the HCC group (2.1%) compared with the non-HCC group (26.7%). LEfSe analysis revealed enrichment of several bacterial species in the HCC group, including *Streptococcus mutans*, *Pseudomonas pisciculyrae*, and *Sphingomonas aracearum*. In stool microbiome analysis, alpha diversity did not differ significantly between the two groups ($P=0.41$). However, several bacterial species such as *Massiliimalia timonensis*, *Streptococcus* spp., and *Alistipes indistinctus* were relatively enriched in patients with HCC.



Conclusions: Patients with decompensated liver cirrhosis and HCC showed reduced microbial diversity in ascitic fluid and distinct microbial signatures compared with those without HCC. These findings suggest that ascites microbiome alterations may reflect disease severity and could potentially serve as biomarkers for HCC-associated disease progression in cirrhosis.

Keywords: Ascites, Microbiome, Hepatocellular Carcinoma, Liver Cirrhosis

OP-85

Trends in Prevalence, Etiology, and Healthcare Costs of Cirrhosis in Korea (2008–2023): A National Population-Based Study

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Aims: Cirrhosis imposes a substantial disease burden, particularly in its decompensated state, which is associated with low survival. Despite its clinical significance, recent national epidemiological data and policy support in Korea remain insufficient. This study aims to analyze 16-year trends in the prevalence, complications, etiology, liver transplantation (LT), mortality, and healthcare costs using data from National Health Insurance Service (NHIS).

Methods: NHIS claims data from 2008 to 2023 were analyzed using KCD-8 codes for cirrhosis (K70.2, K70.3, K74.1–K74.6). Patients were categorized into compensated and decompensated groups based on complications (e.g., ascites, variceal bleeding, hepatic encephalopathy). The outcomes included annual prevalence, etiology, LT rates, mortality, and healthcare resource utilization (costs and length of stay).

Results: A total of 825,490 patients (aged ≥ 20) were analyzed. The prevalence of cirrhosis per 100,000 population increased 1.5-fold, from 346.9 in 2008 to 531.4 in 2023. The male-to-female ratio decreased from 2.6:1 to 1.8:1. Hepatitis B persisted as the leading cause (29.6% in 2008 to 30.0% in 2023), followed by alcoholic liver disease (20.8% to 16.7%). Notably, cirrhosis due to non-alcoholic fatty liver disease (NAFLD) showed a marked increase from 2.3% to 4.9%. The prevalence of hepatocellular carcinoma exhibited a nearly twofold increase (32,825 to 63,250 cases), and annual incidence of LT increased from 542 to 861 cases. Although the average length of stay decreased slightly (38 to 34.5 days), overall inpatient healthcare costs showed a continuous upward trend.

Conclusions: The prevalence of cirrhosis in Korea has significantly increased over 16 years, with a rising proportion of female patients. While viral and alcoholic etiologies remain dom-

inant, the rapidly growing contribution of NAFLD is a notable shift. The increasing of hospitalization costs emphasize the need for enhanced clinical management and targeted public health policies.

Keywords: Liver Cirrhosis, Epidemiology, Etiology, Health Care Costs

Saturday, June 13, 2026, 08:00–09:00

16. MASLD, Basic & Clinical

OP-86

Fumaric Acid as a Novel Metabolite Biomarker for Diagnosis of Metabolic Dysfunction-Associated Steatohepatitis in Obese Subjects

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Aims: Metabolic dysfunction-associated steatohepatitis (MASH) represents the progressive and clinically significant stage of metabolic dysfunction-associated steatotic liver disease (MASLD), closely linked to hepatic fibrosis, liver-related mortality, and cardiometabolic complications. Mitochondrial dysfunction and impaired tricarboxylic acid (TCA) cycle flux are key metabolic features underlying the progression from simple steatosis to steatohepatitis. Fumaric acid, a major intermediate in the TCA cycle, may therefore serve as a potential non-invasive biomarker reflecting mitochondrial dysfunction in MASH.

Methods: A total of 64 patients who underwent histologically confirmed evaluation for MASLD at Gachon University Gil Medical Center between March 2018 and January 2023 were included in this study. The mean age was 65 ± 10 years, 75% were female, and the mean body mass index (BMI) was 37.1 ± 5.9 kg/m². Based on histologic findings, 16 patients were classified as MASH (NAS ≥ 5) and 48 as non-MASH (NAS < 5). Plasma metabolomic profiling was performed to analyze fatty acids, organic acids, and amino acids using GC–MS/MS after derivatization as tert-butyltrimethylsilyl (TBDMS)-, methoxime (MO)-TBDMS-, and ethoxycarbonyl (EOC)-TBDMS derivatives, respectively.

Results: Plasma fumaric acid levels were significantly lower in MASH compared with non-MASH subjects (2.35 vs. 3.80 ng/L, $P<0.01$). When analyzed as a continuous variable, lower fumaric acid levels were independently associated with the presence of MASH (odds ratio 0.52, 95% CI 0.33–0.81, $P=0.004$). A cutoff value of < 2.5 ng/L yielded a sensitivity of 75.0%, specificity of 81.2%, and AUROC 0.781 (95% CI 0.642–0.921,

$P=0.001$) for diagnosis of MASH.

Conclusions: Plasma fumaric acid levels are significantly decreased in histologically confirmed MASH, likely reflecting impaired mitochondrial TCA cycle activity. These findings suggest that fumaric acid may serve as a simple and reliable non-invasive biomarker for identifying MASH among patients with MASLD.

Keywords: Fumaric Acid, Metabolite, Biomarker, Metabolic Dysfunction-Associated Steatohepatitis

OP-87

Extending Stemness and Longevity of Human Chemically Derived Hepatic Progenitors Using a Novel Drug

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Aims: Human chemically derived hepatic progenitors (hCdHs) have been developed through chemical reprogramming of human primary hepatocytes (hPHs) as a promising alternative to liver transplantation. Worldwide, extensive efforts have been made to establish reliable strategies for reprogramming hepatocytes into expandable hepatic progenitor-like cells. However, these approaches have encountered multiple challenges, including progressive phenotypic change, cellular senescence, and limited stability during prolonged *in vitro* culture.

Methods: Approximately 3,000 compounds were surveyed based on prior evidence, from which 12 candidates were selected for experimental validation during hCdH generation. hPHs were reprogrammed using HGF, A83-01, and CHIR99021 (HAC) either in the presence or absence of Drug A, which emerged as the most effective candidate. Drug A-treated hCdHs (Drug A-hCdHs) were compared with control hCdHs across multiple donors and passages.

Results: During serial passaging, hCdHs progressively exhibited phenotypic drift toward a hepatic stellate cell-like state. In contrast, Drug A-hCdHs consistently preserved hepatic progenitor-like features without evidence of such phenotypic conversion. Drug A-hCdHs retained their ability to differentiate into both hepatocytes and cholangiocytes and efficiently formed organoids in three-dimensional culture. Furthermore, hepatocytes isolated from diseased human livers were successfully reprogrammed into hCdHs and could be maintained long term in the presence of Drug A.

Conclusions: These findings demonstrate that Drug A significantly improves the stability, stemness, and longevity of hCdHs during prolonged culture. This pharmacological strategy provides a robust platform for generating patient-specific hepatic progenitors and represents an important step toward the development of regenerative therapies and bioartificial liver systems.

OP-88

Long-Term Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease after Thyroidectomy and Thyroid Hormone Therapy in Thyroid Cancer Survivors: A Nationwide Study

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Aims: As long-term survival continues to improve in thyroid cancer patients, the metabolic consequences of thyroidectomy and thyroid hormone therapy are becoming more important. Although these treatments are essential for cancer management, their long-term impact on metabolic health, including metabolic dysfunction-associated steatotic liver disease (MASLD), has not been fully clarified.

Methods: We conducted a nationwide case–control study using customized data from the Korea National Health Insurance Service, combining insurance claims with standardized health screening records. MASLD was assessed at 5-, 8-, and 10-year follow-ups. Adjusted odds ratios were calculated using logistic regression.

Results: Thyroidectomy was associated with a significantly higher risk of MASLD compared with both matched population controls and thyroid cancer patients who did not undergo surgery. An elevated risk for MASLD was consistently observed at 5-, 8-, and 10-year follow-ups and remained independent of demographic and lifestyle factors. Long-term thyroid hormone therapy further increased the risk. Some metabolic risks, such as overweight/obesity, became significant only at later time points.

Conclusions: Thyroidectomy and long-term thyroid hormone therapy are associated with sustained risk for MASLD in thyroid cancer survivors. These findings highlight the need for personalized hormone management and continued metabolic monitoring.

Keywords: Thyroidectomy, Thyroid Cancer Survivors, Thyroid Hormone Therapy, Metabolic Disorders

OP-89

Emerging Indices Outperform Traditional Fibrosis Scores in Young MASLD across Divergent Screening Goals

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Aims: Although numerous noninvasive indices have been proposed to assess significant fibrosis (SF), none have been validated specifically in young adults with metabolic dysfunction-associated steatotic liver disease (MASLD). This study evaluated their performance in younger patients across two cohorts with distinct screening goals.

Methods: We retrospectively analyzed two MASLD cohorts: a primary care (PC) cohort (n = 972) and a tertiary care (TC) cohort (n = 342). SF was defined as liver stiffness ≥ 7.0 kPa on vibration-controlled transient elastography. The diagnostic performance of emerging indices — fibrosis-8 index, steatosis-associated fibrosis estimator, metabolic-associated fibrosis score-5 — was compared with traditional scores — fibrosis-4 index, aspartate aminotransferase-to-platelet ratio index, and nonalcoholic fatty liver disease fibrosis score.

Results: Across both settings, emerging indices consistently outperformed traditional scores for SF discrimination. The areas under the receiver operating characteristic curves were higher for the emerging indices than for the traditional indices in both cohorts. Decision curve analyses demonstrated that emerging indices provided greater net clinical benefit and larger reductions in unnecessary procedures, with thresholds differing by setting such that lower thresholds favored referral in the PC cohort, whereas higher thresholds were more appropriate for biopsy decisions in the TC cohort. Conventional cut-offs widely used in practice demonstrated limited sensitivity in this population, suggesting that refinement may be required.

Conclusions: Traditional noninvasive fibrosis indices showed limited performance in young adults with MASLD, whereas emerging indices appeared more suitable for achieving the screening goals of referral in PC and biopsy decision-making in TC.

Keywords: Non-Invasive Index, Fibrosis, Metabolic Dysfunction-Associated Steatotic Liver Disease, Young Adults

OP-90

Prospective Evaluation of Steatosis Noninvasive Tests for Two-Year Monitoring in MASLD

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Aims: Noninvasive tests (NITs) are widely used in metabolic dysfunction–associated steatotic liver disease (MASLD), but evidence supporting their longitudinal monitoring performance is limited. We aimed to evaluate whether steatosis-related NITs can track interval changes in steatosis severity over 2 years, using controlled attenuation parameter (CAP) as a surrogate marker. Fibrosis-related NITs were assessed in parallel against liver stiffness measurement (LSM).

Methods: In this single-center prospective study, MASLD patients underwent paired transient elastography at baseline and 2-year follow-up. CAP and LSM were used as surrogate markers of steatosis and fibrosis severity, respectively. Pearson correlation coefficients (r) were calculated for cross-sectional associations at baseline and for longitudinal changes (Δ) between NITs and CAP/LSM.

Results: A total of 277 patients completed 2-year follow-up. Steatosis-related indices demonstrated significant correlations with interval changes in CAP, including Δ FLI (r = 0.38, $P < 0.001$) and Δ HSI (r = 0.24, $P < 0.001$), supporting their ability to track changes in hepatic fat severity over time. In parallel analyses, baseline fibrosis-related NITs correlated with LSM (FIB-4: r = 0.28; NFS: r = 0.19), whereas changes in fibrosis-related indices were not associated with changes in LSM over 2 years (Δ FIB-4 vs Δ LSM: r = 0.03, $P = 0.65$; Δ NFS vs Δ LSM: r = -0.05 , $P = 0.43$).

Conclusions: In a prospective MASLD cohort, steatosis-related NITs (FLI and HSI) tracked 2-year changes in CAP, suggesting utility for longitudinal monitoring of steatosis severity when repeated elastography is not readily available. Fibrosis-related NITs showed cross-sectional associations with LSM, but their change scores did not mirror interval changes in LSM.

Keywords: Noninvasive Test, Metabolic Dysfunction–Associated Steatotic Liver Disease

OP-91

CXCR4-Expressing Peripheral CD8 T Cells Are Activated and Recruited to the Liver in Alcohol-Associated Liver Disease

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Aims: Alcohol-associated liver disease (ALD) is characterized by systemic immune dysregulation and hepatic inflammation. We investigated whether CXCR4-expressing peripheral CD8 T cells represent a distinct activated population in ALD and whether hepatic CXCL12 expression may contribute to their recruitment to the liver.

Methods: Peripheral blood mononuclear cells (PBMCs) from patients with ALD and healthy controls (n=3 per group) were analyzed using single-cell RNA sequencing and multiparameter flow cytometry to characterize CD8 T-cell subsets and CXCR4 expression. Differential gene expression and gene set enrichment analyses were performed to evaluate activation-, cytotoxicity-, and migration-related transcriptional programs. Publicly available datasets were analyzed to assess CXCL12 expression across liver cell populations. CXCL12-driven transwell migration assays were performed to evaluate functional migratory responses of CXCR4-expressing CD8 T cells. In addition, CXCR4 and CXCL12 protein expression was examined by Western blot analysis.

Results: Single-cell analysis revealed expansion of activated/exhausted CD8 T-cell subsets and reduction of naïve CD8 T cells in ALD. CXCR4 expression was preferentially enriched in activated CD8 clusters. CXCR4-expressing CD8 T cells demonstrated increased expression of cytotoxic and activation-associated genes, including GZMB, PRF1, NKG7, and IFNG, together with migration- and positioning-related molecules such as ITGA4, ITGB1, and ICAM1. Gene set enrichment analysis supported coordinated activation and trafficking-related transcriptional programs in CXCR4-positive CD8 T cells. Analysis of liver cell populations demonstrated CXCL12 expression in stromal and non-parenchymal cells. Protein-level analysis further confirmed increased CXCL12 expression in ALD liver samples. In transwell assays, CXCL12 induced preferential migration and enrichment of CXCR4-high CD8 T cells, supporting CXCL12-mediated recruitment.

Conclusions: Peripheral CXCR4-expressing CD8 T cells in ALD display activated and cytotoxic transcriptional profiles. Upregulated CXCL12 expression within the liver microenvironment may facilitate recruitment of these cells, suggesting that CXCR4-associated immune trafficking contributes to immune dysregulation in alcohol-associated liver disease.

Keywords: Alcohol-Associated Liver Disease, CXCR4, CXCL12, CD8 T Cell

Saturday, June 13, 2026, 08:00-09:00

17. Liver Transplantation & ALD

OP-92

Early Postoperative C3a Predicts Early Allograft Dysfunction after Liver Transplantation

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Aims: Early allograft dysfunction (EAD) remains one of the main determinants of short-term outcome after liver transplantation. Despite advances in surgical technique and perioperative care, a substantial proportion of recipients still develop early graft injury. Identification of laboratory markers associated with EAD may improve early postoperative risk stratification. This study aimed to evaluate complement and inflammatory markers associated with EAD after liver transplantation.

Methods: This prospective observational study included 60 adult patients who underwent orthotopic liver transplantation between 2023 and 2025 and 26 healthy controls. EAD within 7 days was defined according to the Olthoff criteria; 16 patients (26.7%) developed EAD. Peripheral blood samples were collected before transplantation and 24 hours after surgery. Serum levels of C3a, C5a, sC5b-9, IL-6, IP-10, and C-reactive protein (CRP) were measured by ELISA. Data are presented as mean $\pm$ SD. Student's t-test, Pearson correlation, and logistic regression were used; $P < 0.05$ was considered significant.

Results: Before transplantation, recipients had significantly higher levels of complement activation markers than healthy controls, including C3a (4215.24 ± 941.32 vs 120.44 ± 16.24 ng/mL), C5a (35.73 ± 3.92 vs 5.92 ± 1.31 ng/mL), and sC5b-9 (681.24 ± 165.34 vs 179.42 ± 28.74 ng/mL) (all $P < 0.001$). At 24 hours after transplantation, patients who developed EAD showed significantly higher C3a levels than those without EAD (5520.12 ± 670.41 vs 2860.41 ± 256.11 ng/mL; $P < 0.01$). IL-6 and IP-10 were also significantly elevated in the EAD group ($P < 0.01$). CRP correlated positively with C3a at 24 hours ($r = 0.31$; $P = 0.018$). In logistic regression analysis, C3a > 4000 ng/mL independently predicted EAD (OR = 3.4; 95% CI 1.3–8.7; $P = 0.008$).

Conclusions: Early postoperative complement activation, particularly elevated C3a, is associated with EAD after liver transplantation. Monitoring C3a may improve early identification of high-risk recipients and support closer postoperative surveillance.

Keywords: Liver Transplantation, Early Allograft Dysfunction, Complement Activation Markers, Postoperative Risk Stratification

OP-93

Body Mass Index ≥ 34 KG/M² Does Not Compromise Safety or Hepatic Regeneration in Living Liver Donors: A Propensity-Matched Cohort Study

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Aims: Thresholds for body mass index (BMI) in the evaluation of living liver donors exhibit considerable intercentre heterogeneity, typically ranging from 30 to 35 kg/m². This variation reflects unresolved uncertainty regarding perioperative risk

among candidates with higher BMI, especially concerning potential complications like hepatic steatosis or metabolic issues, when hepatic steatosis is systematically excluded.

Methods: A retrospective cohort study employing 1:3 propensity score matching, derived via logistic regression. Matching was implemented using a nearestneighbour algorithm with a calliper width of 0.1 standard deviations on the logit of the propensity score.

Results: Median hospital length of stay was modestly longer in the higher BMI group (12.88 versus 10.23 days; mean difference 2.66 days, 95% CI 1.39 to 3.92; $P < 0.001$), attributable predominantly to an elevated incidence of local surgical site infection (13.7% versus 1.9%) and institutional protocols mandating extended observation prior to discharge for donors with elevated BMI rather than hepatic dysfunction. Total bilirubin on postoperative day 1 was 1.01 versus 0.88 mg/dL (mean difference 0.12 mg/dL, 95% CI -0.62 to 0.86 ; $P = 0.747$), and on day 7 was 0.92 versus 0.81 mg/dL ($P = 0.663$). INR on day 1 was 0.88 versus 1.03 (mean difference -0.15 , 95% CI -0.45 to 0.15 ; $P = 0.329$), and on day 7 was 0.97 versus 1.01 ($P = 0.653$).

Conclusions: Among rigorously screened donors in whom hepatic steatosis is excluded, those with BMI ≥ 34 kg/m² exhibit no perioperative mortality, demonstrate normal and parallel hepatic functional recovery relative to lower BMI donors, and present equivalent surgical feasibility.

Keywords: BMI, Steatosis, Living Donor

OP-94

Long-Term Outcomes of the First Donor Hemighepatectomy Using 3D Laparoscopy in Kazakhstan: Experience from a Single Center

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Aims: To evaluate the feasibility and safety of 3D laparoscopic donor hemighepatectomy, to report short-term and long-term outcomes in donors, to highlight the technical innovations and benefits introduced to Central Asia.

Methods: In 2016–2017, the Aktobe Medical Center performed the first donor hemighepatectomies in Kazakhstan utilizing 3D laparoscopic technology, in collaboration with experts from Seoul National University Hospital, led by Dr. Kwang-Woong Lee. Four healthy adult donors underwent right or left hemighepatectomy using 3D laparoscopic guidance. Preoperative evaluation included detailed imaging and functional liver assessment. Perioperative parameters, complications, and postoperative recovery were systematically recorded. Long-term follow-up focused on donor safety, liver regeneration, and

functional outcomes.

Results: All four procedures were completed successfully without intraoperative conversions to open surgery. Average operative time was 2.6 hours, and mean blood loss was 60 mL. No major perioperative complications were observed. Donors resumed normal activities within 3–4 days postoperatively. Follow-up over 6–12 months demonstrated satisfactory liver regeneration, normal liver function tests, and absence of long-term morbidity, highlighting the safety and efficacy of this minimally invasive approach.

Conclusions: This pioneering series represents the first successful implementation of 3D laparoscopic donor hemighepatectomy in Kazakhstan. The positive outcomes in all four donors underscore the feasibility, safety, and advantages of this technique, providing a foundation for expanding living donor liver transplantation programs in Central Asia. Collaboration with experienced international teams was instrumental in achieving these results.

Keywords: Living Donor, Liver Transplantation, Long-Term Outcomes, Laparoscopy, Donor Hemighepatectomy



OP-95

Long-Term Outcomes after Alcohol-Associated Hepatitis among Adults with Type 2 Diabetes Mellitus

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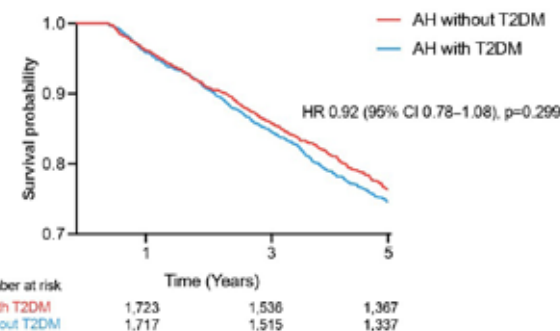
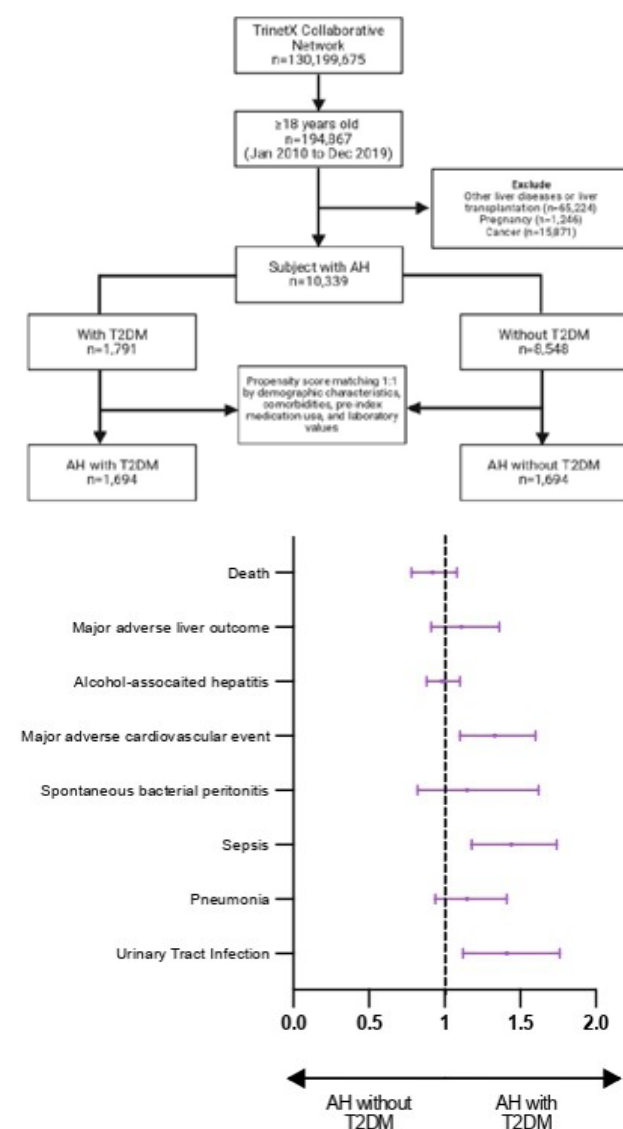
Aims: Type 2 diabetes mellitus (T2DM) is a recognized driver of liver disease progression, but its impact on long-term outcomes after an episode of alcohol-associated hepatitis (AH) remains uncertain. We compared clinical outcomes after AH between patients with and without T2DM.

Methods: We conducted a multicenter, retrospective cohort study using the TriNetX research network. Adults with AH (International Classification of Diseases, Tenth Revision: K70.1) who survived at least 6 months post-diagnosis were included. Cohorts were stratified by T2DM status and matched 1:1 by propensity scores using demographics, comorbidities, labs, and alcohol use disorder treatments. The primary outcome was all-cause mortality. Secondary outcomes included major adverse liver outcomes (MALOs), major adverse cardiovascular events (MACEs), and serious infections. Outcomes were analyzed with Cox proportional hazards models.

Results: After matching, 3,388 AH survivors (1,694 per group) were included. Mortality (17.9% and 17.9%; hazard ratio (HR) 0.92, 95% confidence interval (CI): 0.78–1.08) and MALOs (18.2% and 15.7%; HR 1.11, 95%CI: 0.91–1.36) were similar in patients with AH with and without T2DM. However, T2DM was associated with significantly higher risk of MACEs (20.9% and 14.6%; HR 1.33, 95%CI: 1.10–1.60), sepsis (18.0% and 12.0%; HR 1.44, 95%CI: 1.18–1.74), and urinary tract infection (13.1% and 8.8%; HR 1.41, 95%CI: 1.12–1.76).

Conclusions: Among AH survivors, T2DM was associated with increased risk of cardiovascular events and serious infections, but not with higher mortality or liver-related outcomes. These findings support integrating metabolic risk management into their long-term care.

Keywords: Addiction, Metabolic Syndrome, Alcoholic Hepatitis, Alcohol-Related Liver Disease



OP-96

The Addition of an mTOR Inhibitor Is Associated with Increased Gut Microbial Diversity in Liver Transplant Recipients: A Prospective Pilot Study

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Aims: This study aimed to investigate alterations in gut microbial diversity and taxonomic composition following the initiation of mammalian target of rapamycin (mTOR) inhibitor-based immunosuppression in liver transplant (LT) recipients.

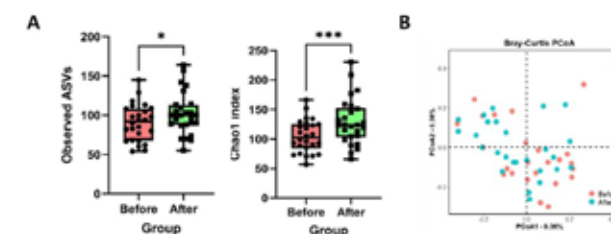
Methods: We prospectively enrolled 30 LT recipients with stable graft function, no history of acute or chronic rejection, and a post-transplant duration of more than five years. All patients were receiving calcineurin inhibitor-based immunosuppression, including tacrolimus or cyclosporine. Following study enrollment, an mTOR inhibitor was initiated in addition to the existing regimen, and patients were followed at three-month intervals. Fecal samples were collected at baseline (prior to mTOR inhibitor initiation) and at 12 months after treatment initiation. The primary outcome was to assess changes in gut microbial diversity and taxonomic composition following the introduction of mTOR inhibitor-based immunosuppression in LT recipients.

Results: Among the 30 enrolled LT recipients, four discontinued mTOR inhibitor therapy due to adverse events. The remaining 26 patients (mean age, 60 years) continued treatment and provided paired fecal samples for longitudinal analysis. Following mTOR inhibitor initiation, post-treatment samples

demonstrated a significant increase in gut microbial alpha diversity, as evidenced by higher observed operational taxonomic units (OTUs) and Chao1 indices (Fig. A). In contrast, beta diversity analysis did not reveal a significant difference in overall microbial community structure after mTOR inhibitor initiation (Fig. B). To identify specific taxonomic alterations, differential abundance analysis was performed using DESeq2. At the family level, more than 20 taxa were significantly enriched following mTOR inhibitor administration. At the genus level, several potentially beneficial taxa, including *Faecalibacterium*, were significantly increased after treatment.

Conclusions: Our findings suggest that the addition of mTOR inhibitor-based immunosuppression is associated with increased gut microbial diversity and distinct compositional alterations LT recipients. Further studies are warranted to elucidate the functional implications and mechanistic pathways underlying microbiome changes following mTOR inhibitor initiation.

Keywords: Liver Transplantation, Mtor Inhibitor, Gut Microbiome



OP-97

Left Lobe Liver Transplantation Using a Flipped Technique: Comparable Survival with Improved Portal Vein Alignment

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Aims: Left lobe liver transplantation (LT) presents technical challenges related to graft orientation and portal vein geometry. The flipped left lobe technique was developed to improve anatomic alignment, but its safety and long-term outcomes compared with the conventional approach remain unclear.

Methods: We retrospectively analyzed adult patients who underwent left lobe LT and compared outcomes between conventional and flipped techniques. Postoperative portal vein angle (PVA) was measured on early postoperative and follow-up computed tomography. Primary outcomes were PVA and vascular complications, while secondary outcomes included graft failure and overall survival. Survival analyses were performed using Cox proportional hazards models and Firth penalized Cox regression, adjusting for clinically relevant covariates.

Results: A total of 43 patients were included. The flipped tech-

nique achieved significantly more favorable postoperative portal vein geometry than the conventional approach, with stable PVA during follow-up. The incidence of vascular complications was comparable between groups. Overall survival and graft survival did not differ between techniques. In multivariable and Firth penalized Cox regression analyses, pretransplant MELD score was the only independent predictor of overall survival and graft failure. Surgical technique and graft orientation were not independently associated with adverse survival outcomes. A more favorable postoperative PVA showed a trend toward reduced graft failure, suggesting a potential mechanistic benefit.

Conclusions: The flipped left lobe technique is not inferior to the conventional approach in terms of survival after left lobe LT. By improving portal vein geometry without increasing vascular complications, it represents a safe surgical alternative with potential structural advantages.

Keywords: Left Lobe Liver Transplantation, Flipped Graft Technique, Portal Vein Angle

Saturday, June 13, 2026, 08:00-09:00

18. HCC, Basic 2

OP-98

Targeting Cell Surface LANCL1 with Monoclonal Antibodies Suppresses Tumorigenesis in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is a prevalent and killing cancer worldwide. Liver tumour-initiating cells (LTICs) are self-renewing sub-populations in HCC, contributing to tumour initiation and treatment resistance. Previously, we have uncovered LANCL1 as a functional cell surface marker that promotes HCC tumour initiation through the FAM49B/Rac1-axis to reduce cellular reactive oxygen species (ROS). In this study, we aim to testify the feasibility of targeting the cell surface LANCL1 by an antibody approach for translational potential in future therapeutic.

Methods: We generated murine monoclonal antibodies (mAb) and evaluated their efficacy *in vitro* using sphere-formation, cytotoxicity, migration, and invasion assays on HCC cell lines, and *in vivo* in an orthotopic HCC model.

Results: Human LANCL1 shares high homology with LANCL2 in the middle region. To generate specific antibodies targeting the N-terminal extracellular region of human LANCL1, the specific peptide corresponding to the 1-42aa region of human

LANCL1 is used as immunogen. By using ELISA on the immunogen, Western blot on the denatured and non-denatured human LANCL1 1-42aa peptide overexpressed in *E. coli* B21 lysate, as well as the non-denatured human full-length LANCL1 protein overexpressed in PLC/PRF/5 lysate, we screened the supernatant derived from the hybridoma clonal cells for different clonal mAbs. We ultimately derived clonal mAbs which were validated by flow cytometry for their binding specificity on LANCL1-overexpressing HCC. We found the mAbs potently inhibited sphere formation, induced significant cytotoxicity, and suppressed migration and invasion of HCC cell lines *in vitro*. *In vivo*, the mAb impaired tumour growth and lung metastasis of PLC/PRF/5 cells in an immunodeficient orthotopic mouse HCC model.

Conclusions: Targeting HCC cell surface LANCL1 by monoclonal antibodies suppressed multiple HCC cell aggressive behaviour and tumour-initiating properties. This provides the solid foundation for developing anti-LANCL1 antibody for clinical translational applications.

Keywords: Hepatocellular Carcinoma, LANCL1, Liver-Tumour Initiating Cells, Antibody

OP-99

Spatially Resolved Transcriptomics Reveals Terminal CD8⁺ T Cell Exhaustion Driven by Chronic Inflammatory Signaling as a Key Determinant of Poor Response to Atezolizumab plus Bevacizumab in Advanced HCC

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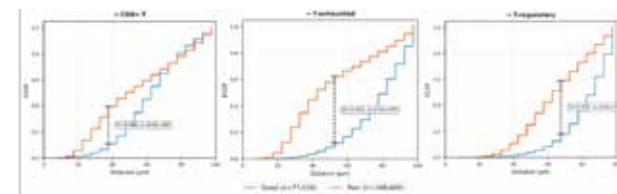
Aims: Atezolizumab plus bevacizumab represents the standard first-line immunotherapy for advanced hepatocellular carcinoma (HCC), yet the tumor microenvironmental (TME) determinants of treatment response remain poorly understood. We performed spatially resolved transcriptomics to characterize the TME in HCC patients stratified by immunotherapy response.

Methods: Tissue microarrays (TMAs) were constructed from resected HCC specimens of 14 patients who received atezolizumab plus bevacizumab for recurrent disease (Good response group, n = 5, best response CR or PR; Poor response group, n = 9, best response SD or PD). Spatial transcriptomics was performed using the Xenium platform, and 15 distinct cell types were identified and characterized.

Results: Good response group exhibited well-differentiated hepatocyte features, with preserved metabolic and secretory functions reflected by expression of CYP17A1 and CYP1A2, alongside enrichment of androgen and xenobiotic metabolism pathways. In contrast, Poor responders demonstrated loss of hepatocyte metabolic identity, upregulation of the invasion marker LAMC2, and prominent cancer-associated fibroblast (CAF)-driven stromal remodeling marked by POSTN expression. Despite elevated chemokine expression (CXCL9, CXCL10) suggestive of active immune recruitment, CD8⁺ and CD4⁺ T cells in poor response group exhibited high LAG3 expression, indicative of an exhausted phenotype. Tumor-associated macrophages (TAMs) in poor response group expressed MARCO, consistent with an immunosuppressive, tumor-promoting polarization. Pathway analysis revealed activation of E2F targets and VEGF signaling in poor response group, alongside chronic JAK/STAT and interferon- γ signaling, which likely drives terminal T cell exhaustion. Nearest-neighbor distance analysis from malignant hepatocytes revealed that T exhausted, T regulatory, and CD8⁺ T cells were all significantly closer to tumor cells in poor response group than in good response group (KS test, $P < 0.001$), with effect sizes of D = 0.505, 0.405, and 0.286, respectively.

Conclusions: Poor immunotherapy response in HCC is not attributable to insufficient T cell infiltration, but rather to a dysfunctional TME in which chronic inflammatory signaling (JAK/STAT, IFN- γ) induces terminal CD8⁺ T cell exhaustion, compounded by spatial proximity of immunosuppressive T exhausted and T regulatory cells to tumor cells, collectively abrogating effective anti-tumor immunity.

Keywords: HCC, Spatial Transcriptomics, Response



Empirical Cumulative Distribution Function (ECDF) of Nearest-Neighbor Distances from Malignant Hepatocytes to CD8⁺ T, T Exhausted, and T Regulatory Cells (within 100 μ m)

OP-100

Development of in Vitro Tumor Microenvironment Model for Immunotherapy Optimization and Synergistic Effects of uPAR Inhibitor in Hepatocellular Carcinoma Immunotherapy

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Aims: The tumor microenvironment (TME) of hepatocellular carcinoma (HCC) is closely associated with metastasis, treatment resistance, and immunotherapy response. However, few cell-based models adequately recapitulate the immune-responsive HCC TME. The urokinase plasminogen activator receptor (uPAR) pathway is involved in tumor progression and TME remodeling. We established *in vitro* 3D HCC TME model for immunotherapy optimization, and determined the synergistic effects of uPAR Inhibitor in HCC immunotherapy.

Methods: Immune-enriched 3D co-culture model of HCC spheroids was generated in 384-well ultra-low attachment plates using Hep3B cells with LX-2 cells, THP-1 monocyte cells, and Jurkat T cells. THP-1 cells were activated with 100 ng/mL rhGM-CSF, 200 ng/mL rhIL-4, 20 ng/mL TNF- α , and 200 ng/mL ionomycin. Spheroids were treated with atezolizumab, uPAR inhibitor (cenupatide), or their combination. Treatment responses were assessed by spheroid size change and live/dead cell imaging.

Results: Activated THP-1-containing spheroids showed a transitional tumor associated macrophage-like phenotype, with reduced CD14, increased CD68, enrichment of the CD14-CD68⁺ population, and co-expression of CD86, CD206, and HLA-DR α . This was accompanied by increased α -SMA and tumor PD-L1 expression, indicating formation of an immunosuppressive and immune checkpoint-targetable microenvironment. In 3D spheroids with only Hep3B cell lines or spheroids containing non-activated THP-1 cells, atezolizumab monotherapy showed little measurable treatment response, whereas responsiveness was observed in the activated THP-1-containing spheroids. After 7 days of treatment under activated THP-1 conditions, addition of a uPAR inhibitor significantly reduced spheroid size (50.7% vs. 15.1% in proportion of size reduction) and viability index (36.2% vs. 75.3% in proportion of live cells) compared to atezolizumab monotherapy.

Conclusions: *In vitro* 3D HCC TME model with activated monocyte cells is a useful platform for immunotherapy optimization. uPAR inhibition synergized the anti-tumor effects of HCC immunotherapy.

Keywords: Hepatocellular Carcinoma, Tumor Microenvironment, 3D Co-Culture Spheroid Model, Upar Inhibitor

OP-101

Multi Cohort Integrative Profiling of Cytochrome P450 Genes Identifies CYP2R1 as a Metabolic and Immunogenomic Biomarker Linking DNA Repair and Myeloid Suppression in Hepatocellular Carcinoma

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cine; 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, South Korea

Aims: Hepatocellular carcinoma (HCC) lacks robust molecular biomarkers that capture its metabolic and immunologic heterogeneity. This study aimed to systematically characterize cytochrome P450 (CYP) gene dysregulation in HCC and to identify CYP-based markers with diagnostic, prognostic, and mechanistic relevance, focusing on CYP2R1 as a potential integrator of metabolism, DNA repair, and tumor immunity.

Methods: Fiftyseven human CYP genes were analyzed in large HCC transcriptomic cohorts, with differential expression, ROC-based diagnostic testing, and Cox regression-based survival modeling. Protein expression and tumor specificity of candidate genes were validated using public immunohistochemistry resources, spatial transcriptomics, and quantitative RT-PCR in paired tumor and nontumor tissues. Coexpression networks, pathway enrichment, and gene set enrichment analyses were used to define CYP2R1-associated programs, and immunecell deconvolution linked CYP2R1 expression to tumor-infiltrating myeloid populations.

Results: CYP genes showed marked, genespecific deregulation in HCC, with several hepatic CYPs being strongly downregulated while CYP2R1 and a small subset were consistently upregulated. CYP2R1 demonstrated high diagnostic accuracy and robust tumorspecific induction at both mRNA and protein levels across independent cohorts. Survival analyses identified CYP2C9 as a favorable and CYP2B6 as an unfavorable independent prognostic marker. High CYP2R1 expression was associated with activation of DNA replication and repair pathways and with transcriptional signatures and inferred infiltration of myeloid-derived suppressor cells.

Conclusions: These data indicate that CYP reprogramming in HCC is highly selective and clinically informative. CYP2R1 emerges as a novel metabolic and immunogenomic biomarker that combines strong diagnostic performance with links to DNA repair activation and myeloid-driven immunosuppression, while CYP2C9 and CYP2B6 provide additional prognostic stratification.

Keywords: CYP2R1, Diagnosis, Prognostic Biomarker, HCC

OP-102

Shelterin Component TPP1 Drives Tumor Progression and Predicts Poor Prognosis in Hepatocellular Carcinoma

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Aims: Telomere dysfunction and the shelterin complex are implicated in cancer, yet the specific functions and interactions of telomerase and shelterin genes in hepatocellular carcinoma (HCC) tumorigenesis remain poorly understood. This study aims to investigate the clinico-biological functions and collaborative contributions of telomerase and shelterin components in hepatocarcinogenesis.

Methods: We analyzed tumor and matched non-tumor tissues from 274 HCC patients who underwent hepatectomy. Telomere-related parameters, including TERT (telomerase reverse transcriptase) expression and telomere length measured by qRT-PCR, telomerase activity assessed by the Telomerase Repeated Amplification Protocol assay, and six shelterin components analyzed by RNA sequencing, were correlated with clinicopathological features. siRNA-mediated knock down of TPP1 (POT1-TIN2 organizing protein) was performed to evaluate its regulatory effect on TERT expression. Findings were externally validated.

Results: TERT and TPP1 were upregulated in tumors with increased telomerase activity and shortened telomere length. Among the shelterin components, TPP1 showed the strongest correlation with TERT, and its expression increased with tumor multiplicity and advancing stage. TPP1 expression also correlated with proliferation-associated genes, consistent with Gene Set Enrichment Analysis suggesting TPP1 involvement in proliferative activity. TPP1 knockdown suppressed TERT protein expression and inhibited HCC cell proliferation, with the strongest anti-proliferative effect observed after dual TERT-TPP1 knockdown. Clinically, high TPP1 expression was associated with significantly earlier HCC recurrence, and co-high expression of TPP1-TERT was linked to significantly worse survival after hepatectomy.

Conclusions: The TERT-TPP1 axis enhances proliferative activity and is associated with aggressive features and poor outcomes in HCC. TPP1 represents a potential therapeutic target and prognostic biomarker for HCC.

Keywords: Telomere, Shelterin, Prognostication, Liver Cancer

OP-103

Clustering of Intrahepatic Cholangiocarcinoma Subtypes Using Whole-Genome Sequencing

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Aims: Intrahepatic cholangiocarcinoma (iCC) accounts for a relatively small proportion of primary liver cancers, and its molecular characteristics remain incompletely characterized. Given the importance of comprehensive molecular-level analyses, this study aimed to identify potential molecular subtypes of

iCC using whole-genome sequencing (WGS) and to correlate these subtypes with clinical features.

Methods: We retrospectively analyzed 59 patients who underwent curative-intent liver resection for iCC between 2013 and 2021. Clustering was performed based on mutational signatures derived from a proprietary WGS pipeline. The resulting molecular clusters were compared with available demographic and clinical data.

Results: Unsupervised clustering based on genomic features identified six distinct molecular subtypes: Cluster 1 (N=31, 52.5%) exhibited a strong CN21 signature without evidence of whole-genome duplication (WGD), and was associated with a high rate of local recurrence (72.0%). Cluster 2 (N=8, 13.6%) was enriched for IDH1/2 and BAP1 mutations, showed WGD, and all patients were classified as small duct type. Cluster 3 (N=8, 13.6%) was enriched for KRAS mutation in the context of WGD, and was associated with significantly elevated preoperative CA 19-9 levels. Cluster 4 (N=5, 8.5%) demonstrated HRD and APOBEC mutational activity; all cases belonged to the large duct type. Cluster 5 (N=4, 6.8%) showed mutational signatures associated with smoking and viral hepatitis exposure (75.0%). Cluster 6 (N=3, 5.1%) exhibited a high indel-to-SBS ratio, and all tumors were localized to the second-order bile duct branches.

Conclusions: Using WGS-based mutational signature analysis, we identified 6 distinct molecular subtypes of iCC, each with unique genomic, clinical, and epidemiologic characteristics.

Keywords: Cluster Analysis, Intrahepatic Cholangiocarcinoma, Whole Genome Sequencing

Saturday, June 13, 2026, 08:00-09:00

19. HCC, Clinical 3

OP-104

Prognostic Factor and Risk Stratification in Hepatocellular Carcinoma: Insights from Cox Regression and Kaplan-Meier Analysis in a Male-Dominated Cohort

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Aims: Hepatocellular carcinoma (HCC) is a significant cause of morbidity and mortality worldwide. This study aims to comprehensively evaluate the prognostic factors influencing survival in patients diagnosed with HCC.

Methods: This is a cross-sectional study aimed at identifying prognostic factors in HCC using Cox regression and Kaplan-Meier analysis. A cohort of 364 predominantly male HCC

patients with a mean age of 61.6 ± 10.9 years was analyzed.

Results: Significant risk factors for mortality included HCV infection, alcoholism, elevated alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA) II levels, and a Child-Pugh score of 8. HCV-positive patients had a hazard ratio (HR) of 2.25. Average survival time was 32.99 ± 31.64 months, with 1, 2, and 3-year survival rates of 73.6%, 44.5%, and 31.3%, respectively. Patients with PIVKA-II levels ≤ 125 mAU/mL had a significantly higher 50% chance of surviving 42 months. Patients with the Barcelona clinic liver cancer (BCLC) stage B1 displayed a higher survival rate, except at the 24-month time point, with BCLC A and B1 groups showing survival rates exceeding 80% in the first year.

Conclusions: The findings provide valuable insights into the prognostic implications and risk stratification in HCC, facilitating personalized treatment decisions and potentially improving patient outcomes.

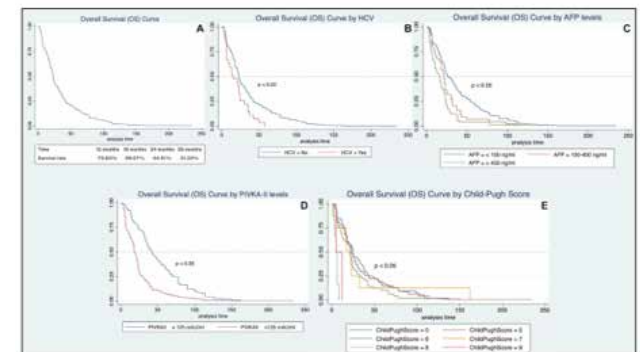


Figure 1. Kaplan-Meier survival curves of statistically significant variables identified in the multivariate analysis ($p < 0.05$). A, Overall survival throughout the follow-up period. B, Overall survival curves of patients with and without HCV throughout the follow-up period. C, Overall survival curves of patients with various AFP levels throughout the follow-up period. D, Overall survival curves of patients with PIVKA-II ≤ 125 and PIVKA-II > 125 mAU/mL throughout the follow-up period. E, Overall survival curves of patients with varying Child-Pugh scores throughout the follow-up period.

Table V. Multivariate analyses of the association between mortality and some factors.

Variable	Hazard ratio (95% CI)	p-value	Variable	Hazard ratio (95% CI)	p-value
Age ≤ 40	1.65 (0.88-3.17)	0.137	Distal metastases		
HCV	2.25 (1.46-3.41)	0.000	Yes	0.47 (0.18-1.35)	0.171
Alcoholism	1.48 (1.06-1.98)	0.017	No	1	
AST (U/L)			Portal		
≤ 80	1		Yes	2.85 (0.88-83.62)	0.778
> 80	0.99 (0.49-1.42)	0.962	No	1	
ALT (U/L)			Location of portal vein thrombosis		
≤ 80	1		No	1	
> 80	1.38 (0.87-1.83)	0.217	VP2	0.52 (0.02-18.27)	0.712
AFP (ng/mL)			VP3	0.43 (0.02-11.51)	0.608
< 100	1		VP4	1.69 (0.05-49.60)	0.760
100-400	1.26 (0.83-1.93)	0.201	Classification according to BCLC stage		
> 400	1.46 (1.04-2.02)	0.028	Very early-stage 0	1	
AFP-L3 (%)			Early-stage A	0.81 (0.31-1.70)	0.599
≤ 10	1		Intermediate stage B1	0.64 (0.26-1.12)	0.121
> 10	1.23 (0.90-1.67)	0.183	Intermediate stage B2	0.85 (0.43-1.70)	0.606
PIVKA II (mAU/mL)			Intermediate stage B3	1.13 (0.49-2.60)	0.766
≤ 125	1		Advanced stage C	1.28 (0.26-6.18)	0.716
> 125	1.50 (1.16-1.95)	0.000	Late-stage D	0.97 (0.17-5.43)	0.978
Tumor size (cm)			Child-Pugh score		
≤ 2	1		0	1	
2-5	1.01 (0.76-1.35)	0.008	1	1.11 (0.82-1.50)	0.426
> 5	1.24 (0.78-1.97)	0.260	2	1.24 (0.81-1.89)	0.316
Number of tumors			3	1.41 (0.69-3.77)	0.265
≤ 3	1		4	6.12 (2.04-21.50)	0.000
> 3	1.90 (0.80-2.50)	0.122	5	2.29 (0.23-7.13)	0.766
Up-to-7					
≤ 7	1				
> 7	1.90 (0.83-2.13)	0.218			

HCV: Hepatitis C virus, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, AFP-L3: Liver-associated alpha-fetoprotein, PIVKA II: Protein induced by vitamin K absence or antagonist-II, BCLC: Barcelona clinic liver cancer, PV: Portal vein.

Table IV. Univariate analysis of the association between mortality and some factors.

Variable	Hazard ratio (95% CI)	p-value	Variable	Hazard ratio (95% CI)	p-value
Male	0.99 (0.74-1.32)	0.959	Number of tumors		
Age ≤ 40	1.98 (1.15-3.47)	0.016	≤ 3	1	
HBV	0.83 (0.63-1.07)	0.152	> 3	1.94 (1.16-2.68)	0.001
HCV	1.75 (1.17-2.60)	0.005	Up-to-7		
Alcoholism	1.58 (1.21-2.05)	0.001	≤ 7	1	
NASH	1.11 (0.75-1.63)	0.582	> 7	2.17 (1.70-2.76)	0.000
INR			Distal metastases		
≤ 1	1		Yes	1.83 (1.00-3.35)	0.048
> 1	1.00 (0.79-1.25)	0.989	No	1	
Total bilirubin (mg/dL)			Portal vein thrombosis		
< 17.1	1		Yes	2.45 (1.65-3.62)	0.000
17.1-34.1	0.96 (0.77-1.20)	0.750	No	1	
> 34.1	1.24 (0.83-1.86)	0.282	Location of portal vein thrombosis		
Albumin (g/d)			No	1	
< 28	2.75 (0.87-8.63)	0.082	VP2	1.78 (0.73-4.31)	0.201
28-35	1.14 (0.84-1.54)	0.274	VP3	2.21 (1.33-3.67)	0.002
> 35	1		VP4	4.97 (2.04-8.37)	0.000
AST (U/L)			Classification according to BCLC stage		
≤ 80	1		Very early-stage 0	1	
> 80	1.49 (1.15-1.93)	0.002	Early-stage A	0.77 (0.50-1.19)	0.238
ALT (U/L)			Intermediate stage B1	0.74 (0.45-1.22)	0.247
≤ 80	1		Intermediate stage B2	1.54 (0.93-2.54)	0.087
> 80	1.62 (1.21-2.18)	0.001	Intermediate stage B3	1.88 (0.93-3.73)	0.066
AFP (ng/mL)			Advanced stage C	2.24 (1.29-3.88)	0.004
< 100	1		Late-stage D	1.80	0.339
100-400	1.55 (1.12-2.14)	0.008	Child-Pugh classification		
> 400	2.15 (1.44-2.81)	0.000	0	1	
AFP-L3 (%)			Child-Pugh A	0.96 (0.75-1.25)	0.759
≤ 10	1		Child-Pugh B	1.65 (0.96-2.85)	0.071
> 10	1.82 (1.45-2.28)	0.000	Child-Pugh score		
PIVKA II (mAU/mL)			0	1	
≤ 125	1		1	0.97 (0.72-1.30)	0.821
> 125	2.20 (1.75-2.77)	0.000	2	1.31 (0.89-1.93)	0.167
Tumor size (cm)			3	0.94 (0.43-2.01)	0.872
≤ 2	1		4	8.90 (3.75-21.55)	0.000
2-5	1.15 (0.90-1.47)	0.247	5	4.50 (1.32-22.87)	0.019
> 5	2.17 (1.58-2.99)	0.000			

HBV: Hepatitis B virus, HCV: Hepatitis C virus, NASH: Non-alcoholic steatohepatitis, INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, AFP-L3: Liver-associated alpha-fetoprotein, PIVKA II: Protein induced by vitamin K absence or antagonist-II, BCLC: Barcelona clinic liver cancer.

Keywords: Hepatocellular Carcinoma, Prognostic Factors, Mortality

OP-105

Real-World Effectiveness of the STRIDE Regimen in Hepatocellular Carcinoma: Initial Experience from a Tertiary Center in Vietnam

Manh Duy Pham, Loc Quang Bui, Huy Le Trinh, Anh Dinh Tran

Hanoi Medical University, Vietnam

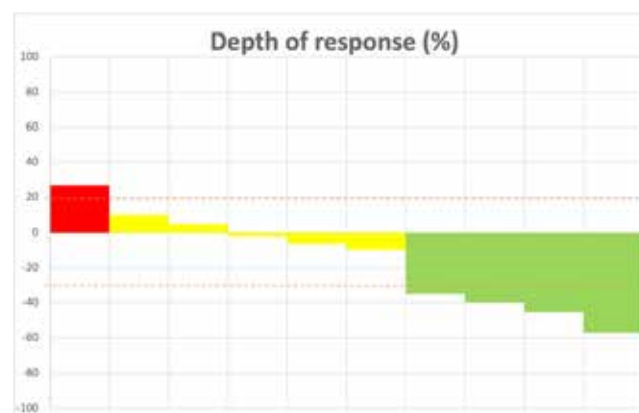
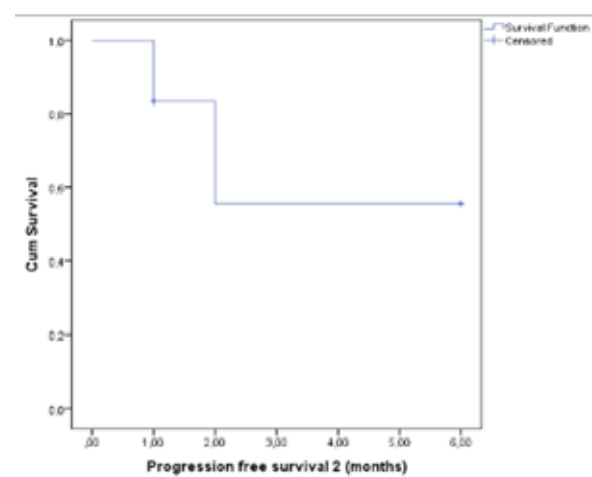
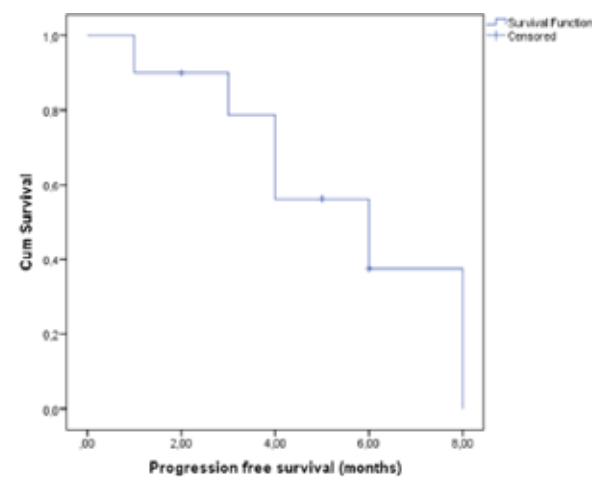
Aims: The STRIDE regimen (Single Tremelimumab Regular Interval Durvalumab) has recently become a first-line standard for advanced hepatocellular carcinoma (HCC). Introduced in Vietnam in April 2025, its clinical adoption remains limited due to the lack of national health insurance coverage and more extensive practitioner experience with the Atezolizumab-Bevacizumab combination. This study reports the first real-world experience at a Vietnamese tertiary center.

Methods: We conducted a descriptive case series of BCLC stage C HCC patients treated with first-line STRIDE at Hanoi Medical University Hospital (April 2025–January 2026). Treatment response was evaluated every 2 cycles using RECIST 1.1. Objective Response Rate (ORR) and Disease Control Rate (DCR) were calculated based on the Best Overall Response (BOR).

Results: Ten patients were enrolled (Median follow-up: 6 months; 80% HBV, 10% HCV, 10% non-viral). Most were Child-Pugh A, with two Child-Pugh B7. The ORR was 40% (all partial responses) and the DCR was 90%. The BOR was achieved at the first assessment for all responders (Time to Response: 2 months); notably, no patients with initial stable disease subsequently converted to a partial response. Median progression-free survival (mPFS) was 6 months (95% CI: 2.1–9.9). Following progression (n=6), five patients transitioned to second-line Lenvatinib and one received palliative care; median PFS2 has not yet been reached. All responders showed corresponding AFP declines. The regimen was well-tolerated with preserved liver function; the only immune-related adverse event was a Grade 1 skin rash (n=1).

Conclusions: Preliminary outcomes of the STRIDE regimen in Vietnam align with the HIMALAYA trial, demonstrating robust disease control and favorable safety. The high rate of early and sustained response provides a strong clinical rationale for adopting this dual immunotherapy, even in self-pay settings.

Keywords: Dual Immunotherapy, Stride Regimen, Hepatocellular Carcinoma



OP-106

Real-World Clinical Outcomes of Nivolumab plus Ipilimumab for Unresectable Hepatocellular Carcinoma: A Multicenter Cohort Study

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Aims: Nivolumab plus ipilimumab (Nivo+Ipi) is a standard first-line therapy for unresectable hepatocellular carcinoma (uHCC). We retrospectively evaluated the clinical outcomes and adverse events of Nivo+Ipi therapy in real-world clinical practice across multiple institutions.

Methods: This study enrolled 17 patients with uHCC who initiated Nivo+Ipi treatment between September 2025 and December 2025. Treatment response was assessed using RECIST version 1.1. Progression-free survival (PFS) and overall survival (OS) were evaluated using the Kaplan-Meier method. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: In the total cohort of 17 patients, the median age was 66 years, and 12 (71%) were male. Child-Pugh class A was observed in 15 patients (88%) and class B in 2 (12%). Barcelona Clinic Liver Cancer (BCLC) stage B and C were reported in 7 (41%) and 10 (59%) patients, respectively. Treatment lines included first-line (n=7, 41%), second-line (n=5, 29%), and third-line (n=5, 29%). Six patients (35%) completed all four doses of ipilimumab. The best overall response (BOR) for all patients was partial response (PR) in 5 (29%), stable disease (SD) in 2 (12%), progressive disease (PD) in 7 (41%), and not evaluable (NE) in 3 (18%). In the first-line setting specifically (n=7), the BOR con-

sisted of PR in 3 (43%), SD in 1 (14%), PD in 2 (29%), and NE in 1 (14%). The median PFS was 4.0 months (95% CI: 1.9–NA) for the entire cohort and 4.0 months (95% CI: 1.6–NA) for first-line cases. Median OS was not reached due to the short follow-up period. Grade ≥ 3 immune-related adverse events occurred in 6 patients (35%), including hepatic toxicity (n=4), adrenal insufficiency (n=1), diarrhea (n=1), proteinuria (n=1), anorexia (n=1), and hyperglycemia (n=1). Steroid therapy was administered to 6 patients (35%).

Conclusions: In real-world practice, Nivo+Ipi therapy achieved an objective response rate of 43% in the first-line setting. However, the median PFS was 4.0 months, with some cases showing early progression. Longer follow-up and further case accumulation are warranted to clarify long-term survival outcomes.

Keywords: Unresectable Hepatocellular Carcinoma, Nivolumab Plus Ipilimumab, Real-World Clinical Outcomes, A Multicenter Cohort Study

OP-107

MRI-Based Surveillance for Hepatocellular Carcinoma Using Risk-Stratified Screening Intervals in Patients with Cirrhosis: A Prospective Cohort Study

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Aims: Current hepatocellular carcinoma (HCC) surveillance relies on semiannual ultrasonography, which has limited sensitivity for early-stage tumor detection and may result in diagnosis of tumor at advanced stages despite regular surveillance. We evaluated the effectiveness of HCC surveillance using gadoteric acid-enhanced MRI at risk-stratified personalized screening intervals in patients with cirrhosis.

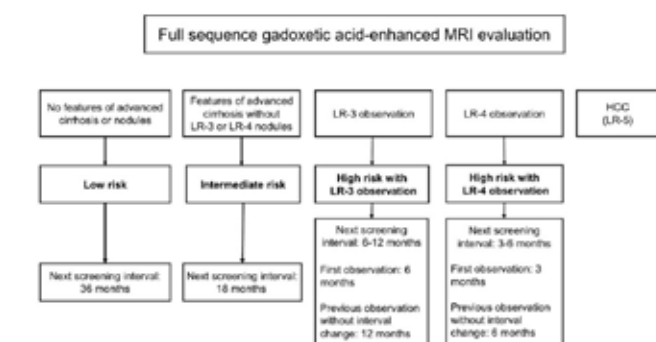
Methods: We prospectively enrolled 86 patients with cirrhosis between May 2021 and October 2022. All patients received HCC surveillance using gadoteric acid-enhanced MRI at risk-stratified screening intervals ranging from 3 to 36 months, according to the assigned risk category based on MRI features (low, intermediate, high risk with LI-RADS LR-3 observations, or high risk with LI-RADS LR-4 observations), for 3 years. The primary outcome was surveillance failure, defined as HCC detected beyond the Milan criteria. Secondary outcomes included the very early-stage detection rate (<2 cm) and the interval cancer rate. Interval cancer was defined as HCC detected outside of scheduled MRI surveillance examinations.

Results: HCC was diagnosed with 13 patients during study period. HCC incidence differed markedly across MRI risk categories, ranging from 1.9 per 100 person-years in patients with low-risk to 73.4 per 100 person-years in those with LR-4 observations. The primary endpoint was met, with no surveillance

failures observed (0%; 95% CI 0–24.7%). Ten cases (76.9%) were identified at very early stage, and there was one interval cancer (7.7%). Compared with a uniform semiannual surveillance strategy, the risk-stratified approach reduced the number of surveillance examinations by 44.2%.

Conclusions: HCC surveillance using gadoteric acid-enhanced MRI at risk-stratified screening intervals resulted in no surveillance failures, a high rate of early-stage tumor detection, and a low incidence of interval cancer. This approach may improve surveillance effectiveness while reducing examination frequency.

Keywords: Hepatocellular Carcinoma, Magnetic-Resonance Imaging, Surveillance



OP-108

Comparative Effectiveness of Subsequent Systemic Therapies after Atezolizumab–Bevacizumab Failure in Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Aims: Atezolizumab plus bevacizumab (Atezo–Bev) has become the standard first-line therapy for advanced hepatocellular carcinoma (HCC). However, optimal subsequent systemic therapy remains unclear. We conducted a systematic review and meta-analysis to compare the effectiveness of subsequent systemic therapies after Atezo–Bev failure.

Methods: Clinical studies investigating systemic therapies administered after Atezo–Bev failure were identified through a systematic search of PubMed, Embase, the Cochrane Library, and Web of Science. Pooled estimates of median overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and grade 3–4 adverse events were calculated using random-effects meta-analysis.

Results: The pooled median OS was 12.42 months (95% confidence interval [CI], 10.02–14.82; $I^2=89.4\%$) for lenvatinib, 7.83 months (95% CI, 6.29–9.36; $I^2=73.6\%$) for sorafenib, 9.19 months (95% CI, 3.60–14.78; $I^2=94.5\%$) for regorafenib, and 9.59 months (95% CI, 4.91–14.27; $I^2=91.4\%$) for cabozantinib. Compared with sorafenib, the pooled risk ratios (RRs) for mortality were 0.64 (95% CI, 0.49–0.84; $I^2=34.2\%$) for lenvatinib, 1.25 (95% CI, 0.33–4.74; $I^2=88.9\%$) for regorafenib, and 0.93 (95% CI, 0.42–2.05; $I^2=60.7\%$) for cabozantinib. The pooled median PFS was 4.74 months (95% CI, 3.76–5.72; $I^2=96.4\%$) for lenvatinib, 2.86 months (95% CI, 2.23–3.48; $I^2=91.2\%$) for sorafenib, 3.05 months (95% CI, 2.42–3.67; $I^2=61.9\%$) for regorafenib, and 3.96 months (95% CI, 1.43–6.50; $I^2=69.8\%$) for cabozantinib. Compared with sorafenib, the pooled RRs for disease progression were 0.58 (95% CI, 0.42–0.80; $I^2=65.3\%$) for lenvatinib and 0.74 (95% CI, 0.51–1.05; $I^2=13.5\%$) for regorafenib. The pooled ORR was 13.0% (95% CI, 9.1–18.1; $I^2=51.0\%$) for lenvatinib, 4.7% (95% CI, 2.5–8.8; $I^2=40.3\%$) for sorafenib, 10.7% (95% CI, 6.0–18.3; $I^2=0.0\%$) for regorafenib, and 7.9% (95% CI, 0.3–69.8; $I^2=0.0\%$) for cabozantinib. The pooled incidence of grade 3–4 adverse events was 36% (95% CI, 29–44%; $I^2=32\%$) with lenvatinib and 34% (95% CI, 28–41%; $I^2=19.6\%$) with sorafenib.

Conclusions: In this meta-analysis, lenvatinib demonstrated the most favorable survival and tumor response outcomes among systemic therapies after Atezo–Bev failure in advanced HCC.

Keywords: Liver Cancer, Second-Line, Chemotherapy, Immunotherapy

OP-109

External Beam Radiotherapy versus Local Ablation Therapy for the Treatment of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Aims: Local ablation therapies (LATs), including radiofrequency ablation (RFA) and microwave ablation (MWA), are established curative options for small hepatocellular carcinoma (HCC), yet their efficacy may be limited in larger tumors or those located in anatomically challenging areas. External beam radiotherapy (EBRT), including stereotactic body radiotherapy (SBRT) and proton beam therapy (PBT), has emerged as a non-invasive alternative, but direct comparative evidence remains limited. This study aimed to compare the efficacy and safety of EBRT with those of LAT in patients with HCC.

Methods: A systematic search of PubMed/MEDLINE, Embase, Cochrane Library, and KoreaMed was conducted through June 2025 in accordance with PRISMA guidelines. Eligible studies included retrospective or prospective comparisons of EBRT (SBRT/PBT) with LAT (RFA/MWA) that reported recurrence or survival outcomes. Pooled hazard ratios (HRs) and odds ratios (ORs) were estimated using a random-effects model. Publication bias was assessed by funnel plots and Egger's test.

Results: Twelve studies involving 2,768 patients were included. EBRT significantly reduced local recurrence compared with LAT (OR 0.36, 95% CI 0.25–0.50; $P < 0.0001$; $I^2 = 0\%$) and improved local progression-free survival (HR 0.41, 95% CI 0.34–0.50; $P < 0.0001$), consistent across tumor sizes ≤ 2 cm and > 2 cm. Progression-free survival favored EBRT (HR 0.80, 95% CI 0.64–1.00; $P=0.049$), whereas overall survival did not differ significantly between the groups (HR 1.24, 95% CI 0.83–1.84; $P=0.291$). Severe toxicities (grade ≥ 3) were comparable between the groups for both acute (OR 0.78, 95% CI 0.27–2.24; $P=0.649$) and late events (OR 1.29, 95% CI 0.85–1.95; $P=0.233$), with EBRT tending toward fewer acute events. No significant publication bias was identified (all $P > 0.05$).

Conclusions: EBRT was associated with better local control without significant differences in survival or toxicity compared with

LAT. These findings support the use of EBRT as a safe, effective, and potentially curative locoregional therapy for appropriately selected patients with liver-confined HCC.

Keywords: Hepatocellular Carcinoma, Stereotactic Body Radiotherapy, Proton Beam Therapy, Radiofrequency Ablation

Saturday, June 13, 2026, 08:00–09:00

20. Biliary and Pancreatic Disease & Others

OP-110

Self-Supervised Learning Model Integrates Plain and Contrast-Enhanced CT for Preoperatively Identifying Gangrenous Cholecystitis: A Multicenter Study

Guandou Yuan, Qingping Guo, Shengjie Xie, Siyang Li, Jinpeng Zheng, Haiqing Yang, Songqing He

Division of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

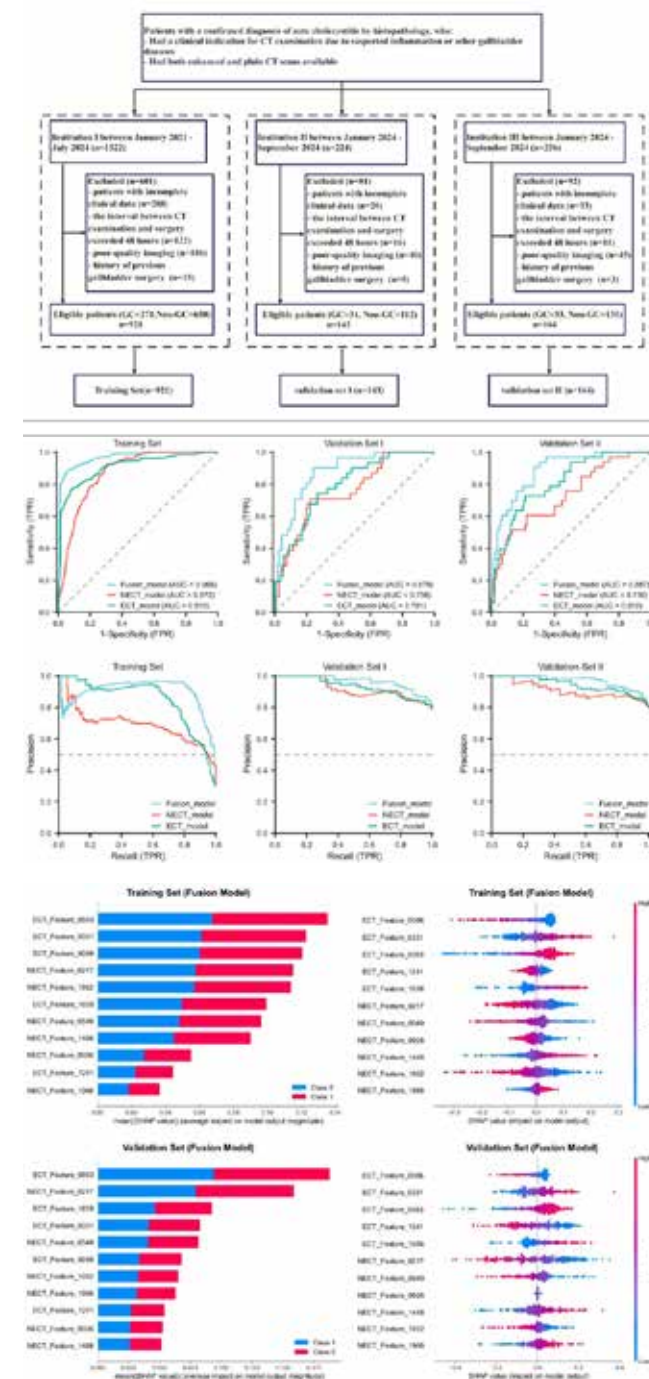
Aims: Gangrenous cholecystitis (GC) is a severe complication of acute cholecystitis that requires prompt surgical intervention. However, its preoperative diagnosis remains challenging due to the limitations of traditional imaging techniques. This study aims to develop a self-supervised learning (SSL) model to preoperatively identify GC using both plain and contrast-enhanced CT images.

Methods: This was a retrospective, multicenter cohort study conducted from January 2021 to September 2024. A total of 7368 CT images from 1228 patients (training set: 921 patients; independent validation set: 307 patients) were retrospectively analyzed. We developed an SSL model using seResNet-50 framework, trained on unenhanced and contrast-enhanced CT images, to predict the presence of GC preoperatively. The model leverages unlabeled data to pretrain the network, and is then fine-tuned on a limited set of annotated images. After feature extraction and selection, we developed three models for predicting GC, including a fusion model, an enhanced CT (ECT) model, and a non-enhanced CT (NECT) model. Performance was assessed using accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

Results: The fusion model demonstrated robust performance in preoperative GC prediction. In the training set, the fusion model achieved an AUC of 0.965, a sensitivity of 88%, and a specificity of 95% in detecting GC. In Validation Set I, the fusion model had an AUC of 0.879, surpassing the enhanced and non-enhanced models (AUCs: 0.791, 0.756, respectively). Similarly, in Validation Set II, the fusion model achieved an AUC of 0.887, significantly better than the ECT and NECT models

(AUCs: 0.810, 0.730). The model also provided interpretable analyses by detecting subtle features of gangrenous changes in the CT images, facilitating clinical decision-making.

Conclusions: We developed a fusion SSL model for preoperative prediction of gangrenous cholecystitis using both unenhanced and contrast-enhanced CT scans. The model's high diagnostic performance suggests its clinical applicability in improving early diagnosis and timely risk stratification of GC.



Keywords: Gangrenous Cholecystitis, Self-Supervised Learning, Cholecystectomy, Biliary Surgery, Retrospective Cohort Study

OP-111

Staged Minimally Invasive Strategy for the Management of Complicated Gallstone Disease in Pregnancy

Onlasyn Ibekenov¹, **Daulet Kyzhyrov²**, Bolatbek Baymakhanov¹, Shokan Kaniev¹, Erlan Abrashev¹, Mazhit Abdykadyrov¹

¹The National Scientific Center of Surgery Named after A. N. Syzganov (NSCS), KAZAKHSTAN; ²Kazakh National Medical University Named after S.D. Asfendiyarov - Kaznmu, Kazakhstan

Aims: Management of complicated gallstone disease during pregnancy represents a challenging clinical problem, requiring a careful balance between timely surgical intervention and fetal safety. Advances in minimally invasive techniques, including endoscopic and laparoscopic approaches, have expanded therapeutic options. This study aimed to evaluate the outcomes of surgical management in pregnant patients.

Methods: From 2022 to 2025, 37 pregnant patients with complicated gallstone disease were treated at the A.N. Syzganov National Scientific Center of Surgery. The mean age was 37.6 years (range 21–49). Gestational age at admission: first trimester — 3 patients; second — 24; third — 10. All patients presented with abdominal pain. Obstructive jaundice occurred in 24 (64.8%), with total bilirubin 25.7–148.9 $\mu\text{mol/L}$. Elevated C-reactive protein was noted in 10 (27%), and increased aminotransferases in 19 (51.3%). Ultrasonography confirmed choledocholithiasis in 30 (81.1%) and acute cholecystitis in 7 (18.9%). Descriptive statistical analysis was performed using IBM SPSS Statistics

Results: A staged management strategy was applied in 20 patients (54.1%): stage 1 — ERCP with endoscopic sphincterotomy; stage 2 — laparoscopic cholecystectomy (LC) 3–6 days later. Ten patients (27%) underwent ERCP alone; LC was postponed due to absence of gallbladder stones (3) or high preterm labor risk (1). Six patients with destructive cholecystitis underwent LC without prior ERCP. Two late-pregnancy cases had percutaneous cholecystostomy as a bridge to postpartum LC.

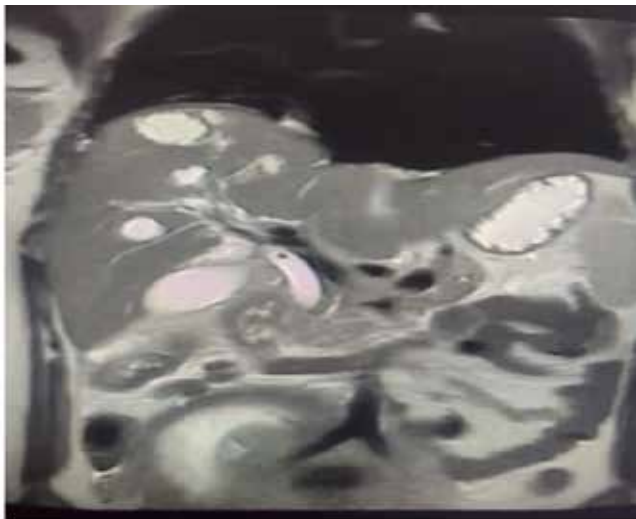
Complications included perforation of a choledochal cyst, managed with biliary stenting and conservative therapy. One intrauterine fetal demise occurred three days after ERCP in a patient with severe cholangitis and biliary pancreatitis. All other pregnancies resulted in term delivery via spontaneous vaginal birth.

Conclusions: A staged minimally invasive approach appears effective and, based on our experience, safe. ERCP with endoscopic sphincterotomy provides reliable biliary decompression, while laparoscopic cholecystectomy can be safely performed at any stage of pregnancy when indicated, with favorable ma-

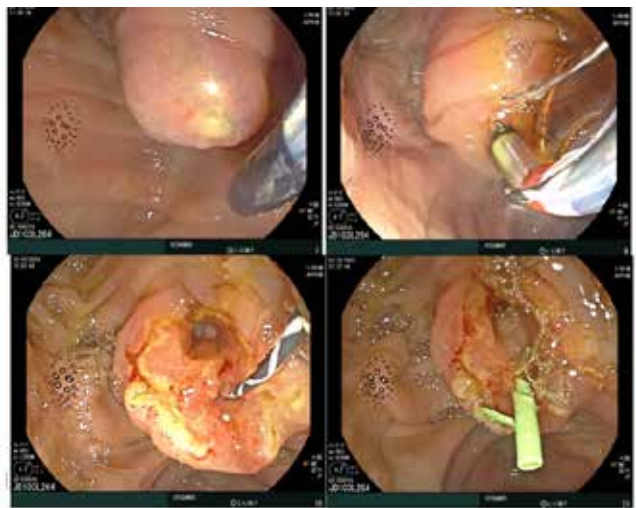
ternal and fetal outcomes.

Table 1. Distribution of surgical procedures among pregnant patients (n=37)

Type of surgery	Number of patients	Surgical treatment (n=37)		
		I	II	III
Two-stage surgery 1) ERCP, EST with choledocholith -extraction 2) Laparoscopic cholecystectomy (LC) performed 3–5 days later	18	-	13	5
ERCP, EST with choledocholith - extraction	9	1	5	3
Laparoscopic cholecystectomy (LC)	5	2	6	-
Percutaneous transhepatic biliary drainage (PTBD)	2	-	-	2



Acute calculous cholecystitis. Stone in the distal common bile duct with features of acute pancreatitis. Cholangitic liver abscesses and right-sided exudative pleuritis.



The common bile duct (CBD) is slightly enlarged, with an impacted stone visualized at the ampulla. During contrast cholangiography, the CBD diameter is up to 1.2–1.3 cm, with a 0.8 cm stone in the terminal part. EST was performed up to 0.7 cm. Three stones were extracted using a Dormia basket. For prophylactic purposes, a pancreatic stent (5 Fr, up to 4 cm in length) was placed.

Keywords: Gallstone Disease, Pregnancy, Complications of the Gallstone Disease, Choledocholithiasis

OP-112

Survival Analysis of Peritoneal Metastasis in Pancreatic Cancer Receiving Hyperthermic Intraperitoneal Chemotherapy

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Aims: Peritoneal metastasis (PM) of pancreatic cancer is associated with a poor prognosis. The survival rates of patients with PM are markedly low, highlighting the need for alternative therapeutic strategies. Thus, we aim to explore the effectiveness of hyperthermic intraperitoneal chemotherapy (HIPEC) as a treatment modality for peritoneal metastatic pancreatic cancer.

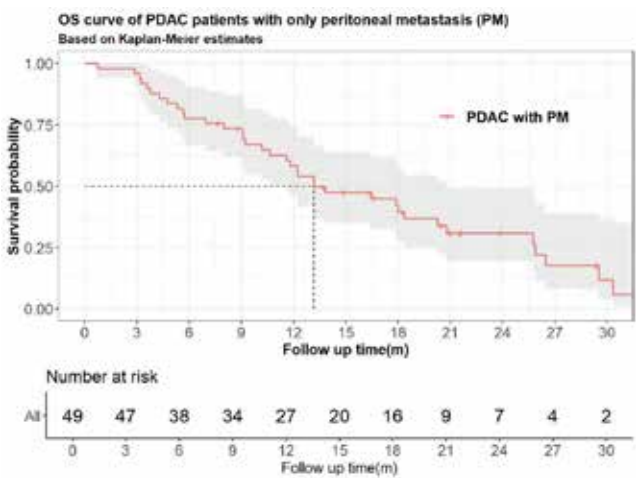
Methods: Patients with peritoneal metastatic pancreatic cancer confirmed by pathology, without other organs metastasis, received HIPEC treatment. Hyperthermic chemotherapy catheters were placed in the abdominal cavity during exploratory surgery, and patients received HIPEC with 90 mg cisplatin. Patients received either intravenous or oral chemotherapy after HIPEC.

Results: A total of 49 pancreatic ductal adenocarcinoma patients with PM receiving HIPEC from February 2023 to October 2024 was included. Among them, 16 patients had tumors located in the head or neck of the pancreas, 28 patients had tumors in the body or tail of the pancreas and 2 patients with multi-focal lesions. Notably, 3 patients had post-pancreaticoduodenectomy peritoneal metastasis. Eighteen patients had received prior systemic chemotherapy before HIPEC. All patients underwent subsequent systemic chemotherapy after HIPEC. Conversion surgery was performed when peritoneal metastases disappeared and pancreatic lesion was resectable. One patient received distal pancreatectomy after 2 times of HIPEC and 4 cycles of nab-paclitaxel and gemcitabine. The median survival time for all patients was 13.2 months. The 6-month survival rate was 77.6%, and the 1-year survival rate was 58.3%.

Conclusions: Despite the poor prognosis associated with PM of pancreatic cancer, the combination of HIPEC and adjuvant chemotherapy offers potential therapeutic benefit. Further studies, including larger randomized trials, are necessary to better define the role of HIPEC in the management of peritoneal metastatic pancreatic cancer and to optimize treatment protocols.

Keywords: Pancreatic Cancer, Peritoneal Metastasis, Hyperther-

mic Intraperitoneal Chemotherapy



OP-113

Antibiotic Prophylaxis in Emergency Cholecystectomy: A Systematic Review and Meta-Analysis with Trial Sequential Analysis

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Aims: The value of antibiotic prophylaxis in emergency cholecystectomy remains uncertain. We performed a systematic review and meta-analysis of randomized controlled trials to assess whether antibiotics reduce postoperative infectious complications and whether trial sequential analysis (TSA) materially changes interpretation.

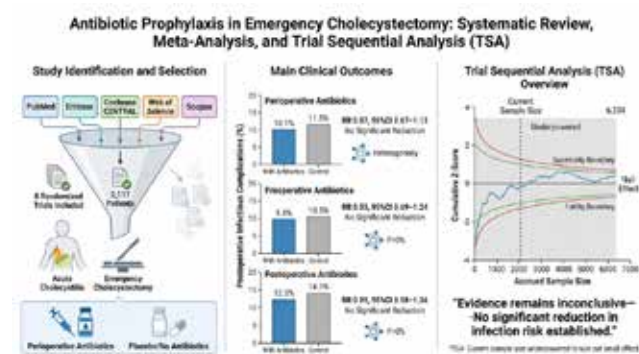
Methods: PubMed, Embase, Cochrane CENTRAL, Web of Science, and Scopus were searched for randomized trials enrolling patients with Tokyo-guideline-defined acute cholecystitis undergoing emergency cholecystectomy and comparing perioperative antibiotics with placebo or no antibiotics. The primary outcome was total postoperative infectious complications. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Prespecified subgroup analyses examined preoperative and postoperative antibiotic use. TSA was performed for the primary outcome using a two-sided alpha of 5%, power of 80%, and an anticipated relative risk reduction of 20%.

Results: Eight randomized trials, including 2,117 patients, were analyzed. Perioperative antibiotics did not significantly reduce total postoperative infectious complications versus control (RR 0.87, 95% CI 0.67–1.13; $I^2=0\%$). No significant benefit was found with preoperative antibiotics (RR 0.69, 95% CI 0.45–1.08; $I^2=8\%$) or postoperative antibiotics (RR 0.99, 95% CI 0.71–1.38; $I^2=0\%$).

TSA showed that the accrued information size remained below the required information size (2,117 vs about 6,334 patients), and no superiority or futility boundary was crossed. However, this indicates limited conclusiveness, not evidence of benefit.

Conclusions: Current randomized evidence does not show a significant or clinically meaningful reduction in postoperative infectious complications with perioperative antibiotic prophylaxis for emergency cholecystectomy. Although TSA suggests the evidence remains underpowered to exclude a small effect with certainty.

Keywords: Antibiotic Prophylaxis, Emergency Cholecystectomy, Meta-Analysis



OP-114

A Safe and Oncologic Feasibility of Laparoscopic Pancreaticoduodenectomy for Pancreatic Cancer: Experience from a Developing Country without Robotic Platforms

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Aims: This study aims to evaluate the efficacy and oncologic outcomes of laparoscopic pancreaticoduodenectomy (LPD) utilizing a left-posterior superior mesenteric artery (SMA) first-approach, combined with circumferential lymphadenectomy around the SMA and common hepatic artery (CHA), and total mesopancreas (MP) dissection for pancreatic ductal adenocarcinoma (PDAC). The procedure was implemented in a developing country without access to robotic surgical platforms.

Methods: A prospective study was conducted on 47 PDAC patients who underwent LPD with the described technique between January 2021 and December 2025. Patient demographics, operative details, pathological findings, recurrence patterns, and survival outcomes were analyzed.

Results: The median age was 58.9 ± 8.9 years (range 35–70), with 54.1% over 60. Mean operative time was 426.2 ± 78.5

minutes; SMA-first approach averaged 99.9 ± 27.7 minutes. Mesopancreas metastasis was observed in 29.7%, and reactive fibrosis in 45.9%. Mean harvested LNs were 32.4 ± 12.2 , including 7.1 ± 5.6 left-sided SMA LNs; Metastatic involvement of left-sided SMA LNs was found in 5 cases (13.5%). Pancreatic fistula occurred in 22.6%, mostly grade A; one required conversion. One case had refractory diarrhea. The mean postoperative hospital stay was 14.1 days, and there was no 90-day mortality. In multivariate analysis, metastasis of left-sided SMA LNs was the only independent predictor of both disease-free and overall survival ($P < 0.05$).

Conclusions: LPD with the left posterior SMA first approach, combined arterial circumferential lymphadenectomy and total mesopancreas dissection for PDAC, is a feasible and effective strategy to achieve favorable oncological outcomes, even in resource-limited settings lacking robotic surgical systems.

Keywords: Laparoscopic Pancreaticoduodenectomy, Artery First-Approach, Arterial Circumferential Lymphadenectomy, Total Mesopancreas

OP-115

Low Prealbumin Predicts Early Recurrence after Pancreatic Cancer Surgery: A Retrospective Cohort Study

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Aims: This study aimed to identify predictors of early recurrence after curative-intent resection for pancreatic ductal adenocarcinoma, with a particular focus on the prognostic value of preoperative prealbumin.

Methods: Fifty-seven patients who underwent pancreaticoduodenectomy or radical antegrade modular pancreatectomy for PDAC between March 2021 and December 2023 were retrospectively reviewed. Early recurrence was defined as recurrence within 1 year after surgery. Clinicopathologic and nutritional variables were analyzed using univariate and multivariate Cox proportional hazards models. Clinical differences between early-recurrence and non-recurrence groups were also assessed.

Results: In the univariate analysis, N2 stage (HR 3.43, $P=0.033$), resection margin <1 mm (HR 2.78, $P=0.023$), and prealbumin <20 mg/dL (HR 3.31, $P=0.016$) were significantly associated with early recurrence. Multivariate analysis identified low prealbumin as the only independent predictor (HR 4.82, $P=0.005$). Group comparison further demonstrated higher frequencies of margin <1 mm (55.0% vs. 21.6%, $P=0.011$) and prealbumin <20 mg/dL (68.4% vs. 31.3%, $P=0.010$) in the early recurrence group. Other variables were not significantly different.

Conclusions: Low preoperative prealbumin level was the sole independent risk factor for early recurrence after curative PDAC resection. Margin status and nodal burden were associated with recurrence but lacked independent significance. Incorporating nutritional assessment into perioperative management may improve risk stratification and guide personalized postoperative surveillance.

Keywords: Pancreatic Neoplasms, Recurrence, Malnutrition, Biomarkers

THE LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
in conjunction with EALA

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POSTER EXHIBITION

PE-1~PE-1	Autoimmune Liver Disease
PE-1~PE-1	Acute Liver Failure and Drug-Induced Liver Injury
PE-1~PE-4	Alcohol-Related Liver Disease, Basic
PE-1~PE-2	Liver Cirrhosis, Portal Hypertension with Cx. Basic
PE-1~PE-12	Liver Cirrhosis, Portal Hypertension with Cx. Clinical
PE-1~PE-3	HBV, Basic
PE-1~PE-5	HBV, Clinical
PE-1~PE-2	HCV, Basic
PE-1~PE-4	HCV, Clinical
PE-1~PE-12	MASLD, Basic
PE-1~PE-25	MASLD, Clinical
PE-1~PE-16	Others, Medical
PE-1~PE-40	Liver Cancer, Basic
PE-1~PE-35	Liver Cancer, Clinical
PE-1~PE-30	Liver Transplantation
PE-1~PE-46	Biliary and Pancreatic Surgery
PE-1~PE-13	Liver Surgery
PE-1~PE-7	Others, Surgical



1. Autoimmune Liver Disease

PE-1

Metagenomic Identification of Gut Microbial Signatures as Non-Invasive Diagnostic Markers in Autoimmune Hepatitis and Primary Biliary Cholangitis

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Aims: Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are chronic immune-mediated liver diseases in which gut microbiome alterations may contribute to pathogenesis via the gut–liver axis. This study aimed to identify gut microbial strains that distinguish AIH and PBC from healthy controls and to assess their potential as diagnostic biomarkers.

Methods: Stool samples and clinical data were obtained from 25 patients with AIH, 25 with PBC, 10 with AIH–PBC overlap, and 30 healthy controls at Ajou University Hospital. Shotgun metagenomic sequencing was performed for gut microbiome profiling. Species-level candidates with relatively higher abundance in each disease group than in healthy controls were selected. LEfSe was applied with an LDA score ≥ 2.0 and an FDR-adjusted $p \leq 0.05$, and analyses were restricted to species passing prevalence filter and CPM normalization to ensure robust detection.

Results: Gut microbiome composition and diversity differed significantly between healthy controls and the AIH, PBC, and AIH+PBC groups. In total, 26 strains in AIH, 24 in PBC, and 27 in the AIH-PBC met the LEfSe criteria and were defined as core microbial signatures, each consistently increased relative to healthy controls. ROC analysis demonstrated meaningful discriminatory performance, with four strains for AIH (AUC ≥ 0.70), five for PBC (AUC ≥ 0.66), and fourteen for AIH+PBC (AUC ≥ 0.70 , all $P < 0.05$).

Conclusions: These findings suggest that disease-specific gut microbial signatures may serve as non-invasive diagnostic biomarkers for AIH, PBC, and AIH–PBC overlap. Larger, independent cohorts and integrative models combining multiple taxa will be required to validate and refine these microbiome-based biomarkers for clinical application.

Keywords: Autoimmune Hepatitis, Primary Biliary Cholangitis, Diagnostic Biomarkers, Gut Microbiome

2. Acute Liver Failure and Drug-Induced Liver Injury

PE-1

Acute Liver Injury following Self-Poisoning with Glory Lily (*Gloriosa Superba*) and a Detergent Containing Potassium Permanganate (KMnO₄) and Oxalic Acid (H₂C₂O₄)

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Aims: Self-poisoning with plants and household products has become a severe public health issue in Sri Lanka. Glory Lily (*Gloriosa superba*) is one such poisonous plant that contains colchicine. It is subject to enterohepatic circulation and has a reported average case fatality rate of around 15% following self-poisoning. A detergent containing potassium permanganate (KMnO₄) and oxalic acid (H₂C₂O₄) has become a popular agent amongst the youth for self-poisoning and has been reported around 24% case fatality. Through this, we report the acute hepatotoxicity of glory lily and the detergent following self-poisoning.

Methods: Patients admitted to the general hospitals of the Southern province of Sri Lanka following self-poisoning with glory lily (n=16) and the detergent (n=63) were considered. Clinical and laboratory parameters [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin] were evaluated.

Results: Most of the patients poisoned with both agents were females (glory lily 10/16, detergent 34/63). The median age of the glory lily poisoned group and the detergent poisoned group was 22 years and 23 years, respectively. Their median ALT, AST, ALP, and total bilirubin were 42 U/L, 21 U/L, 193 U/L, and 21.00 $\mu\text{mol/L}$, respectively, for the glory lily-poisoned group. The same parameters for the detergent-poisoned group were 24 U/L, 37 U/L, 146 U/L and 14.00 $\mu\text{mol/L}$, respectively. No deaths were reported for the glory lily-poisoned patients, while one death was noted in the other group.

Conclusions: Modestly elevated levels of ALT and AST in the glory lily-poisoned group indicated mild hepatocellular injury. A mild increase in direct bilirubin suggested impaired hepatic processing and excretion of bile pigments in the same group. Elevated ALP was also noted, which may indicate cholestatic involvement. Glory lily ingestion (which contains colchicine) caused potentially reversible liver injury. However, the acute liver injury following the detergent poisoning was not prominent.

Keywords: *Gloriosa Superba*, Colchicine, Liver Injury, Detergent

Table 1: Basic Demographic, clinical and laboratory data

Parameter	Glory Lily-poisoned group (n=16)	Detergent-poisoned group (n=63)
Female (%)	62	54%
Age (years) — Median and IQR	22 (18-30)	23 (19-31)
Time to hospital admission since poisoning (hrs)	5 (3-22)	3 (1-5)
Systolic pressure (mmHg) — Median and IQR	110 (110-120)	110 (110-120)
Diastolic pressure (mmHg) — Median and IQR	80 (70-80)	70 (70-80)
Pulse (beats per minute)	80 (80-91)	76 (68-82)
ALT (U/L) — Median and IQR	42 (35-79)	24 (17-36)
AST (U/L) — Median and IQR	21 (15-127)	37 (31-45)
ALP (U/L) — Median and IQR	193 (184-298)	146 (136-250)
Total Bilirubin ($\mu\text{mol/L}$) — Median and IQR	21 (16-25)	14 (9-25)

3. Alcohol-Related Liver Disease, Basic

PE-1

The Mechanisms of the ASGR1–Clathrin Axis in Hepatocyte Phagocytosis of Erythrocytes Driving Iron Overload in Alcoholic Liver Disease

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Aims: To determine whether the ASGR1–Clathrin axis mediates hepatocellular phagocytosis of damaged erythrocytes and thereby drives intrahepatic iron overload in alcoholic liver disease (ALD), and to elucidate the underlying molecular mechanism as a basis for potential therapeutic targets.

Methods: Clinical correlation analysis of serum ASGR1 in 675 ALD patients; characterization of hepatocellular erythrophagocytosis and ASGR1 expression in an ALD mouse model by histology and immunostaining; *in vitro* gain- and loss-of-function studies in hepatocytes to assess effects of ASGR1 modulation on erythrophagocytosis and involvement of clathrin-dependent pathways; generation of liver-specific ASGR1 knockout and overexpression mice; quantitative hepatic iron measurement by ICP-MS; live-cell imaging of erythrophagocytosis; and targeted molecular interventions (RNAi, pharmacological inhibitors, and rescue experiments) to define pathway

Results: Preliminary clinical analysis showed a significant positive correlation between serum ASGR1 and disease course in 675 ALD patients. In the ALD mouse model, hepatocellular erythrophagocytosis incidence reached 40.1% with marked upregulation of ASGR1 in liver tissue. *In vitro*, ASGR1 knockdown reduced hepatocyte uptake of damaged erythrocytes, whereas ASGR1 overexpression increased uptake; mechanistic

assays indicate activation of a clathrin-dependent phagocytic pathway downstream of ASGR1. Planned *in vivo* experiments and ICP-MS quantification will test whether these ASGR1-mediated effects produce measurable hepatic iron accumulation.

Conclusions: Available clinical and experimental data support a model in which alcohol-induced erythrocyte damage up-regulates hepatocellular ASGR1, and the ASGR1–Clathrin axis promotes hepatocyte erythrophagocytosis that contributes to hepatic iron overload in ALD. This project will rigorously validate that mechanism in liver-specific genetic models and quantitative iron assays, potentially revealing novel targets for prevention and treatment of ALD-associated iron overload.

Keywords: Iron Overload, ASGR1, Clathrin, Efferocytosis

PE-2

Biophysical Modeling of Alcohol-Dependent ASIC1a Channel Current and Its Role in ER Stress–Mediated Hepatocyte Injury

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Aims: Alcohol-associated liver disease (ALD) is a progressive hepatocellular disorder caused by chronic or excessive ethanol exposure, ultimately leading to endoplasmic reticulum (ER) stress, hepatocyte apoptosis, and liver failure. Increasing evidence suggests that acid-sensing ion channel 1a (ASIC1a), a proton-gated cation channel permeable to Ca²⁺, is upregulated during alcohol exposure and contributes to intracellular Ca²⁺ overload. However, the quantitative relationship between alcohol concentration, membrane potential, and ASIC1a-mediated current remains poorly characterized. We developed a mechanistic biophysical model to define how alcohol-dependent ASIC1a expression modulates channel current and downstream ER stress signaling.

Methods: A conductance-based ion channel model was constructed incorporating:

1. Alcohol-dependent steady-state ASIC1a expression
2. Hill-type modulation of channel conductance
3. Voltage-dependent current using the equation $I = g(A)(V - E_{\text{rev}}) = g(A)(V - E_{\text{rev}})$

where alcohol concentration regulates ASIC1a expression, membrane potential determines driving force, and E_{rev} represents Ca²⁺ reversal potential. A 3D computational surface was generated to quantify channel current across physiologically relevant alcohol concentrations (0–100 mM) and membrane potentials (–80 to +40 mV).

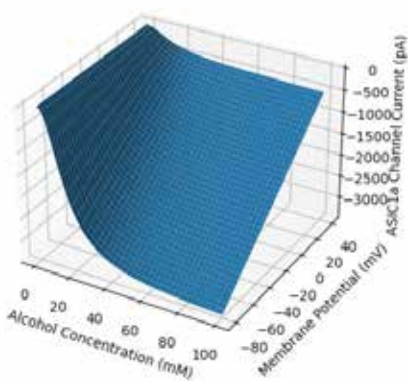
Results: The model demonstrates a nonlinear increase in ASIC1a conductance with rising alcohol concentration, characterized by sigmoidal activation kinetics. Channel current increas-

es markedly at hyperpolarized potentials due to enhanced electrochemical driving force, while current reverses near the Ca^{2+} equilibrium potential. The 3D surface reveals a synergistic interaction between alcohol concentration and membrane voltage, indicating a threshold region where small increases in alcohol produce disproportionately large increases in Ca^{2+} current. This amplification predicts enhanced intracellular Ca^{2+} accumulation capable of triggering ER stress and ER-phagy. The generated 3D image illustrates ASIC1a channel current as a nonlinear surface dependent on both alcohol concentration and membrane potential, highlighting voltage-dependent amplification at high alcohol exposure.

Conclusions: This biophysical model provides quantitative evidence that alcohol-induced upregulation of ASIC1a can significantly amplify Ca^{2+} influx in hepatocytes, particularly under hyperpolarized membrane conditions. The results support a mechanistic framework in which alcohol enhances ASIC1a-mediated Ca^{2+} entry, promoting ER stress activation and ER-phagy, thereby contributing to hepatocyte injury in ALD. Targeting ASIC1a may therefore represent a rational upstream therapeutic strategy for preventing alcohol-induced liver damage.

Keywords: Alcohol-Associated Liver Disease, ASIC1A, Calcium Influx, Biophysical Modeling

ASIC1a Current vs Alcohol and Membrane Potential



PE-3

Integrative Transcriptomic Network Analysis Identifies Ferroptosis-Associated CXCL8 (IL-8) and Enables Therapeutic siRNA Design in Alcohol-Related Liver Disease

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Aims: Alcohol-related liver disease (ALD) involves inflammation, oxidative stress, and metabolic dysregulation. Ferroptosis, an iron-dependent lipid peroxidation-driven cell death, has

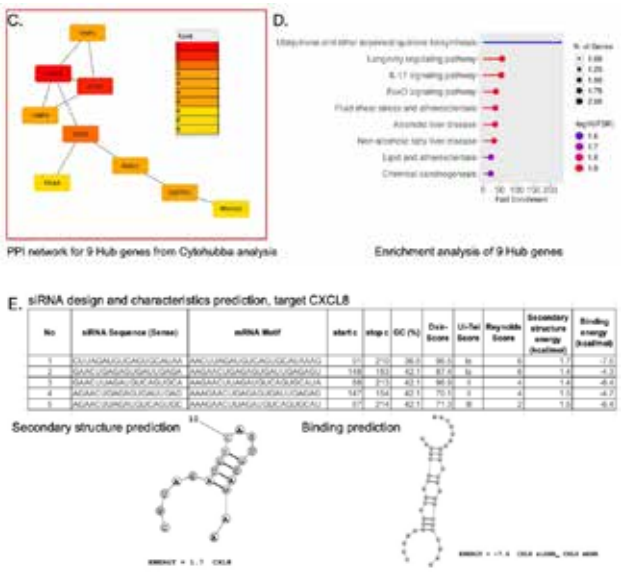
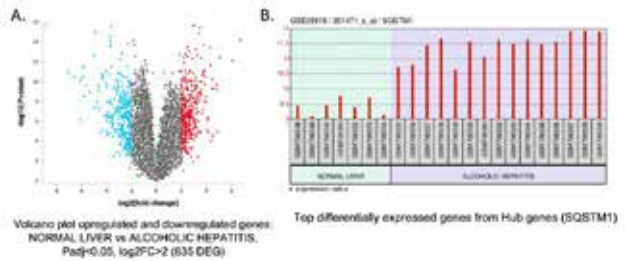
emerged as a key mechanism, but its regulatory genes and therapeutic targets in ALD remain unclear. This study aimed to identify ferroptosis-associated hub genes in alcoholic hepatitis and propose small interfering RNA (siRNA) candidates targeting key drivers.

Methods: Gene expression data from the Gene Expression Omnibus were analyzed, including samples from normal liver (n=7) and alcoholic hepatitis (n=15). Differentially expressed genes (DEGs) were identified using a threshold-adjusted $P < 0.05$, $|\log_2\text{FC}| > 2$ (635 DEGs, Figure 1A), and upregulated genes (293) were intersected with experimentally validated human ferroptosis-related genes (603) from FerrDb. Protein-protein interaction networks were constructed using STRING, and hub genes were identified via CytoHubba in Cytoscape. Functional enrichment analysis was performed, and siRNA targeting of the top hub gene was designed using siDirect with secondary structure and binding energy evaluation.

Results: A total of 15 ferroptosis-related DEGs were identified, with 11 forming a connected network. Nine hub genes were detected, including CXCL8, LCN2, SOD2, NQO1, and SQSTM1 (Figure 1C). Enrichment analysis revealed pathways related to ALD, IL-17 signaling, and oxidative stress (Figure 1D), supporting a role for inflammation-redox interactions in disease progression. CXCL8 was selected as a therapeutic target. Although CXCL8 has been reported to exert anti-ferroptotic effects via activation of antioxidant pathways, its strong pro-inflammatory role in ALD suggests that its inhibition may reduce inflammation-driven oxidative stress and indirectly modulate ferroptosis. Five siRNA candidates were generated, with the top candidate demonstrating optimal GC content, high predicted efficacy, and strong binding affinity (Figure 1E). These findings suggest that targeting inflammatory mediators may indirectly modulate ferroptosis in ALD.

Conclusions: The integrative transcriptomics approach provides insights into ferroptosis-driven mechanisms. CXCL8 was identified as a key ferroptosis-associated hub gene, highlighting a potential siRNA candidate for targeted therapy in ALD.

Keywords: Alcohol-Related Liver Disease, Ferroptosis, SiRNA Therapeutics, CXCL8



PE-4

Survival of Patients with Nodular Regenerative Hyperplasia: A Mayo Clinic Platform Use Case

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Aims: The Mayo Clinic Platform (MCP) is Mayo Clinic's enterprise-level data and analytics infrastructure designed to enable healthcare innovation using large-scale clinical data. It provides aggregated de-identified patient data and enables tools for analytics, artificial intelligence, and research, allowing collaborations between Mayo and external partners. In this work, we demonstrate its use for investigation of rare conditions such as nodular regenerative hyperplasia (NRH) of the liver.

Methods: Using the MCP, a search for patients with biopsy confirmed NRH with or without cirrhosis was conducted. For comparison, an equivalent search for biopsy confirmed, non-NRH cirrhosis was performed. Comparison between these two cohorts was conducted using MCP analytic tools.

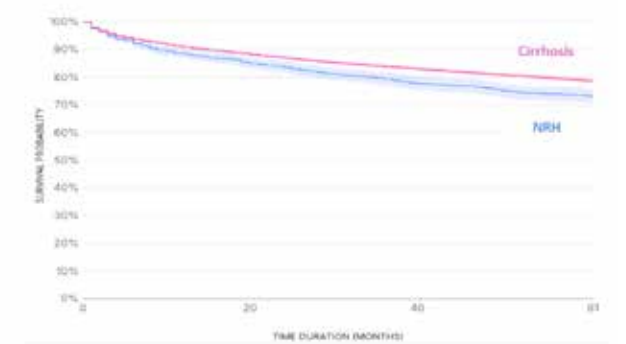
Results: Out of 8,171,580 unique patients included in MCP, 1,294 patients were identified in the NRH cohort and 14,907 patients in the non-NRH cirrhosis cohort. The average age and sex demographics were similar between the two groups. Total bilirubin, INR, ALT and AST were higher and platelet count was lower in the non-NRH cirrhosis group. Albumin was similar between the two groups. Most notably, survival probability at 61 months in the NRH cohort was near 82% compared to near 89% in the non-NRH cirrhosis group.

Conclusions: MCP is an innovative and user-friendly tool, which harnesses the power of artificial intelligence and data networks; it can be utilized to study rare diseases such as NRH. As

demonstrated in our current study, liver synthetic function was better preserved in the NRH cohort; however, survival probability was markedly lower in the NRH cohort. This emphasizes the importance of timely evaluation to determine the underlying etiology of NRH, which would allow for disease directed monitoring and therapy that may lead to improved survivability in this group.

Keywords: Nodular Regenerative Hyperplasia, Cirrhosis, Data Network, Artificial Intelligence

Figure 1. Survival Probability Comparison



Legend: NRH (nodular regenerative hyperplasia)

Table 1. Demographics and laboratory assessment

	NRH	Cirrhosis
Age	56.4 (43.6-65.2)	57.9 (48.0-65.2)
Female	49%	45%
Platelets	130.2 (73.9-213.0)	114.3 (67.1-190.8)
Total bilirubin	1.3 (0.6-3.0)	2.4 (1.0-6.0)
INR	1.2 (1.1-1.6)	1.4 (1.1-1.9)
Albumin	3.3 (3.0-3.8)	3.3 (2.8-3.7)
ALT	46 (24-93)	49 (29-87)
AST	39 (25-58)	49 (33-69)

Legend: NRH (nodular regenerative hyperplasia), INR (international normalized ratio), ALT (alanine aminotransferase), AST (aspartate aminotransferase)

4. Liver Cirrhosis, Portal Hypertension with Cx. Basic

PE-1

Altered T Cell Immune Profile and Its Prognostic Implications in Children with Portal Hypertension: A Pilot Study

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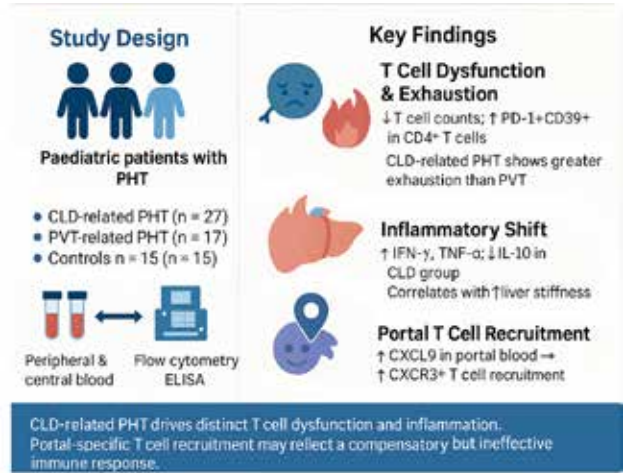
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Aims: Portal hypertension (PHT) is associated with systemic inflammation, yet T cell immune alterations in children remain poorly characterized. We aimed to define quantitative and qualitative T cell changes in children with PHT and examine their relationship with clinical outcomes.

Methods: We prospectively enrolled 44 paediatric PHT (27 chronic liver disease (CLD) related-, 17 portal vein thrombosis (PVT) related-) and 15 liver disease-free controls. Plasma and peripheral blood mononuclear cells (PBMCs) were analysed to assess immune markers, cytokines, and T cell profiles. Statistical analyses examined group differences and correlations with liver stiffness and bleeding history.

Results: CLD-related PHT showed reduced T cell counts and increased CD39/CD38 expression in CD8⁺ and double-negative (DN) T cells. PVT-related PHT exhibited CXCR3 downregulation in DN T cells and CCR4 upregulation in CD4⁺ T cells. Both PHT groups demonstrated elevated CD39 expression, more exhausted CD4⁺ T cells (PD-1⁺CD39⁺), and a pro-inflammatory shift in non-CD8 T cells with higher IFN- γ production and lower IL-10. In CLD-related PHT, soluble CD25 decreased, while PD-L1, IFN- γ , and TNF- α increased, correlating with liver stiffness. Portal plasma CXCL9 exceeded peripheral levels, associated with CXCR3⁺ T cell recruitment but reduced effector function. In bleeding PHT, plasma OPN was reduced, whereas ICAM-1, sCD163, and VCAM were elevated; T cells showed CCR4⁺ enrichment, CD39/CD38 upregulation, and a pro-inflammatory phenotype.



Conclusions: Children with CLD-related PHT exhibit a pro-inflammatory immune milieu driving T cell functional alterations. Distinct immune profile in bleeding patients implicates

as potential biomarkers of prognosis and therapeutic targets in paediatric PHT.

Keywords: Portal Hypertension, T Cell Dysfunction, Immune Milieu, Biomarkers

PE-2

Therapeutic Effects of Empagliflozin in a Murine Model of TAA-Induced Liver Fibrosis

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Aims: Liver fibrosis is a progressive pathological condition characterized by excessive extracellular matrix deposition and chronic inflammation. Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor widely used for the treatment of type 2 diabetes, has recently been suggested to exert anti-inflammatory and anti-fibrotic effects beyond glycemic control. This study aimed to investigate the therapeutic potential of empagliflozin in a murine model of thioacetamide (TAA)-induced liver fibrosis.

Methods: Liver fibrosis was induced in mice by intraperitoneal injection of thioacetamide (TAA, 200 mg/kg) twice weekly for 8 weeks. Empagliflozin (10 mg/kg/day) was administered orally starting 2 weeks after the first TAA injection and continued daily throughout the experimental period. At the end of treatment, liver tissues and serum samples were collected. Histological changes were assessed using H&E and Sirius Red staining. Serum biochemical markers, including liver enzymes, were measured. The expression of fibrosis-related markers (e.g., α -SMA, collagen type I) and inflammatory mediators (e.g., TNF- α , IL-1 β) was evaluated by molecular and immunohistochemical analyses.

Results: Empagliflozin treatment significantly attenuated TAA-induced liver injury, as evidenced by improved hepatic architecture and reduced collagen deposition. Serum levels of liver enzymes were markedly decreased in the empagliflozin-treated group compared to the TAA-only group. Furthermore, empagliflozin suppressed the expression of fibrogenic markers, including α -SMA and collagen type I, and reduced the expression of pro-inflammatory cytokines. These findings suggest that empagliflozin mitigates both fibrotic progression and hepatic inflammation in TAA-induced liver fibrosis.

Conclusions: Empagliflozin exerts protective effects against TAA-induced liver fibrosis in mice, potentially through the suppression of fibrogenic activation and inflammatory responses. These results highlight the therapeutic potential of empagliflozin as a candidate anti-fibrotic agent in chronic liver disease.

Keywords: Liver Fibrosis, Empagliflozin

5. Liver Cirrhosis, Portal Hypertension with Cx. Clinical

PE-1

Analysis of Lesions of Liver in Postmortem Cases in Indian Population

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Aims: Lesions of liver cause significant morbidity and mortality even without causing significant sign & symptom. Liver biopsy may not give the exact picture. Autopsy study may be a better choice.

Methods: Retrospective analysis of histopathological findings of autopsy cases was done during year 2017 -20. Only those cases were selected, which showed positive histopathological finding in heart, lung, liver, spleen, kidney and brain. Total 70 cases were taken. The age group was between 4 days to 77 years. Male and female were 52 and 18 respectively. Out of total 70 cases, 41 showed significant lesions in liver, which were analyzed.

Results: Most common lesion was moderate to severe degree of Hepatic steatosis which showed foci of cirrhosis 14/70 (20%). Grossly most of the cases were mixed type of cirrhosis; macronodular & micronodular. Next prominent group of diseases were cirrhosis (9/70)12.8%. Other common diseases were chronic hepatitis & granuloma 4/70 (5.7%) each. Cardiac cirrhosis was seen in 2/70 cases, which was confirmed by finding fibrosis in myocardium. Nonalcoholic hepatic steatosis was seen a case of 11 months old male baby who presented with umbilical granuloma on gross examination and lung also showed pneumonic features. Other conditions were hydatid cyst, metastasis from primary cancer of unknown origin and Acute inflammatory cell infiltration in chronic hepatitis were seen in 1/70 cases.

Conclusions: Histopathological examination of Post mortem specimens is conducted at limited centers in our country. This diminishes opportunity of medical professionals to learn about liver pathology.

Keywords: Liver Biopsy, Liver Diseases, Postmortem Study

PE-2

Rule-out Cut-off of 2D-Shear Wave Elastography for Excluding Significant Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Two-dimensional shear-wave elastography (2D-SWE) is a practical method for assessing liver fibrosis. However, an optimal cut-off value to rule out significant fibrosis ($\geq F2$) in metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. This study aimed to determine the evidence-based rule-out cut-off through diagnostic meta-analysis.

Methods: A systematic review was of MEDLINE, EMBASE, and Cochrane CENTRAL was performed through December 2025 for studies evaluating 2D-SWE with liver biopsy as the reference standard. Pooled sensitivity, specificity, and summary area under the receiver operating characteristic curve (sAUC) were estimated. The rule-out cut-off was defined as the highest threshold achieving pooled sensitivity $\geq 80\%$. External validation was performed using an independent clinical cohort.

Results: Twenty-two studies involving 3,171 adults with biopsy-proven MASLD were analyzed. The sAUC was 0.84 (95% confidence interval (CI), 0.81-0.87), with pooled sensitivity 79.6% and specificity 76.0%. The rule-out cut-off of 6.6 kPa (95% CI, 5.4-8.2) achieved sensitivity 80.0% and specificity 70.7%. At this threshold, negative predictive value exceeded 95% at prevalences of 5% and 10%. Diagnostic performance was generally preserved across subgroups, but was modestly attenuated in populations with greater metabolic burden and in studies using Supersonic ultrasound platforms. External validation (n=163) demonstrated consistent sensitivity (0.86) and specificity (0.68).

Conclusions: 2D-SWE demonstrated good diagnostic accuracy for significant fibrosis in MASLD. A liver stiffness of 6.6 kPa can reliably rule out significant fibrosis. As 2D-SWE can be integrated into conventional ultrasound systems, it may facilitate broader implementation of fibrosis screening beyond specialized centers.

Keywords: Fibrosis, 2D Share Wave Elastography, Cutoff

PE-3

Development and External Validation of an Explainable AI Model for Predicting Hepatic Decompensation in Chronic Liver Disease

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of Laboratory Medicine, Etugen Medical University, Mongolia

Aims: Hepatic decompensation represents a major turning point in the clinical course of chronic liver disease (CLD), yet early identification of high-risk patients remains challenging. We aimed to develop and externally validate an explainable artificial intelligence (AI) model for predicting hepatic decompensation using real-world clinical and laboratory data, and to evaluate its incremental value beyond MELD-Na.

Methods: A total of 450 patients with CLD from two independent laboratories were included (Molor Clinic: n=254; NB Clinic: n=196). Molor Clinic was used for model development and internal validation, while NB Clinic served as an independent external validation cohort. Clinical and biochemical variables were integrated into a Light Gradient Boosting Machine (LightGBM) model. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), C-index, calibration analysis, and decision curve analysis. Prognostic performance was evaluated using Cox proportional hazards modeling. Model interpretability was assessed using SHapley Additive exPlanations (SHAP).

Results: In the external validation cohort, the AI model achieved an AUC of 0.87, significantly outperforming MELD-Na (AUC 0.77, $P<0.01$). Integration of the AI score with MELD-Na further improved discrimination (C-index 0.88). Patients classified as high-risk demonstrated a significantly increased incidence of hepatic decompensation (hazard ratio 3.5, 95% CI 2.1–5.8, $P<0.001$). SHAP analysis identified serum albumin, bilirubin, platelet count, and sodium as the strongest contributors to risk prediction. Decision curve analysis confirmed superior net clinical benefit across clinically relevant threshold probabilities.

Conclusions: We developed and externally validated an explainable AI-based prognostic model that significantly improves risk stratification for hepatic decompensation beyond MELD-Na. This independently validated, real-world model may support earlier intervention and optimized clinical decision-making in chronic liver disease.

Keywords: Hepatic Decompensation, Chronic Liver Disease, Cirrhosis, Prognostic Model

PE-4

Correlation of Lactate-Albumin Ratio Multiple by Age with Short- and Long-Term Survival in Patients with Cirrhosis Combined with Sepsis

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Aims: The lactate-albumin ratio has been proven relevance in

the prognosis of patients with renal failure or heart failure. This study focused on the correlation between lactate-albumin ratio multiple by age (LAA) and short- and long-term survival in patients with cirrhosis combined with sepsis.

Methods: We extracted patient data based on the Medical Information Market for Intensive Care (MIMIC-IV) database. Using the median LAA values as the dividing threshold, the entire dataset was separated into two groups, and the Kaplan-Meier (K-M) curve and restricted cubic splines (RCS) were applied to analyze the correlation between LAA and survival outcomes at 7-day, 28-day, 1-year. Additionally, we constructed a clinical prediction model based on COX regression and performed internal validation using Receiver Operating Characteristic (ROC) curves to assess the predictive value of LAA for survival outcomes at the specified time points.

Results: A total of 1515 patients diagnosed with cirrhosis combined with sepsis were enrolled. K-M survival curves showed that patients with LAA ≥ 2.71 had lower survival rates at 7-day, 28-day, and 1-year. The hazard ratio for 7-day survival was 3.236 (95% CI: 2.369 - 4.421), for 28-day survival was 2.131 (95% CI: 1.780 - 2.552), and for 1-year survival was 1.643 (95% CI: 1.427 - 1.891). Additionally, RCS and ROC curve analyses demonstrated a potential non-linear relationship between LAA and survival in cirrhosis with sepsis. LAA demonstrated predictive value for 7-day and 28-day survival outcomes, with area under the curve values as follows: 7-day (Train: 0.726, test: 0.596); 28-day (Train: 0.648, Test: 0.65).

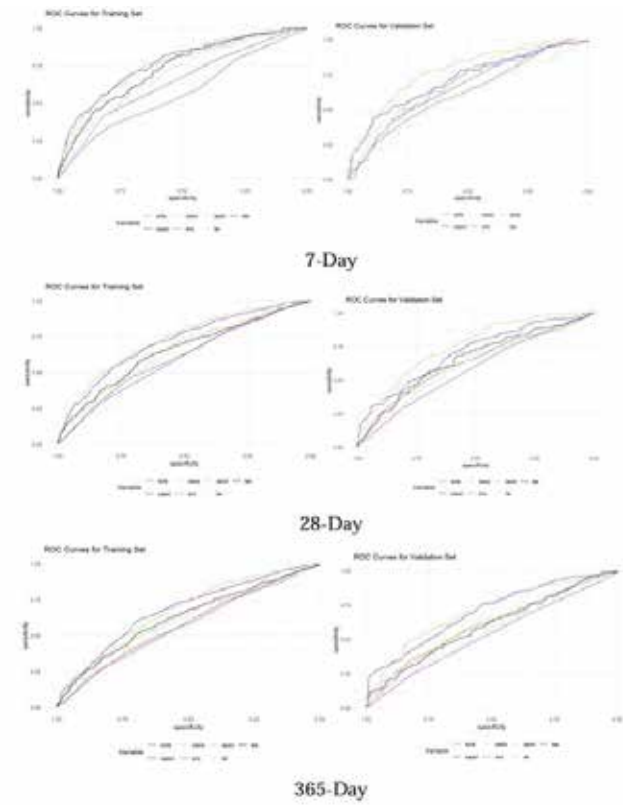


Figure 1.

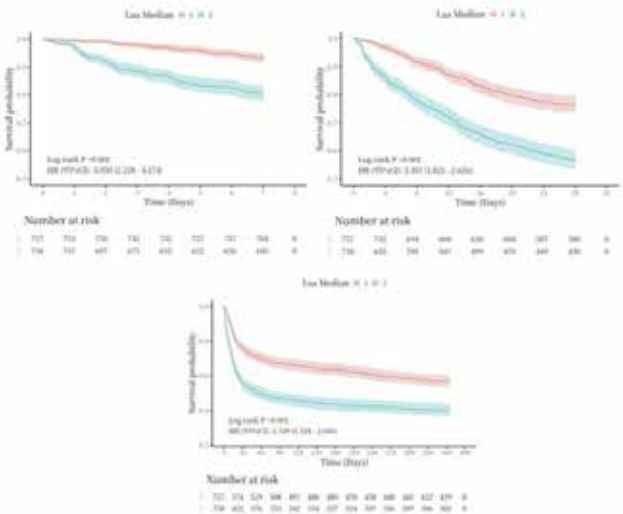


Figure 2.

Name	Dataset	Day7		Day28		Day365	
		AUC	95%CI	AUC	95%CI	AUC	95%CI
APACHE	Train	0.765	[0.723, 0.807]	0.731	[0.699, 0.763]	0.678	[0.646, 0.71]
APACHE	Test	0.756	[0.713, 0.84]	0.754	[0.709, 0.799]	0.705	[0.658, 0.753]
LAA	Train	0.726	[0.683, 0.77]	0.648	[0.612, 0.684]	0.625	[0.591, 0.658]
LAA	Test	0.596	[0.515, 0.677]	0.65	[0.597, 0.704]	0.598	[0.546, 0.65]
LAR	Train	0.698	[0.651, 0.744]	0.638	[0.602, 0.673]	0.598	[0.565, 0.632]
LAR	Test	0.673	[0.601, 0.745]	0.611	[0.554, 0.666]	0.56	[0.507, 0.613]
OASIS	Train	0.742	[0.696, 0.787]	0.657	[0.622, 0.692]	0.617	[0.583, 0.65]
OASIS	Test	0.707	[0.639, 0.756]	0.645	[0.59, 0.7]	0.617	[0.566, 0.668]
SAPSII	Train	0.764	[0.721, 0.807]	0.715	[0.682, 0.747]	0.678	[0.64, 0.71]
SAPSII	Test	0.71	[0.634, 0.787]	0.704	[0.653, 0.754]	0.701	[0.654, 0.748]
SIRS	Train	0.64	[0.593, 0.687]	0.593	[0.56, 0.627]	0.573	[0.541, 0.605]
SIRS	Test	0.663	[0.599, 0.717]	0.577	[0.525, 0.629]	0.534	[0.484, 0.584]
SOFA	Train	0.567	[0.515, 0.62]	0.608	[0.572, 0.643]	0.571	[0.537, 0.605]
SOFA	Test	0.619	[0.542, 0.696]	0.628	[0.571, 0.683]	0.606	[0.554, 0.657]

Figure 3.

Conclusions: Our study suggests that lower LAA levels were associated with better survival outcomes in patients with cirrhosis and sepsis. LAA may serve as a useful prognostic predictor, deepening our understanding of the association between serum biomarkers and inflammatory diseases.

Keywords: Sepsis, Liver Cirrhosis, Disease Prognosis Assessment, Lactate-Albumin Ratio

PE-5

Association between Platelet-Albumin-Bilirubin Index and Mortality in Cirrhotic Patients Combined with Sepsis: A Retrospective Cohort Study from the MIMIC-IV Database

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Qiong Yan¹, Xiaomin Shi¹, Mingming Deng¹, Fangfang Yuan³, Xiaowei Tang¹

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Aims: The platelet-albumin-bilirubin (PALBI) index has demonstrated efficacy in hepatic function assessment. However, its association with clinical outcomes in cirrhotic patients with sepsis remains underexplored. This study was aimed to analyze the prognostic correlation between PALBI index and mortality.

Methods: We extracted patient data based on the Medical Information Market for Intensive Care (MIMIC-IV) database. Study participants were categorized into three groups, and the Kaplan-Meier (K-M) curve and restricted cubic splines (RCS) were applied to analyze the correlation between PALBI and survival outcomes at 7-day, 28-day, 1-year. Receiver Operating Characteristic (ROC) curves was used to assess the predictive value of PALBI for survival outcomes at the specified time points.

Results: This study included 1,758 patients diagnosed with cirrhosis combined with sepsis. Kaplan-Meier survival curves revealed that patients in Group 3 had shorter survival times and higher risks of adverse outcomes at corresponding time points compared to Groups 1 and 2. ROC curve analysis demonstrated the predictive value of the PABLI index for prognosis across multiple time periods (AUC: 0.634, 0.646, and 0.615, respectively). Based on univariate Cox regression analysis, we constructed a multivariate Cox regression model using variables screened at $P<0.05$. This model demonstrated that the PALBI index was an independent predictor of prognosis in patients with sepsis and cirrhosis at 7 days (HR: 1.82, 95%CI [1.50 - 2.21], $P<0.001$), and 28 days (HR: 1.78, 95%CI [1.56 - 2.02], $P<0.001$). RCS curves analysis further suggested potential nonlinear relationships in the prognostic associations. Validation confirmed that the PABLI index correlates with clinical outcomes in cirrhotic patients with sepsis.

Conclusions: In our study, the PALBI score was identified as an independent risk factor for prognosis in cirrhotic patients with sepsis and can be integrated into clinical risk stratification.

Keywords: Sepsis, Liver Cirrhosis, Disease Prognosis Assessment, Platelet-Albumin-Bilirubin Index

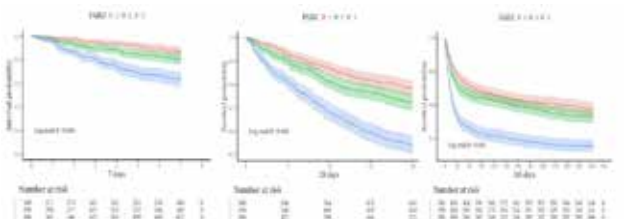


Figure 1

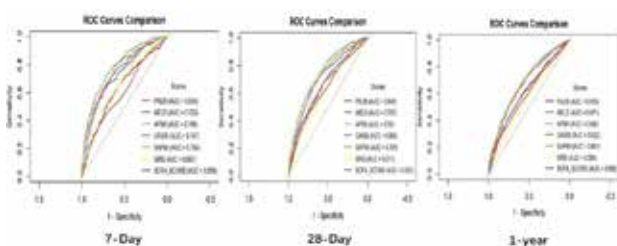


Figure 2

Name	Dataset	Day 7		Day 28		Day 365	
		AUC	95%CI	AUC	95%CI	AUC	95%CI
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SOFA	Test	0.619	[0.542, 0.696]	0.628	[0.573, 0.683]	0.606	[0.554, 0.657]

Figure 3

PE-6

Identification of Four Novel Patient Subgroups with Distinct Mortality and Quality of Life Using Machine Learning Tools in Acutely Decompensated Cirrhosis

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Aims: This study sought to implement an unsupervised machine learning (ML) approach to cluster patients admitted for acute insults of decompensated liver cirrhosis (LC), based on their distinct clinical features and laboratory findings. This clustering is generated to foster the subsequent analysis of differences concerning long-term mortality and self-reported outcomes.

Methods: A sizable cohort of patients with decompensated LC from two tertiary hospitals was analyzed using the k-prototypes algorithm, including demographic, clinical, and biochemical data. The retrieved clusters were associated with metrics like 1-year all-cause mortality and multidimensional frailty. Furthermore, a pipeline designated as practical decision motivation and support (PROMPT) based on a supervised ML model, that is, a random forest, has been constructed to allo-

cate new patients to these clusters, taking reduced variables into account.

Results: A total of 1002 patients were enrolled for final analyses, with a median age of 65 years and 51.7% female. The major etiologies of LC were immune-related reasons, and gastroesophageal variceal bleeding (GEVD) represented the predominant complication. Four different clusters (1-4) have been identified with distinct phenotypes according to demographic-clinical and biochemical parameters. Cluster 3 was the most advanced in age, the most prevalent in infection rates, and the highest probabilities concerning 1-year all-cause mortality. Cluster 1 was characterized by RFH-NPT-defined malnutrition risk, and deteriorated hepatopathy severity evaluated by MELD-Na scores, alongside a higher prevalence of ascites/hepatic encephalopathy. Cluster 2 exhibited a female predominance and prevalently concomitant GEVD complication. Cluster 4 included improved biochemical profiles as indicative of higher albumin levels, the lowest MELD-Na scores, and better survival. The PROMPT, using five pivotal variables, represented an AUC of at least 0.7.

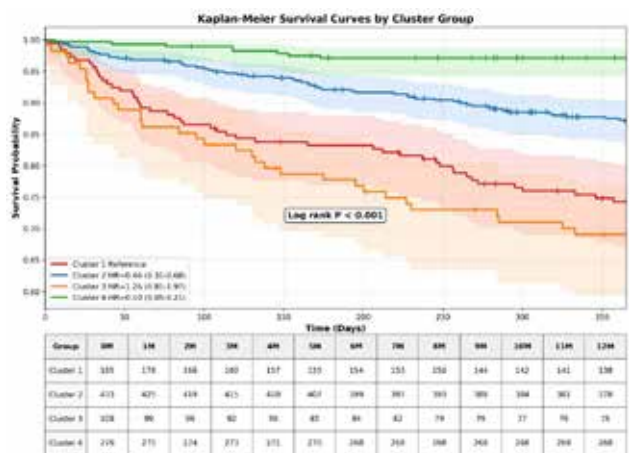


Figure 1

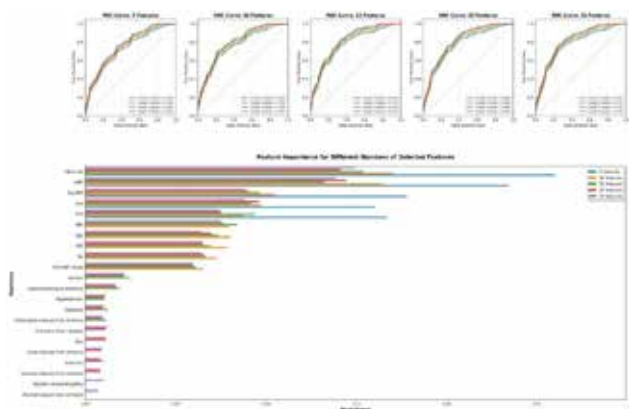


Figure 2



Figure 3

Conclusions: ML approaches are sufficiently capable of clinical-biochemically clustering LC patients with acute decompensation, closely connected to prognostication and frailty.

Keywords: Machine Learning, Cluster, Liver Cirrhosis, Prognosis

PE-7

Hidden Chloride Load from Packaged Broth Activates Macula Densa Signaling and Vasopressin Release Worsening Edema and Hyponatremia in Cirrhosis

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Aims: Dilutional hyponatremia in advanced cirrhosis reflects impaired solute-free water excretion driven largely by non-osmotic vasopressin release, while emerging hepatology literature suggests chloride may carry additional prognostic information beyond sodium alone. We evaluated whether combined hyponatremia-hypochloremia identifies a more severe fluid-retention phenotype in decompensated cirrhosis.

Methods: We built this reviewer-safe draft around a real open dataset previously used for cirrhosis electrolyte research from MIMIC-III, an openly available ICU database from Beth Israel Deaconess Medical Center. Adults with cirrhosis were identified, and admission chloride <99 mEq/L and sodium <135 mEq/L within 24 hours defined exposure. Multivariable logistic regression, LOWESS trend analysis, Bonferroni-adjusted subgroup testing, likelihood-ratio comparison, and ROC analysis were prespecified; external validation is feasible in the newer open MIMIC-IV and multicenter eICU-CRD resources.

Results: In the published open MIMIC-III cirrhosis cohort, 1,216 critically ill patients were included. ICU mortality was 18.8%, and 199 (16.4%) had hyponatremia. Mortality was 34.2% in hyponatremia versus 15.8% without it. After adjustment for age, MELD, SOFA, organ support, AKI, hemoglobin, platelet

count, white blood cell count, and sodium, chloride remained independently associated with ICU death (per 1 mEq/L increase, $P=0.002$), whereas sodium lost significance. Chloride discriminated mortality better than sodium (AUC 0.800 vs 0.744, $P<0.001$). Patients with combined hyponatremia and hyponatremia had 36.6% mortality versus 16.1% with neither abnormality and 14.6% with hyponatremia alone.

Conclusions: This version is stronger than a diet-only framing because it uses measurable, reproducible open-data variables with a clear biologic link to vasopressin-mediated water retention. Its clinical use is immediate: earlier recognition of chloride-sensitive decompensation, sharper diuretic and fluid review, better triage for refractory ascites pathways, and more targeted escalation toward transplant-focused care.

Keywords: Cirrhosis, Vasopressin, Hyponatremia, Ascites

PE-8

Seven-Day Clinical Trajectory as a Predictor of 90-Day Mortality in Patients with ACLF: A Multicenter Study from the KACLIF Cohort

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Aims: Although the concept of early clinical trajectory in acute-on-chronic liver failure (ACLF) has been emphasized in recent guidelines, including those of the European Association for the Study of the Liver (EASL), data-driven evidence validating the prognostic value of early changes remains limited. We aimed to evaluate whether dynamic clinical changes within the first 7 days after ACLF diagnosis predict 90-day mortality, using the Korean Acute-on-Chronic Liver Failure (KACLIF) cohort.

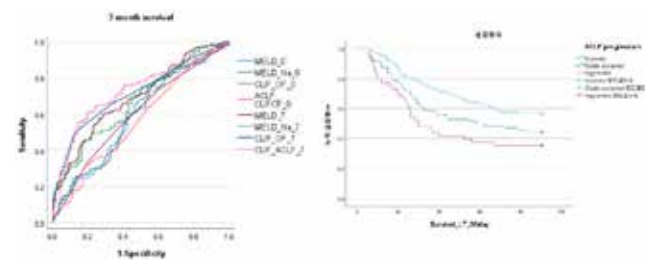
Methods: This was a post hoc analysis of a nationwide, multicenter retrospective cohort involving patients with ACLF enrolled in the KACLIF study. We assessed changes in key clinical variables—including organ failure scores, serum bilirubin, creatinine, INR, and hepatic encephalopathy—between day 0 and day 7. Patients were categorized into three groups: improvement, stable, or worsening, based on 7-day clinical ACLF-CLIF score. The primary outcome was 90-day mortality.

Results: Among 262 patients with evaluable 7-day data, those with worsening trajectories had significantly higher 90-day mortality compared to stable or improving groups ($P<0.004$).

Patients with ACLF grade 2–3 at day 7 showed higher mortality (78%). Notably, ACLF grade assessed at day 7 demonstrated better prognostic discrimination than ACLF grade at admission (Harrell's C-index 0.66 vs 0.58). In multivariate analysis, a worsening clinical trajectory within the first 7 days (Model1, sustained stage HR = 1.46, aggravated stage HR = 2.60, $P < 0.001$) was an independent predictor of mortality after the adjustment of Age, Sex, MELD score.

Conclusions: Early dynamic changes in clinical parameters within the first 7 days following ACLF diagnosis have prognostic value independent of baseline status. This trajectory-based assessment may help identify high-risk patients who require early consideration for liver transplantation. These findings support the clinical importance of early monitoring and decision-making and provide empirical evidence for the 7-day time window emphasized in international ACLF guidelines.

Keywords: Acute Onchronic Liver Failure, Liver Cirrhosis, Portal Hypertension, Decompensation



PE-9

Prognostic Value of the HOPE-EVL Score for Mortality in Patients with Acute Esophageal Variceal Bleeding Treated with Endoscopic Variceal Ligation

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*Vietnam Interventional Gastroenterological Endoscopy Society

Aims: To evaluate the prognostic value of the HOPE-EVL score in predicting 30-day mortality in patients with acute esophageal variceal bleeding after endoscopic variceal ligation (EVL).

Methods: A retrospective–prospective cohort study was conducted in 213 patients with acute esophageal variceal bleeding who underwent EVL at the Digestive & Hepatobiliary Center, Bach Mai Hospital. The HOPE-EVL score was calculated after EVL to stratify patients into risk groups. Patients were followed for 30 days to evaluate early rebleeding and mortality. The predictive performance of the HOPE-EVL score for 30-day mortality was assessed using ROC curve analysis.

Results: The overall 30-day mortality rate was 12.2%. The HOPE-EVL score was significantly associated with clinical characteristics and treatment outcomes. The incidence of early rebleeding increased progressively across risk groups, occurring in 7.6% of patients in the low-risk group, 22.9% in the middle-risk group, and 55% in the high-risk group ($P < 0.05$). A marked difference in 30-day mortality was observed across HOPE-EVL risk groups, with rates of 1.3%, 22.9%, and 80% in the low-, middle-, and high-risk groups, respectively ($P < 0.05$). The HOPE-EVL score demonstrated excellent prognostic performance for 30-day mortality, with an area under the ROC curve (AUC) of 0.95 (95% CI: 0.909–0.988; $P < 0.05$).

Conclusions: The HOPE-EVL score is a valuable tool for predicting 30-day mortality in patients with acute variceal bleeding after EVL, supporting early risk stratification and guiding clinical management.

Keywords: Hope-EVL, Acute Variceal Bleeding, Esophageal Varices, Cirrhosis

PE-10

Diagnostic Performance of Raw versus Age-Education Adjusted QuickStroop for PHES-Defined Minimal Hepatic Encephalopathy in Cirrhosis

Akash Roy¹, Utkarsh Bhattad¹, Shruti Keyal¹, Awanish Tewari¹, Nikhil Sonthalia¹, Sarthak Chakrabarti¹, Sourish Roy¹, Rajat Khandelwal¹, Anand Kulkarni², Uday Chand Ghoshal¹, Jasmohan Bajaj³, Rajender Reddy⁴, Mahesh Kumar Goenka¹

¹Institute of Gastrosciences and Liver Transplantation, Apollo Multispecialty Hospitals, Kolkata, India 700054; ²Department of Hepatology, Asian Institute of Gastroenterology, Hyderabad, India 500032; ³Department of Medicine, Virginia Commonwealth University and Richmond VA Medical Center, Richmond, Virginia, USA; ⁴Division of Gastroenterology and Hepatology, University of Pennsylvania, 2 Dulles, Liver Transplant Office 3400 Spruce Street, Philadelphia, PA 19104, USA.

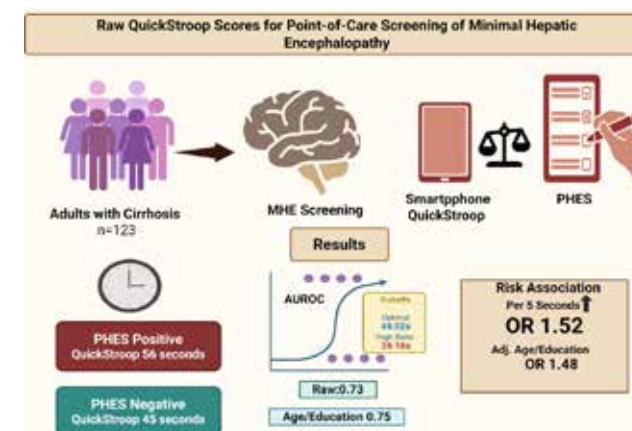
Aims: Minimal hepatic encephalopathy (MHE) remains underdiagnosed in routine clinical care, and testing remains limited due to time restrictions. QuickStroop is a novel point-of-care app-based test proposed as a rapid MHE assessment tool. We evaluated the diagnostic performance of raw QuickStroop against the Psychometric Hepatic Encephalopathy Score (PHES) defined MHE and assessed whether adjustment for age and education improved discrimination.

Methods: In this single-center diagnostic accuracy study, adult patients with cirrhosis (aged 18–70 years) who underwent both PHES and QuickStroop were included. PHES positivity was defined as a score ≤ 5 . analysis. The diagnostic performance of raw QuickStroop and its incremental value after adjustment for age and education were evaluated using area under the receiver operating characteristic curve (AUROC), logistic regression, and decision curve analysis.

Results: Among 123 patients, 64 (52.0%) were PHES positive. QuickStroop values were higher in PHES-positive patients (56.09 [44.00–65.17] vs 45.00 [38.00–50.07] s; $P < 0.001$). Raw QuickStroop showed moderate discrimination for PHES-defined MHE (AUC 0.739, 95% CI 0.651–0.827). The Youden-optimal cutoff was 49.02 s (sensitivity 70.3%, specificity 74.6%), whereas a high-sensitivity cutoff of 39.18 s yielded 90.6% sensitivity and 28.8% specificity. Each 5-second increase in QuickStroop was associated with higher odds of PHES-defined MHE, both unadjusted (OR 1.52, 95% CI 1.28–1.86) and after adjustment for age and education (OR 1.48, 95% CI 1.24–1.84; both $P < 0.001$). Adding age and education produced only a small, non-significant AUCROC gain (0.756 vs 0.739; $P = 0.331$).

Conclusions: QuickStroop demonstrated fair diagnostic performance for PHES-defined MHE. Age-education adjustment provided minimal incremental value beyond raw QuickStroop, supporting the practical utility of the raw test in this setting.

Keywords: Minimal Hepatic Encephalopathy, Quickstroop, MHE



PE-11

Spleen Stiffness Measurement vs Conventional Non-Invasive Markers as Predictors of Esophageal Varices in Advanced Chronic Liver Disease: A Multivariate Analysis

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Aims: Esophageal varices (EV) represent a major complication of clinically significant portal hypertension (CSPH) in advanced chronic liver disease (ACLD). Screening endoscopy remains the gold standard for EV detection but is invasive and resource-in-

tensive. Spleen stiffness measurement (SSM) has emerged as a promising non-invasive alternative; however, comparative data against conventional markers including APRI, FIB-4, and platelet count from Southeast Asian populations, especially in Indonesia remain limited. The aims is to compare the diagnostic accuracy of SSM against conventional non-invasive markers for predicting EV, and to identify independent predictors of EV and CSPH in a large ACLD cohort.

Methods: A cross-sectional study was conducted on 485 patients with advanced chronic liver disease who underwent transient elastography and esophagogastroduodenoscopy (EGD) at Tertiary Hospital, Makassar, Indonesia. Diagnostic accuracy was assessed by ROC analysis with Youden Index; DeLong test compared AUC values between SSM and conventional markers (APRI, FIB-4, platelet count, albumin). Agreement between SSM classification (CSPH: SSM ≥ 40 kPa) and endoscopic EV grading was evaluated using Cohen's Kappa. Independent predictors were identified using backward conditional logistic regression.

Results: EV were present in 197 patients (40.6%). SSM demonstrated excellent diagnostic accuracy for predicting EV (AUC = 0.912; optimal cut-off 40.10 kPa; sensitivity 87.3%; specificity 95.5%; negative predictive value 91.7%), significantly outperforming platelet count (AUC = 0.716), FIB-4 (AUC = 0.677), APRI (AUC = 0.672), and albumin (AUC = 0.508) by DeLong test (all $P < 0.001$). Near-perfect agreement was observed between SSM classification and endoscopic EV grading (Cohen's $\kappa = 0.836$), with 91.7% of non-CSPH patients having no varices and 93.0% of CSPH patients having EV Grade ≥ 1 . On multivariate analysis, independent predictors of EV were SSM per 10 kPa increment (OR = 2.401; 95% CI: 2.038–2.829; $P < 0.001$), Hepatitis C etiology (OR = 5.916; 95% CI: 1.331–26.291; $P = 0.020$), and low platelet count (OR = 2.083; 95% CI: 1.208–3.593; $P = 0.008$), with Nagelkerke $R^2 = 0.636$. APRI, FIB-4, age, sex, BMI, and albumin were eliminated from the model once SSM was included. Independent predictors of CSPH were Hepatitis C (OR = 7.875; $P < 0.001$), low platelet count (OR = 2.579; $P < 0.001$), high APRI (OR = 2.207; $P = 0.001$), age ≥ 50 years (OR = 2.005; $P = 0.001$), and Hepatitis B etiology (OR = 1.712; $P = 0.032$).

Conclusions: SSM at a 40.10 kPa cut-off significantly outperforms all conventional non-invasive markers for predicting EV in advanced CLD, validating the Baveno VII threshold in a Southeast Asian population. SSM is the dominant independent predictor of EV, explaining 63.6% of its variance in combination with Hepatitis C etiology and platelet count. A negative predictive value of 91.7% supports SSM-based endoscopy-sparing strategies in clinical practice.

Keywords: Spleen Stiffness Measurement, Esophageal Varices, Portal Hypertension, Non-Invasive Markers

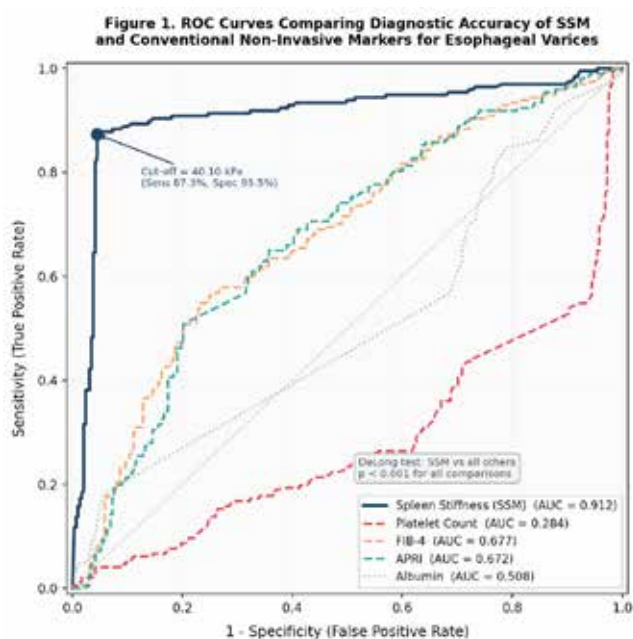


Figure 1. ROC.

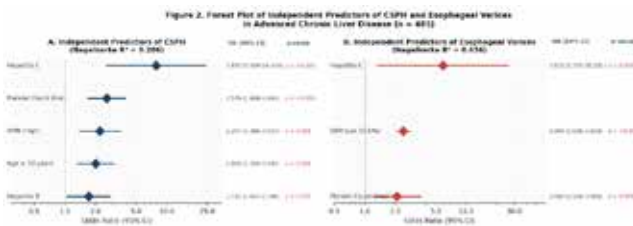


Figure 2. ForestPlot-Resha's Mac mini.

PE-12

Portal Hypertensive Ischemic Enteropathy without Mesenteric Thrombosis: Reversible with TIPS Despite Extreme Hyperlactatemia

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Aims: Current EASL guidelines designate arterial lactate ≥ 12 mmol/L as a futility criterion for rescue transjugular intrahepatic portosystemic shunt (TIPS). However, this threshold was derived from variceal hemorrhage cohorts and may not apply to portal hypertensive ischemic enteropathy (PHIE), where hyperlactatemia reflects mesenteric venous congestion rather than irreversible end-organ failure. We report the case series of PHIE without mesenteric thrombosis managed with urgent TIPS despite extreme hyperlactatemia.

Methods: Three consecutive patients with decompensated cirrhosis presenting with bowel wall edema with or without pneumatosis intestinalis, without arterial occlusion or superior mesenteric vein thrombosis, underwent urgent rescue TIPS. Serial arterial lactate measurements and CT imaging were obtained before and after the procedure.

Results: In Case 1 (56/F, MELD 30), pneumatosis intestinalis resolved completely within 4 hours post-TIPS, with lactate normalizing from 7.8 to 1.8 mmol/L within 72 hours. The patient was bridged to re-transplantation. In Case 2 (63/F, MELD 28), lactate normalized from 16.6 to 1.9 mmol/L within 5 days with resolution of bowel wall edema. In Case 3 (63/M, MELD 34), lactate normalized from 15.5 to 2.4 mmol/L with radiologic improvement; however, focal gastric antrum ischemia that had progressed beyond reversibility prior to intervention led to perforation and death on post-TIPS day 8.

Conclusions: PHIE represents a severe, reversible manifestation within the spectrum of portal hypertensive enteropathy. Post-TIPS lactate clearance provides mechanistic proof that hyperlactatemia in PHIE is driven by venous congestion. The EASL lactate futility threshold should not be applied to this clinical entity. In PHIE, the severity of radiologic findings should prompt urgent decompression, not withholding of treatment.

Keywords: Portal Hypertension, Transjugular Intrahepatic Portosystemic Shunt, Hyperlactatemia, Liver Transplantation

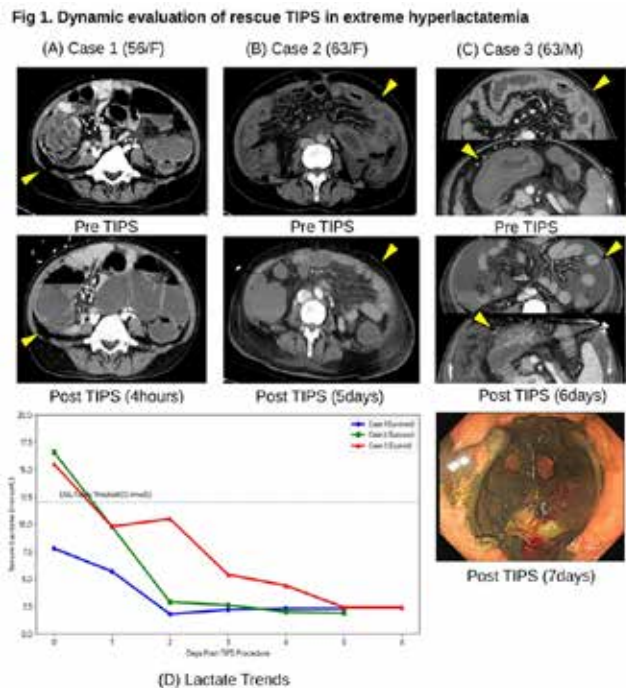


Figure 1.

6. HBV, Basic

PE-1

Identification of Aberrantly Expressed Genes in Hepatocellular Carcinoma Associated with Chronic Hepatitis Virus Infections: A Transcriptomic Analysis

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Aims: Chronic infections with hepatitis B (HBV), hepatitis C (HCV), and hepatitis D (HDV) viruses continue to be a significant cause of hepatocellular carcinoma (HCC) globally. The persistent inflammatory response and progressive liver injury induced by the hepatitis viruses establish a molecular context that is conducive to carcinogenesis. However, the key genes involved in virus-induced HCC pathogenesis remain unknown. In the present study, we employed publicly available GEO data on the transcriptomes of HCC patients infected with HBV, HCV, and HDV viruses and sought to identify the potential biomarkers and therapeutic targets associated with the diseases.

Methods: Herein, the total eight microarray datasets including 848 patients samples (comprising Virus and tumor samples) were analysed using the GEO2R tool existing in GEO database. The predicted DEGs were further subjected to Functional annotation and pathway enrichment analysis by using Enrichr tool. Successively, Protein-Protein Interaction analysis was performed by Cytoscape software, and the top 10 most significant hub nodes were identified. In this study, molecular docking, molecular dynamics (MD) simulations and MM-GBSA binding free energy calculations were systematically conducted using the Schrödinger software suite to evaluate the potential anti HBV, HCV, HDV activity of plant-derived small molecules ob-

tained from the NPASS database.

Results: The GEO2R analysis resulting in the identification of nearly 1100 aberrantly expressed genes among HBV, HCV, HDV and normal control samples. Enrichment analysis indicated that these targets are mainly involved in pathways related to Cell cycle, P53 signaling pathway, and Viral carcinogenesis. Network analysis identified hub genes in nine centrality and most frequently occurring hub gene Anillin, Actin Binding Protein (ANLN) was considered as plausible target for subsequent identification of inhibitors. Docking studies showed that Isodarpavinol B, Dihydrobinetin and Blapsin B exhibited stronger binding affinities than sorafenib (reference compound) toward ANLN. Molecular dynamics Trajectory analyses (RRMSD, RMSF PCA, FEL, and DCCM) and MM/GBSA calculations further confirmed ANLN target as stable and energetically favourable interactions, primarily driven by van der Waals, hydrophobic, and electrostatic forces.

Conclusions: Conclusively, findings from our study postulates Isodarpavinol B, Dihydrobinetin and Blapsin B targeting elevated ANLN levels which may contribute as potential inhibitors for HBV, HCV, HDV associated patients.

Keywords: Anillin, Actin Binding Protein (ANLN), Differentially Expressed Genes (DEGs), Hepatitis Virus Infections

PE-2

Six Concurrent Layers of Effector Suppression in the Immune Tolerant Phase of Chronic Hepatitis B: A Tissue-Separated Single-Cell Transcriptomic Analysis

Young Min Park

Liver Research Initiative, Korea

Aims: The immune tolerant (IT) phase of chronic hepatitis B virus (HBV) infection is conventionally regarded as immunologically inert. This study aimed to characterize IT immunopathogenesis through tissue-separated single-cell reanalysis, focusing on mechanisms that may prevent effector conversion despite immune engagement.

Methods: This study is a tissue-separated reanalysis of the GSE182159 single-cell RNA sequencing open-dataset originally published by Zhang et al (Gut 2023;1:153-167, DOI: 10.1136/gutjnl-2021-325915). We analyzed 243,000 immune cells from paired liver and blood samples of 23 donors (NL n=6, IT n=6, IA n=5, AR n=3, CR n=3) using the ITLAS (Integrated Transcriptomic Landscape Analysis System) analytical workflow [GitHub: github.com/choccoba/ITLAS] on Google Colaboratory with NVIDIA A100 GPU. Liver and blood were analyzed separately. Donor-level Mann-Whitney U tests with stratified FDR correction were applied to 196 candidate genes across 6 lineages. Oaxaca-Blinder decomposition verified per-cell expression changes versus subcluster composition shifts.

Results: IT immune cells showed active antigen recognition (HLA class II, FDR q<0.01), signaling activation (JAK1/MTOR), and interferon response (MX1/ISG15, IT-specific, FDR q<0.005), yet effector conversion was absent. Six concurrent transcriptomic patterns associated with effector suppression were identified: myeloid co-expression of immunoregulatory genes (TGFB1/LGALS9), upregulation of DNA methylation regulators (DNMT1/DNMT3A/TET2), dissociation of mTOR from glycolytic gene expression, IT-specific SOCS1/3 downregulation with concurrent JAK-STAT activation, liver-specific TOX/TOX2 up-regulation with tissue-opposite directionality, and pan-tissue PRDM1 downregulation. Decomposition confirmed 94.4% of findings were per-cell dominant.

Conclusions: The IT phase may be characterized by active immune engagement coupled with multiple concurrent transcriptomic patterns individually consistent with effector suppression. These hypothesis-generating findings suggest that combination strategies targeting multiple pathways may warrant further investigation.

Keywords: Hepatitis B Virus, Immune Tolerance, Single-Cell Rna Sequencing, Effector Suppression

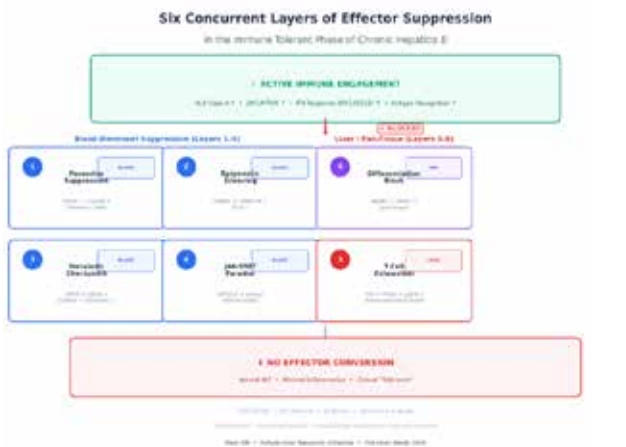


Figure 1. Graphical



Figure 2. Paradox.

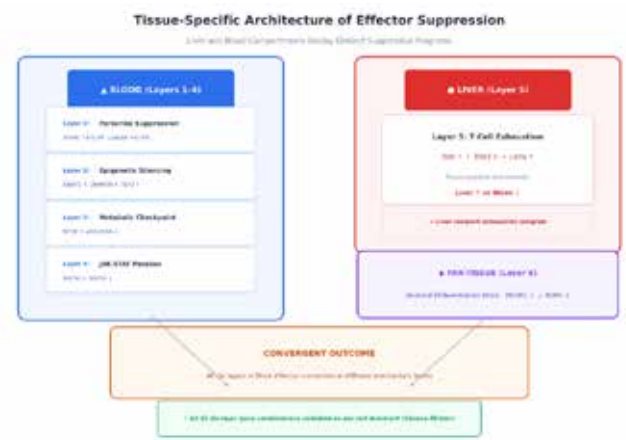


Figure 3. Tissue architecture.

PE-3

Deep Learning-Guided Discovery of the YKEFGAS Motif and AI-Assisted Capsid Assembly Modulator Design for Hepatitis B Virus

Young Min Park
Liver Research Initiative, Korea

Aims: As part of an HBV foundation modeling study, we developed CNN and Transformer deep learning models for genotype classification and explored their interpretability through attention weight analysis. Rather than targeting a predetermined therapeutic endpoint, we systematically investigated which genomic regions the models prioritized for genotype discrimination. This hypothesis-free, data-driven exploration led to the unexpected discovery of a highly conserved motif within the Core protein, which was subsequently identified as residing within the capsid assembly modulator (CAM) binding domain, prompting further investigation of its druggability and therapeutic potential.

Methods: We analyzed 18,247 HBV sequences from GenBank (filtered to 2,147 high-quality samples). CNN and Transformer models were trained for genotype classification (A–H) with attention extraction and Grad-CAM analysis. Shannon entropy independently validated attention findings. AlphaFold2 Multimer predicted Core protein dimer structures. CB-Dock2 blind docking evaluated 22 compounds. Fragment-based optimization from a patent-free scaffold was performed with comprehensive ADMET profiling (SwissADME, pkCSM, SwissTargetPrediction). Claude AI (Anthropic) facilitated all workflow stages.

Results: Both models achieved >95% accuracy (CNN 95.5%, Transformer 96.3%), with Transformer showing superior genotype discrimination. Attention analysis converged on the YKEFGAS motif (residues 6–12) as the most conserved region, cross-validated by Shannon entropy (0.02–0.15 vs. domain

average 0.45). The S12T polymorphism distinguished genotypes B/C (S12: 98.5%) from genotype A (T12: 96.2%). AlphaFold2 revealed this motif at the dimer interface with a ~30 Å³ druggable void. All 22 docked compounds contacted TYR6, confirming target relevance. Fragment-based optimization yielded YM-005, a novel benzimidazole achieving −8.6 kcal/mol (94.5% of clinical candidate GLS4).

Conclusions: Starting from model interpretability analysis, this study demonstrates how AI-driven genomic exploration can lead to biologically meaningful discoveries and therapeutic hypotheses. The systematic workflow—from deep learning attention to lead compound design—provides a reproducible framework for AI-assisted drug target identification. YM-005 requires experimental validation; second-generation optimization revealed fundamental efficacy-safety trade-offs, honestly reflecting current computational limitations.

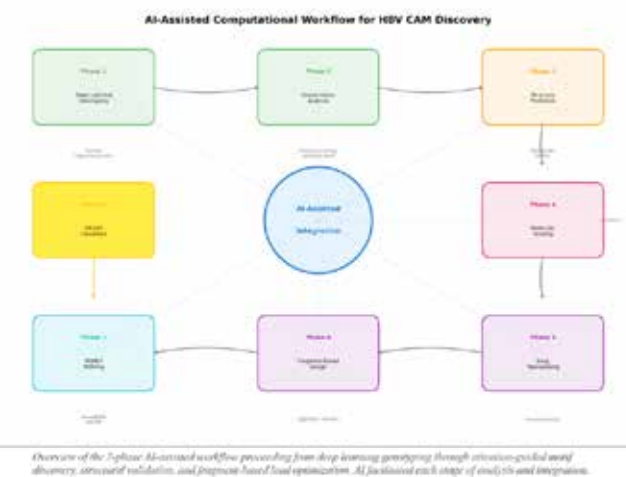


Figure 1.

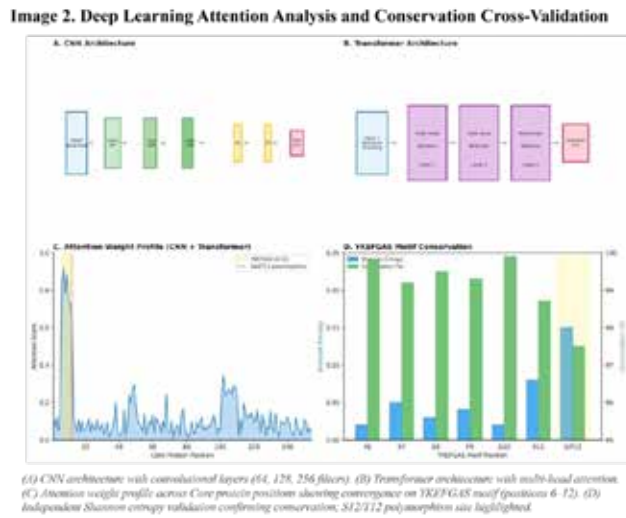


Figure 2. Deep Learning Attention Analysis and Conservative Cross-Validation.

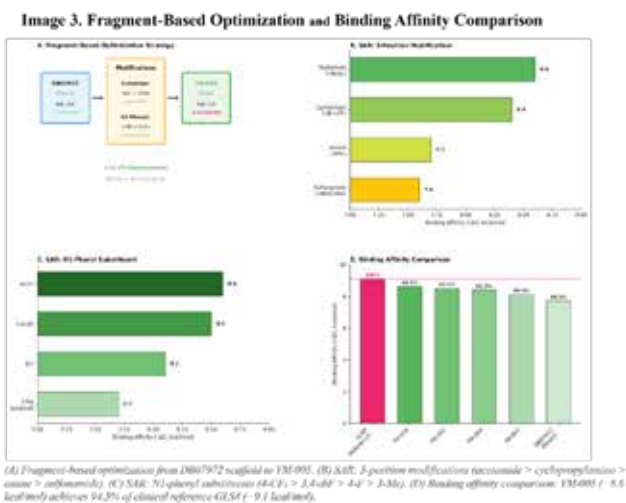


Figure 3. Fragment-Based Optimization and Binding Affinity Comparison.

<Disclosure: AI-assisted tools were used for workflow support and language refinement. All study design, result interpretation, and scientific conclusions were determined by the author. All results are computational and require experimental validation.>

Keywords: Hepatitis B Virus, Ykefgas MOTIF, Deep Learning Interpretability, AI-Assisted Drug Discovery

7. HBV, Clinical

PE-1

HBsAg Quantification in CHB Patients Treated with ETV, TDF or TAF and Association with the Risk of HCC

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Aims: This study evaluated the clinical implications of hepatitis B surface antigen quantification (qHBsAg) in patients with chronic hepatitis B (CHB) treated with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF). We specifically aimed to identify the association between qHBsAg levels and the risk of developing hepatocellular carcinoma (HCC).

Methods: Between January 2009 and December 2023, clinical data and qHBsAg levels were analyzed for 279 patients (ETV: n=65, TDF: n=164, TAF: n=50) who initiated antiviral therapy.

Results: During a mean follow-up period of 43.2 months, 105 patients (44.8%) achieved either a >50% reduction in qHBsAg or a qHBsAg level <1,000 IU/mL after one year of treatment. Patients meeting these criteria showed a significantly lower

incidence of HCC ($P<0.032$) and decompensated cirrhosis ($P<0.023$) compared to those who did not. There were no significant differences in HCC development ($P=0.290$) or qHBsAg reduction rates ($P=0.204$) among the ETV, TDF, and TAF groups. Multivariate analysis identified the Child-Turcotte-Pugh (CTP) score ($P=0.043$) as an independent predictor of HCC development.

Conclusions: A significant reduction in qHBsAg (>50% decrease or level <1,000 IU/mL) at one year of antiviral therapy is associated with a lower risk of HCC and decompensated cirrhosis. Monitoring qHBsAg levels can serve as a valuable predictive marker for long-term clinical outcomes in CHB patients treated with ETV, TDF, or TAF.

Keywords: Chronic Hepatitis B, Hepatocellular Carcinoma, Hbs Ag Quantification, Entecavir, Tenofovir Disoproxil Fumarate; Tenofovir Alafenamide

PE-2

Hepatitis D Virus Seroprevalence among HBsAg Positive Patients in a Major Australian Tertiary Referral Centre

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Aims: To determine the seroprevalence of hepatitis D virus infection among HBsAg positive patients attending a major tertiary referral centre in Sydney, Australia.

Methods: This retrospective observational study included adult patients with confirmed HBsAg positivity managed through a tertiary hepatology service. Demographic and laboratory data were extracted from electronic medical records. Patients who underwent serological testing for anti-HDV antibodies were included in the analysis. Descriptive statistics were used to summarise demographic characteristics and HDV seroprevalence was calculated among tested HBsAg-positive individuals.

Results: A total of 555 patients included in the database were HBsAg-positive. Among these, 379 patients (68.3%) underwent HDV serological testing. The mean age of tested patients was 53.2 years (SD 12.6), with a near even sex distribution. Anti-HDV antibodies were detected in 4 patients, yielding an HDV seroprevalence of 1.06%. Overall, HDV infection was uncommon in this study population.

Conclusions: Hepatitis D virus (HDV) is a defective RNA virus that requires hepatitis B virus (HBV) surface antigen for viral assembly and transmission. HDV co-infection is associated with accelerated progression to cirrhosis and hepatocellular carcinoma. The prevalence of HDV infection among hepatitis

B surface antigen (HBsAg)-positive patients varies widely by geographic region and population. In Australia, contemporary data on HDV seroprevalence in large metropolitan tertiary-care centres remain limited.

The seroprevalence of HDV infection among HBsAg-positive patients in a major Sydney tertiary referral cohort was low but non-zero. These findings are consistent with Australia's low HDV endemicity and contrast with higher prevalence rates reported from endemic regions. Nonetheless, the presence of HDV infection in a large, diverse tertiary-care population supports continued screening of HBsAg-positive patients, particularly those from high-risk or endemic backgrounds, in accordance with current international guidelines.

Keywords: Hepatitis D Virus, Hepatitis B Surface Antigen, Seroprevalence, Tertiary Care Centre

PE-3

Sarcopenia Delays Early Virological Response but Does Not Affect Long-Term Prognosis in Patients with Chronic Hepatitis B and Liver Cirrhosis

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Aims: To investigate the clinical significance of sarcopenia on virological response (VR) and long-term prognosis in treatment-naïve chronic hepatitis B (CHB) patients with liver cirrhosis (LC).

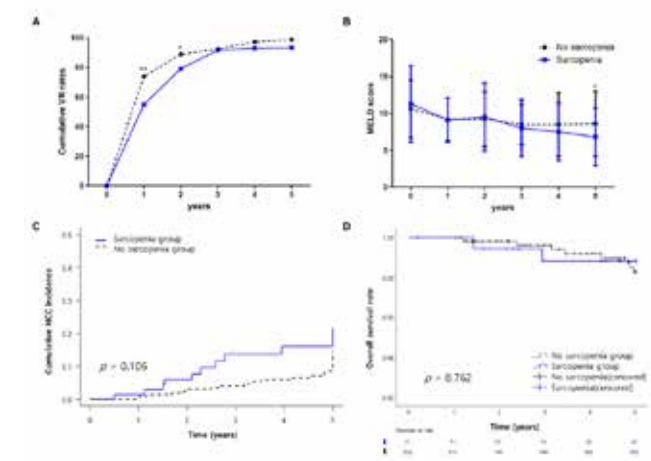
Methods: We retrospectively reviewed data from treatment-naïve CHB patients who had started antiviral therapy from 2007 to 2018 at Jeonbuk national university hospital. Eligible patients were diagnosed with LC and maintained antiviral therapy for more than a year. L3 skeletal muscle index (L3-SMI) was calculated by computed tomography and sarcopenia was defined using the gender quartile method (cut-off: <46.0 cm²/m² for males and <35.37 cm²/m² for females).

Results: A total of 283 patients (sarcopenic group 71, non-sarcopenic group 212) were enrolled. The sarcopenia group was significantly older and had a higher frequency of alcohol history compared to the non-sarcopenia group. The mean initial HBV NDA levels and MELD scores were not different between the groups. The cumulative VR rates were significantly lower in the sarcopenia group at 1 and 2 years, indicating a delay in viral suppression. However, VR rates became comparable after 3 years of continuous therapy. There was no difference in serial MELD scores, cumulative HCC incidence, or overall survival rate

between the two groups. Consistent trends were observed in subgroup analyses of patients with sarcopenic obesity and those aged ≥60 years. In multivariate analysis for 5-year overall survival, baseline Log HBV DNA, VR at 1 year, MELD score, and HCC development were independent prognostic factors, whereas sarcopenia was not.

Conclusions: Sarcopenia in patients with CHB-LC tends to delay the achievement of early virological response but does not affect MELD score alteration, HCC incidence, or long-term survival. Preservation of liver function and early viral suppression are more critical for prognosis than muscle mass in this population.

Keywords: Sarcopenia, Hepatitis B, Chronic, Antiviral Agents, Treatment Outcome



PE-4

Comparison of Quantitative HBsAg Decline between Entecavir and Tenofovir Alafenamide in Patients with Chronic Hepatitis B

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Aims: Entecavir (ETV) and tenofovir alafenamide (TAF) are widely used first-line nucleos(t)ide analogues for chronic hepatitis B (CHB) treatment, offering potent viral suppression and a high barrier to resistance. Nevertheless, direct comparisons of their effects on quantitative hepatitis B surface antigen (HBsAg) reduction remain limited. This study aimed to evaluate differences in HBsAg decline as well as renal and metabolic safety profiles between ETV and TAF therapy in CHB patients.

Methods: We retrospectively reviewed 1,342 consecutive CHB patients who were treated with either ETV or TAF at a tertiary referral center between January 2007 and December 2021.

Among them, 493 patients met the inclusion criteria and were analyzed (ETV, n = 169; TAF, n = 324). The primary outcome was the change in quantitative HBsAg levels at 12 and 24 months after treatment initiation. Secondary outcomes included longitudinal changes in estimated glomerular filtration rate (eGFR), serum phosphorus levels, and low-density lipoprotein (LDL) cholesterol.

Results: The median absolute decrease in quantitative HBsAg levels did not differ significantly between the two treatment groups at 12 and 24 months. However, the proportion of patients achieving a >10% reduction in HBsAg was higher in the TAF group compared with the ETV group at both 12 months (63.0% vs. 55.8%) and 24 months (81.7% vs. 65.1%). Renal function was better preserved in the TAF group, with stable eGFR values at 24 months, whereas the ETV group showed a significant decline (0.0 vs. -6.0, $P=0.003$). In addition, serum phosphorus levels were better maintained with TAF ($P=0.003$). Changes in LDL cholesterol were comparable between the two groups.

Conclusions: Among patients with CHB, TAF therapy was associated with a higher proportion of patients achieving meaningful quantitative HBsAg reduction and demonstrated a more favorable renal safety profile compared with ETV, without significant differences in lipid changes.

Keywords: Chronic Hepatitis B, Quantitative Hbsag, Entecavir, Tenofovir Alafenamide

PE-5

Longitudinal Renal Function Trajectories in Chronic Hepatitis B Patients on Anti-Viral Treatment: A Nationwide Population-Based Study in Korea

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Aims: Patients with chronic hepatitis B (CHB) infection often require lifelong anti-viral therapy using nucleot(s)ide(NUC) analogues. Long duration of NUC can encounter decrease of renal function depending on the NUC agents. Tenofovir disoproxil, tenofovir alafenamide (TAF) and entecavir (ETV) have been considered as safe and highly efficacious agent, however there have been scarce data regarding long term outcome in large population. We aimed to investigate the longitudinal renal function trajectory in CHB patients undergoing treatment with TDF, TAF or ETV.

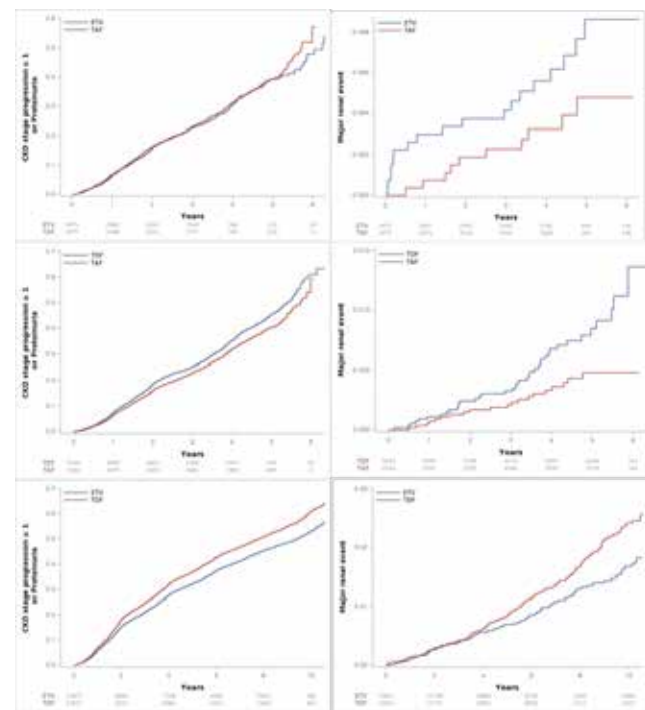
Methods: Utilizing data from the Korea National Health Insurance Service, we identified 34,576 patients treated with TDF,

25,615 patients treated with ETV and 6,789 patients treated with TAF. The primary outcome was the progression of chronic kidney disease (CKD), defined as an advancement of CKD by at least one stage and the presence of overt proteinuria. Propensity score (PS) matching was employed for outcome comparisons. Patients with previous history of other NUC, no data of renal function, presence of proteinuria at anti-viral treatment, previous history of end stage renal disease, dialysis and kidney transplantation, and decompensated liver cirrhosis.

Results: In the 1:1 PS-matched cohort comprising 2,675 patient pairs, no statistically significant difference was observed in CKD stage progression ≥ 1 or development of proteinuria between the TAF and ETV groups (9.11 vs. 9.27/100 person-years [PYs]; HR 1.02, $P=0.70$) however, in the PS-matched cohort of 11,873 patient pairs of ETV and TDF groups, TDF showed significantly higher risk for CKD stage progression ≥ 1 or proteinuria (7.69 vs 9.19/100person years, HR 1.215, $P<0.001$). Furthermore, in the PS-matched cohort of 5,339 patient pairs of TAF and TDF groups, TDF showed higher risk for CKD stage progression ≥ 1 or proteinuria (9.34 vs 10.76/100person years, HR 1.148, $P<0.001$).

Conclusions: In this large-scale, PS-matched analysis, long-term treatment with TAF showed no significant difference compared to ETV in CKD progression, major renal events, or hepatocellular carcinoma incidence. These findings suggest that TAF and ETV have comparable renal safety and oncologic outcomes in patients with CHB.

Keywords: HBV, Renal Function, Big Data, Anti-Viral Treatment



8. HCV, Basic

PE-1

Molecular Epidemiology, Genotype Distribution, and Public Health Burden of Hepatitis C Virus in Nepal: A Review

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Aims: Hepatitis C virus (HCV) infection remains a major global public health concern, particularly in low- and middle-income countries. Nepal has a low overall prevalence but a high disease burden in major risk groups such as people who inject drugs (PWID) and HIV patients. Limited molecular surveillance and fragmented epidemiological reporting have hindered a thorough knowledge of HCV transmission patterns in Nepal.

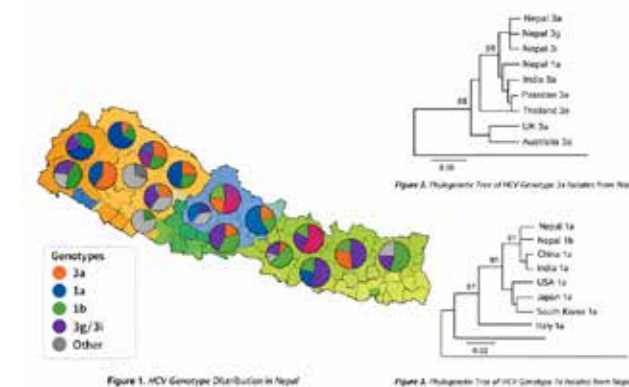
Methods: A narrative review was undertaken using available literature, national surveillance reports, and molecular epidemiological studies related to HCV in Nepal from 2000 to 2025. Data were extracted on prevalence, Genotype distribution, diagnostic approaches, and Public health implication.

Results: According to available evidence indicates that the estimated HCV prevalence in Nepal's general population is around 0.38%, whereas prevalence among PWID ranges from 27% to 42%, demonstrating concentrated transmission within high-risk groups. Molecular epidemiological investigations consistently show genotype 3a as the predominant circulating genotype, followed by genotypes 1a and 1b, suggesting geographical similarities with South Asian transmission patterns. Recent sequencing-based investigations, such as partial genome sequencing and limited whole-genome techniques, have identified emerging subtypes and resistance-associated substitutions (RAS) that alter the response to direct-acting antiviral (DAA) medications. Molecular diagnostic tools such as reverse transcription polymerase chain reaction (RT-PCR), real-time PCR, and sequencing technologies have greatly improved detection sensitivity and genotype characterization; however, these technologies remain centralized in reference laboratories and are not widely available in peripheral health-care settings.

Conclusions: HCV infection in Nepal remains concentrated in specified high-risk populations, with genotype 3 dominating and growing genetic diversity. Although diagnostic capacity has increased over the past decade, there are still gaps in national molecular surveillance and equal access to advanced diagnostics. To attain vital viral hepatitis eradication objectives by 2030, national hepatitis control programs must strengthen

laboratory infrastructure, enhance sequencing-based monitoring, and integrate molecular epidemiology.

Keywords: Molecular Epidemiology, Genotype Distribution, Public Health, Hepatitis C



PE-2

Multimodal Artificial Intelligence for Prognostic Prediction in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Aims: The development of artificial intelligence (AI), particularly multimodal approaches integrating imaging and clinical data, has shown great potential in improving prognosis prediction in patients with hepatocellular carcinoma. However, results vary across studies, and a comprehensive quantitative synthesis is lacking. This study aims to evaluate the prognostic performance of multimodal AI models and their clinical implications in hepatocellular carcinoma through a systematic review and meta-analysis approach.

Methods: This study was conducted in accordance with the PRISMA 2020 guidelines. A literature search was conducted in PubMed, Scopus, and Web of Science databases until March 2026. Studies that met the inclusion criteria were those that used AI (machine learning, deep learning, or radiomics) to predict prognosis in hepatocellular carcinoma patients and reported performance metrics such as area under the curve (AUC) or concordance index (C-index). The analysis was performed using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and sensitivity analysis and publication bias evaluation were performed.

Results: Five original studies were included in the quantitative meta-analysis. The AUC values for each study ranged from 0.75

to 0.91. Pooling results showed that the multimodal AI model had good prognostic performance, with a pooled AUC of 0.815 (95% CI: 0.78–0.85). There was moderate to high heterogeneity between studies ($I^2 = 68\%$). Clinically, the AI model significantly improved patient risk stratification, with high-risk groups having an approximately 2–3-fold increased risk of mortality (Hazard Ratio [HR] ~2.0–3.5) compared to low-risk groups. This model also showed potential in predicting recurrence and supporting therapeutic decision-making, including the selection of candidates for resection, transplantation, and systemic therapy.

Conclusions: Multimodal AI models have demonstrated good performance in predicting the prognosis of hepatocellular carcinoma and hold significant potential for supporting clinical decision-making. However, heterogeneity across studies and limited external validation indicate the need for further research with more standardized designs. The integration of new technologies such as large language models represents a future research opportunity.

Keywords: Hepatocellular Carcinoma, Artificial Intelligence, Prognosis, Multimodal AI

9. HCV, Clinical

PE-1

Hepatic Biochemical Abnormalities in Chronic Hepatitis C Patients: Insights from a Tertiary Hospital in Nepal

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Aims: Chronic hepatitis C (CHC) is a major global public health concern. Chronic hepatitis C cause liver damage, cirrhosis, and liver carcinoma, leading to alterations in hepatic biochemical parameters. Data on liver biochemical abnormalities among patients with chronic hepatitis C in Nepal are limited. This study aimed to evaluate hepatic biochemical abnormalities in CHC patients attending a tertiary care hospital in Nepal.

Methods: This retrospective cross-sectional study included patients diagnosed with CHC who underwent liver function testing between 2018 and 2025 at a tertiary care hospital in Nepal. Ethical approval was obtained from KIST Medical College. Demographic and laboratory data were extracted from hospital records. Data were analyzed using SPSS version 17.0. Continuous variables are presented as mean $\pm$ SD, categorical

variables as n (%), and one-sample t-tests were used to compare mean values with reference ranges. A p value < 0.05 was considered statistically significant.

Results: A total of 105 patients were included. Elevated liver enzymes were common, with aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase increased in 44.8%, 39.1%, and 30.5% of patients, respectively. Total and direct bilirubin were elevated in approximately one-quarter of patients. Low serum albumin and reduced total protein were observed in 29.0% and 16.2% of patients, respectively. Mean values of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were above reference ranges, while mean albumin and total protein were below normal. All differences were statistically significant ($P < 0.001$).

Conclusions: Chronic hepatitis C is associated with common hepatic biochemical abnormalities, particularly elevated liver enzymes and reduced markers of liver synthetic function. Regular monitoring of liver biochemical parameters is essential for effective clinical assessment and management, especially in resource-limited settings.

Keywords: Chronic Hepatitis C, Liver Function Tests, Hepatic Biochemical Abnormalities, AST

PE-2

Real-World Effectiveness and Safety of 8-Week Glecaprevir/Pibrentasvir for Persons Who Inject Drugs and with Human Immunodeficiency Virus Infection Patients from Taiwan Nationwide HCV Registry

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Aims: The once-daily, oral, fixed-dose, direct-acting antiviral glecaprevir/pibrentasvir (G/P) is indicated for chronic hepatitis C (CHC) infection with HCV genotypes 1–6 in patients. Person who inject drugs (PWID) and human immunodeficiency virus (HIV) patients are special populations with high HCV prevalence. As Taiwan government is committed to eliminating HCV by 2025, this study aimed to measure the real-world evidence for PWID and HIV patients using 8-week G/P in Taiwan HCV Registry (TACR).

Methods: The TACR is an ongoing nationwide registry program organized and supervised by Taiwan Association for the Study of the Liver (TASL), which aims to set up a database and biobank of patients with CHC in Taiwan. Data was analyzed as of 31 May 2025 for CHC patients with CKD treated with G/P. Effectiveness reported as sustained virologic response at post-treatment week 12 (SVR12) was assessed by modified intention-to-treat (miTT) populations that excluded patients who lost to follow-up or without SVR12 data. Safety profile was assessed in the ITT population.

Results: Overall, 743 patients received 8-week G/P regimen (ITT) and 661 of which had SVR12 data available (miTT). The overall SVR12 rate was 98.2% (649/661) in the miTT population. For selected subgroups including patients with PWID, HIV, GT3, PWID and HIV, the SVR12 rate was 98.4% (496/504), 97.4% (153/157), 97.5% (78/80), respectively. Adherence rate $\geq 80\%$ for PWID, HIV, PWID and HIV patients were 99.5% (552/580), 100% (163/163), 98.7% (148/150). Overall, 9.2% (68/743) of the patients experienced adverse events (AEs) in the ITT population. Three patients (0.4%) experienced serious adverse events and only two (0.3%) resulted in permanent drug discontinuation. None of them were considered as treatment drug related. The most frequent AEs ($>5\%$) was fatigue (6.2%). Laboratory abnormalities of Grade 3 and 4 for bilirubin, AST, and ALT were all less than 0.7%. Liver, kidney and HCV RNA level were all significantly improved at week 4 and SVR12 for all PWID and HIV patients.

Conclusions: In this real-world Taiwanese cohort, 8-week G/P therapy was effective and well-tolerated in PWID and HIV patients. Benefits of HCV cure for short-term liver, kidney function and HCV RNA level were also observed for both PWID and HIV patients.

Keywords: Hepatitis C, Glecaprevir/Pibrentasvir, Human Immunodeficiency Virus, Persons Who Inject Drugs

PE-3

Risk of Pancreatic Cancer between Hepatitis C and Non-Hepatitis C Cohorts in Korea, 2002-2024

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Aims: To examine and compare the incidence of pancreatic cancer in HCV and Non-HCV cohorts in Korea

Methods: Using the National Health Insurance Service Claims Data from 2002 to 2024, an HCV cohort was established by selecting 20-89 years old among patients with HCV infection (ICD-10, Acute HCV, B17.1; chronic HCV, B18.2) records from 2005 to 2021, and for comparison, a non-HCV cohort was established by matching gender and age at a ratio of 1:20 among those without history of HCV, HBV, or HIV. A total of 3,471,700 subjects (166,025 HCV; 3,305,675 non-HCV) were selected and followed up until December 31, 2024. The end-point was the occurrence of pancreatic cancer (ICD-10, C25) or death, whichever comes first. Time-to-event analyses were performed using Cox proportional hazards models adjusted for age, sex, comorbidities, lifestyle habits, and competing risk of death.

Results: The 20-year cumulative incidence was higher in the HCV cohort (0.64%) compared to that in non-HCV cohort (0.48%). Compared to non-HCV cohort, the HCV cohort had a 1.62-fold higher risk of pancreatic cancer after adjustment for age and sex. With additional adjustments for comorbidities, body mass index, smoking, drinking, and competing risk, the HCV cohort had a 1.38 times higher risk of developing pancreatic cancer than the non-HCV cohort.

Conclusions: This study may suggest that HCV infection is a systemic disease that requires continuous monitoring for both hepatic and extrahepatic complications. Considering the infection itself and the underlying health conditions on HCV patients, attention to the risk of extrahepatic cancers, such as pancreatic cancer, is necessary.

Keywords: Pancreatic Cancer, HCV

PE-4

Clinical Manifestations of Acute Hepatitis C Virus Infection with Syphilis Co-Infection

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Aims: Mongolia, as a country with a high burden of liver disease caused by viral infections, has prioritized reducing the spread of viral hepatitis and sexually transmitted infections (STIs) in line with the WHO strategy for 2022–2030. Orders A/133 (2023) and A/18 (2024) issued by the Ministry of Health mandate that healthcare providers initiate screening of hospitalized patients for hepatitis B and C viruses, syphilis, and HIV infection. Among infectious diseases registered in Mongolia, STIs rank among the leading causes, with more than 40% of reported cases being newly diagnosed syphilis. Hepatitis C virus (HCV) infection

and syphilis are transmitted via the parenteral route, can lead to chronic disease, and co-infection represents a serious condition that accelerates liver damage and negatively affects treatment outcomes. Syphilis infection places additional stress on liver function and exacerbates HCV-related inflammation. This study aimed to investigate how syphilis co-infection affects the biochemical and clinical course of acute hepatitis C virus infection.

Methods: A retrospective, hospital-based cross-sectional study design was used. A total of 74 patients diagnosed with acute hepatitis C virus infection and treated at the National Center for Communicable Diseases between 2025 and 2026 were randomly selected. Data were collected from medical records. Patients were divided into two groups based on syphilis serology results: HCV mono-infection and HCV with syphilis co-infection. Differences between variables in the two groups were analyzed using the T-test, with statistical analysis performed using SPSS version 26. A p-value <0.05 was considered statistically significant.

Results: Of the study participants, 17 (23%) had syphilis co-infection. There were no statistically significant differences in age and sex between the groups ($P=0.982$). In the co-infected group, 23.5% had high RPR titers (indicative of active/new infection). Clinically, general signs of infection and intoxication (35.3%), fatigue (100%), dyspeptic syndrome (100%), and intoxication syndrome (100%) were predominant. Biochemical analysis showed significantly higher levels in the co-infected group compared to the mono-infected group: total bilirubin (192.4 vs 110.5 $\mu\text{mol/L}$, $P<0.01$), alkaline phosphatase (245.8 vs 132.1 U/L, $P=0.004$), and ALT (1240.5 vs 850.2 U/L, $P=0.03$). Kaplan–Meier analysis demonstrated that the mean time for ALT normalization was longer in the co-infected group (26.4 days) compared to the mono-infected group (20.7 days) ($P=0.006$), indicating prolonged recovery.

Table 1. General characteristics of the study participants

№	Parameters	Subcategory	Total n (%)	Acute C hepatitis		P value
				TPHA +/n	TPHA -/n	
Selected demographic and anthropometric parameters						
1	Age		35.6±15.39	35.3±11.8	35.7±16.4	0.032*
2	Sex	Male	39(52.7)	9(52.9)	30(52.6)	0.982
		Female	35(47.3)	8(47.1)	27(47.4)	
3	BMI		24.3±5.09	25.9±5.37	23.8±4.94	0.295
4	Marriage		41(55)	9(53)	32(56)	
Risk factors identified through the epidemiological questionnaire						
1	Blood or blood product transfusion		1(1.4)	0(0)	1(1.8)	0.272
2	Surgical procedures/operations		30(40.5)	8(47.1)	22(36.8)	0.382
3	Drug use		3(4.1)	0(0)	3(5.3)	0.046
4	IV treatment		5(6.8)	1(5.9)	4(7)	0.746
5	Dental procedures		13(17.6)	2(11.8)	11(19.3)	0.117
6	Tattooing		21(28.4)	4(23.5)	17(29.8)	0.246
7	Piercing		4(5.4)	1(5.9)	3(5.3)	0.846
8	History of family member with hepatitis		6(8.1)	2(11.8)	4(7)	0.227
Clinical symptoms and syndromes						
1	Fatigue syndrome		67(91)	17(100)	50(87.7)	0.001*
2	Dyspeptic syndrome		71(96)	17(100)	54(94.7)	0.046*
3	Right upper quadrant pain		60(81)	15(88.2)	45(78.9)	0.066
4	Intoxication syndrome		70(95)	17(100)	53(93)	0.018*
5	Jaundice		73(99)	17(100)	56(98.2)	0.272
6	Cholestatic syndrome		33(45)	9(52.9)	24(42.1)	0.585
7	Hemorrhagic syndrome		3(4)	1(5.9)	2(3.5)	0.397
	Total		74	17	67	

*p < 0.05 was considered statistically significant.

Table 2. Laboratory parameters among study participants with TPHA-positive (+) serology									
Parameters	At the time of hospital admission		P value	Hospitalization day 54-21		P value	At the time of hospital discharge		P value
	TPHA +/n	TPHA -/n		TPHA +/n	TPHA -/n		TPHA +/n	TPHA -/n	
ALT	1240.5±470.2	850.2±229.5	0.03*	358.0±95.8	258.2±67.6	0.075	43.7±26.9	90.4±119.3	0.367
AST	768.0±521.5	612.9±233.0	0.004*	347±1039	173±262	0.019*	34.1±15.4	54.7±65.5	0.143
Total bilirubin	192.4±45.2	110.5±38.6	<0.001*	67±76.6	65±81.4	0.755	31±15.9	31±18.9	0.709
Alkaline phosphatase (ALP)	245.8±88.4	132.1±62.3	0.004*	143±38.3	105±43.2	0.146	140±44.7	115±37.8	0.851

Conclusions: Syphilis co-infection worsens the clinical course of acute hepatitis C, deepens jaundice and cholestatic syndrome, and prolongs the normalization of biochemical parameters.

Keywords: Acute Hepatitis C, Syphilis, Co-Infection, Cytolysis, Cholestasis

10. MASLD, Basic

PE-1

Dynamic Immune Landscape of NAFLD Highlights pDCs as Predictive Biomarkers for Disease Progression

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Aims: To provide a comprehensive, stage-resolved characterization of hepatic immune cell dynamics across the NAFLD spectrum and to identify immune-cell-derived signatures that can serve as diagnostic or risk-stratification tools for NASH.

Methods: We performed an integrative reanalysis of publicly available single-cell RNA-seq datasets from the Gene Expression Omnibus encompassing liver samples across NAFLD stages (simple steatosis → NASH → cirrhosis). Key findings were validated in independent human datasets and in experimentally induced murine NASH models. Using pDC-associated gene signatures, we built and tested a diagnostic model across multiple validation cohorts.

Results: Immune cell composition underwent extensive remodeling across disease stages, with plasmacytoid dendritic cells (pDCs) exhibiting the most pronounced transcriptional and numerical shifts. We discovered a distinct pDC subset co-expressing GZMB and TPM2 that was specifically enriched in NASH samples; this GZMB⁺TPM2⁺ signature was reproducible in independent human datasets and in murine NASH models. A diagnostic model based on pDC gene signatures achieved robust performance in multiple validation cohorts.

Conclusions: These results uncover a previously underappreciated role for GZMB⁺TPM2⁺ pDCs in NASH pathogenesis and provide a reproducible pDC-derived signature that may aid early diagnosis and risk stratification in NAFLD.

Keywords: Diagnostic Markers, Immune Landscape, NAFLD, PDCS

PE-2

Defective Mitochondria Trigger Hepatic Stellate Cell Transdifferentiation to Promote Liver Fibrosis

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Aims: Liver fibrosis is a hallmark of chronic liver disease, characterized by activated hepatic stellate cells (aHSCs). Quiescent HSCs (qHSCs) transdifferentiate into proliferative, myofibroblast-like cells, acquiring enhanced extracellular matrix-producing capacity that drives fibrogenesis. During this process, extensive metabolic reprogramming imposes a substantial burden on mitochondria. We investigated compensatory mitochondrial retrograde signaling as a critical regulatory axis driving HSC activation.

Methods: Primary murine HSCs were treated with mitochondrial toxins at various doses and time points. To examine the mechanistic basis of HSC activation, primary HSCs were transfected with siRNA against key transcription regulators of mitochondrial function. Fibrogenic transdifferentiation of HSCs was analyzed by RT-qPCR and Western blotting.

Results: In primary murine HSCs undergoing spontaneous activation *in vitro*, mitochondrial mass increased, as evidenced by elevated TOM20 immunostaining intensity and MitoTracker Green staining. However, the mitochondrial membrane potential examined by TMRE exhibited relatively weaker signals in aHSCs compared to qHSCs, indicating a mismatch between total mitochondrial mass and functional mitochondrial capacity. aHSCs also displayed increased mitochondrial protein accumulation, reflecting impaired mitochondrial proteostasis. Genes and proteins associated with downstream mitochondrial dysfunction signaling were markedly upregulated. This pattern was recapitulated in RNA-sequencing datasets from fibrotic patient livers. Mechanistically, silencing key transcriptional regulators of mitochondrial quality control and mitochondrial retrograde signaling pathway prevented induction of fibrogenic genes, such as Acta2, in HSCs.

Conclusions: Our data demonstrate that defective mitochondria transmit regulatory signals contributing to HSC transdifferentiation and highlight the mitochondrial quality control pathway as a critical mediator of this process. These findings suggest that targeting the mitochondrial retrograde signaling may provide a potential therapeutic approach for treating liver fibrosis.

Keywords: Liver Fibrosis, Hepatic Stellate Cell (HSC)

PE-3

Bile Acid Homeostasis Restoration by MK53 Peptide Ameliorate Metabolic-Associated Steatohepatitis in Experimental Models

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH) are growing global health concerns characterized by hepatic lipid accumulation and metabolic imbalance. Bile acid metabolism plays a key role in linking metabolic stress to liver inflammation and fibrosis. We previously identified a stress-induced molecular chaperone involved in MASLD progression and developed the MK53 antagonist peptide to restore hepatic lipid homeostasis. This study further investigates the effects of MK53 on cholesterol metabolism and bile acid homeostasis in a GAN diet-induced mouse model of MASH.

Methods: A GAN diet-induced mouse model of MASH was used to evaluate liver function, insulin tolerance, and glucose homeostasis. Bile and serum samples were collected to measure bile acid levels by LC–MS/MS. An *in vitro* cell model was employed to investigate the underlying mechanisms.

Results: Our preliminary data showed that p53 was translocated to nucleus to promote expression of small heterodimer partner (SHP) leading to suppression of CYP7A1/CYP7B1 expression in hepatic cells under nutrient overload, linking these changes to altered cholesterol metabolism in the MASH model. Administration of MK53 restores the hepatic bile acid synthesis and reduced serum levels of taurine conjugated bile acids. The rebalancing of bile acid profiles correlated with a marked reduction in hepatic inflammation.

Conclusions: Our findings suggest that MK53 peptide represents a potential therapeutic strategy for MASH, in part, via rebalancing bile acid synthesis.

Keywords: MASH, Bile Acid, Mk53 Peptide, LIPID Metabolism

PE-4

Liver Stiffness Impairs Hepatic Lipid Transport via Mechanorepression of LXRA in MASLD

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Aims: Liver fibrosis is characterized by increased tissue stiffness. However, the mechanism by which extracellular matrix stiffening regulates hepatocyte function is poorly defined. This study aimed to investigate how liver stiffness modulates hepatocyte

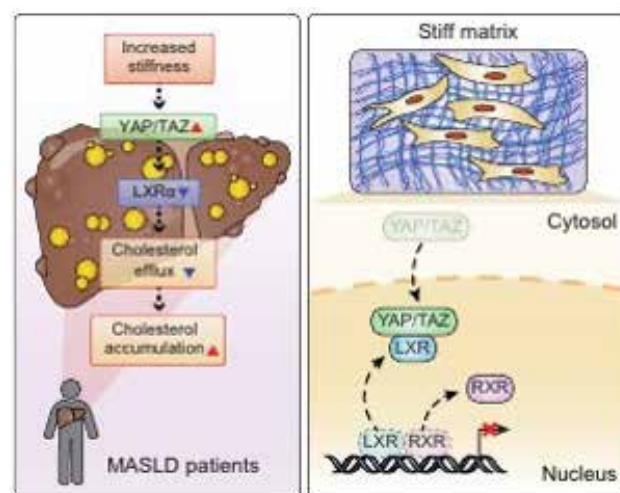
metabolism, focusing on mechanosensitive regulation of cholesterol transport.

Methods: Mouse primary hepatocytes were cultured on soft (1 kPa) or stiff (20 kPa) polyacrylamide hydrogel substrates and subjected to metabolomic, transcriptomic, and biochemical analyses. To validate the mechanistic basis *in vivo*, hepatocyte-specific Yap/Taz knockout mice were examined in a cholesterol-induced fibrosis model. The findings were confirmed using liver biopsies from Boramae MASLD cohort.

Results: Hepatocytes cultured on a stiff matrix showed impaired cholesterol efflux compared with those on a soft matrix. Hepatocyte-specific Yap/Taz deletion protected mouse livers from cholesterol accumulation and fibrosis progression. Mechanistically, nuclear YAP suppressed the induction of LXR α target genes. LXR α suppression occurred even when YAP-TEAD interaction was disrupted, indicating that the LXR α regulation by YAP does not require classical YAP transactivation. Consistent with these findings, an inverse correlation between LXR α and YAP target genes was observed in MASLD patient samples.

Conclusions: Elevated liver stiffness functionally rewires hepatocyte cholesterol handling through YAP/TAZ-mediated repression of LXR α signaling. These findings identify liver stiffness as an active metabolic determinant in MASLD rather than a simple surrogate of fibrosis severity. Targeting this mechanotransduction pathway may represent a therapeutic strategy for MASLD with high liver stiffness.

Keywords: Liver Stiffness, Yap/Taz, Cholesterol, LXR α



PE-5

Zfp469 Deletion Attenuates Liver Fibrosis by Down-regulating Extracellular Matrix Production in Hepatic Stellate Cells

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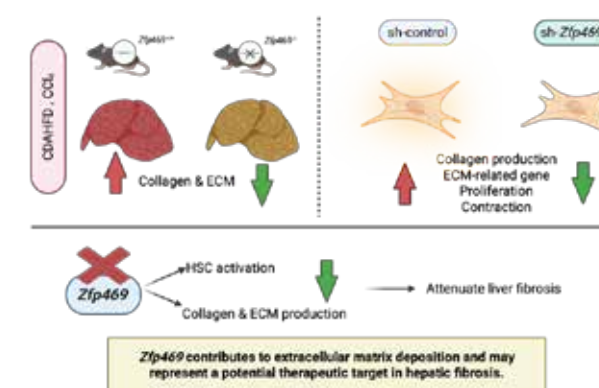
Aims: Liver fibrosis results from chronic liver injury and is characterized by excessive extracellular matrix (ECM) deposition. *Zfp469* has been implicated in connective tissue regulation. However, its role in hepatic fibrogenesis remains unclear. This study investigated the functional impact of *Zfp469* deletion in murine models of liver fibrosis and explored its cellular expression using single-cell transcriptomic analysis.

Methods: *Zfp469* knockout (KO) mice and wild-type (WT) littermates were subjected to two fibrosis models. For diet-induced injury, mice were fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for 10 weeks. For toxin-induced fibrosis, mice received intraperitoneal carbon tetrachloride (CCl₄) injections twice weekly for 4 weeks. Liver tissues were collected for histological evaluation. Fibrosis was assessed using Masson's trichrome and Sirius Red/Fast Green staining. Hepatic lipid accumulation in the CDAHFD model was evaluated by Oil Red O staining. The single-cell RNA-sequencing datasets were analyzed to determine the cellular distribution of *Zfp469* and its association with ECM-related genes. For *in vitro* studies, primary mouse hepatic stellate cells (HSCs) were transduced with shRNA targeting *Zfp469* (sh-*Zfp469*) or control shRNA to evaluate fibrogenic activation and phenotype.

Results: Re-analysis of single-cell transcriptomic demonstrated that *Zfp469* expression was enriched in activated hepatic stellate cells and positively correlated with ECM-related genes. Both CDAHFD feeding and CCl₄ treatment induced marked collagen deposition in WT mice, as shown by Masson's trichrome and Sirius Red/Fast Green staining. In contrast, *Zfp469* KO mice exhibited reduced collagen accumulation compared with WT controls in both models. Oil Red O staining confirmed hepatic lipid accumulation in the CDAHFD model. *In vitro*, *Zfp469* knockdown in primary HSCs suppressed activation-associated gene expression and collagen production compared with control cells.

Conclusions: *Zfp469* deletion attenuates liver fibrosis in both diet- and toxin-induced models and reduces HSC activation *in vitro*. Together with single-cell analysis showing HSC-enriched expression and correlation with ECM-related gene, these findings suggest that *Zfp469* contributes to ECM deposition during chronic liver injury and may used as a potential therapeutic target in hepatic fibrosis.

Keywords: ZFP469, Liver Fibrosis, Hepatic Stellate Cells, Extracellular Matrix



PE-6

Gut Microbiota-Derived Nicotinamide Compounds Regulate Fatty Acid β -Oxidation and Inflammation in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent metabolic disorder with a significant global health burden. Emerging evidence suggests that gut microbiota-derived metabolites may regulate host metabolism and inflammation. However, the mechanisms by which these metabolites influence MASLD progression remain incompletely understood. This study aimed to investigate the therapeutic potential of nicotinamide-related microbial metabolites—nicotinamide (NAM), nicotinic acid (NA), and nicotinamide riboside (NR)—in regulating lipid metabolism, inflammation, and intestinal barrier function in MASLD.

Methods: Gut microbiota-derived metabolites were identified using untargeted metabolomic profiling based on LC-Orbitrap mass spectrometry. The biological effects of NAM, NA, and NR were evaluated using integrated *in vitro*, *in vivo*, and *in silico* approaches. Cellular experiments were conducted in AML12 hepatocytes, RAW264.7 macrophages, Caco-2 intestinal epithelial cells, and 3T3-L1 adipocytes. A Western diet-induced MASLD mouse model was used to assess metabolic and inflammatory responses. Gene and protein expression were analyzed using quantitative real-time PCR and western blotting, and potential molecular interactions were predicted through network pharmacology and molecular docking analyses.

Results: NAM, NA, and NR significantly increased the expression of key regulators of fatty acid β -oxidation, including ACOX1, CPT1, PGC-1 α , and AMPK. These changes were associated with enhanced fatty acid oxidation and reduced lipid

accumulation in hepatocytes and adipocytes. In macrophages, treatment suppressed inflammatory responses by reducing pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β . In addition, these metabolites increased the expression of intestinal tight junction-related proteins, including occludin and zonula occludens-1, suggesting improved intestinal barrier integrity. Computational analyses further indicated potential interactions between nicotinamide-related metabolites and metabolic regulators involved in lipid metabolism.

Conclusions: Our findings demonstrate that nicotinamide-related microbial metabolites may alleviate MASLD through multiple mechanisms, including enhancement of fatty acid β -oxidation, suppression of inflammatory signaling, and improvement of intestinal barrier function. These results highlight the important role of microbiota-derived metabolites in host metabolic regulation and suggest that NAM, NA, and NR may represent promising therapeutic candidates for MASLD management. Targeting gut microbiota–host metabolic interactions may provide a novel strategy for the prevention and treatment of MASLD and related metabolic disorders.

Keywords: Microbial Metabolites, Nonalcoholic Fatty Liver Disease, Nicotinic Acids, Nicotinamide Riboside

PE-7

Strain-Specific Effects of *Lactobacillus acidophilus* Improve Hepatic and Microbial Dysregulation in MASLD and Diabetes

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D) are closely linked to gut-liver axis dysfunction, yet the mechanistic contribution of gut microbiota remains incompletely defined. We investigated whether *Lactobacillus acidophilus* alleviates hepatic and metabolic abnormalities through modulation of gut microbiota and downstream metabolic pathways.

Methods: Human stool samples were collected from healthy controls (HC, n=63), healthy controls with diabetes (HC+DM, n=35), patients with metabolic dysfunction-associated steatohepatitis (MASH, n=58), and patients with MASH and diabetes (MASH+DM, n=22), and microbial composition was analyzed by 16S rRNA profiling. *L. acidophilus*, identified from the human cohort analysis, was further evaluated in Western diet (WD)-fed mice and ob/ob diabetic mice. Mice received oral gavage of *L. acidophilus* (1×10^9 CFU, twice weekly), with metformin as a positive control. Hepatic histology, serum biochemical parameters, oral glucose tolerance test, qPCR, and microbiome profiling were performed.

Results: In the human cohort, dysbiosis worsened with disease severity, and *Lactobacillus* abundance decreased from HC (0.12%) to MASH (0.09%). Notably, among *Lactobacillus* species examined, *L. acidophilus* uniquely exhibited an early and significant decrease in HC+DM compared with HC ($P<0.01$).

In WD-fed mice, *L. acidophilus* reduced hepatic steatosis and inflammatory injury (NAS: NCD, 0; WD, 7.1; La, 5.2) and significantly lowered hepatic cholesterol levels ($P=0.0486$). *L. acidophilus* restored intestinal barrier markers, reduced hepatic inflammation, and regulated lipid metabolism, accompanied by partial recovery of WD-induced dysbiosis. In ob/ob diabetic mice, *L. acidophilus* improved glucose homeostasis (OGTT AUC: Con, 45733; La, 36888; Met, 36510). *L. acidophilus* also enhanced hepatic AMPK activation, consistent with reduced lipogenesis and gluconeogenesis.

Conclusions: *L. acidophilus* improved hepatic steatosis, lipid dysregulation, and glucose intolerance across MASLD and T2D models, supporting its potential as a microbiome-based therapeutic candidate through gut microbiota modulation and AMPK-associated metabolic regulation.

Keywords: MASLD, Type 2 Diabetes, Lactobacillus Acidophilus, Gut–Liver Axis, Gut Microbiota

PE-8

Hepatocellular NOX2 Aggravates Metabolic Dysfunction-Associated Steatotic Liver Disease by Disrupting Mitochondrial Homeostasis and Lipid Metabolic Process

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Aims: The interplay between oxidative stress and mitochondrial dysfunction substantially promoted the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). However, its underlying mechanism and core molecular events have not been fully identified. The NADPH oxidase 2 (NOX2) in hepatocytes is increasingly recognized as a contributor to the pathogenesis of MASLD. Therefore, we sought to investigate the role of NOX2 in modulating mitochondrial homeostasis and subsequent lipid accumulation in MASLD.

Methods: The expression level and cellular source of NOX2 were estimated in hepatic tissues from CDAHFD-induced mouse models mimicking MASH. Functional studies were implemented using hepatocyte-specific NOX2 knockout mouse models, along with the AML12 hepatocyte cell line. Furthermore, the effects of pharmacological NOX2 inhibition using GSK2795039 were assessed both *in vivo* and *in vitro*.

Mitochondrial alterations, hepatic steatosis/lipid accumulation, and regulatory pathways were evaluated via histological, molecular, and metabolomics techniques.

Results: NOX2 expression was significantly elevated in murine models and PA-treated AML12 cells, positively correlating with disease severity. Hepatic NOX2 deficiency mitigated CDAHFD-induced steatosis and fibrotic changes, in alignment with mitochondrial morphology, dynamics, and respiratory functional recovery. Additionally, deleting NOX2 can attenuate hepatocellular mtDNA release and suppress the downstream inflammatory cGAS-STING pathway. Transcriptomic and metabolomic analyses indicated that NOX2 may impair lipid metabolism, leading to cholesterol accumulation in liver tissues, and that increased SOAT1 expression, which modulates lipid droplets, was mechanistically involved. Pharmacological inhibition of NOX2 with GSK2795039 similarly ameliorated MASH histological damages in both murine and hepatocyte models.

Conclusions: NOX2 serves as an executor by instigating oxidative stress-dictated mitochondrial dysfunction and inflammatory activities, promoting lipid accumulation and MASH progression. It is promising to target NOX2 as a therapeutic strategy for MASLD.

Keywords: NOX2, Oxidative Stress, Mitochondria, Lipid Metabolism

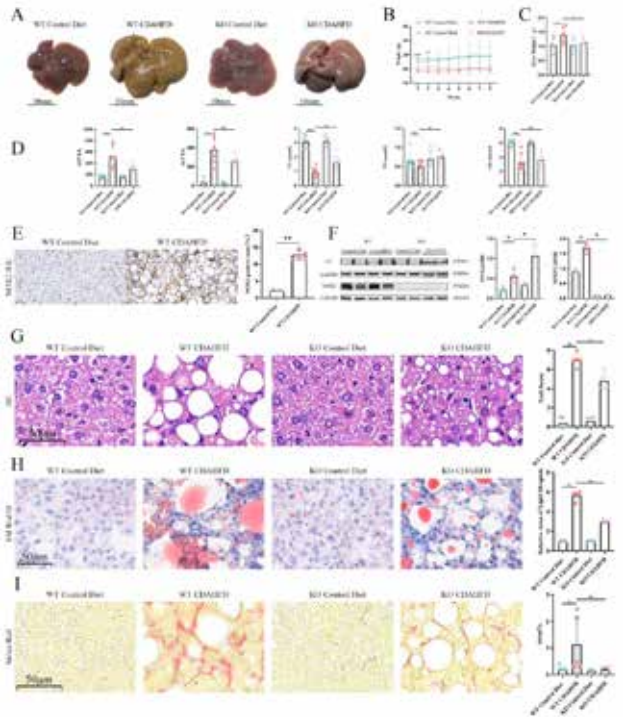


Figure 1.

PE-9

Diagnostic Accuracy of Noninvasive Tests for Hepatic Steatosis in MASLD: An Umbrella Review

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Aims: To synthesize and critically appraise evidence from systematic reviews and meta-analyses on the diagnostic accuracy of non-invasive tests (NITs) for detecting hepatic steatosis in adults with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: PRISMA 2020-compliant umbrella review. PubMed/MEDLINE, Embase, Scopus, Web of Science and the Cochrane Library were searched to February 2026. We included reviews/meta-analyses of diagnostic accuracy for steatosis (S1 or higher) assessing imaging, serum biomarkers or artificial intelligence (AI), using biopsy or MRI-PDFF as reference standards (ultrasound accepted only as a 'soft' reference for population biomarker studies). Methodological quality was assessed with AMSTAR 2, overlap with corrected covered area (CCA), and a sensitivity analysis was restricted to high-confidence reviews.

Results: Thirty-one reviews/meta-analyses were included across MRI (MRI-PDFF, H-MRS), quantitative ultrasound (UDFF, attenuation coefficient, ATI), transient elastography-controlled attenuation parameter (CAP), conventional ultrasound/HRI, CT, serum scores (FLI, HSI, LAP, TyG, TyG-BMI, VAI) and AI models. MRI platforms showed the highest accuracy (AUROC >0.95; MRI-PDFF AUROC 0.97). Quantitative ultrasound performed well (UDFF AUROC 0.93; attenuation coefficient AUROC 0.89-0.97) and generally outperformed CAP (AUROC 0.82-0.92). With hard reference standards, serum biomarkers showed moderate performance (FLI AUROC about 0.80; HSI 0.75-0.83), while higher estimates using soft standards had lower certainty. AI models achieved pooled AUROC 0.97 but had substantial methodological limitations. Overlap ranged from moderate (CCA 5.2% in biomarkers) to high (CCA 14.8% in CAP); high-confidence-only synthesis did not change the main conclusions.

Conclusions: MRI-PDFF is the most accurate NIT for steatosis in MASLD. Next-generation quantitative ultrasound offers the best balance of accessibility and accuracy, while serum biomarkers remain useful for population screening. A stepwise pathway (serum screening -> ultrasound confirmation -> MRI arbitration) may optimize clinical workflows and resource use.

Keywords: MASLD, Hepatic Steatosis, Diagnostic Accuracy, Mri-Pdff, Quantitative Ultrasound, Cap

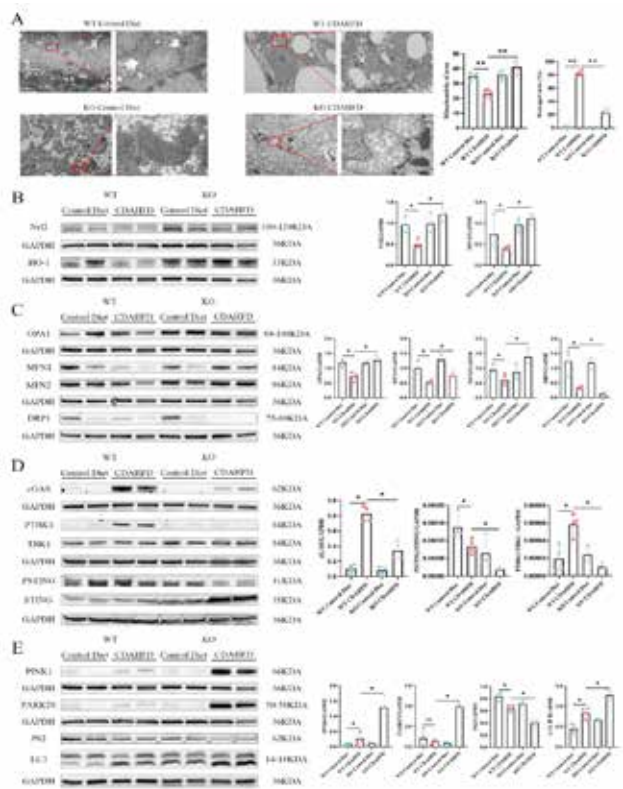


Figure 2.

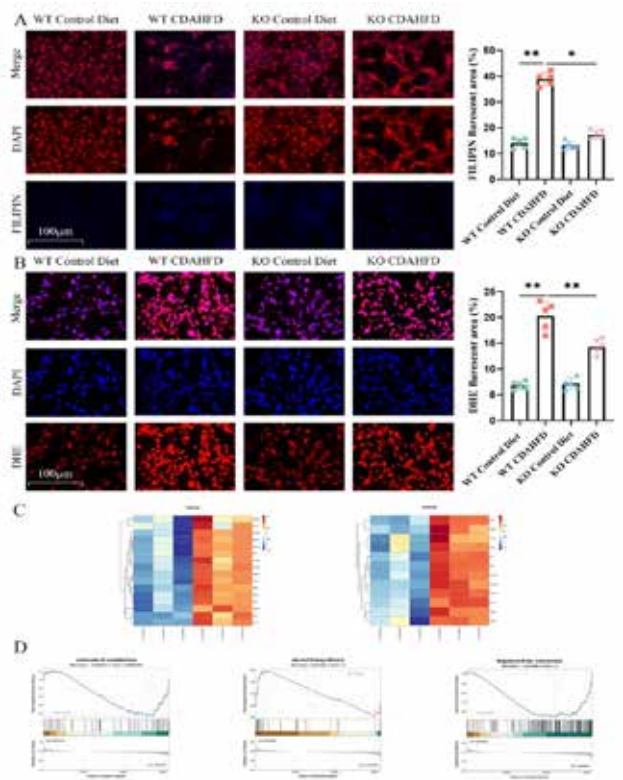


Figure 3.

PE-10

SGK1 Inhibition Attenuates Liver Fibrosis by Suppressing Hepatic Stellate Cell Activation

Hye-Young Seo, Ji Yeon Park, Jae Seok Hwang, Mi-Kyung Kim, Byoung Kuk Jang

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Aims: Serum- and glucocorticoid-regulated kinase 1 (SGK1) is a serine/threonine kinase belonging to the AGC kinase family and is activated by stress and growth factor signaling pathways. SGK1 has been implicated in inflammatory and fibrotic responses in several organs; however, its role in hepatic fibrosis remains unclear. In this study, we investigated whether SGK1 is upregulated in liver fibrosis and whether pharmacological inhibition of SGK1 attenuates fibrogenic responses in hepatic stellate cells.

Methods: Liver fibrosis was induced by thioacetamide (TAA) injection for 8 weeks, and SGK1 mRNA expression was analyzed using real-time RT-PCR. SGK1 mRNA levels were also evaluated in liver tissues of patients with Metabolic dysfunction-associated steatohepatitis (MASH). LX2 cells were stimulated with TGF- β to induce fibrogenic signaling, and the effects of SGK1 inhibitors were evaluated using western blot analysis. In addition, primary mouse hepatic stellate cells were treated with SGK1 inhibitors, and α -SMA expression was evaluated as a marker of stellate cell activation.

Results: SGK1 mRNA levels were increased in liver tissues from patients with MASH. SGK1 expression was also significantly upregulated in the livers of TAA-injected mice. Importantly, in LX2 cells, TGF- β stimulation markedly increased CTGF expression, which was attenuated by SGK1 inhibitor treatment. Similarly, in primary hepatic stellate cells, SGK1 inhibitor treatment decreased α -SMA expression, indicating suppression of stellate cell activation.

Conclusions: Taken together, these findings demonstrate that SGK1 is upregulated in fibrotic mouse livers and in human liver fibrosis. Pharmacological inhibition of SGK1 attenuated TGF- β -induced fibrogenic responses in hepatic stellate cells, suggesting that SGK1 may represent a potential therapeutic target for liver fibrosis.

Keywords: SGK1, Liver Fibrosis, Hepatic Stellate Cells

PE-11

Maternal Obesity Induced Trained Immunity on the Development of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in Offspring

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Aims: MASLD is a leading cause of chronic liver disease, strongly linked to metabolic disorders. Maternal obesity and a high-fat diet (HFD) during pregnancy can induce lasting epigenetic changes, predisposing offspring to MASLD. Additionally, trained immunity may amplify inflammatory responses, further influencing disease progression.

This study examines how maternal obesity affects liver fat deposition in offspring, focusing on epigenetic programming and immune reprogramming in MASLD susceptibility.

This study aims to investigate how maternal obesity, induced by a high-fat diet (HFD), affects liver fat accumulation and metabolic programming in offspring. Specifically, it will examine key epigenetic modifications and the role of trained immunity in MASLD pathogenesis.

Methods: Pregnant mice are subjected to a high-fat diet (HFD) to induce obesity, while a control group is maintained on a standard diet. The induction of trained immunity during pregnancy and lactation is assessed through various markers, including cytokine profiles and immune cell reprogramming. Following birth, the offspring are weaned onto either a standard diet or an HFD. Liver samples are collected at various stages to measure fat deposition, histological changes, and metabolic markers. Additionally, epigenetic modifications such as DNA methylation and histone acetylation are analyzed to understand the persistence and transmission of these changes.

Results: Maternal HFD induces mild fatty liver changes in neonatal offspring, as observed through H&E, Trichrome, and Oil-red-O staining. Adult offspring, particularly those in the HCH group, which were exposed to maternal HFD, chow diet, and later re-exposed to HFD, exhibit greater fat accumulation and larger lipid droplets compared to controls. Maternal diet influences hepatic macrophage heterogeneity, leading to an increased presence of pro-inflammatory M1 macrophages in the periportal region of HFD-exposed offspring. Trained Kupffer cells display spatial heterogeneity, suggesting early-life metabolic priming and immune reprogramming. Histone modifications, including H3K14ac, H3K27ac, and H3K4me3, along with PPAR- γ activation, are observed in the offspring liver, supporting the hypothesis of persistent epigenetic memory. DNA methylation changes, particularly Fgf21 promoter hypomethylation, suggest that early-life epigenetic programming contributes to metabolic dysregulation later in life. Maternal HFD exposure leads to elevated levels of pro-inflammatory cytokines, including IL-6, TNF- α , and IL-1 β , in offspring, indicating a primed inflammatory state. Increased oxidative stress markers are detected, particularly in the HCH group, exacerbating MASLD progression. Offspring exposed to a secondary dietary insult in adulthood demonstrate exacerbated steatosis, fibrosis, and inflammatory responses, indicating that maternal diet-induced metabolic programming amplifies susceptibility to later-life metabolic stressors.

Conclusions: Maternal HFD induces trained immunity and epigenetic remodeling, leading to increased hepatic inflammation, metabolic dysregulation, and heightened susceptibility to MASLD in offspring. The HCH group exhibits the most severe phenotype, supporting the idea that early-life metabolic priming exacerbates the effects of later dietary challenges. Targeting epigenetic modifications and immune reprogramming may provide potential strategies for preventing MASLD.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease, Maternal Obesity, Trained Immunity, Metabolic Programming

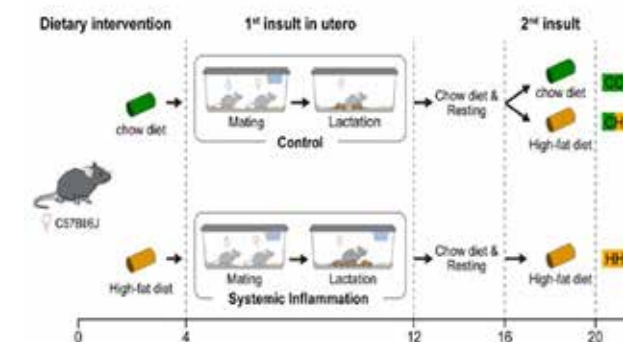


Figure 1.

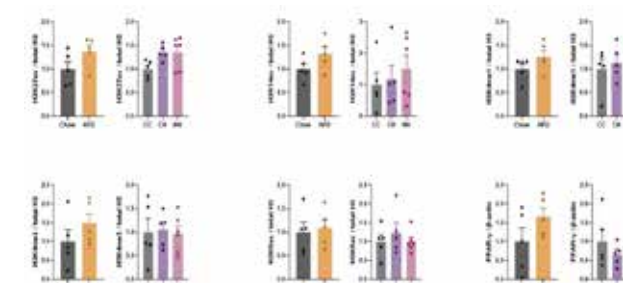


Figure 2.

PE-12

Reversal of Hepatic Stellate Cell Activation Is Facilitated by Regression-Associated Hepatokine

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Aims: Liver fibrosis is a major cause of mortality in chronic liver disease. Although hepatic stellate cell (HSC) is a central driver of fibrogenesis, therapeutic strategies aimed at preventing HSC activation have shown limited efficacy. In contrast, fibrosis regression represents an endogenous repair program with important therapeutic potential, during which activated HSCs revert to an inactive state. However, the mechanisms underlying

HSC inactivation during regression remain poorly understood. Here, we investigated whether HSC inactivation is a passive process or an actively regulated event, and sought to identify the cellular mechanisms that promotes HSC inactivation during liver fibrosis regression.

Methods: To determine whether liver microenvironment during fibrosis regression facilitates HSC inactivation, we employed a hepatic HSC engraftment model and compared the rate of HSC inactivation in livers recovering from fibrosis versus normal livers. Furthermore, we used co-culture and conditioned media systems to test whether hepatocytes from recovering livers secrete soluble factors that promote HSC inactivation.

Results: We found that fibrosis-resolving hepatic milieu markedly accelerated HSC inactivation following hepatic HSC engraftment, indicating that HSC inactivation is not merely a result of losing activation signals, but rather a facilitated process. Mechanistically, hepatocytes from recovering livers secreted soluble molecules that promoted HSC inactivation. These findings suggest that hepatocytes act as drivers of liver fibrosis resolution through paracrine signaling that promote reversal of HSC transdifferentiation.

Conclusions: Our study proposes the first rational mechanism for HSC inactivation during liver fibrosis regression and identifies a hepatocyte-driven signaling pathway as a critical driver. These findings lay the foundation for a new therapeutic paradigm in liver fibrosis. Rather than focusing solely on suppressing HSC activation, accelerating HSC inactivation through hepatocyte-derived signal may represent a novel therapeutic strategy. In addition, these factors secreted from hepatocytes may represent promising antifibrotic drug candidates.

Keywords: Hepatic Stellate Cell Inactivation, Liver Fibrosis Regression

11. MASLD, Clinical

PE-1

Sedentary Behavior, Recreational Activity and Mortality Risk among US Adults with Metabolic Dysfunction Associated Steatotic Liver Disease: A Cohort Study

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Aims: This study aimed to investigate the association between sedentary behavior (SB) and all-cause and cardiovascular (CVD)

mortality among U.S. adults with metabolic dysfunction-associated steatotic liver disease (MASLD), and to examine whether vigorous recreational activity modifies this relationship.

Methods: 14,409 adults with MASLD enrolled in NHANES 2007-2018. SB was characterized by sitting time and categorized as <4, 4-6, 6-8, or ≥8 hours/day, while vigorous activity was defined as engaging in ≥10 minutes/week. Mortality outcomes were determined through linkage with the NDI. Multivariable Cox proportional hazards models were used to estimate HRs, and survival probabilities were examined using Kaplan-Meier curves. Subgroup analyses assessed potential effect modification by vigorous activity.

Results: Over a mean follow-up of 80 months, 1,293 all-cause deaths and 337 CVD deaths were documented. Prolonged sitting time was positively associated with all-cause and CVD mortality, with stratified analyses indicating significant effect modification by vigorous activity. Among participants without vigorous activity, sitting ≥8 hours/day was associated with higher risks of all-cause (HRs =1.573, 95% CI: 1.320-1.874, *P*<0.001) and CVD mortality (HRs=1.608, 95% CI: 1.128-2.293, *P*=0.009), accompanied by lower survival probabilities (all-cause, log-rank *P*<0.001; CVD, log-rank *P*=0.015). However, among individuals engaging in vigorous activity, SB was not significantly associated with either of the mortality outcomes.

Conclusions: Prolonged SB is linked to elevated risks of all-cause and CVD mortality among individuals with MASLD; however, engagement in vigorous recreational activity may mitigate this risk. These results underscore the significance of reducing sedentary time and promoting vigorous exercise in this high-risk population.

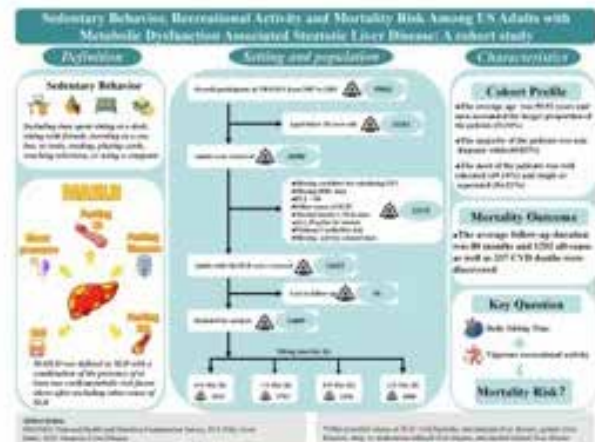


Figure 1: Overview of the study design and participant selection procedure. MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; BMI: Body Mass Index; TG: Triglyceride; HDL: High-Density Lipoprotein; NHANES: National Health and Nutrition Examination Survey; FLI: Fatty Liver Index; SLD: Steatotic Liver Disease

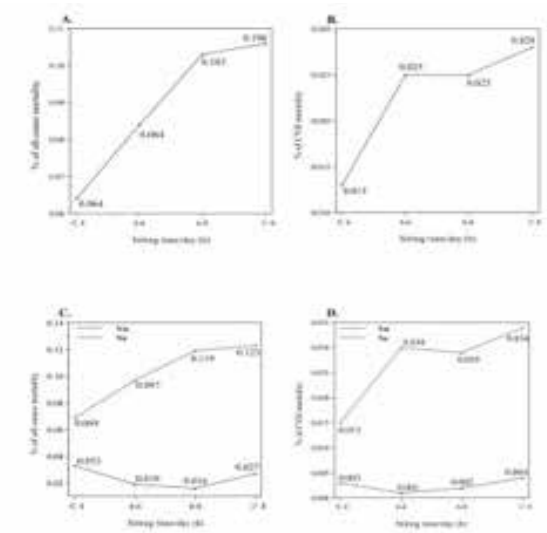


Figure 2: A-B Prevalence of all-cause and CVD mortality among MASLD patients across different daily sitting time, respectively; C-D Prevalence of all-cause and CVD mortality among participants across different daily sitting time stratified by vigorous recreational activity status, respectively, among which red indicates participants without vigorous activity, while blue indicates participants with vigorous activity. CVD: Cardiovascular Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease

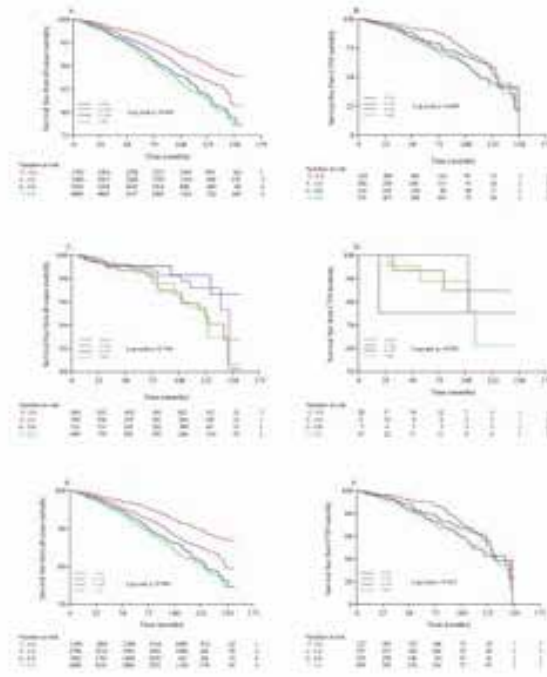


Figure 3: A-B Kaplan-Meier survival analysis curves among MASLD patients for all-cause and CVD mortality, respectively; C-D Kaplan-Meier survival analysis curves among MASLD patients with vigorous activity for all-cause and CVD mortality, respectively; E-F Kaplan-Meier survival analysis curves among MASLD patients without vigorous activity for all-cause and CVD mortality, respectively. CVD: Cardiovascular Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease

Keywords: MASLD, Sedentary Behavior, Vigorous Recreational Activity, Mortality

PE-2

Association of Endothelial Activation with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Unraveling the Mediating Role of Hepatic Enzymes in a National Cohort

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Aims: Endothelial dysfunction plays a key role in the development of metabolic dysfunction-associated steatotic liver disease (MASLD). However, the prognostic value of endothelial activation and stress index (EASIX), a novel biomarker reflecting multisystem endothelial dysfunction, for evaluating MASLD risk remains uncertain. This study aimed to: (1) examine the relationship between EASIX and MASLD risk, and (2) determine the mediating effects of hepatic enzymes in this association.

Methods: We analyzed data from 29,275 adults in NHANES (2007-2018), of whom 14,033 (47.9%) had MASLD. MASLD was diagnosed using FLI score ≥60, a validated predictor of hepatic steatosis based on metabolic parameters. Nonlinear relationships were examined using restricted cubic splines (RCS), and logistic regression models calculated odds ratios (ORs). Causal mediation analysis determined the proportion mediated by hepatic enzymes.

Results: Fully adjusted logistic regression analyses showed that individuals in the highest EASIX quartile had 16% higher odds of MASLD (OR 1.16; 95% CI: 1.00-1.33). RCS analysis demonstrated a significant J-shaped relationship (*P*-nonlinear<0.001). Subgroup analyses indicated stronger associations among participants under 65 years old, females, and Mexican Americans. Causal mediation analysis found that gamma-glutamyl transferase explained 67.1% of the total association, followed by alanine aminotransferase (42.2%), aspartate aminotransferase (32.9%), and alkaline phosphatase (28.1%).

Conclusions: Endothelial dysfunction, as measured by EASIX, is significantly associated with MASLD risk, with hepatic enzymes mediating a large part of this relationship. These results establish EASIX as a readily available biomarker that reflects multisystem endothelial dysfunction relevant to MASLD development and helps identify high-risk patients who may benefit from endothelial-targeted treatments.

Keywords: MASLD, Endothelial Dysfunction, Easix, Hepatic Enzymes, Mediation Analysis

Table 1. Sample size and baseline characteristics of MASLD patients stratified by sitting time per day from NHANES 2007-2018

Variables	Total (n=14409)	Sitting time/day (h)				P
		<4 (n=3792)	4-6 (n=3361)	6-8 (n=2556)	≥8 (n=4090)	
Age (years)	50.924 ± 16.633	49.358 ± 15.466	51.405 ± 17.030	51.943 ± 17.484	51.317 ± 16.743	<0.001
BMI (kg/m ²)	34.045 ± 6.277	33.245 ± 5.633	33.624 ± 5.930	34.268 ± 6.401	34.845 ± 6.798	<0.001
Male, n(%)	7714 (53.536)	2012 (53.059)	1803 (53.645)	1290 (54.754)	2609 (63.245)	0.586
PIR	2.434 ± 1.594	1.981 ± 1.432	2.351 ± 1.539	2.423 ± 1.608	2.746 ± 1.657	<0.001
Race/Ethnicity, n(%)						<0.001
Mexican American	2743 (19.037)	1168 (30.802)	650 (19.339)	367 (15.577)	558 (13.388)	
Non-Hispanic White	5881 (40.815)	1101 (29.035)	1346 (40.048)	1068 (43.331)	2366 (48.286)	
Non-Hispanic Black	3037 (21.077)	682 (17.985)	699 (20.797)	533 (22.623)	1123 (22.918)	
Others	2748 (19.071)	841 (22.178)	666 (19.816)	388 (16.409)	853 (17.408)	
Education level, n(%)						<0.001
Less than high school	3765 (26.661)	1468 (39.293)	918 (27.869)	535 (23.170)	844 (17.646)	
High school diploma	3418 (24.203)	948 (25.375)	871 (26.442)	558 (24.366)	1041 (21.785)	
More than high school	6939 (49.136)	1320 (35.332)	1585 (45.689)	1216 (52.663)	2808 (60.580)	
Marital status, n(%)						0.019
Married	6466 (45.787)	1695 (45.357)	1441 (43.759)	1094 (47.405)	2236 (46.739)	
Single or separated	7656 (54.213)	2042 (54.643)	1852 (56.241)	1214 (52.609)	2548 (53.261)	
Vigorous activity, n(%)	2379 (16.511)	603 (15.902)	564 (16.781)	363 (15.407)	849 (17.327)	0.130
Moderate activity, n(%)	5253 (36.456)	1344 (35.443)	1263 (37.578)	857 (36.375)	1789 (36.501)	0.318
Drinking, n(%)	9020 (62.806)	2177 (63.065)	2143 (68.955)	1488 (61.101)	3212 (70.454)	<0.001
Smoking status, n(%)						<0.001
Never	7519 (52.698)	2140 (56.976)	1721 (51.682)	1180 (50.666)	2478 (51.061)	
Former	3961 (27.761)	911 (24.255)	956 (28.769)	456 (21.367)	1438 (29.631)	
Now	2748 (19.540)	705 (18.770)	653 (19.610)	493 (21.348)	937 (19.308)	
DM, n(%)	3048 (25.995)	934 (24.631)	843 (25.082)	618 (26.231)	1249 (26.388)	0.218
Hypertension, n(%)	6682 (46.438)	1530 (40.623)	1562 (46.557)	1144 (48.619)	2446 (49.959)	<0.001
CHD, n(%)	1277 (9.040)	257 (6.873)	282 (8.561)	242 (10.485)	496 (10.366)	<0.001

Abbreviations: MASLD: metabolic dysfunction-associated steatotic liver disease; BMI: body mass index; PIR: poverty income ratio; DM: diabetes mellitus; CHD: coronary heart disease

Table 2. Association between daily sitting time and all-cause mortality among MASLD patients stratified by vigorous activity status

Vigorous activity		Sitting time/day (h)			
		<4 (HR, 95% CI), P	4 to 6 (HR, 95% CI), P	6 to 8 (HR, 95% CI), P	≥8 (HR, 95% CI), P
Yes	Crude model ¹	Reference	0.666 (0.319, 1.301), 0.280	0.595 (0.239, 1.484), 0.266	1.004 (0.550, 1.834), 0.989
	Model 1 ²	Reference	0.497 (0.235, 1.053), 0.068	0.534 (0.210, 1.357), 0.188	0.905 (0.473, 1.729), 0.762
	Model 2 ³	Reference	0.456 (0.213, 0.973), 0.042	0.506 (0.196, 1.307), 0.160	0.801 (0.410, 1.564), 0.516
No	Crude model ¹	Reference	1.541 (1.291, 1.839), <0.001	1.948 (1.623, 2.338), <0.001	2.138 (1.825, 2.505), <0.001
	Model 1 ²	Reference	1.172 (0.970, 1.415), 0.101	1.439 (1.183, 1.749), <0.001	1.789 (1.506, 2.125), <0.001
	Model 2 ³	Reference	1.038 (0.855, 1.260), 0.706	1.288 (1.035, 1.572), 0.013	1.573 (1.320, 1.874), <0.001

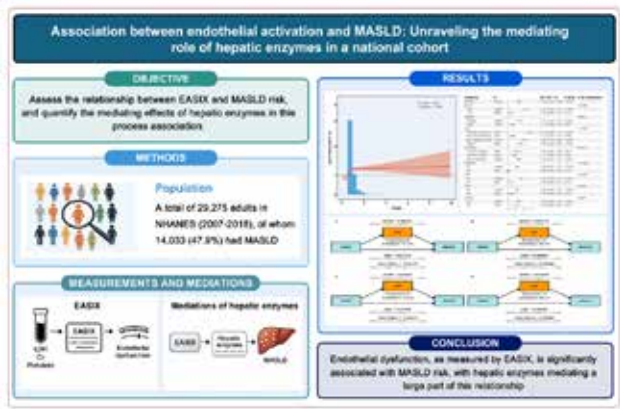
¹Crude model: adjusted for none.
²Model 1: adjusted for age, race, education level and PIR.
³Model 2: adjusted for age, race, education level, PIR, smoking status, alcohol drinking history, DM, hypertension, CHD, and moderate activity. *P* < 0.05 presents significant difference.

Table 3. Association between daily sitting time and cardiovascular mortality among MASLD patients stratified by vigorous activity status

Vigorous activity		Sitting time/day (h)			
		<4 (HR, 95% CI), P	4 to 6 (HR, 95% CI), P	6 to 8 (HR, 95% CI), P	≥8 (HR, 95% CI), P
Yes	Crude model ¹	Reference	0.859 (0.077, 9.526), 0.902	2.448 (0.221, 27.066), 0.465	1.600 (0.291, 8.786), 0.588
	Model 1 ²	Reference	1.543 (0.086, 27.700), 0.768	6.615 (0.218, 201.113), 0.278	3.276 (0.296, 36.294), 0.334
	Model 2 ³	Reference	4.184 (0.021, 825.428), 0.596	10.293 (0.102, 1043.132), 0.322	17.430 (0.051, 5966.152), 0.337
No	Crude model ¹	Reference	1.571 (1.104, 2.235), 0.012	1.249 (0.854, 1.828), 0.252	1.677 (1.209, 2.326), 0.002
	Model 1 ²	Reference	1.427 (0.988, 2.063), 0.058	1.195 (0.806, 1.773), 0.376	1.577 (1.121, 2.219), 0.009
	Model 2 ³	Reference	1.499 (1.025, 2.194), 0.037	1.225 (0.815, 1.842), 0.329	1.608 (1.128, 2.293), 0.009

¹Crude model: adjusted for none.
²Model 1: adjusted for age, race, education level and PIR.
³Model 2: adjusted for age, race, education level, PIR, smoking status, alcohol drinking history, DM, hypertension, CHD, and moderate activity. *P* < 0.05 presents significant difference.

MASLD: metabolic dysfunction-associated steatotic liver disease; PIR: poverty income ratio; DM: diabetes mellitus; CHD: coronary heart disease; h: hour; HR: Hazard ratio.



PE-3

Plasma Transcriptomic Signatures of Metabolic-Associated Steatotic Liver Disease across Egypt, Palestine and the United Arab Emirates: A Multi-Country Pilot Study

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Aims: Metabolic-associated steatotic liver disease (MASLD) is a major non-communicable liver disease in Arab countries, where access to timely, non-invasive diagnosis remains limited. We aimed to characterise shared and context-specific plasma transcriptomic signatures of MASLD in three Arab settings as a first step towards a liquid-biopsy-based risk-stratification tool.

Methods: Adults aged 25–60 years were recruited from specialist clinics in Egypt, Palestine and the United Arab Emirates and classified as MASLD with fibrosis, MASLD without fibrosis or healthy controls using harmonised clinical, metabolic, biochemical, imaging and non-invasive fibrosis criteria. Plasma from 30 participants (10 per country spanning these phenotypes) underwent whole-transcriptome RNA sequencing to profile coding and non-coding RNAs. Standardised bioinformatics pipelines were applied for quality control, alignment, quantification, differential-expression analysis and pathway enrichment, using false-discovery-rate control to identify significantly dysregulated transcripts and enriched pathways.

Results: Preliminary analyses identified a core set of dysregulated microRNAs and mRNAs consistently associated with MASLD across all three countries, alongside country-specific patterns that may reflect local genetic structure, diet and other exposures. Enriched pathways included lipid handling, insulin signalling, inflammatory signalling and fibrogenesis, supporting their plausibility as mediators of disease progression and fibrosis.

Conclusions: This pilot demonstrates the feasibility of harmonised, liquid-biopsy-based omics in diverse Arab health systems and provides a shortlist of candidate biomarkers for qRT-PCR validation and incorporation into a multivariable prediction algorithm to distinguish MASLD from health and flag individuals at high risk of fibrosis without liver biopsy. It exemplifies South–South collaboration in precision hepatology and is funded by the Arab Research & Innovation Co-Funded Alliances (ARICA) Initiative under the Federation of Arab Scientific Research Councils.

Keywords: Metabolic-Associated Steatotic Liver Disease, Transcriptomics, microRNAs, Liquid Biopsy, Arab Populations

PE-4

Risk-Associated and Clinically Informative Biomarkers for Cardiovascular Risk Stratification in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with atherosclerotic cardiovascular disease (ASCVD), yet the magnitude of cardiovascular risk across various disease labels and the clinical utility of readily available risk-associated markers remains unclear.

Methods: We searched PubMed, Embase, Web of Science, and the Cochrane Library from 1 January 2000 to 30 September 2025. Observational studies, as well as randomized trials contributing baseline cross-sectional observational data, were included. We pooled relative effects for (i) 10-year ASCVD high-risk classification as defined by established risk engines and (ii) incident major adverse cardiovascular events (MACE). Heterogeneity (I^2 and τ^2), small-study effects (funnel plots and Egger's tests), and leave-one-out sensitivity analyses were assessed. Risk of bias was evaluated using customized Newcastle–Ottawa Scales.

Results: Fifty-two studies were included. Compared with non-steatotic comparators, steatotic liver disease was associated with a higher overall cardiovascular burden (pooled relative effect 2.02, 95 % CI 1.90–2.14). When stratified by outcome, pooled effects were 1.91 (95 % CI 1.60–2.29) for predicted 10-year ASCVD high-risk classification and 1.74 (95 % CI 1.43–2.12) for incident MACE. Associations were consistent across disease labels, including nonalcoholic fatty liver disease (NAFLD; 1.98, 95 % CI 1.81–2.16), with higher but less precise estimates observed for nonalcoholic steatohepatitis (NASH; 3.60, 95 % CI 1.16–6.04). Readily available bio markers may help complement established ASCVD risk scores by refining cardiovascular risk stratification in individuals with MASLD. Several readily

available markers were informative for cardiovascular risk: Fatty Liver Index (FLI) ≥ 60 (hazard ratio [HR] 1.61, 95 % CI 1.12–2.11) and ≥ 30 (HR 1.39, 95 % CI 1.11–1.66); Fibrosis-4 index (FIB-4) ≥ 1.30 (HR 2.25, 95 % CI 1.84–2.65); blood pressure $\geq 130/85$ mmHg (HR 2.16, 95 % CI 1.81–2.51); triglyceride–glucose index (TyG) > 8.716 (HR 1.40, 95 % CI 1.26–1.54); and type IV collagen 7S ≥ 5 ng/mL (HR 2.37, 95 % CI 1.45–4.29). Compared with controls, MASLD was also associated with an adverse biomarker profile, including higher high-sensitivity C-reactive protein (hs-CRP) (+1.06 mg/L), homeostasis model assessment of insulin resistance (HOMA-IR) (+1.65), alanine aminotransferase (ALT) (+8.89 U/L), aspartate aminotransferase (AST) (+6.10 U/L), gamma-glutamyl transferase (GGT) (+13.23 U/L), total cholesterol (TC) (+9.05 mg/dL), triglycerides (TG) (+48.33 mg/dL), low-density lipoprotein cholesterol (LDL-C) (+8.46 mg/dL), glycated hemoglobin (HbA1c) (+0.43 %), and lower high-density lipoprotein cholesterol (HDL-C) (8.41 mg/dL).

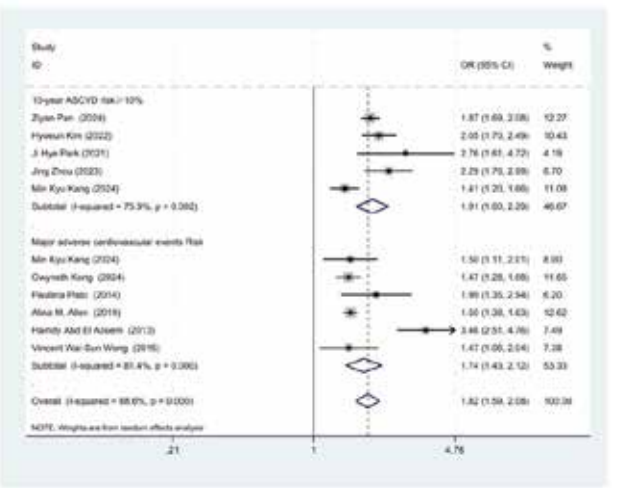


Figure 3.

Conclusions: MASLD is associated with an approximate twofold increased risk of cardiovascular events, but this association varies based on population and clinical context. A concise and pragmatic panel—FIB-4, FLI, blood pressure, and triglyceride–glucose index, with type IV collagen 7S where available (and NAFLD-LFS in selected settings)—may complement established ASCVD risk assessment and support earlier, risk-guided prevention in routine MASLD care.

Keywords: MASLD, Atherosclerotic Cardiovascular Disease, Major Adverse Cardiovascular Events, Biomarkers

PE-5

CT Attenuation–Based Hepatic Steatosis Assessment Using 3D Organ Segmentation: Impact of Tube Voltage and Need for Cutoff Adjustment

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Aims: To investigate the impact of tube voltage on CT attenuation–based parameters derived from 3D organ segmentation for hepatic steatosis assessment and to evaluate the feasibility of applying tube voltage–specific cutoff values.

Methods: This single-center retrospective study included 795 adults who underwent both liver CT and MR spectroscopy–proton density fat fraction (MRS-PDFF). The cohort comprised dual-energy CT (DECT; n=398) and single-energy CT (SECT; n=397) datasets. Using automated organ segmentation, volumetric liver attenuation and liver-minus-spleen attenuation differences were measured on pre-contrast and post-contrast

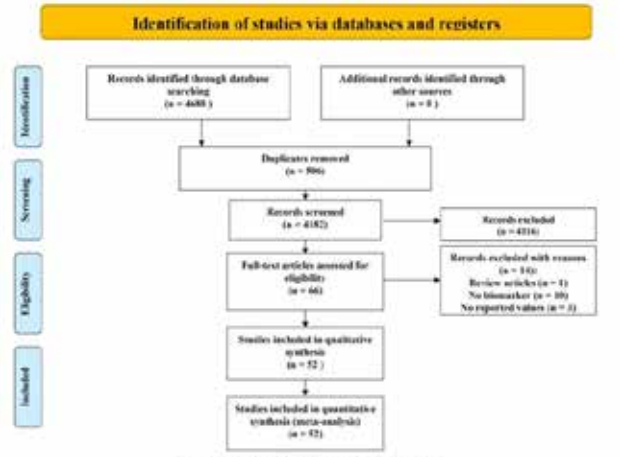


Figure 1.

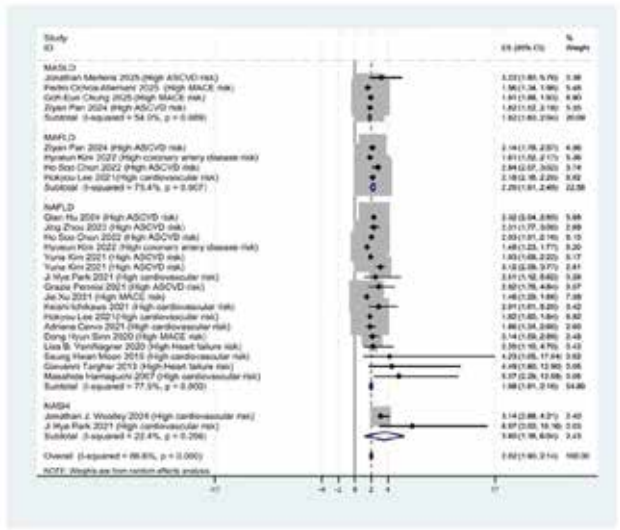


Figure 2.

portal venous phase images. In the DECT cohort, paired 120-kVp-equivalent (120-kVp-E) and 80-kVp images were used to derive ($n=147$) and validate ($n=251$) linear regression equations for tube voltage adjustment, with agreement quantified using intraclass correlation coefficients (ICCs). Hepatic steatosis was defined as MRS-PDFF $\geq 5\%$. Cutoff values for hepatic steatosis classification were derived at 120 kVp in the SECT dataset and applied to paired DECT data in the validation dataset using tube voltage-specific adjusted cutoffs; diagnostic performance was assessed using sensitivity and specificity.

Results: Volumetric liver attenuation and liver-minus-spleen attenuation differences measured on both pre-contrast and post-contrast images demonstrated strong correlations between 120-kVp-E and 80-kVp images ($r=0.921-0.975$; all $p < 0.001$). In the validation dataset, regression-adjusted values showed excellent agreement with measured 80-kVp values (ICCs, 0.966–0.992), with mean differences ≤ 0.7 HU. When tube voltage-specific cutoff values were applied to paired data, corresponding sensitivity and specificity were comparable between 120-kVp-E and 80-kVp images.

Conclusions: CT attenuation-based parameters for hepatic steatosis assessment are significantly affected by tube voltage; therefore, applying tube voltage-specific adjusted cutoff values is essential for reliable classification across varying kVp settings. This approach enables more flexible and robust opportunistic assessment of hepatic steatosis in routine clinical CT examinations regardless of protocol heterogeneity.

Keywords: Hepatic Steatosis, 3D Segmentation, Computed Tomography, Tube Voltage

PE-6

Association of PNPLA3/FTO Gene Polymorphisms with Hepatic Steatosis: Mongolian Subjects

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a complex condition that results from multiple risk factors. In recent years, genetic risk factors for MASLD have been extensively studied, particularly the PNPLA3 gene, which is strongly associated with MASLD progression. The FTO gene is a common cause of obesity and may increase the risk of MASLD. We aimed to investigate the association of PNPLA3/FTO gene polymorphisms in individuals with MASLD and without MASLD.

Methods: We included 150 participants aged from: 100 with

MASLD and 50 relatively healthy controls. We determined the four SNPs, including rs738409 and rs2896019 in PNPLA3, and rs9939609 and rs17817449 in FTO, employing the PCR-RFLP technique.

Results: The frequency of PNPLA3 rs738409 CG/GG was significantly higher in the case group compared with controls (64% vs. 38%). Moreover, there was a significant in the frequency of rs2896019 TG/GG between the study groups (69% vs. 52%). For FTO rs9939609, the AT/AA genotype was more common in cases than in controls (47% vs. 24%), whereas rs17817449 did not differ significantly between groups. We conducted a combined risk-genotype analysis and found that the co-occurrence of PNPLA3 rs738409 CG/GG and rs2896019 TG/GG was more frequent in MASLD cases (55% vs. 30%) than in controls. Participants with this co-occurrence had a 2.8-fold higher risk of developing MASLD than those without (OR = 2.8). On the contrary, combined FTO risk genotypes, rs9939609 AT/AA + rs17817449 TG/GG, were not significantly different between study groups (OR = 1.9). The percentage of participants with all SNPs was 15% in cases and 4% in controls. In addition, participants with all SNPs had a markedly increased risk of MASLD (OR = 4.2). We also categorized participants by the number of detected risk genotypes into 5 groups (None SNPs, 1 SNP, 2 SNPs, 3 SNPs, and 4 SNPs). Body weight, BMI, and WC, ALT, GGT, triglycerides, LDL-C, and HDL-C were significantly different among groups.

Conclusions: The PNPLA3 rs738409 (CG/GG), rs2896019 (TG/GG), and FTO rs9939609 (AT/AA) genotypes were correlated with increased risk of MASLD. Significantly, individuals harboring four concurrent SNPs had the highest probability of developing MASLD.

Keywords: MASLD, PNPLA3, FTO, Mongolia

PE-7

Prevalence and Risk Factors of Metabolic Dysfunction-Associated Steatotic Liver Disease among Adults with Hyperuricemia in Vietnam

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Aims: Hyperuricemia is a growing global concern associated with metabolic disorders. Metabolic dysfunction-associated steatotic liver disease (MASLD) frequently coexists with hyperuricemia, yet data on its prevalence and risk factors in Vietnamese populations are limited. This study aimed to determine the prevalence and independent predictors of MASLD among hyperuricemic patients in Vietnam.

Methods: A cross-sectional study was conducted on 264 hyperuricemic patients between May 2023 and June 2024. MASLD

was diagnosed and graded for steatosis severity using Controlled Attenuation Parameter (CAP) scores via FibroScan. Multivariate logistic regression evaluated demographic, clinical, and biochemical factors to identify independent predictors of MASLD.

Results: The prevalence of MASLD was 58.3%. Among all patients, 25.4% had mild (Grade 1), 16.3% had moderate (Grade 2), and 16.7% had severe (Grade 3) hepatic steatosis. Higher BMI (OR: 1.35; 95% CI: 1.21–1.53; $P < 0.001$) and triglycerides (OR: 1.23; 95% CI: 1.05–1.47; $P = 0.013$) were independent predictors. BMI moderately correlated with CAP scores ($r = 0.322$; $P < 0.001$). Uric acid levels showed a statistically significant but weak correlation with hepatic steatosis ($r = 0.102$, $P < 0.05$; regression $R^2 = 0.17$).

Conclusions: MASLD is highly prevalent in hyperuricemic Vietnamese patients, with BMI and triglycerides as key predictors. Clinicians should consider routine hepatic evaluation for early MASLD detection in this population. These findings underscore the importance of interventions targeting obesity and lipid metabolism to reduce MASLD burden in this population.

Keywords: Hyperuricemia, Non-Alcoholic Fatty Liver Disease, Metabolic Diseases

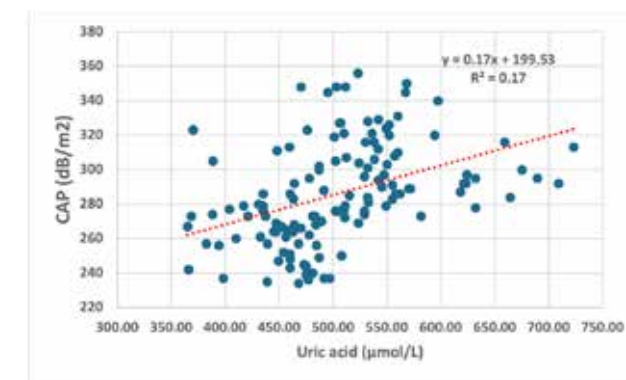


Figure 1.

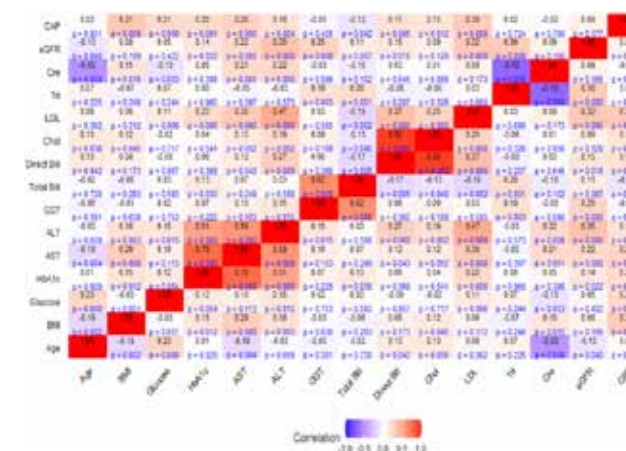


Figure 2.

PE-8

Evaluating the ZJU Index's Effectiveness in Predicting All-Cause Mortality among US Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease: A Comparative Analysis with Triglyceride-Glucose to Waist-to-Height Ratio

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Aims: Metabolic dysfunction-associated Steatotic liver disease (MAFLD) is an increasingly recognized global health concern. Previous studies have established the effectiveness of Triglyceride-Glucose to Waist-to-Height Ratio (TyG-WHtR) in predicting all-cause mortality in MAFLD individuals. This study aimed to introduce the novel ZJU index and evaluate its performance in comparison to TyG-WHtR.

Methods: The study utilized data from the National Health and Nutrition Examination Survey (NHANES), all individuals eligible for mortality analyses between 1999 and 2018. Missing data were filled in using exclusion criteria and multiple imputation. We utilized Cox regression analyses, restricted cubic spline (RCS), Kaplan-Meier survival curves, subgroup analyses, and receiver operating characteristic curve (ROC) curves to assess the association between the ZJU index and TyG-WHtR with all-cause mortality in the adults of United States.

Results: This study included 8336 adults with MASLD, with a mean age of 48.82 years. Cox regression analysis revealed that both the ZJU index (HR = 1.50, 95% CI = 1.19-1.89) and TyG-WHtR (HR = 1.55, 95% CI = 1.21-2.00) were significantly associated with all-cause mortality, with stronger associations observed in higher quartiles. An S-shaped nonlinear relationship between TyG-WHtR and mortality was identified. Kaplan-Meier survival curves further validated that higher values of both indices were associated with reduced survival probabilities. ROC indicated that both were effective in predicting all-cause mortality (ZJU index: AUC = 0.828 at 3 years, 0.839 at 5 years and 0.854 at 10 years; TyG-WHtR: AUC = 0.830 at 3 years, 0.840 at 5 years and 0.855 at 10 years). Although TyG-WHtR demonstrated slightly superior predictive efficacy, both the ZJU index and TyG-WHtR proved valuable in predicting mortality in MASLD patients, with the ZJU index emerging as a novel and robust predictor.

Conclusions: Both ZJU index and TyG-WHtR are highly effective and robust predictors of all-cause mortality in patients with MASLD.

Keywords: ZJU Index, Triglyceride-Glucose to Waist-to-Height Ratio, All-Cause Mortality, Comparative Analysis

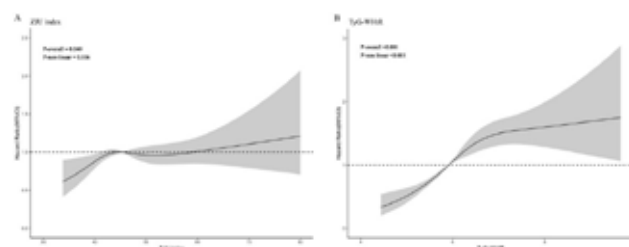


Figure 1.

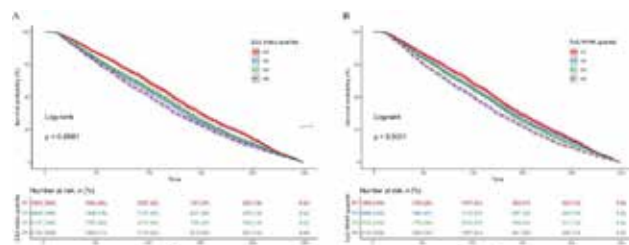


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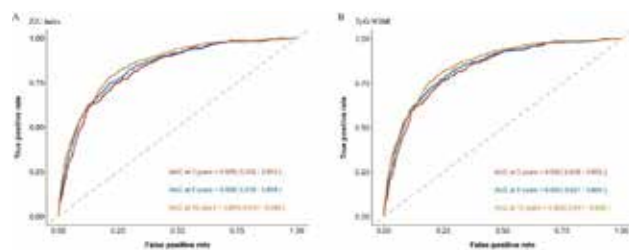


Figure 3.

PE-9

Comparison of Effectiveness between Phentermine/Topiramate and Liraglutide in Obese Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: Anti-obesity drugs improve hepatic inflammation in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to compare the effects of phentermine/topiramate and liraglutide in obese MASLD patients.

Methods: This retrospective study included 438 obese MASLD patients who received phentermine/topiramate (n=320) or liraglutide (n=118) for more than 12 months. Steatosis was assessed using the hepatic steatosis index (HSI) and controlled attenuation parameter (CAP). Fibrosis was assessed using the fibrosis index based on four factors (FIB-4) and liver stiffness (LS). Changes in steatosis and fibrosis were compared at 12 months after treatment.

Results: After propensity score (PS) matching, 108 patients were equally assigned to the two treatment groups. After 12 months of treatment, HSI (40.584→36.556 in phentermine/topiramate; 40.284→39.347 in liraglutide) and CAP (321→299 dB/m in phentermine/topiramate; 306→288 dB/m in liraglutide) decreased significantly in both groups (all $P < 0.05$). However, FIB-4 (0.838→0.717; $P = 0.025$) and LS (6.0→4.9 kPa; $P = 0.011$) decreased significantly only in the liraglutide group. The phentermine/topiramate group showed a significantly greater reduction in steatosis from baseline to 12 months, as assessed by HSI (−9.32% vs. −1.87%; $P < 0.001$) and CAP (−10.15% vs. −5.22%; $P < 0.001$), compared with the liraglutide group. In contrast, the percent changes from baseline to 12 months in FIB-4 (1.58% vs. −3.83%; $P = 0.297$) and LS (−7.37% vs. −12.50%; $P = 0.144$) were not significantly different between the two groups.

Conclusions: In obese patients with MASLD, phentermine/topiramate resulted in greater improvement in hepatic steatosis; however, fibrosis regression was comparable between the treatment groups.

Keywords: Fibrosis, Liraglutide, Metabolic Dysfunction-Associated Steatotic Liver Disease, Phentermine/Topiramate, Steatosis

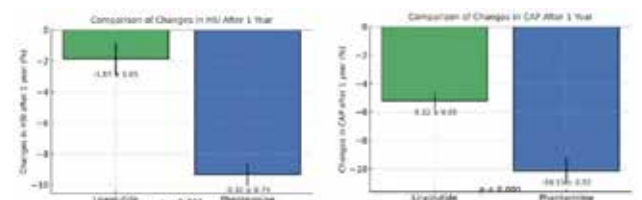


Figure 1. Comparison of steatosis improvement in obese MASLD patients treated with liraglutide and phentermine/topiramate (A) HSI (B) CAP

PE-10

Automated Staging of Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Using Deep Learning and Explainable AI

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Aims: Accurate staging of hepatic fibrosis is critical for the management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH). The current non-invasive tests often lack the precision of histology. This study is aimed to develop and validate a deep learning framework for the automated staging of liver fibrosis (F0–F4) from ultrasound imaging, incorporating Explainable AI to ensure the clinical transparency and reliability.

Methods: A total of 6,330 ultrasound images categorized from F0–F4 were utilized. A ResNet-18 architecture was implemented using transfer learning with ImageNet-1K initialization. The dataset was split into 80% training, 10% validation, and an 10% independent hold-out test set. Data augmentation using random rotation/flipping was used to ensure probe-angle invariance. Model performance was evaluated using AUROC, sensitivity, specificity, and F1-scores. To address clinical interpretability, Grad-CAM was applied to visualize the parenchymal features driving the AI's staging decisions, and calibration plots were generated to assess model reliability.

Results: On the independent test set (N=633), the model achieved an overall diagnostic accuracy of 92% and a multi-class AUROC of 0.93. For the critical identification of Cirrhosis (F4), the model demonstrated a sensitivity of 95% and a Specificity of 93.45%. The F1-scores for intermediate stages (F1–F3) ranged from 0.94 to 0.95. Calibration analysis showed high concordance between predicted and observed probabilities ($R^2 = 0.96$). Grad-CAM heatmaps confirmed that AI prioritized medically relevant textures, such as parenchymal nodularity and echogenicity, while ignoring non-clinical artifacts.

Conclusions: The MASLD-Net framework provides a highly accurate, non-invasive solution for fibrosis staging that meets the diagnostic needs of the current MASLD/MASH therapeutic era. By providing both near-perfect diagnostic metrics and visual “glass-box” explanations via Grad-CAM, this tool offers a scalable alternative to invasive biopsy and a significant enhancement over conventional non-invasive scores like FIB-4.

Keywords: MASLD, Deep Learning, Explainable AI, Grad-Cam

PE-11

From Gums to Liver: Association between Periodontal Health and Fatty Liver Risk among Metal-Exposed Industrial Workers

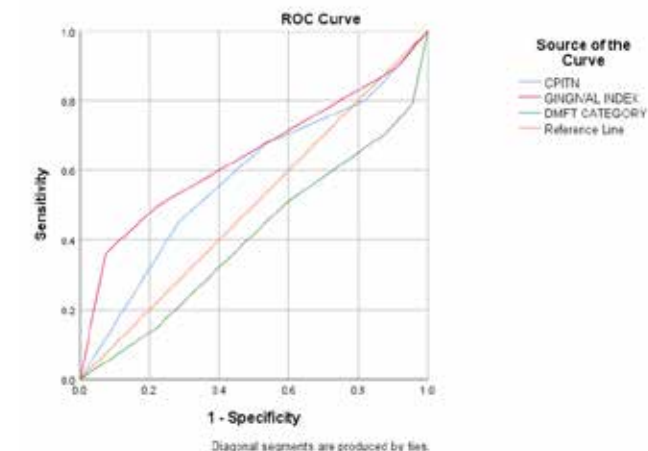
Rahmath Meeral¹, Hemanth Kumar², Prathyusha Mahanta³

¹Department of Public Health Dentistry, Saveetha Dental College and Hospital; ²Department of Public Health Dentistry, Saveetha Dental College and Hospital, India

Aims: Occupational exposure to heavy metals has been increasingly implicated in systemic inflammatory conditions and metabolic disorders. Emerging evidence suggests a possible “oral–liver axis,” where periodontal disease may contribute to systemic inflammation and metabolic dysfunction, potentially increasing the risk of non-alcoholic fatty liver disease (NAFLD). Industrial workers exposed to metal dust and fumes may represent a high-risk population for both oral diseases and metabolic liver disorders. This study aimed to assess the association between periodontal health indicators and predicted NAFLD risk among metal-exposed industrial workers.

Methods: A cross-sectional study was conducted among 250 industrial workers with documented occupational exposure to metal dust and fumes. Data on demographic characteristics, occupational exposure history, smoking status, and protective practices were collected using a structured questionnaire. Oral health assessment included the Community Periodontal Index of Treatment Needs (CPITN), Gingival Index (GI), and Decayed-Missing-Filled Teeth (DMFT) score. NAFLD risk was estimated using the Fatty Liver Index (FLI). Descriptive statistics, Pearson correlation analysis, chi-square tests, and receiver operating characteristic (ROC) curve analysis were performed to examine associations and predictive performance of oral health indicators for NAFLD risk.

Results: The mean age of participants was 38.37 ± 11.98 years, with a majority being male (70.8%). Severe periodontitis was observed in 38.8% of workers, while mild gingivitis was present in 50.4%. High and very high DMFT scores were recorded in 53.6% of participants. Overall, 62.0% of workers were classified as having a high probability of NAFLD based on the FLI. A significant association was observed between periodontal status and NAFLD risk. Workers with severe periodontitis demonstrated a markedly higher prevalence of predicted NAFLD (72.2%) compared with those with healthy gingiva (66.7%) or gingival inflammation (63.6%) ($\chi^2 = 12.97$, $P = 0.011$). Gingival index categories also showed a strong association with NAFLD, with severe gingivitis demonstrating the highest proportion of NAFLD likelihood (88.9%) ($\chi^2 = 29.39$, $P < 0.001$). DMFT categories showed a statistically significant association with NAFLD risk ($\chi^2 = 14.83$, $P = 0.005$). ROC curve analysis demonstrated moderate predictive ability for gingival index (AUC = 0.641), followed by CPITN (AUC = 0.577), while DMFT category showed lower discriminatory ability (AUC = 0.408). These findings indicate that periodontal indicators may serve as useful markers for metabolic liver risk in occupational settings.



Conclusions: Periodontal disease and gingival inflammation were significantly associated with predicted NAFLD risk among metal-exposed industrial workers. The findings highlight the

importance of integrating oral health screening within occupational health programs to facilitate early identification of individuals at risk for metabolic liver disease.

Keywords: Occupational Metal Exposure, Gingival Index, Liver, Periodontitis

PE-12

TyG Index as a Marker of Metabolic Liver Injury in Patients with Type 2 Diabetes Mellitus: A Cross Sectional Study

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Aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is increasingly recognized as a major hepatic complication in patients with type 2 diabetes mellitus (T2DM). Insulin resistance plays a central role in its pathogenesis. The triglyceride–glucose (TyG) index has emerged as a simple and practical surrogate marker of insulin resistance and has been proposed as a potential indicator of metabolic liver injury. This study aimed to evaluate the association between TyG index and liver enzyme abnormalities in patients with T2DM.

Methods: A cross-sectional study was conducted among patients with T2DM enrolled in a primary care program. Clinical and laboratory parameters including age, glycated hemoglobin (HbA1c), triglycerides, alanine aminotransferase (ALT), and TyG index were collected. Metabolic liver injury was defined as ALT levels >40 U/L. The association between TyG index and liver enzyme elevation was analyzed using chi-square test, while the correlation between TyG index and ALT levels was evaluated using Spearman correlation analysis.

Results: A total of 78 patients with T2DM were included in the study. The mean age was 58.19 ± 10.81 years, and 62.8% were female. The mean HbA1c level was $8.72 \pm 2.25\%$, while the mean triglyceride level was 179.59 ± 112.11 mg/dL. The mean TyG index was 9.35 ± 0.65 . Elevated ALT levels were observed in 9% of patients, whereas 82.1% of patients had a high TyG index. However, chi-square analysis showed no significant association between TyG index and metabolic liver injury ($P=0.443$). Spearman correlation analysis also demonstrated a weak and non-significant correlation between TyG index and ALT levels ($r = 0.108$, $P=0.347$).

Conclusions: A high TyG index was commonly observed among patients with T2DM, reflecting a high burden of metabolic risk. However, TyG index was not significantly associated with liver enzyme elevation in this cohort. Further studies with larger populations are needed to clarify the potential role of TyG index as a marker of metabolic liver injury.

Keywords: TYG Index, Type 2 Diabetes Mellitus, Metabolic Liver Injury, MASLD

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
age	78	29,00	85,00	58,1923	10,81492
HbA1c (%)	78	4,00	14,00	8,7218	2,24879
Trygliceride	78	36,70	720,90	179,5910	112,10931
ALT	78	5,300	158,900	19,83333	23,708904
TyG	78	7,61	11,25	9,3546	,64687
Valid N (listwise)	78				

Table 1.

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,589 ^a	1	,443		
Continuity Correction ^b	,063	1	,801		
Likelihood Ratio	,527	1	,468		
Fisher's Exact Test				,603	,368
Linear-by-Linear Association	,582	1	,445		
N of Valid Cases	78				

a. 1 cells (25,0%) have expected count less than 5. The minimum expected count is 1,26.
b. Computed only for a 2x2 table

Table 2.

Correlations			TyG	ALT
Spearman's rho	TyG	Correlation Coefficient	1,000	,108
		Sig. (2-tailed)		,347
	N		78	78
ALT		Correlation Coefficient	,108	1,000
		Sig. (2-tailed)	,347	
	N		78	78

Table 3.

PE-13

CT-Measured Waist Circumference as a Surrogate Marker of Histologic Disease Activity in Hepatic Steatosis

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Aims: MASLD has emerged as a leading cause of chronic liver disease worldwide. Accurate assessment of histologic disease activity requires liver biopsy, which is invasive and impractical for repeated monitoring, while reliable non-invasive markers remain lacking. Waist circumference, reflecting visceral fat accumulation more directly than BMI and self-measurable in routine clinical settings, may serve as a practical surrogate. This study aimed to evaluate the association between CT-measured waist circumference and histologic disease activity assessed by NAS, and to compare its performance against BMI in individuals with hepatic steatosis.

Methods: We retrospectively analyzed 324 patients who un-

derwent cholecystectomy with intraoperative liver biopsy at Soonchunhyang University Cheonan Hospital (April 2023–November 2025). Hepatic steatosis was confirmed histologically, and NAS was calculated according to the Kleiner criteria. Significant histologic activity was defined as NAS ≥ 3 . CT-measured waist circumference was obtained from preoperative abdominal CT at the L3 vertebral level by two blinded investigators. Logistic regression analyses were performed to evaluate associations of BMI and CT-measured waist circumference with NAS ≥ 3 , with multivariable models adjusted for age, sex, diabetes, hypertension, and dyslipidemia. Subgroup analyses were conducted according to obesity status (BMI <25 vs. ≥ 25 kg/m²), and discriminative performance was evaluated using ROC curve analysis with DeLong test comparisons.

Results: Among 324 participants, 126 (38.9%) had significant histologic activity (NAS ≥ 3). In univariable analysis, both BMI (OR 1.12 per 1 kg/m², 95% CI 1.05–1.18, $P < 0.001$) and CT-measured waist circumference (OR 1.04 per 1 cm, 95% CI 1.02–1.06, $P < 0.001$) were significantly associated with NAS ≥ 3 , with comparable AUCs (0.626 vs. 0.641; DeLong test $P=0.432$). When both measures were included simultaneously, waist circumference retained its significant association (OR 1.04, 95% CI 1.00–1.08, $P=0.025$), whereas BMI did not (OR 1.01, $P=0.822$). (Fig. 1) In multivariable analysis adjusted for cardiometabolic covariates, waist circumference remained independently associated with NAS ≥ 3 (OR 1.04, 95% CI 1.02–1.06, $P < 0.001$). (Fig.2) This association persisted in the non-obese subgroup (BMI <25 kg/m²), where each 1-cm increase in waist circumference was associated with a 7% increase in the odds of significant histologic activity (OR 1.07, 95% CI 1.02–1.12, $P=0.009$). (Fig.3)

Conclusions: CT-measured waist circumference was independently associated with histologic disease activity in patients with hepatic steatosis and remained informative in non-obese individuals, outperforming BMI in multivariable analysis. These findings suggest that waist circumference may serve as a practical and clinically meaningful surrogate marker for monitoring hepatic inflammatory activity, particularly in patients for whom body weight-based assessment is insufficient.

Keywords: Steatotic Liver Disease, Waist Circumference, CT, MASLD

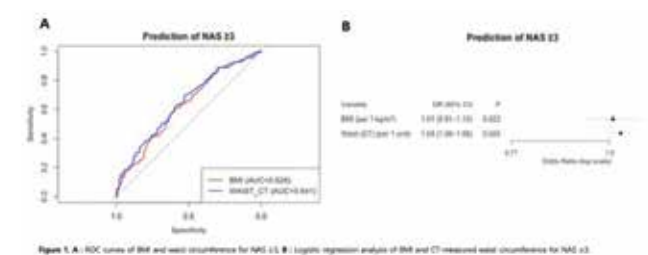


Figure 5. A: ROC curves of BMI and waist circumference for NAS ≥ 3 . B: Logistic regression analysis of BMI and CT-measured waist circumference for NAS ≥ 3 .

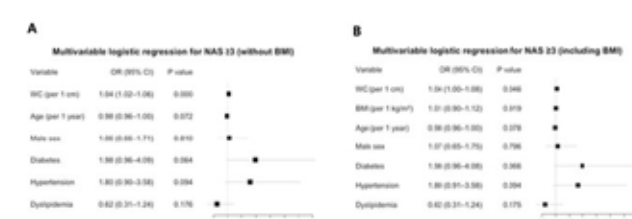


Figure 2. A: Multivariable logistic regression analysis for predicting NAS ≥ 3 without BMI. B: Multivariable logistic regression analysis for predicting NAS ≥ 3 including BMI.

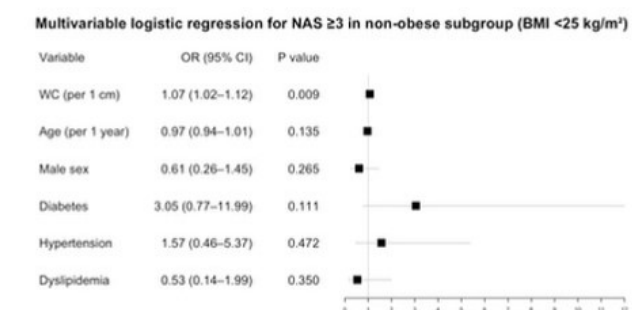


Figure 3. Multivariable logistic regression analysis for predicting NAS ≥ 3 in the non-obese subgroup (BMI <25 kg/m²).

PE-14

Hidden Burden of Metabolic Dysfunction–Associated Steatotic Liver Disease in Asymptomatic Adults: A Large Community-Based Screening Study from Rural Nepal

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Aims: Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) is an increasingly important cause of chronic liver disease worldwide. However, data from rural populations in low-resource countries remain limited. This study aimed to estimate the burden of previously undiagnosed MASLD among asymptomatic adults participating in a community health screening program in rural western Nepal.

Methods: A cross-sectional screening study was conducted between 1 March and 14 June 2025 during community health camps in rural western Nepal (Annapurna, Machhapuchchhre, Madi, and Rupa Rural Municipalities). Participants underwent anthropometric measurements, blood pressure assessment, fasting blood glucose testing, and lipid profile analysis. Abdominal ultrasonography using portable ultrasound was performed to detect hepatic steatosis. MASLD was diagnosed based on ultrasound evidence of steatosis with overweight/

obesity (BMI ≥ 23 kg/m²), diabetes mellitus, or at least two metabolic risk abnormalities.

Results: A total of 1,396 individuals were screened. The mean age was 46.8 ± 14.7 years, and 57% were male. Mean body mass index was 25.2 ± 3.8 kg/m². Mean waist circumference was 90 ± 3.5 cm in males and 88 ± 4.9 cm in females. Hypertension and dyslipidemia were present in 13.2% and 16.6% of participants.

MASLD was identified in 277 individuals, corresponding to a prevalence of 19.8% (95% CI: 17.7–21.9). Prevalence was similar between males and females (19.6% vs 20.2%). Most affected individuals were asymptomatic and had not previously undergone liver evaluation.

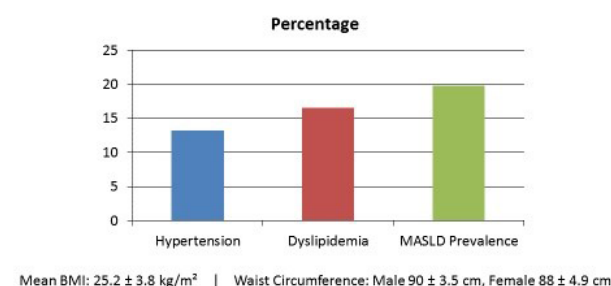
Conclusions: MASLD represents a substantial but largely unrecognized health burden in rural Nepal. Community-based screening programs incorporating portable ultrasound and metabolic assessment may facilitate early detection and support preventive strategies to reduce future chronic liver disease in underserved populations.

Keywords: Community Screening, Hepatic Steatosis, Metabolic Dysfunction–Associated Steatotic Liver Disease, Metabolic Risk Abnormalities

Figure 1. Community Screening and Detection of MASLD in Rural Nepal



Figure 2. Metabolic Risk Factors and MASLD Prevalence in Study Population



PE-15

Hepatic Steatosis Linked to Cancer Therapy in the Indian Population

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Aims: Chemotherapy-induced liver injury is one of the most common causes of mortality in cancer patients. One of the processes leading to the formation of fatty livers is hepatic steatosis, which is brought on by chemotherapy drugs. In this study, we are evaluating the development of fatty liver during the therapy for ovarian cancer.

Methods: A prospective study was conducted on cases of ovarian cancer with normal liver function tests that developed fatty livers after getting chemotherapy.

Results: We studied 200 cases of ovarian cancer, out of which 31 (15%) cases developed fatty liver secondary to therapy for ovarian cancer. The average age at which fatty liver develops is 49.2 years. Among various clinical parameters, only weight and body surface area (BSA) did show a statistically significant correlation ($P=0.05$) with the development of fatty liver. The patients who had PFI for more than 15 months also showed the development of FL ($P=0.03$) (table 1).

Conclusions: The development of fatty liver following chemotherapy follows a common mechanism, but the process is fast. This may be due to an altered metabolic process. Here also weight and BSA are associated with the development of fatty liver. Following chemotherapy, progression-free interval has also shown a significant correlation with the development of fatty liver.

Keywords: Fatty Liver, Ovarian Cancer, Chemotherapy

PE-16

Clinical Trajectory and Predictors of Progression in Compensated Metabolic Dysfunction-Associated Steatohepatitis

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Aims: Metabolic dysfunction-associated steatohepatitis (MASH) is an emerging cause of chronic liver disease worldwide and is increasingly recognized in Asian populations. However, data describing the clinical trajectory and predictors of disease progression among patients with compensated MASH in Mon-

golia remain limited. Understanding factors associated with disease progression is essential for improving risk stratification and early clinical intervention.

Methods: We conducted a retrospective cohort study of patients diagnosed with compensated MASH at a tertiary referral center in Mongolia between 2023 and 2025. Baseline demographic, metabolic, and laboratory variables were collected, including age, sex, body mass index, diabetes status, and liver function markers. Non-invasive fibrosis indices, including FIB-4 and MELD scores, were calculated. Patients were followed longitudinally to evaluate clinical outcomes, including hepatic decompensation, liver-related hospitalization, and mortality. Kaplan–Meier survival analysis and Cox proportional hazards models were used to identify predictors of disease progression. Subgroup analyses were performed according to metabolic risk burden and urban–rural residence.

Results: A total of 87 patients with compensated MASH were included, with a median follow-up of 2.4 years. During the follow-up period, 45 patients (51.8%) experienced at least one liver-related clinical outcome. Patients with a higher metabolic risk burden, particularly those with obesity and diabetes, demonstrated a significantly increased risk of disease progression. Elevated FIB-4 scores were independently associated with adverse outcomes (HR 2.31, 95% CI 1.25–4.27, $P=0.008$). Subgroup analyses suggested differences in clinical trajectories between patients residing in urban and rural regions, potentially reflecting disparities in metabolic profiles and access to healthcare services.

Conclusions: These findings suggest that compensated MASH patients in Mongolia demonstrate heterogeneous clinical trajectories influenced by metabolic risk factors and fibrosis severity. Risk stratification using metabolic indicators and non-invasive fibrosis scores may facilitate early identification of high-risk patients and support targeted clinical management strategies.

Keywords: Metabolic Dysfunction-Associated Steatohepatitis (MASH), Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Disease Progression, Fib-4 Score

PE-17

Segmental Fatty Liver as a Diagnostic Clue for Primary Sclerosing Cholangitis

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Aims: Hepatic steatosis is typically a diffuse process driven by systemic metabolic factors. However, regional heterogeneity in fat distribution may reflect localized alterations in portal hemodynamics or biliary pathology. We report a case in which

segmental fatty liver distribution provided a diagnostic clue for primary sclerosing cholangitis (PSC).

Results: A 32-year-old man presented with asymptomatic abnormal liver function tests. He had obesity (BMI 30.9 kg/m²) and dyslipidemia. Laboratory evaluation showed a cholestatic pattern (AST 73 U/L, ALT 69 U/L, ALP 290 U/L, GGT 1,109 U/L). Imaging studies, including ultrasonography (Figure 1) and computed tomography (Figure 2), demonstrated fatty infiltration predominantly in the right hepatic lobe with relative fat sparing in segments 1 and 4.

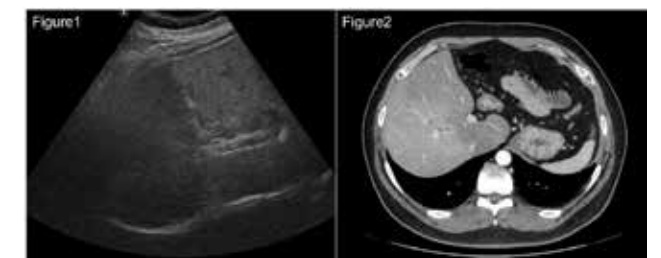
FibroScan revealed advanced fibrosis (TE 11.8 kPa) and severe steatosis (CAP 369 dB/m) in the right lobe. The patient was initially managed as metabolic dysfunction-associated steatohepatitis (MASH); however, persistent cholestatic liver enzyme abnormalities prompted liver biopsy.

Histopathologic findings showed marked regional discrepancy: segment 4 demonstrated macrovesicular steatosis with preserved bile ducts, whereas segment 5 showed relative fat sparing accompanied by ductular reaction and inflammatory changes. Cytokeratin 7 immunostaining confirmed abnormal ductular proliferation in segment 5.

Magnetic resonance cholangiopancreatography (MRCP) subsequently revealed multifocal intrahepatic bile duct strictures, leading to the diagnosis of PSC.

Conclusions: Segmental variation in hepatic fat distribution may reflect localized alterations in portal perfusion associated with biliary disease. In patients with metabolic risk factors, the presence of focal fat sparing or heterogeneous steatosis—especially when accompanied by a cholestatic liver profile—should raise suspicion for underlying cholangiopathies such as PSC. Recognition of this imaging-pathologic dissociation can facilitate earlier diagnosis and appropriate evaluation.

Keywords: Primary Sclerosing Cholangitis, Segmental Hepatic Steatosis, Fat Distribution Heterogeneity



PE-18

Causal Forests Reveal Older Adults with MASLD and High Visceral Adiposity Deriving the Strongest Fibrosis Improvement after Structured Weight Loss

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Aims: Weight reduction is a cornerstone in MASLD care, yet fibrosis response varies widely among older adults. We examined whether treatment benefit clusters within specific metabolic phenotypes rather than being uniformly distributed.

Methods: We analyzed NHANES after pandemic data (transient elastography, DXA, metabolic panels, weight-history modules). MASLD was defined using elastography-based steatosis with metabolic criteria. Structured weight-loss exposure was derived from physician advice combined with active weight-control behavior. Causal forests with doubly robust adjustment estimated heterogeneous treatment effects, with sensitivity analyses using alternate fibrosis thresholds, overlap restriction, and competing-risk exclusion of viral hepatitis and heavy alcohol use.

Results: Among 1,742 older adults with MASLD, significant fibrosis prevalence reached 12.1%. Only 43.2% reported active weight-loss attempts despite counseling exposure in 61.5%. Visceral adiposity (DXA trunk fat) showed strong correlation with stiffness ($r=0.41$), while insulin resistance amplified this gradient (interaction $\beta=0.27$, $SE=0.08$). Causal forests identified a high-response subgroup ($\approx 28\%$) with central obesity, diabetes, and elevated triglycerides, showing estimated fibrosis attenuation equivalent to 1.8–2.3 kPa reduction under weight-loss exposure, compared with <0.6 kPa in low-response profiles. Model discrimination for identifying high-benefit individuals reached AUC 0.79, with sensitivity 0.76 and specificity 0.71. Subanalysis showed stronger effects in non-cirrhotic strata (R^2 improvement 0.18) and attenuation in sarcopenic phenotypes.

Conclusions: The advantage of this approach lies in targeting intervention intensity to those most likely to gain fibrosis benefit, rather than applying uniform counseling. This enables clinically actionable stratification, improves efficiency of lifestyle programs, and supports precision-based MASLD management in aging populations.

Keywords: Weight Loss, Visceral Adiposity, Insulin Resistance, Fibrosis

PE-20

Night Shift Eating, Sleep Fragmentation, and Sarcopenic Obesity Accelerate Fibrotic MASLD in Older Adults With Multimorbidity

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Aims: Fibrotic MASLD in older adults is usually framed through

obesity alone, although meal timing, sleep disruption, and muscle-fat imbalance may better capture progression in multimorbid aging. We examined whether these factors converge around higher fibrosis burden in older adults.

Methods: We analyzed datasets from a UK Biobank prospective night-shift cohort (281,280 workers), an older-adult NHANES sleep-MASLD analysis (4,731 participants), an NHANES 2017–2018 VCTE sarcopenia-fibrosis study (1,831 adults), and a longitudinal older-adult meal-timing cohort (2,945 participants) linking later eating patterns with multimorbidity.

Results: Over a median 12.1 years in UK Biobank, 2,555 incident NAFLD cases occurred usual/permanent night-shift work carried a 1.27-fold higher risk, and some night shifts a 1.12-fold higher risk versus never/rarely. In older NHANES participants, sleeping <6 hours was associated with 21% higher MASLD prevalence, >8 hours with 38% higher prevalence, and sleep disorders with a 2.38-fold higher prevalence, spline analysis showed a U-shaped curve with a turning point at 7 hours. In NHANES 2017–2018, 664 of 1,831 participants had MASLD and 89 had significant fibrosis; sarcopenia prevalence was 11.7% in MASLD versus 3.8% in non-MASLD, and sarcopenia independently associated with significant fibrosis (OR 6.10). Combined with low physical activity, fibrosis odds rose to 7.91, with prolonged sedentary time, to 4.32. In the older-adult meal-timing cohort, multimorbidity clustered with later breakfast timing, and 10-year survival was 86.7% in late eaters versus 89.5% in early eaters.

Conclusions: The practical advantage of this framework is identifying a modifiable triad beyond body weight alone. Clinically, it supports fibrosis-focused screening that integrates meal timing, sleep assessment, and sarcopenic obesity in older multimorbid adults.

Keywords: MASLD, Night Eating, Sarcopenic Obesity, Fibrosis

PE-21

Impact of Metabolic Dysfunction Associated Steatotic Liver Disease on Hepatocellular Carcinoma Risk in Patients with Chronic Viral Hepatitis: A Nationwide Cohort Study

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Aims: We investigated the association between metabolic dysfunction-associated steatotic liver disease (MASLD) on hepatocellular carcinoma (HCC) and other liver-related outcomes in patients with chronic hepatitis B (CHB) or chronic

hepatitis C (CHC) using a nationwide cohort.

Methods: This retrospective cohort study used the Korean National Health Information Database. Adults newly diagnosed with CHB or CHC between 2009 and 2013 were included if health check-up data enabling MASLD assessment were available within two years. MASLD was defined as hepatic steatosis (Fatty Liver Index ≥ 60) with at least one cardiometabolic risk factor. A 1:3 frequency matching by index year, age, sex, and hepatitis type, as well as propensity score matching weights were used to control observed confounding between groups and outcomes.

Results: Among 187,847 patients with chronic viral hepatitis who met the inclusion criteria, 20,098 (10.7%) had concurrent MASLD at baseline. After matching, 72,648 patients were included in the final analysis (MASLD: 18,117; non-MASLD: 54,531). During up to 10 years of follow-up, patients with MASLD showed a higher incidence of HCC than those without MASLD (3.12 vs. 2.21 per 1,000 person-years). MASLD was associated with higher risks of HCC (adjusted hazard ratio [aHR] 1.33; 95% CI 1.20–1.48), decompensated cirrhosis (aHR 1.43; 95% CI 1.32–1.56), liver transplantation (aHR 1.70; 95% CI 1.10–2.65), and liver-related mortality (aHR 1.58; 95% CI 1.37–1.82). In contrast, metabolic dysfunction was not associated with liver-related outcomes in patients without MASLD. Within MASLD as well, individual metabolic risk factors were not associated with increased risks of liver-related outcomes.

Conclusions: MASLD was independently associated with increased risks of HCC and adverse liver outcomes among patients with CHB or CHC. Metabolic dysfunction in the absence of MASLD, and individual metabolic risk factors within MASLD, were not associated with additional risk.

Keywords: Metabolic Dysfunction Associated Steatotic Liver Disease, Chronic Viral Hepatitis, Hepatocellular Carcinoma

PE-22

Association of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) with GERD Prevalence and Endoscopic Severity in Primary Care

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Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic metabolic disorder linked to extrahepatic complications, including gastroesophageal reflux disease (GERD). However, data from primary care settings comparing GERD symptoms and objective endoscopic findings in MASLD patients remain limited. This study aimed to evaluate the association between ultrasound-diagnosed MASLD and the prevalence of symptomatic and erosive GERD.

Methods: A cross-sectional study was conducted on 46 patients (MASLD, $n=23$; Control, $n=23$) at a primary care clinic in Korea. MASLD was diagnosed via abdominal ultrasound. We assessed the prevalence of typical GERD symptoms (heartburn and acid regurgitation) and evaluated objective mucosal damage using esophagogastroduodenoscopy (EGD) based on the Los Angeles (LA) classification.

Results: The MASLD group demonstrated a significantly higher overall prevalence of GERD symptoms compared to the control group (60.9% vs. 26.1%, $P=0.020$). Specifically, typical symptoms such as heartburn (47.8% vs. 17.4%, $P=0.038$) and acid regurgitation (43.5% vs. 13.0%, $P=0.016$) were markedly more frequent in MASLD patients. Furthermore, endoscopic evaluation revealed that erosive esophagitis (LA Class A or B) was significantly more prevalent in the MASLD cohort (34.8% vs. 8.7%, $P=0.035$), indicating a higher degree of objective mucosal injury.

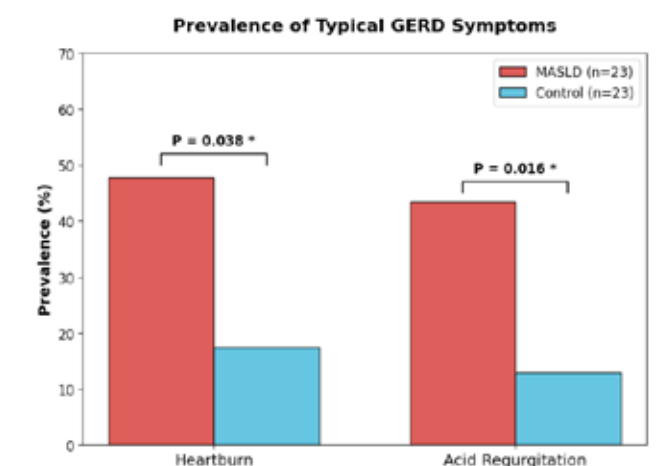


Figure 1.

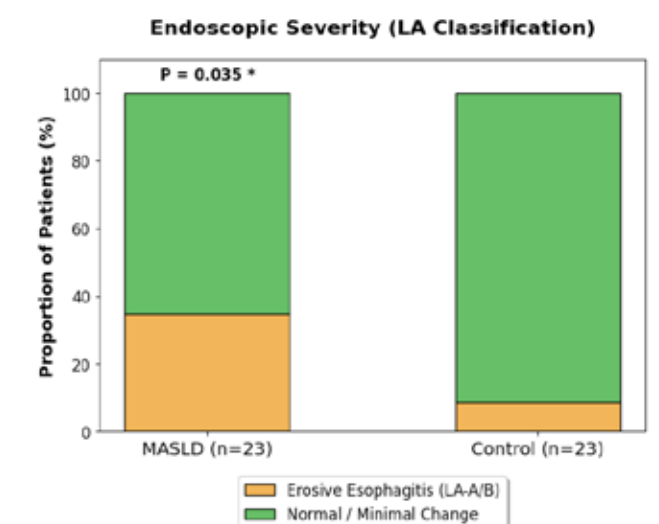


Figure 2.

Conclusions: In the primary care setting, MASLD is a significant predictor for both the symptomatic manifestation and endo-

scopic severity of GERD. These findings highlight the need for comprehensive screening, suggesting that upper gastrointestinal endoscopy and proactive symptom evaluation should be integrated when managing patients with MASLD.

Keywords: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Gastroesophageal Reflux Disease (GERD)

PE-23

Prevalence, Clinical Characteristics, and Liver Fibrosis Burden of MASLD in a Central European Population – Findings from the Białystok plus Study

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Aims: This study aimed to assess the prevalence, clinical profiles, and liver fibrosis burden of MASLD cohort in a representative population from Central and Eastern Europe.

Methods: This study is part of the Białystok PLUS (Polish Longitudinal University Study), an ongoing, prospective, population-based cohort study. From a random sample of 2,572 adult residents of Białystok, Poland, participants diagnosed with MASLD and no liver steatosis were selected. These groups were compared using anthropometric, epidemiological, and clinical data.

Results: 558 participants were diagnosed with MASLD accounting for 21.7% of the study population and 1,731 (67.3%) individuals presented no liver steatosis. MASLD was predominantly associated with obesity, diabetes mellitus and arterial hypertension. Significant liver fibrosis (Liver stiffness measurement $\geq$ F2) was more frequent in MASLD cohort (15.64%) compared to no steatotic participants (5.12%), ($P < 0.001$) with cirrhosis rates observed in 0.58% of MASLD participants, and 0.12% of controls ($P = 0.093$).

Conclusions: MASLD is highly prevalent in this Central and Eastern European population and is strongly associated with metabolic comorbidities. Individuals with MASLD exhibit a significantly higher burden of liver fibrosis compared with those without steatosis, indicating an increased risk of disease progression. These findings highlight the need for early identification and targeted management of MASLD in the general population.

Keywords: MASLD, Liver Diseases, Cardiometabolic, Poland

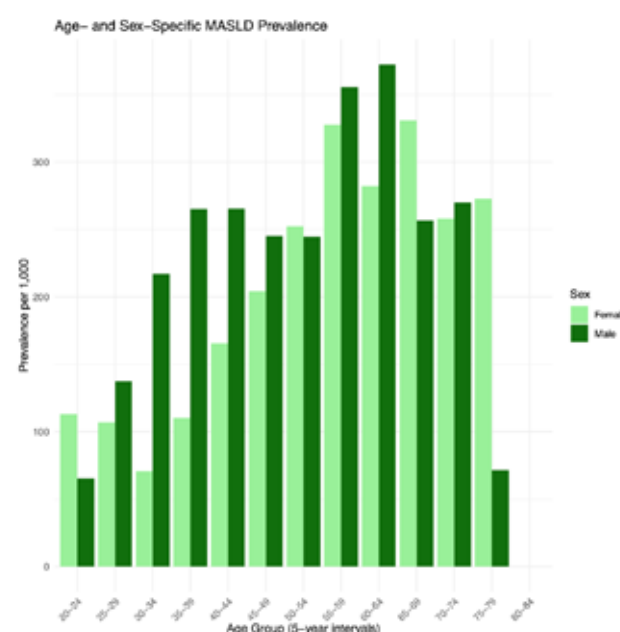


Figure 1.

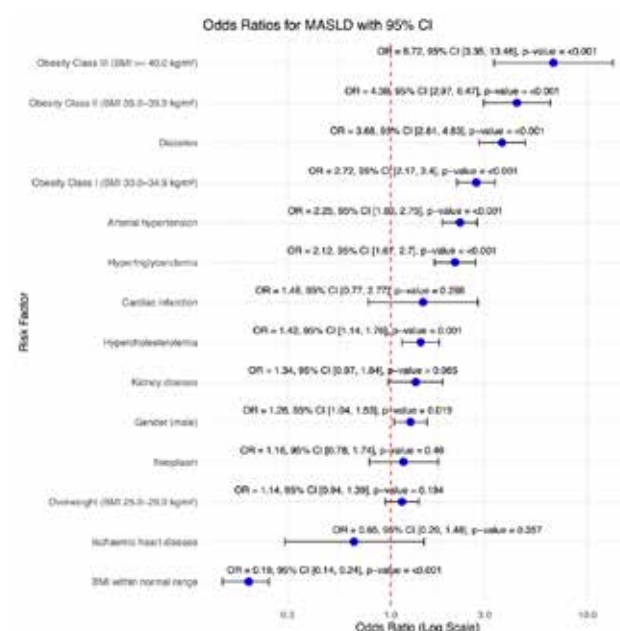


Figure 2.

PE-25

Small Vulnerable Newborns Have Higher Risk of Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Meta-Analysis

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Aims: Metabolic dysfunction-associated steatotic liver disease

(MASLD), formerly designated nonalcoholic fatty liver disease (NAFLD), has emerged as the leading aetiology of chronic liver disease worldwide. Early-life exposures may critically shape long-term hepatic metabolic trajectory. Preterm birth, low birthweight (LBW), and small for gestational age (SGA) status are biologically plausible antecedents of MASLD through mechanisms including adipose tissue dysfunction, insulin resistance programming, and altered hepatic lipid metabolism. However, robust quantitative synthesis of this association is lacking.

Methods: We conducted a pre-registered systematic review and meta-analysis following PRISMA guidelines. Medline, EMBASE, and Web of Science were searched through 11 March 2025 for studies examining associations between birthweight, gestational age, birthweight-for-gestational-age, and risk of MASLD. Dual independent reviewers screened citations and abstracted data. Pooled odds ratios (ORs) were derived using DerSimonian–Laird random-effects models stratified by exposure category. Heterogeneity was quantified using the I^2 statistic.

Results: Of 3,794 publications identified, 46 underwent full-text evaluation, and 37 were included in the qualitative synthesis. Eleven studies ($n = 12,580$ individuals) contributed to the quantitative meta-analysis. Preterm birth was associated with a statistically significant 2.47-fold increased odds of MASLD (OR 2.47; 95% CI 1.76–3.45; 3 studies, $n = 2,972$). SGA status similarly conferred a 2.46-fold elevated risk (OR 2.46; 95% CI 1.44–4.20; 7 studies, $n = 10,336$). LBW was not independently associated with MASLD after pooling (OR 1.47; 95% CI 0.83–2.60; 4 studies, $n = 3,788$), suggesting that gestational age and proportionality of fetal growth rather than absolute birthweight may be the critical determinants.

Conclusions: Preterm birth and SGA status each confer an approximately 2.5-fold increased lifetime risk of MASLD, underscoring the clinical importance of adverse perinatal growth trajectories as hepatic disease determinants. These findings provide evidence for a developmental programming hypothesis of MASLD pathogenesis and call for targeted hepatic surveillance and structured lifestyle intervention programs in high-risk birth cohorts.

Keywords: MASLD, NAFLD, Preterm Birth, Low Birthweight, Small For Gestational Age, Developmental Origins, Meta-Analysis, Hepatic Steatosis, Perinatal Programming

12. Others, Medical

PE-1

Albumin-Bilirubin Score for Predicting the Risk of Progression to End-Stage Liver Disease and All-Cause Mortality in Elderly Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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Aims: The metabolic dysfunction-associated steatotic liver disease (MASLD) is a recently proposed novel nomenclature highlighting the importance of cardiometabolic abnormalities. This study aimed to evaluate the prognostic utility of the albumin-bilirubin (ALBI) score for predicting the long-term risk of progression to end-stage liver disease (ESLD) and all-cause mortality in elderly patients with MASLD.

Methods: A retrospective, single-center cohort study of 412 consecutive elderly patients (age ≥ 65 years) with MASLD between January 2018 and December 2020 was performed. The ALBI score was calculated at baseline through albumin level and total bilirubin, and categorized into grade 1 (ALBI ≤ -2.60 , $n=109$), grade 2 (ALBI > -2.60 to ≤ -1.39 , $n=197$), and grade 3 (ALBI > -1.39 , $n=106$). The primary endpoint was a composite outcome of progression to ESLD (defined by hepatic decompensation events or MELD-Na score ≥ 15) or death. Multivariable Cox proportional hazards models were used to assess the association between ALBI grade and outcomes by reporting hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: There were 297 men (72.1%) and a mean age of 71 ± 3 years. Over a median follow-up of 41 months, 68 patients (16.5%) reached the composite endpoint. The cumulative incidence of the composite outcome was significantly higher with increasing ALBI grade (6.4% for grade 1, 12.7% for grade 2, and 34.0% for grade 3; log-rank $P < 0.001$). In multivariable analysis, the HRs (95% CIs) for those with grade 2 and grade 3 ALBI were 1.45 (1.09–1.78) and 2.87 (2.42–3.19), respectively (P for trend < 0.001). Receiver-operating characteristic curves demonstrated an area under the curve of 0.71 for ALBI score to predict the composite outcome.

Conclusions: Our finding support the incorporation of ALBI score, a simple and non-invasive tool, into routine clinical practice to enhance risk stratification and guide more aggressive management in high-risk individuals.

Keywords: Albumin-Bilirubin Score, All-Cause Mortality, End-Stage Liver Disease, Metabolic Dysfunction-Associated Steatotic Liver Disease

PE-2

Leveraging Decentralization, Integration, and Task-Shifting to Achieve Micro-Elimination of Hepatitis C among Prisoners in Northern India

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Aims: Hepatitis C virus (HCV) infection is highly prevalent among incarcerated individuals, yet diagnosis and treatment remain challenging in correctional settings. A decentralized, integrated, and task-shifting approach can overcome these barriers. This project utilized a novel prison-based model for HCV micro-elimination, leveraging the existing public health infrastructure to streamline care and accelerate treatment initiation.

Aim: To evaluate the feasibility and effectiveness of a decentralized testing utilizing HCV self-testing (HCVST), decentralized treatment, task-shifting to pharmacists, and integrated HCV/HIV testing through National AIDS Control program (NACP), with support from National Viral Hepatitis Control Program (NVHCP), for Hepatitis C micro-elimination within a prison setting in Northern India.

Methods: A micro-elimination project was conducted across four major jails in Uttarakhand state of India, from Aug 2024-Aug 2025, offering HCVST. Reactive HCVST results led to RNA testing and liver fibrosis assessment via onsite transient elastography (TE) using portable TE machine. Drones aided sample collection and direct-acting antiviral (DAA) delivery and teleconsultation supported constant handholding. Confirmed active infections were treated with DAA therapy, following NVHCP guidelines. A usability study of HCVST kits was also conducted among 100 inmates (Figure 1).

Results: Of 4050 inmates (96.7% male; mean age: 35 ± 13 years), 40.9% were from Haridwar, 25.1% from Dehradun, 20.4% from Haldwani and 13.6% from Roorkee. Overall, 138 (3.41%) tested positive for HCVST, with 67% (92/132) positives from Haridwar, 14% (20/132) from Dehradun and 18% (26/132) from Roorkee. Key reported behaviors included sharing toothbrushes/shaving tools (38.1%) and unsafe sex (14.6%). HCV positivity was significantly higher among those sharing needles [Risk in exposed = 56.9% (33/58), OR: 5.1; 95% CI: 2.9–9.0], using unprescribed injectable drugs [Risk = 52.1% (37/71), OR: 4.3; 95% CI: 2.3–7.5], unsafe sex [Risk = 15.4% (70/455), OR: 11.9; 95% CI: 7.9–17.8], tattooing (OR: 6.2; 95% CI: 2.3–16.6), and sharing personal items (OR: 3.7; 95% CI: 2.4–5.5). Logistic regression identified unsafe sex (OR: 8.6; 95% CI: 4.9–15.1), needle sharing (OR: 7.2; 95% CI: 2.1–25.0), and injectable drug use (OR: 3.8; 95% CI: 1.2–11.9) as independent predictors ($P < 0.05$). Out of 138 Anti-HCV positive, 117/138 (85%) were tested for

HCV RNA, 106/117 (90%) were HCV RNA positive (median HCV RNA-30,245 IU/mL (range 262–625,463)). Significant liver fibrosis (TE > 12 kPa) was observed in 15 cases. 74/106 (70%) individuals were put on DAA treatment, only 21/74 (28%) completed treatment and SVR-12 rate was 95%. The only reason for drop outs at different level of cascade of care was “release from the prison”. Overall usability of HCVST kits was 80%, with high acceptability and some challenges with sample collection requiring assistance.

Conclusions: This project demonstrated feasibility of utilizing HCVST to screen and link inmates to hepatitis C care within a correctional setting which has high burden. Model of care was effective in delivering comprehensive care with innovative approaches contributing to national elimination goals. Next step is to collect and document data on complete cascade of care including SVR-12 and to make the model of care self-sustainable.

Keywords: Hepatitis C, Micro-Elimination, Prisoners



Figure 1.

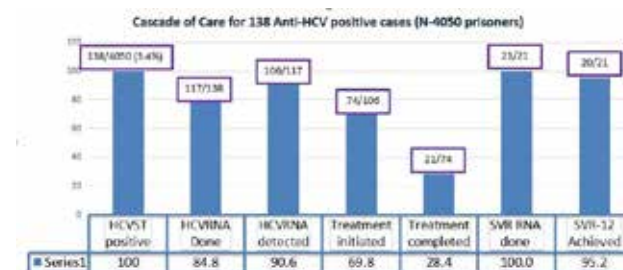


Figure 2.

PE-3

A Multifaceted Approach to Combat Liver Diseases: The Preventive Hepatology Initiative at AIIMS Rishikesh

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Aims: Liver Diseases remain a significant public health challenge globally and in India. Achieving control of liver diseases requires comprehensive strategies encompassing prevention, early detection, and effective treatment. This abstract describes the multifaceted preventive hepatology program at AIIMS Rishikesh and its contributions towards combating liver diseases.

Methods: The AIIMS Rishikesh preventive hepatology program employs a multi-pronged approach: 1) Community-based screening camps for viral hepatitis, steatotic liver disease (SLD), and patterns of alcohol consumption, targeting both general populations and high-risk groups. 2) Active case finding through family member screening of liver disease patients (MASLD, ARLD, hepatitis B and C). 3) Integration with the National Programs on viral hepatitis and SLD to provide comprehensive and affordable care. 4) Implementation of micro-elimination projects, such as targeted screening and treatment within a district prison. 5) Cutting-edge research, including cohort studies and cluster randomized controlled trials evaluating the effectiveness of public health interventions.

Results: Since Dec 2021, preventive hepatology clinic has provided care to 1500 patients (300 HBV, 200 HCV, 200 ALD and 800 NAFLD) at the tertiary care center and screened 3500 individuals through numerous community screening camps, (900 in urban, 900 in rural, 500 in urban slum, and 1200 in a prison) and linked to care through the national programs. Screening of 4500 family members of 1500 patients has proven highly effective in active case detection and linkage to care. The disaggregated proportion for SLD was 30-50%. Over 40% family members had either HBsAg or Anti-HBc positivity among family members of HBV patients. The prison micro-elimination project among 1200 prison inmates has demonstrated the feasibility of targeted interventions using HCV self-testing, identifying 138 Anti-HCV positives and initiating treatment in 74 HCV RNA-positive individuals. A portable fibroscan was used for fatty liver screening, and the AUDIT questionnaire for alcohol screening and quantification, to enable risk stratification and early intervention. Integration with national programs has maximized resource utilization and program reach.

Conclusions: The AIIMS Rishikesh preventive hepatology program is playing a vital role in India's efforts to combat liver disease. Through community outreach, active case finding, research, micro elimination projects, and integration with national programs, the initiative is contributing to improved access to care and reduced disease burden. The program's comprehensive strategy offers a valuable model for other institutions working towards a healthy liver initiative.

Keywords: Preventive Hepatology, Public Health, Comprehensive Liver Care, Liver Awareness



Figure 1.

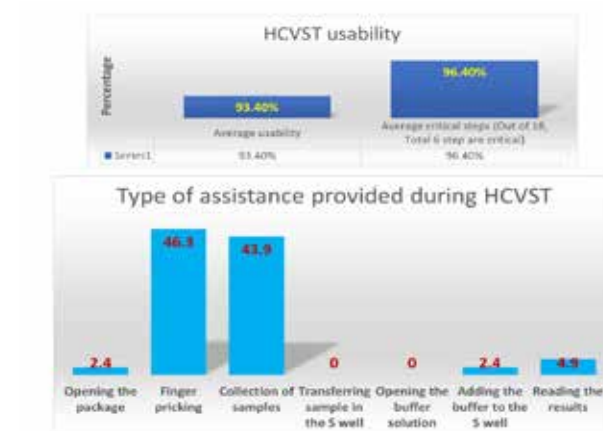


Figure 2.

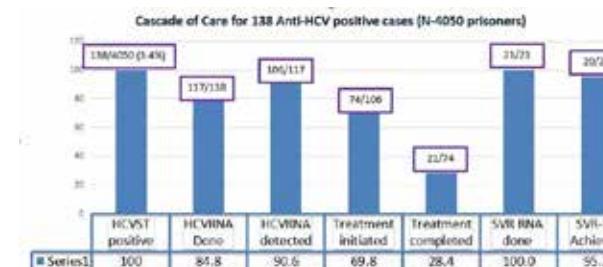


Figure 3.

PE-4

Impact of a National Transplant Coordination Program on Organ Donation Activity in Kazakhstan

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Aims: Organ transplantation is an established treatment for end-stage renal, hepatic, cardiac, and respiratory failure. However, organ shortage remains a major barrier to the expansion of transplant activity in Kazakhstan. The first kidney transplantation in Kazakhstan was performed in 1979. Although technically successful, the absence of adequate immunosuppressive therapy led to early graft rejection and patient death. System-

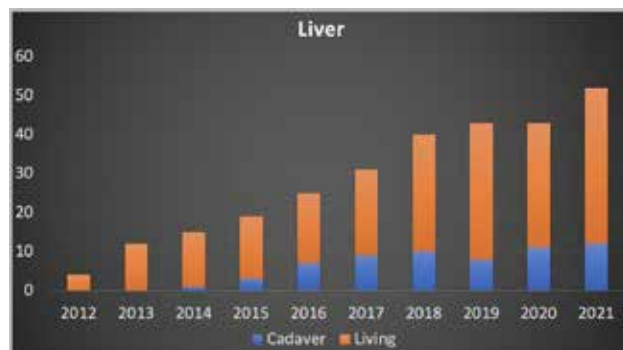
atic development of transplant services began approximately 10 years ago following implementation of a government-supported national transplant program under the Ministry of Health.

Methods: A national transplant coordination system was established, introducing dedicated transplant coordinators in all donor-designated hospitals. These coordinators oversee donor identification, organ procurement, and logistical processes. Data regarding transplant activity and program expansion were analyzed up to mid-2022.

Results: Currently, 11 transplant centers operate across Kazakhstan. Since implementation of the coordination program, more than 1,000 transplantations have been performed. Significant increases were observed in kidney, liver, and heart transplantation activity following the establishment of the national coordination framework. The structured organization of donor identification and procurement contributed to improved transplant accessibility.

Conclusions: The implementation of a centralized transplant coordination program in Kazakhstan was associated with increased organ donation and transplantation activity. Continued development of this system may help address the persistent organ shortage and further expand transplant services nationwide.

Keywords: Transplant, Organ Donation, Coordination



PE-5

The Influence of Limited Time Feeding on the mRNA Expression of the IL-6 Gene and CYP 11A1 Protein within the Cells of the Ileum Epithelium, Alongside the Rhythmic Dynamics of Gut Microbiota in Prediabetic States

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Aims: The Investigate the Effect of TRF on lipid, glucose me-

tabolism, mRNA expression of IL-6 gene and Cyp11A1 protein expression in IECs and rhythmic expression of gut microbiota in terms of relative abundance.

Methods: After model validation, mice were shifted in further different groups according to time restricted feeding and as Adlibitum feeding manner for further 8 weeks. To see the relative abundance and expression of gut microbiota at different time points, collected Fecal samples of Morning, Afternoon, Evening and Night (AMEN) timings in both group and in control group. Ileum (Intestinal) epithelial cells were isolated from each group. Cyp11a1 expression was done by western blot and mRNA by qPCR.

Results: We found that the cyp11a1 expression decreases in mice fed on TRF manner as compare to the mice fed in an Adlibitum manner. mRNA expression of IL-6 was found be high in Adlibitum group and it was effectively decreased in TRF group. Expression of Firmicutes and Actinobacteria was higher in 70% HSr + HFr Adlibitum group. They are abundantly present in all 4 time points (AMEN) fecal samples of 70% HSr + HFr Adlibitum mice. Moreover, Relatively higher throughout the day in 70% HSr + HFr Adlibitum as compare to 70% HSr + HFr TRF mice. Expression of Bifidobacteria and bacteroides was higher in 70% HSr + HFr TRF group in evening and morning fecal samples.

Conclusions: Decreased expression of Cyp11a1 protein and IL-6 gene in IE cells may regulate the steroid (cortisol) secretion which in turn regulates the glucose and lipid metabolism.

Keywords: CYP11A1, ILEUM (INTESTINAL) EPITHELIAL CELLS, MICROBIOME

PE-6

Ethics of Interaction with Chinese Liver Transplantation

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International Coalition to End Transplant Abuse in China

Aims: An initial aim is to point out the gravity and scope of organ transplant abuse in China and global complicity in that abuse. The specific aim is to propose for the global liver transplantation profession an ethics policy and practices for interaction with Chinese liver transplantation by comparing and assessing ethical policies already developed and ethical practices already engaged by other components of the global transplant profession on this matter. The aim is further, to demonstrate, through adoption of these policies and practices, how complicity with organ transplant abuse in China can be avoided.

Methods: The particular ethical statements of the global transplantation profession which would be considered and as-

sessed are:

- 1) The Transplantation Society Ethics Committee Policy Statement of 2006 on the Chinese Transplantation Program,
- 2) The International Society for Heart and Lung Transplantation of 2022 ethical statement addressing interactions between national and foreign transplant health professionals
- 3) The Policy statement of Canadian Society of Transplantation and Canadian Society of Nephrology on organ trafficking.

For ethical practices, the presentation would consider and address particular activities In Canada, the UK, Australia, Israel and Tawian.

Results: There are advantages and limitations to each of the policies and practices to be canvassed. Something, for the liver transplant profession, is better than nothing. The best result would be to draw on the best of the policies and practices canvassed. The presentation would suggest what that best result might be.

Conclusions: Right now the global liver transplant profession does not have an ethics policy directed to interaction with Chinese transplantation, either specifically or as part of a general policy. The global liver transplant society needs to consider what should be done on this subject.

Keywords: Ethics, Transplant Abuse, China

PE-7

Humoral Immune Imbalance in Chronic Liver Disease after COVID-19

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Aims: Persistent immune disturbances after COVID-19 may influence the course of chronic liver disease, but their humoral profile remains insufficiently characterized. We aimed to compare immunoglobulin and interferon patterns in patients with chronic hepatitis after COVID-19 and in patients with liver cirrhosis.

Methods: Sixty patients aged 30–65 years with chronic liver disease were examined: 20 patients with chronic hepatitis after COVID-19 and 40 patients with liver cirrhosis. Thirty healthy individuals served as controls. Serum levels of IgG, IgA, IgM, IFN- α , and IFN- γ were measured by ELISA. Statistical analysis was performed using Student's *t*-test, and $P < 0.05$ was considered significant.

Results: Both patient groups demonstrated a disturbed humoral immune profile compared with controls. In liver cirrhosis, IgG decreased to 9.7 ± 0.33 g/L versus 11.6 ± 0.43 g/L in controls, while IgA decreased to 1.16 ± 0.05 g/L versus 1.35 ± 0.20 g/L ($P < 0.05$). IgM increased to 1.90 ± 0.26 g/L compared with 1.21 ± 0.12 g/L in controls ($P < 0.05$). In chronic hepatitis after

COVID-19, IgG remained reduced (9.91 ± 0.69 g/L), IgA was also decreased (1.11 ± 0.06 g/L), and IgM reached the highest level among the study groups (2.05 ± 0.47 g/L), exceeding both controls and cirrhosis patients ($P < 0.05$). IFN- α was elevated in both cirrhosis and post-COVID chronic hepatitis, but was higher in the post-COVID group (39.2 ± 1.58 vs 37.16 ± 2.18 pg/mL). IFN- γ was increased in both groups and tended to be higher in cirrhosis (36.16 ± 3.05 vs 34.5 ± 1.82 pg/mL).

Conclusions: Chronic liver disease is accompanied by humoral immune imbalance, but patients with chronic hepatitis after COVID-19 demonstrate a more pronounced IgM- and IFN- α -oriented response. These findings suggest persistent immune activation after SARS-CoV-2 infection and support continued hepatologic follow-up in this group.

Keywords: Chronic Liver Disease, COVID-19, Humoral Immunity, Interferons

PE-8

A Rare Case of Acute Hepatitis E Virus Infection

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Aims: To present a rare case of acute HEV infection with its clinical and laboratory characteristics

Methods: A 56-year-old female was hospitalized at the National Center for Communicable Diseases from October 2 to October 30, 2025, for 28 days. The diagnosis was established based on detailed medical history, physical examination, and laboratory investigations. Serological confirmation was achieved through detection of anti-HEV IgM antibodies.

Results: The patient presented with a 5-day history of fever, anorexia, nausea, vomiting, epigastric pain, abdominal distension, dark-colored urine, and generalized fatigue. Physical examination revealed bilateral scleral icterus and epigastric tenderness. Her past medical history included an episode of jaundice in 1989. She had completed a full hepatitis B vaccination series, reported regular consumption of untreated tap water at her workplace, and had undergone dental extraction one month prior to admission.

Biochemical analysis demonstrated markedly elevated liver enzymes: AST 1506.8 U/L, ALT 4493.6 U/L, and direct bilirubin 73.0 μ mol/L. Urinalysis revealed urobilinogenuria and bilirubinuria. Serologic testing was negative for HAV-IgM, HBsAg, and anti-HCV, whereas anti-HEV IgM was positive, confirming acute HEV infection. After 28 days of treatment, liver enzyme levels normalized (AST 25.5 U/L, ALT 40.3 U/L), and bilirubin levels decreased, indicating resolution of hepatocellular injury and

cholestasis.

Conclusions: Although rare in our country, acute HEV infection should be considered in the differential diagnosis of acute viral hepatitis, as its clinical presentation and biochemical profile may resemble other viral hepatitis infections. Detection of anti-HEV IgM is essential for definitive diagnosis. HEV is transmitted through contaminated water, undercooked animal meat, and blood exposure. The infection is preventable, and most patients achieve complete recovery with appropriate supportive management.

Keywords: Hepatitis E Virus, Acute Hepatitis, Rare Case, Water-borne Infection

PE-9

Health-Related Quality of Life and Associated Factors in Outpatients with Chronic Liver Disease: A Cross-Sectional Study at 108 Military Central Hospital

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Aims: To evaluate health-related quality of life (HRQoL) among outpatients with chronic liver disease using the EQ-5D-5L/EQ-VAS instruments and to identify associated factors at 108 Military Central Hospital in 2025.

Methods: A cross-sectional descriptive study was conducted in 251 outpatients with chronic liver disease. HRQoL was assessed using the Vietnamese versions of EQ-5D-5L and EQ-VAS, covering five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Demographic characteristics, comorbidities, and clinical symptoms were collected. Group comparisons were performed using t-tests and ANOVA. Multivariable linear regression analysis was applied to identify independent predictors of HRQoL.

Results: The mean EQ-5D-5L index score was 0.8478 (SD 0.2122), and the mean EQ-VAS score was 80.8 (SD 14.9), indicating generally preserved quality of life. However, more than 50% of patients reported at least mild anxiety/depression, and approximately 45% experienced pain or discomfort. Male patients accounted for 73.3% of the cohort; individuals aged 45–59 and ≥60 years represented 42.2% and 33.1%, respectively. Most patients had mild disease severity (MELD <11: 97.6%). Hepatitis B was present in 78.5%, hepatitis C in 10.4%, hepatocellular carcinoma in 31.1%, and cirrhosis in 25.5%. Female patients demonstrated higher EQ-5D-5L scores than males (0.858 vs. 0.820; $P=0.007$), while EQ-VAS scores showed no significant difference ($P=0.357$). Lower HRQoL was observed among older patients, those with lower income, and individuals with comorbidities. Pain/discomfort and anxiety/depression were strongly associated with reduced HRQoL. Multivariable regression identified older age, low income, stage 1–2 chronic kidney disease, abdominal

distension, muscle cramps, pain, anxiety, hepatocellular carcinoma, limited multidimensional support, and poor disease awareness as independent predictors of poorer HRQoL ($P<0.05$).

Conclusions: Although HRQoL remains relatively good among predominantly mild outpatient cases, psychological burden and symptom distress remain substantial. Symptom control and psychosocial support should be prioritized in outpatient management, particularly for elderly, low-income, and comorbid patients. Integrating symptom management, patient education, and multidimensional support into routine care may significantly improve HRQoL in individuals with chronic liver disease.

Keywords: Chronic Liver Disease, Health-Related Quality of Life, EQ-5D-5L

PE-10

Hidden Burden of Liver Diseases amongst Sanitation Staff of a Tertiary Care Institute in Northern India

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Aims: The rising burden of liver diseases like steatotic liver diseases (SLD), harmful intake of alcohol, infection with Hepatitis B (HBV) and C (HCV) viruses are emerging public health problems in low-income occupational groups, yet remain underdiagnosed. Sanitation staff represent a vulnerable population with high exposure to health care associated infections (HAIs), lifestyle and metabolic risk factors, but limited access to preventive health screening. We aim to determine the proportion of liver diseases and to identify its sociodemographic and biochemical predictors among sanitation staff in a tertiary care institute in North India.

Methods: A cross-sectional study was conducted among 360 sanitation staff. Sociodemographic characteristics, lifestyle factors, anthropometry, viral markers and biochemical parameters were recorded. Hepatic steatosis and fibrosis staging were assessed using elastography-based liver stiffness measurement (LSM). Alcohol consumption was assessed using AUDIT questionnaire and all were tested for HIV, HBsAg and Anti-HCV. Associations for liver diseases were evaluated using chi-square tests, and independent predictors were identified through multivariable logistic regression analysis.

Results: A total of 360 sanitation staff were included (52.2% females), with the majority aged 30–39 years (46.4%). Overweight and obesity were present in 36.9% and 30.3%, respectively, and dyslipidaemia was observed in 71.1%. Hypertension was noted in 22.5%, while 20.0% had prediabetes and 9.2% had diabetes mellitus. The prevalence of SLD was 72.5%

(261/360). Significant fibrosis (F2–F4) was identified in 36.9%, including 12.8% with advanced fibrosis (F3–F4). On bivariate analysis, BMI category ($P<0.001$), tobacco use ($P=0.038$), fibrosis stage ($P=0.002$), and BARD score ($P=0.010$) were significantly associated with SLD. In multivariable analysis, obesity independently predicted SLD (AOR 3.49; 95% CI: 1.62–7.50; $P=0.001$). Other sociodemographic and lifestyle variables were not significant after adjustment. In the biochemical model, AST (SGOT) remained independently associated (AOR 0.98; 95% CI: 0.96–0.99; $P=0.028$), while other metabolic parameters were not independently significant. Viral marker prevalence was 0.55% for HBsAg and 1.94% for Anti-HCV; all subjects tested negative for HIV. Additionally, one-third of the cohort (126/360) reported significant alcohol consumption.

Conclusions: A substantial hidden burden of liver diseases was observed among sanitation staff, with over one-third demonstrating significant liver fibrosis. Obesity and altered liver enzyme levels (AST) emerged as independent predictors of SLD. These findings highlight an underrecognized occupational health risk and underscore the need for routine metabolic and hepatic screening, along with targeted workplace-based preventive strategies and early lifestyle modification interventions in this vulnerable population.

Keywords: Preventive Hepatology, Screening, Sanitary Workers, Public Health



Figure 1.



Figure 2.

PE-11

Beta-2 Adrenergic Signaling Drives Early Hepatocyte Proliferation via TNFR2 and Neutrophil Recruitment

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Aims: Liver regeneration requires tightly coordinated early signaling and rapid immune remodeling. Although catecholamine elevation is a hallmark of the systemic stress response, its functional role in initiating hepatocyte proliferation remains unclear. This study investigated whether catecholamine signaling through specific adrenergic receptors regulates early liver regeneration.

Methods: Transcriptomic changes in liver resection patients were analyzed using public datasets. In our in-house liver donor cohort, circulating catecholamines and immune cells were assessed before and on postoperative day 1 (POD 1). Mechanistic studies were performed using partial hepatectomy in wild-type (WT), *Adrb2*-knockout, and hepatocyte-specific *Adrb2* knockout mice. Early regenerative responses were characterized using transcriptomics, western blotting, immunohistochemistry. Primary neutrophils were isolated for assessing cytokine production and migration.

Results: Analysis of human public RNA sequencing data revealed enriched neuroactive ligand receptor interactions, especially *ADRB2* and TNF signaling within two hours of liver resection. Our liver donor cohort showed peripheral neutrophils and TNF levels increased remarkably on POD 1. Interestingly, a significant catecholamine increase was observed in donors with a higher liver regeneration rate (LRR), whereas not in lower LRR group, suggesting catecholamine-mediated signaling may be a critical early driver in regeneration. In WT mice, rapid elevations in hepatic catecholamines were accompanied by neutrophil infiltration and TNF α production. These findings were supported by bulk RNA sequencing, showing early up-regulation of *Adrb2*, *Tnfr2* and enriched TNF signaling pathway. Conversely, *Adrb2*-knockout mice exhibited abrogation of these regenerative signatures, with suppressed TNFR2 and JNK. Consistently, hepatocyte-specific *Adrb2*-knockout mice exhibited decreased neutrophil migration, TNF α production and delayed hepatocyte proliferation.

Conclusions: This study redefines catecholamines as essential biochemical switches governing early liver regeneration. By activating ADRB2/TNFR2 signaling pathway and neutrophil recruitment, hepatocytes enter the proliferative priming stage after liver injury. These findings suggest that enhancing ADRB2

signaling could provide a novel strategy in promoting liver regeneration capacity in patients.

Keywords: Liver Regeneration, Beta-2 Adrenergic Receptor, Neutrophil, Partial Hepatectomy

PE-12

Frailty and Sarcopenia Modify the Prognostic Impact of Liver Disease in Community-Dwelling Older Adults: A Prospective Cohort Study

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Aims: While the clinical significance of frailty and sarcopenia is well-established in advanced liver disease, their impact on community-dwelling older adults with relatively mild liver disease remains unclear. We aimed to investigate the prevalence of these geriatric syndromes according to liver disease status and examine their impact on mortality and long-term hospitalization.

Methods: We conducted a prospective population-based study of community-dwelling adults aged ≥ 65 years from 2014 to 2020 in Korea. The prevalence of frailty and sarcopenia was compared according to the presence of liver disease. Multivariable Cox proportional hazards models were used to examine the associations of frailty and sarcopenia with all-cause mortality and long-term hospitalization among participants with liver disease, adjusting for potential confounding factors.

Results: Among 1,886 participants, 513 (27.2%) had liver disease, the majority of whom were non-cirrhotic. Liver disease alone was not independently associated with the baseline prevalence of frailty or sarcopenia, nor with all-cause mortality or long-term hospitalization in multivariable analyses. However, among participants with liver disease, frailty and sarcopenia were independently associated with a 3.62-fold (95% CI, 2.04–6.43) and 2.41-fold (95% CI, 1.49–3.91) increased risk of the composite outcome of all-cause mortality or long-term hospitalization, respectively.

Conclusions: In community-dwelling older adults, liver disease per se does not appear to dictate adverse outcomes. However, the coexistence of frailty or sarcopenia markedly increased the risks of mortality and long-term hospitalization. These findings underscore the importance of geriatric assessment and targeted interventions addressing functional decline in older adults with even mild liver disease.

Keywords: Frailty, Sarcopenia, Older Adults, Liver Disease

PE-13

Dietary Red Meat Consumption, Viral Hepatitis Status, and Serum Ferritin Levels: A Cross-Sectional Analysis

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Aims: Serum ferritin reflects both iron storage and hepatic inflammatory activity. Chronic viral hepatitis and dietary heme iron intake may independently contribute to hyperferritinemia and fibrosis progression. We aimed to evaluate the independent and interactive effects of viral hepatitis (HBV, HCV), red meat consumption patterns, fibrosis stage, and steatosis severity on serum ferritin levels.

Methods: A total of 262 participants were included (124 viral-negative, 71 HBV-positive, 67 HCV-positive). All patients had available data on serum ferritin, transient elastography-based fibrosis staging (F0–F4), steatosis grading (S0–S3), and predominant red meat consumption (horse, sheep, cow, goat). Hyperferritinemia was defined as ferritin ≥ 300 ng/mL and severe hyperferritinemia as ≥ 1000 ng/mL. Due to non-normal distribution, ferritin values were analyzed as median (IQR). Group comparisons were performed using Kruskal–Wallis testing. Multivariable logistic regression identified independent predictors of hyperferritinemia.

Results: Hyperferritinemia (≥ 300 ng/mL) was present in 44% and severe hyperferritinemia (≥ 1000 ng/mL) in 11%. Median ferritin levels were significantly higher in viral hepatitis compared with controls (HBV 372 ng/mL [IQR 168–688], HCV 418 ng/mL [210–756] vs 228 ng/mL [102–412]; $P < 0.001$). Severe hyperferritinemia occurred in 14% of HBV and 18% of HCV patients versus 6% of controls ($P = 0.004$). Ferritin increased stepwise with fibrosis stage (214 ng/mL in F0–F1, 344 in F2, 518 in F3, and 804 in F4; p -trend < 0.001), with advanced fibrosis (F3–F4) strongly associated with elevated ferritin (median 642 vs 268 ng/mL; $P < 0.001$; $\rho = 0.41$, $P < 0.001$). Steatosis was associated with ferritin on univariate analysis ($P = 0.01$) but not after fibrosis adjustment. Ferritin varied by predominant meat consumption ($P = 0.003$), highest among horse meat consumers (468 ng/mL [210–880]) compared with sheep (395 ng/mL), cow (258 ng/mL), and goat (212 ng/mL). Severe hyperferritinemia was most frequent in horse meat consumers

(18%, $P = 0.01$). The association between horse meat intake and elevated ferritin was amplified in viral hepatitis patients (interaction $P = 0.02$). On multivariable analysis, advanced fibrosis (OR 3.56, 95% CI 2.01–6.29, $P < 0.001$), HCV infection (OR 2.21, 95% CI 1.27–3.85, $P = 0.005$), HBV infection (OR 1.74, 95% CI 1.01–3.00, $P = 0.046$), and horse meat consumption (OR 2.08, 95% CI 1.18–3.65, $P = 0.01$) independently predicted hyperferritinemia.

Conclusions: Serum ferritin elevation in chronic liver disease reflects a multifactorial process driven by viral infection, fibrosis severity, and dietary heme iron exposure. HCV demonstrated the strongest association with hyperferritinemia, while horse meat consumption independently predicted elevated ferritin levels, particularly in patients with advanced fibrosis.

These findings suggest a synergistic interaction between inflammatory liver injury and dietary iron intake in modulating iron storage biomarkers. Prospective studies are needed to determine whether dietary modification influences ferritin levels and fibrosis progression in chronic viral hepatitis.

Keywords: Serum Ferritin, Hyperferritinemia, Red Meat Consumption, Chronic Viral Hepatitis, Liver Fibrosis, Dietary Heme Iron, Steatosis

PE-14

Global, Regional, and National Burdens of Acute Viral Hepatitis in Adolescents and Young Adults Aged 15-39 Years from 2000 to 2021: A Trend Analysis

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Aims: Acute viral hepatitis (AVH) remains a major global health challenge. This study aims to provide comprehensive global estimates of the AVH burden among adolescents and young adults aged 15–39 years from 2000 to 2021.

Methods: This trend analysis utilizes data from the Global Burden of Disease (GBD) 2021 database, examining case numbers, age-standardized incidence rates (ASIR), prevalence rates (ASPR), years lived with disability (ASYSR), and their average annual percentage changes (AAPCs) for AVH, stratified by country, region, sex, and socio-demographic index (SDI). Joinpoint regression analysis identifies significant shifts in global trends.

Results: Over the past two decades, the global ASIR and ASPR of AVH among individuals aged 15–39 have declined. In 2021, AHA was the most common AVH subtype globally, followed by AHB, AHE, and AHC. Regionally, Central Sub-Saharan Africa had the highest ASIR and ASYSR, while Andean Latin America saw the largest increases. Nationally, Somalia had the highest ASIR in 2021, and Bolivia experienced the most significant increase from 2000 to 2021. Low-SDI regions had the highest AVH bur-

den in 2021, but the low-middle SDI group saw the greatest decrease. Males had a higher overall ASIR than females, with a more substantial decline in ASIR for males. Adolescents aged 15–19 had the highest ASIR in 2021, and the largest ASIR decrease was observed in those aged 20–24.

Conclusions: The data from GBD 2021 highlight a significant decline in AVH incidence from 2000 to 2021 and underscore the need for tailored, cost-effective interventions to mitigate AVH's impact.

Keywords: Acute Viral Hepatitis, Epidemiology, Socioeconomics, Adolescents and Young Adults

PE-15

Time-Resolved Analysis of Early Hepatic Injury Responses Using Precision-Cut Liver Slices

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Aims: Liver fibrosis is a conserved wound healing response to injury, yet its study is often limited by reductionist cell-based models. Precision-cut liver slices (PCLS) provide a promising *ex vivo* platform by preserving native tissue architecture. However, the biological relevance of spontaneous fibrogenic activation in PCLS remains debated. This study aimed to characterize these temporal responses and evaluate PCLS as a physiologically relevant platform for antifibrotic drug discovery.

Methods: Murine PCLS were cultured *ex vivo* for up to 5 days. We performed temporal transcriptomic profiling using RNA sequencing at multiple time points (Days 0, 1, 2, 3, and 5). Bioinformatic analyses including likelihood ratio testing (DESeq2) and unsupervised hierarchical clustering, identified dynamic gene modules. These findings were validated through molecular assays including qPCR and Western blotting to assess fibrogenic marker expression. The concordance between PCLS signatures and *in vivo* liver injury models (human and murine) was evaluated using cosine similarity based comparative enrichment analysis.

Results: PCLS exhibited a dynamic transcriptional trajectory initiated by the early activation of innate immune and damage-associated pathways (Days 1–2), followed by progressive induction of extracellular matrix remodeling and myofibroblast activation programs (Days 3–5). Modular analysis revealed that these sequential transcriptional shifts highly correlate with gene expression patterns observed in multiple *in vivo* liver injury models and human fibrotic tissues. Furthermore, pharmacological screening identified candidate compounds that significantly attenuated the injury driven fibrogenic program in PCLS, demonstrating the model's utility for drug evaluation.

Conclusions: Spontaneous fibrogenesis of PCLS recapitulates

key molecular features of *in vivo* liver fibrosis. Our findings support PCLS as a robust, physiologically relevant *ex vivo* platform for studying early fibrogenic mechanisms and screening potential antifibrotic therapeutics.

Keywords: Liver Fibrosis, Precision-Cut Liver Slices, Transcriptomics

PE-16

Evaluation of the Enzymatic Profile and Clinical Spectrum of Patients with Suspected Liver Disease Presenting to a Tertiary Care Center in Pokhara, Nepal

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Aims: To evaluate the enzymatic profile and clinical spectrum of patients with suspected liver disease presenting to a tertiary care center in Pokhara, Nepal.

Methods: This cross-sectional study included 150 patients with clinically suspected liver disease attending a tertiary care hospital in Pokhara. Demographic details, clinical presentations, and liver function parameters, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and albumin, were recorded. Data were analyzed using descriptive statistics to determine the pattern of enzyme abnormalities and their clinical correlation.

Results: Out of 150 patients, 96 (64%) were male and 54 (36%) were female. The most common clinical presentations were jaundice (90, 60%), abdominal pain (75, 50%), and fatigue (72, 48%). Elevated ALT and AST levels were observed in 105 (70%) and 112 (74.7%) patients, respectively, suggesting a predominance of hepatocellular injury. Elevated ALP was noted in 60 (40%) patients. Hyperbilirubinemia was present in 95 (63.3%) cases, while hypoalbuminemia was observed in 68 (45.3%). The hepatocellular pattern was the most common (82, 54.7%), followed by cholestatic (40, 26.7%) and mixed pattern (28, 18.6%). Alcohol-related liver disease (55, 36.7%) and viral hepatitis (48, 32%) were the leading suspected etiologies.

Conclusions: Hepatocellular injury is the most prevalent pattern among suspected liver disease patients in this setting. Liver enzyme abnormalities correlate well with clinical presentations, emphasizing the importance of early biochemical assessment for effective management.

Keywords: Liver Enzymes, ALT, AST, Cross-Sectional Study, Liver Disease, Hepatocellular Injury, Cholestasis, Pokhara, Nepal

Variable	Frequency (n)	Percentage (%)
Total Patients	150	100
Gender		
Male	96	64.0
Female	54	36.0
Clinical Features		
Jaundice	90	60.0
Abdominal Pain	75	50.0
Fatigue	72	48.0
Nausea/Vomiting	58	38.7
Ascites	40	26.7
Liver Enzyme Abnormalities		
Elevated ALT	105	70.0
Elevated AST	112	74.7
Elevated ALP	60	40.0
Hyperbilirubinemia	95	63.3
Hypoalbuminemia	68	45.3
Pattern of Liver Injury		
Hepatocellular	82	54.7
Cholestatic	40	26.7
Mixed	28	18.6
Probable Etiology		
Alcohol-related liver disease	55	36.7
Viral hepatitis	48	32.0
Non-alcoholic fatty liver disease	30	20.0
Others	17	11.3

13. Liver Cancer, Basic

PE-1

The Mongolian Anomaly and the Southeast Asian Cluster: Mapping the 2022 Liver Cancer Epidemic across Asia

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Aims: Liver and intrahepatic bile duct carcinoma represents a critical oncological burden in Asia. This study elucidates the sexual dimorphism and regional heterogeneity of its incidence in 2022.

Methods: We analyzed incidence data extracted from the 2022 global cancer observatory (GLOBOCAN) database, covering 47 Asian countries/territories. Indices included Age-Standardized Rates (ASR) per 100,000 and absolute case volumes, stratified by sex.

Results: The analysis reveals profound geographic variance and consistent male predominance. Mongolia exhibits hyper-endemic status, recording the highest ASRs globally (Male: 113.46; Female: 80.95). A significant high-incidence cluster was identified in Southeast Asia (Cambodia, Thailand, Vietnam), where male ASRs exceed 34.0. China bears the highest absolute disease burden (>367,000 combined cases), driven by population size rather than extreme ASRs relative to Mongolia. Conversely, South and West Asian nations (e.g., India, Israel) show the lowest incidence (ASR <5.0). Sexual disparity is pro-

nounced, with male-to-female ratios exceeding 3:1 in high-incidence zones.

Conclusions: The 2022 data highlights a persistent public health crisis in East and Southeast Asia. The extreme incidence in Mongolia and the massive volume in China necessitate stratified health policies prioritizing viral hepatitis eradication and targeted surveillance in high-risk male populations.

Keywords: Liver Neoplasms, Asia, Epidemiology, Gender Disparity

PE-2

A Novel Inhibitor Suppresses Hepatocellular Carcinoma Progression by Targeting sEV Secretion via the RBBP7/GLDC Pathway

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Aims: Hepatocellular carcinoma (HCC) remains a leading global health challenge, with particularly high incidence in Asia. Emerging evidence underscores the essential role of small extracellular vesicles (sEVs) in modulating intercellular communication within the HCC tumor microenvironment by transferring molecular cargoes between cancer cells and surrounding cells.

Methods: A chemical library screen was performed to identify inhibitors of sEV secretion from metastatic HCC cells using Amplified Luminescent Proximity Homogeneous Assay (alphaLISA), targeting CD63 and CD9 as sEV markers. Fluorescence from bead proximity quantified sEV levels in conditioned medium. Mass spectrometry identified protein targets of the lead compound. Multivesicular body (MVB) counts per cell were determined by transmission electron microscopy, and lysosome-endocytic cargo fusion assessed via colocalization of Dextran-AF488 and Magic Red cathepsin B dye.

Results: Compound 1G2 was identified as a potent attenuator of sEV release in HCC cells, reducing MVB numbers while promoting endolysosomal fusion and thereby impairing sEV secretion. Proteomic analysis revealed RB binding protein 7 (RBBP7) as a critical regulator of sEV biogenesis and secretion. RBBP7 knockdown significantly decreased sEV production, lowered MVB abundance, and enhanced endolysosomal fusion, linking RBBP7 to intracellular trafficking pathways that control sEV dynamics. RBBP7 knockdown upregulated glycine decarboxylase (GLDC), and rescue of GLDC expression in RBBP7 knockdown cells restored sEV secretion, confirming GLDC's downstream

involvement in this pathway. Clinical data showed RBBP7 up-regulation in HCC tissues and positive correlations with sEV biogenesis-related proteins. Furthermore, 1G2 suppressed *in vivo* tumor growth, indicating therapeutic potential.

Conclusions: These findings demonstrate that the novel compound 1G2 effectively suppresses HCC progression by inhibiting sEV secretion through modulation of the RBBP7/GLDC pathway and endolysosomal trafficking. By targeting this axis, 1G2 disrupts tumor-promoting intercellular communication, offering promising therapeutic potential for HCC management and highlighting small-molecule inhibition of sEV dynamics as a viable strategy against cancer progression.

Keywords: Hepatocellular Carcinoma, Small Extracellular Vesicles, Endolysosomal Fusion, Biogenesis of Small Extracellular Vesicles

PE-3

Proteomic Characterization of Integrin β 4-Enriched Lung-Targeting Small Extracellular Vesicle-Corona Complex along Pulmonary Metastasis of Hepatocellular Carcinoma

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Aims: Pulmonary metastasis of hepatocellular carcinoma (HCC) represents a frequent clinical manifestation in late-stage patients, significantly impairing patients' survival prospects. Previously, we demonstrated that small extracellular vesicles derived from metastatic HCC cells (met HCC-sEV) interact with lung tissues to promote pre-metastatic niche formation and facilitate pulmonary metastasis. This interaction is mediated by integrin β 4, which is enriched in met HCC-sEV and functions to facilitate their targeting and accumulation in lung tissues. Protein corona are layers of proteins absorbed onto sEV surface, influencing their interactions with different tissues. In this study, we aim to elucidate how integrin β 4 and its associated corona proteins contribute to their lung-targeting ability.

Methods: sEVs were isolated from integrin β 4-overexpressing cells by differential ultracentrifugation. Fetal bovine serum (FBS) was incubated with the isolated sEVs for the formation of sEV-corona complex, which was subjected to mass spectrometry analysis for protein profiling.

Results: Protein profiling identified 4540 sEV proteins, among which 155 proteins were differentially expressed comparing to control sEV. Pathway enrichment and gene ontology analysis discovered the involvement of biological processes and molecular functions highly relevant to the binding of integrin β 4 to extracellular matrix rich in lung tissues, and revealed a subset

of proteins (LAMA1, LAMA5, LAMB1, LAMB2 and LAMC1) immensely participating in these processes. For corona proteins, 106 FBS proteins were identified to interact with sEV, among which 5 proteins (ORM1, LTF, APOC2, HSPG2 and BHMT) were remarkably enriched in integrin β 4-overexpressing sEVs. *In silico* binding analysis predicted prospective interaction between integrin β 4 and the corona proteins.

Conclusions: We identified interacting corona proteins potentially contributing to the lung-targeting ability of integrin β 4-enriched sEVs. This study provides insights on targeting these associated proteins to prevent the interaction of met HCC-sEV with lung tissues and thereby abrogating pulmonary metastasis of HCC.

Keywords: Small Extracellular Vesicle, Protein Corona, Liver Cancer, Metastasis

PE-4

Targeting Dickkopf-1 Unlocks Synergistic Antitumor Immunity with PD-L1 Blockade in Hepatocellular Carcinoma

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Aims: Dickkopf-1 (DKK1), a secreted Wnt antagonist, is frequently overexpressed in hepatocellular carcinoma (HCC) and has been implicated in tumor progression. However, its role in immune regulation and therapeutic response remains unclear. We investigated the immunomodulatory function of DKK1, its association with programmed death-ligand 1 (PD-L1), and the potential benefit of DKK1 inhibition combined with anti-PD-L1 therapy.

Methods: We employed patient samples, human HCC cell lines with DKK1 knock-out (KO) or overexpression, and a syngeneic murine HCC model. PD-L1 expression was assessed by immunohistochemistry, western blotting, and qRT-PCR. T-cell activity was evaluated through Jurkat co-culture assays and cytokine secretion. The pharmacologic DKK1 inhibitor WAY-262611 was tested alone or in combination with anti-PD-L1 *in vitro* and *in vivo*.

Results: High DKK1 expression correlated with increased PD-L1 levels in human HCC tissues and cell lines, while DKK1 KO reduced PD-L1 expression. Co-culture experiments revealed that DKK1 suppressed Jurkat T-cell viability and IFN- γ production.

Treatment with WAY-262611 downregulated PD-L1 expression and reduced tumor cell migration. *In vivo*, Hepa1-6 DKK1 tumors displayed enhanced growth suppression when treated with combined DKK1 inhibition and anti-PD-L1, compared with either agent alone. Dual blockade significantly increased CD8⁺ T-cell infiltration and reduced immune evasion.

Conclusions: DKK1 promotes immune escape in HCC by up-regulating PD-L1 and impairing T-cell function. Pharmacologic inhibition of DKK1 augments the antitumor efficacy of PD-L1 blockade, suggesting that DKK1 is a promising therapeutic target and biomarker for immunotherapy combinations in HCC.

Keywords: Hepatocellular Carcinoma, DKK1, PD-L1, Immune Evasion

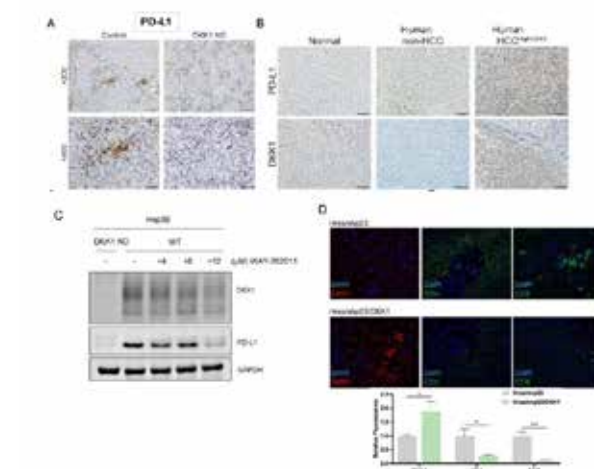


Figure 1.

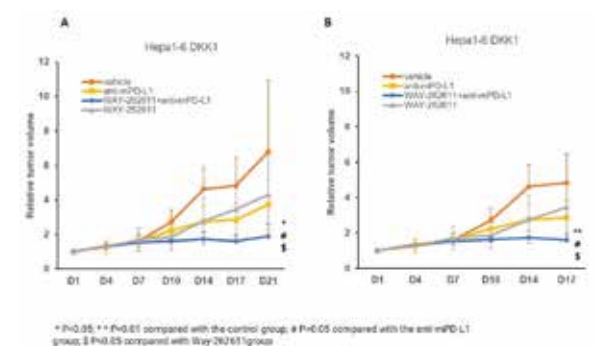


Figure 2.

PE-5

Identification of a Metastasis-Associated snoRNA with Therapeutic Potential in Hepatocellular Carcinoma

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Aims: Small nucleolar RNAs (snoRNAs) are emerging as important regulators of gene expression and cellular homeostasis beyond their canonical role in ribosomal RNA modification. However, the functional and therapeutic relevance of snoRNAs in hepatocellular carcinoma (HCC) metastasis remains largely unexplored. This study aimed to identify and characterize a metastasis-associated snoRNA with diagnostic and therapeutic in HCC.

Methods: A metastasis-associated snoRNA (snR#1) was identified through transcriptome profiling of HCC tissues. Expression levels were measured performed by qRT-PCR in HCC tissues and serum samples. TCGA transcriptome data were analyzed to evaluate pathway enrichment according to snR#1 expression levels using gene set enrichment analysis. Functional studies were performed using siRNA- and antisense oligonucleotide (ASO)-mediated silencing in HCC cell lines, and metastatic potential was evaluated in an *in vivo* mouse model. RNA sequencing was conducted following ASO-mediated silencing to identify transcriptional changes and enriched pathways.

Results: snR#1 was significantly overexpressed in HCC tissues and serum samples and showed markedly higher expression in patients with vascular invasion. TCGA transcriptome analysis revealed that patients with high snR#1 expression exhibited significant enrichment of proliferative gene sets, including G2M_CHECKPOINT, MITOTIC_SPINDLE, and E2F_TARGETS. Functional studies demonstrated that siRNA-mediated knockdown of snR#1 showed minimal effects, whereas ASO-mediated silencing markedly suppressed proliferation, migration, and invasion in two HCC cell lines. In addition, ASO treatment significantly reduced lung metastatic burden in an *in vivo* mouse model. RNA sequencing analysis following ASO-mediated silencing identified OXIDATIVE_PHOSPHORYLATION as the top enriched pathway among differentially expressed genes.

Conclusions: These findings identify snR#1 as a metastasis-associated snoRNA with diagnostic and prognostic potential in HCC. The strong anti-metastatic effect of ASO-mediated silencing together with transcriptome signatures associated with proliferative and metabolic programs suggest that snR#1 represents a promising therapeutic target for inhibiting HCC metastasis.

Keywords: Snorna, Hepatocellular Carcinoma, Metastasis, Antisense Oligonucleotide

PE-6

Kuan-Sin-Yin Enhances Anti-PD1 Efficacy in Hepatocellular Carcinoma by Promoting CD8⁺ T Cell Infiltration and Cytotoxic Function

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Aims: Immune checkpoint inhibitors show limited efficacy in hepatocellular carcinoma (HCC). This study investigates whether the traditional Chinese medicine formula Kuan-Sin-Yin (KSY) enhances anti-PD-1 therapy in HCC through immunomodulation.

Methods: Anti-tumor effects of KSY were evaluated in subcutaneous and orthotopic HCC models in C57BL/6 mice, with or without anti-PD-1. Immune infiltration was assessed by flow cytometry; intra-tumoral Granzyme B (GZB) and cytokines by ELISA. KSY components were identified via LC-MS, and their targets predicted using SwissTargetPrediction. These were integrated with HCC-related and tumor microenvironment-related genes from public databases (Genecards, OMIM, TCGA). KSY's effect on CD8⁺ T cells was examined in co-cultures with HCC cells or organoids. Proliferation/apoptosis were evaluated by EDU/TUNEL. Transcriptomics and western blotting were performed on KSY-treated CD8⁺ T cells.

Results: KSY showed no direct cytotoxicity on HCC cells *in vitro*, but suppressed tumor growth in both models at medium/high doses and synergized with anti-PD-1. It promoted infiltration of B cells, NK cells, macrophages, CD4⁺ T cells, and CD8⁺ T cells, with marked increase in CD8⁺ T cells in combination therapy, accompanied by elevated intra-tumoral GZB, IFN- γ , TNF- α , and IL-2. Bioinformatics implicated apoptosis as a key pathway, confirmed by TUNEL. KSY did not affect CD8⁺ T cell proliferation but upregulated *Ccr5*, *Ccr7*, *Tnf*, *Ifng*, and notably *Gzmb* transcription. Co-culture experiments confirmed that KSY-primed CD8⁺ T cells, and to a lesser extent their supernatant, directly induced HCC cell and organoid apoptosis. Mechanistically, KSY activated p53 in CD8⁺ T cells, increasing p-p53 and GZB. Pifithrin- α , a p53 inhibitor, reversed GZB upregulation and tumor cell apoptosis in co-cultures.

Conclusions: KSY remodels the HCC immune microenvironment and synergizes with anti-PD-1 by activating p53 in CD8⁺ T cells, enhancing their infiltration and cytotoxic function. KSY represents a promising immunomodulator for HCC combination therapy.

Keywords: Hepatocellular Carcinoma, Kuan-Sin-Yin, CD8⁺ T Cells, P53 Signaling Pathway

PE-7

Circular RNA SCAP Regulates Genomic Stability and PARP Inhibitor Sensitivity in Hepatocellular Carcinoma via the let-7b-5p/RAD51C Axis

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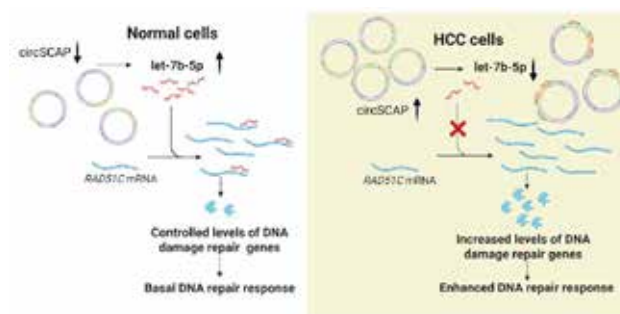
Aims: The robust DNA damage response machinery in hepatocellular carcinoma (HCC) is a primary driver of therapeutic resistance. Our prior research demonstrated that circular RNA SCAP (circSCAP) facilitates DNA replication; however, its role in DNA repair and its potential as a therapeutic target remain unexplored. This study aimed to elucidate how circSCAP impacts DNA repair and affects the response to poly (ADP-ribose) polymerase (PARP) inhibitors.

Methods: We performed transcriptomic profiling of circSCAP-knockdown HCC cells using RNA sequencing (GSE310080). DNA repair functionality was evaluated through γ -H2AX immunofluorescence and neutral comet assays. Chemosensitivity to PARP inhibitors, including olaparib and rucaparib, was determined via IC50 assays. The mechanistic interactions between circSCAP, let-7b-5p, and RAD51C were mapped using bioinformatic predictions, dual-luciferase reporter assays, and clinical correlation analysis.

Results: RNA sequencing and Gene Set Enrichment Analysis revealed a global downregulation of DNA repair processes following circSCAP depletion, characterized by reduced expression of key mediators such as *BRCA1*, *ATM*, *RAD51C*, and *TONSL*. *Silencing circSCAP impaired homologous recombination, leading to an accumulation of double-strand breaks as evidenced by increased γ -H2AX foci and DNA fragmentation. Consequently, circSCAP depletion profoundly sensitized HCC cells to olaparib and rucaparib. Mechanistically, we identified that circSCAP functions as a molecular sponge for let-7b-5p. Let-7b-5p directly targets the 3' untranslated region of RAD51C, and its high expression correlates with favorable patient survival. Clinical data confirmed a negative correlation between let-7b-5p and RAD51C; notably, RAD51C is upregulated in tumor tissues, and high expression is linked to poor overall survival.*

Conclusions: Our findings identify the circSCAP/let-7b-5p/RAD51C axis as a critical safeguard of genomic stability in HCC. Inhibiting circSCAP effectively induces a “BRCAness” state, offering a logical synthetic lethality approach to enhance the sensitivity of HCC cells to PARP inhibitors.

Keywords: Circular RNA, Hepatocellular Carcinoma, PARP Inhibitor, DNA Repair



PE-12

Epigenetic Regulation of Laminin- γ 2 Monomer Promotes Metastatic Potential in Hepatocellular Carcinoma

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Aims: Serum laminin- γ 2 monomer (Lm- γ 2m) is a predictive biomarker for hepatocellular carcinoma (HCC) development in patients achieving sustained virological response after HCV infection and for extrahepatic metastasis in early-stage HCC (Hepatology 2021). However, the molecular mechanisms regulating Lm- γ 2 expression in HCC remain unclear. We investigated whether promoter DNA methylation epigenetically regulates Lm- γ 2 expression and contributes to metastatic potential.

Methods: DNA methylation status of the Lm- γ 2 promoter was analyzed by bisulfite sequencing in five HCC cell lines (JHH-2, JHH-4, JHH-7, HuH-7, HepG2) and two immortalized hepatocytes (TTNT-16, THLE-5B). Functional regulation by methylation was examined using 5-aza-2'-deoxycytidine (5-Aza-dC) treatment and *in vitro* methylation luciferase assays. Highly metastatic HepG2 subclones were established via *in vivo* lung metastasis selection, and promoter methylation was compared with parental cells.

Results: Lm- γ 2m expression was elevated in JHH-2 and JHH-4 cells but low in JHH-7, HuH-7, HepG2, and immortalized hepatocytes. Correspondingly, promoter methylation levels were lower in high-expressing cells, indicating an inverse correlation between methylation and expression. Treatment with 5-Aza-dC induced Lm- γ 2m expression in a concentration-dependent manner. *In vitro* CpG methylation of the Lm- γ 2 promoter significantly suppressed luciferase activity in JHH-4 cells. Furthermore, highly metastatic HepG2 subclones exhibited increased Lm- γ 2m expression accompanied by promoter demethylation compared with the parental cells.

PE-14

The Effect of Exomeres on Cancer Stemness in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is a hypervascular tumor characterized by frequent recurrence and metastasis, partly driven by cancer stem cells (CSCs) that possess self-renewal ability, differentiation, and therapy-resistant properties. Intercellular communication within the tumor microenvironment plays a vital role in promoting tumor progression, with extracellular vesicles and nanoparticles (EVPs) serving as key mediators of this process. Recently, exomeres, an emerging subtype of extracellular nanoparticle has been discovered. Given the considerable importance of EVP in human cancers, the potential functions of exomere warrants in-depth investigation.

Methods: Exomeres were isolated from normal hepatocytes and HCC cell lines with varying metastatic potential and characterized by Western blotting and transmission electron microscopy. Their effects were evaluated using *in vitro* assays for self-renewal, CSC marker expression, chemosensitivity, proliferation, migration, and invasion, as well as *in vivo* tumorigenicity analyses. To explore underlying mechanisms, proteomic profiling was performed on exomeres and recipient-cell lysates, followed by functional validation of candidate proteins.

Results: Exomeres derived from HCC cells, but not from normal hepatocytes, enhanced CSC traits in recipient cells by increasing self-renewal, upregulating CSC markers, and decreasing sensitivity to chemotherapeutic agents. They also significantly promoted proliferation, migration, invasion, and tumor-forming capacity. Proteomic analysis of exomeres identified RUVBL1 as an exomere-enriched protein whose abundance correlated with the metastatic potential of the parental HCC cells. Importantly, exomeres with reduced RUVBL1 showed markedly attenuated ability to induce malignant behaviors and CSC-like properties.

Conclusions: HCC-derived exomeres function as potent intercellular signals that drive tumor aggressiveness and stemness, with RUVBL1 emerging as a key effector. These findings expand the understanding of exomere-mediated communication in HCC and suggest exomere-associated RUVBL1 as a candidate biomarker and therapeutic target for HCC management.

Keywords: HCC, Exomere, Cancer Stemness, RUVBL1

Conclusions: Promoter DNA methylation negatively regulates Lm- γ 2m expression in HCC. Epigenetic demethylation enhances Lm- γ 2m expression and is associated with increased metastatic potential, suggesting a mechanistic link between epigenetic regulation and HCC progression.

Keywords: DNA Methylation, Hepatocellular Carcinoma, Laminin-Gamma2 Monomer

PE-13

Brown Adipose Tissue Activation Suppresses Hepatocellular Carcinoma via Metabolic Competition and PI3K/AKT/mTOR Inhibition

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Aims: To evaluate whether activating brown adipose tissue (BAT)—a highly glucose-consuming thermogenic organ—can inhibit hepatocellular carcinoma (HCC) progression and to explore potential mechanisms, including metabolic competition and downstream oncogenic signaling suppression.

Methods: A murine HCC model was treated with the selective β 3-adrenergic receptor agonist CL-316,243 to activate BAT, with tumor burden assessed at endpoint. BAT activation status was supported by UCP1-related readouts. Tumor tissues were analyzed for PI3K/AKT/mTOR signaling and glycolysis-associated gene expression. *In vitro*, stromal vascular fraction (SVF) from murine BAT was differentiated into brown adipocytes and co-cultured with RIL-175 c-Myc liver cancer cells in a β 3-agonist-independent setting to test tumor cell proliferation effects.

Results: Pharmacological BAT activation reduced HCC tumor burden, suppressed the PI3K/AKT/mTOR pathway, and down-regulated glycolysis-related genes in tumor tissue. *In vitro*, co-culture with differentiated brown adipocytes inhibited proliferation of liver cancer cells without β 3-agonist exposure, supporting a direct tumor-suppressive role of brown adipocytes beyond any compound-specific antitumor effect.

Conclusions: BAT activation is a promising anti-HCC strategy that may exploit tumors' glycolytic dependence by limiting nutrient availability and dampening oncogenic metabolic signaling. BAT-targeted pharmacology and BAT-mimetic approaches—including endocrine/paracrine mediators such as batokines, BAT-derived small extracellular vesicles—warrant further translational investigation in liver cancer.

Keywords: Brown Adipose Tissue, Hepatocellular Carcinoma, Small Extracellular Vesicles, PI3K/AKT/MTOR

PE-15

Identification of *Streptococcus Salivarius* as a Novel Biomarker for Predicting and Enhancing PD-1 Responses in Hepatocellular Carcinoma

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Aims: Immune checkpoint inhibitor (ICI) therapy, including PD-1 inhibitors, benefits only a small subset of hepatocellular carcinoma (HCC) patients due to unreliable biomarkers and immune resistance. Research on the gut-liver axis suggests that gut microbiota may enhance ICI efficacy, underscoring the need to identify specific microbiota for effective combinatorial strategies.

Methods: Fecal samples from 67 HCC patients receiving PD-1-based therapy including 20 responders and 47 non-responders were profiled using metagenomic sequencing. The *in vivo* role of *Streptococcus salivarius* (*S. salivarius*) was examined in PD-1 refractory mouse HCC model, and the effect on immune tumor microenvironment (TME) was evaluated by immunofluorescence staining, FISH, quantitative PCR, mass spectrometry, and single-cell RNA sequencing (scRNA-seq) with immune profiling. Additionally, *S. salivarius* conditioned medium (SACM) was used to assess its direct effects on immune cells *in vitro*.

Results: *S. salivarius* was significantly enriched in the fecal samples of anti-PD-1 responder HCC patients, forming interconnected network with three other *Streptococcus* species that contribute to PD-1 sensitivity. Daily oral administration of *S. salivarius* reduced tumor burden in a PD-1-refractory HCC model. scRNA-seq and immune profiling revealed that *S. salivarius* enhanced CD8 T cell infiltration in the TME, particularly promoting the recruitment of naïve CD8 T cells and effector memory T cells (TEM) while suppressing exhausted PD-1+TIM3+ CD8 T cells. Further FISH analysis revealed the infiltration of extracellular *S. salivarius* in the tumor, coinciding with CD8 T cell infiltration. Additionally, SACM stimulated CD8 T cells *in vitro*, increasing the proportions of naïve, central memory (TCM), TEM, and activated CD8 T cells. Metabolomic profiling revealed that citrulline was elevated in *S. salivarius*-enriched samples, correlating consistently with PD-1 sensitivity in HCC patients.

Conclusions: Our findings show that *S. salivarius* sensitizes PD-1 treatment by enhancing CD8 T cell infiltration and activation, supporting its combination with anti-PD-1 therapy in HCC treatment.

Keywords: Immunotherapy, Gut Microbiota, Tumor Microenvironment, Hepatocellular Carcinoma

PE-16

High Methionyl-tRNA Synthetase 1 Expression Is an Independent Predictor of Early Recurrence after Curative Resection in Hepatocellular Carcinoma

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Aims: Methionyl-tRNA synthetase 1 (MARS1) has been implicated in tumor progression and oncogenic signaling across multiple malignancies. However, its prognostic significance in hepatocellular carcinoma (HCC) remains unclear. This study aimed to evaluate the association between tumoral MARS1 expression and recurrence outcomes following curative resection in HCC.

Methods: We retrospectively analyzed 134 patients who underwent curative surgical resection for HCC. MARS1 expression was assessed by immunohistochemistry and quantified using H-score. High expression was defined as the upper tertile (H-score ≥ 210.6). Recurrence-free survival (RFS) was analyzed using Kaplan–Meier and Cox proportional hazards models. Multivariate analyses were adjusted for tumor size, microvascular invasion (MVI), alpha-fetoprotein (AFP), and BCLC stage.

Results: Forty-four patients (33%) were classified as MARS1-high. Median RFS was significantly shorter in the MARS1-high group compared with the MARS1-low group (15.3 vs. 41.3 months). In univariate analysis, high MARS1 expression was associated with increased recurrence risk (HR 2.06, 95% CI 1.32–3.21, $P=0.001$). In multivariate analysis adjusting for established prognostic factors, MARS1-high remained an independent predictor of recurrence (adjusted HR 2.46, 95% CI 1.51–3.99, $P=0.00027$). Tumor size was also independently associated with recurrence (HR 1.14 per cm increase, $P=0.0018$), whereas MVI, AFP, and BCLC stage were not statistically significant in the fully adjusted model.

Conclusions: High intratumoral MARS1 expression is independently associated with early recurrence following curative resection in HCC. These findings suggest that MARS1 may serve as a novel biomarker for recurrence risk stratification and potentially reflect aggressive tumor biology in HCC.

Keywords: Hepatocellular Carcinoma, Mars1, Recurrence-Free Survival, Biomarker

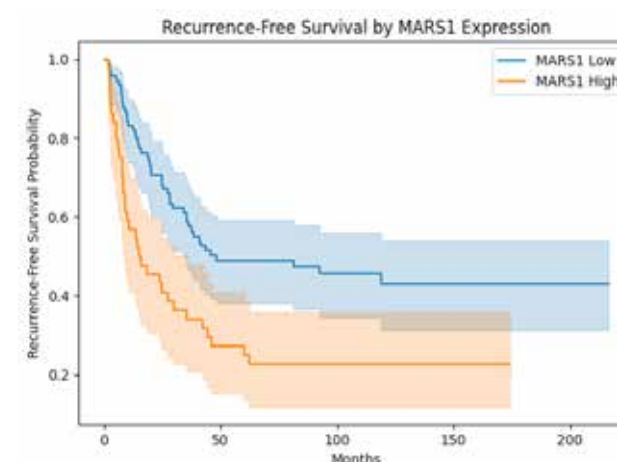


Figure 1. Kaplan–Meier curves for recurrence-free survival according to MARS1 expression.

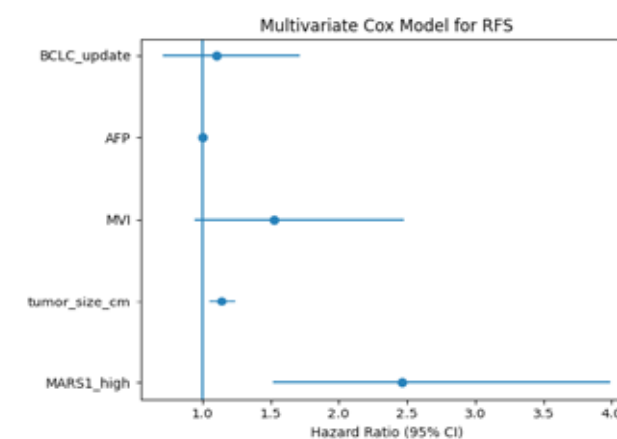


Figure 2. Multivariate Cox proportional hazards analysis for recurrence-free survival.

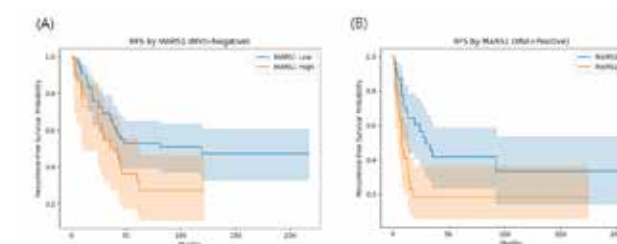


Figure 3. Stratified analysis of recurrence-free survival according to microvascular invasion status.

PE-17

Integrated Proteomic and Transcriptomic Profiling of IL-4/IL-13-Conditioned Macrophage Secretome in Hepatocellular Carcinoma

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Aims: Increased IL-4 levels have previously been observed in patients with hepatocellular carcinoma (HCC). Based on this clinical observation, we characterized IL-4/IL-13-conditioned macrophage secretome using integrated proteomic and transcriptomic approaches and evaluated its impact on tumor progression *in vivo*.

Methods: U937-derived macrophages were stimulated with IL-4 and IL-13 and analyzed using quantitative LC–MS/MS-based secretome proteomics. Conditioned media were administered for five consecutive days to Huh7 xenograft-bearing nude mice. Tumor growth was evaluated, followed by bulk RNA-seq analysis of xenograft tumors.

Results: IL-4/IL-13 stimulation induced anti-inflammatory mediators and TREM2 expression and resulted in substantial remodeling of the macrophage secretome. Proteomic analysis identified upregulation of proteins associated with lipid metabolism and extracellular matrix organization, with MMP12 emerging as the most prominently increased secreted factor. *In vivo*, administration of conditioned media significantly increased tumor volume and weight. Integrative analysis of secretome proteomics and xenograft bulk RNA-seq demonstrated that MMP12 was selectively increased in mouse-derived reads within tumor tissues and represented the only overlapping molecule between datasets.

Conclusions: IL-4/IL-13 stimulation is associated with macrophage secretome remodeling and enhanced tumor growth *in vivo*. MMP12 may represent a mediator linking cytokine-induced macrophage activation to tumor microenvironment alterations in HCC.

Keywords: Hepatocellular Carcinoma, Tumor-Associated Macrophages, Secretome

PE-18

Novel Copper(II) Complexes for Synergistic Tumor Immunotherapy via Cuproptosis, Apoptosis, and Chemodynamic Therapy

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Aims: Hepatocellular carcinoma (HCC) ranks among the highly malignant tumors. Although immunotherapy has made remarkable progress, the immunosuppressive tumor microenvironment (TME) still poses a significant hurdle to effective treatment. Cuproptosis, apoptosis and chemodynamic therapy, can synergistically induce immunogenic cell death (ICD). This mechanism facilitates the promotion of antitumor immune responses.

Methods: MTT, western blot, electron paramagnetic resonance (EPR) spectroscopy, transmission electron microscopy (TEM), flow cytometry, ELISA.

A	IC ₅₀ (μM)					
	Huh-7	HCC-LM3	MHCC-97H	AGS	A549	MIHA
A'1	> 20	> 20	> 20	> 20	> 20	> 20
A'2	> 20	> 20	> 20	> 20	> 20	> 20
A'3	> 20	> 20	> 20	> 20	> 20	> 20
A'4	> 20	> 20	> 20	> 20	> 20	> 20
A1C	8.0 ± 0.7	4.6 ± 0.1	> 20	8.5 ± 1.1	7.9 ± 0.6	> 20
A2C	13.2 ± 1.1	7.4 ± 0.3	> 20	9.3 ± 0.4	8.2 ± 0.5	> 20
A3C	5.7 ± 0.6	3.9 ± 0.1	7.3 ± 0.7	8.4 ± 0.5	12.4 ± 1.2	4.8 ± 0.4
A4C	12.9 ± 0.6	6.5 ± 0.1	12.4 ± 3.5	13.1 ± 1.1	9.0 ± 0.2	4.3 ± 0.4
A1B	2.3 ± 0.8	1.8 ± 0.1	4.0 ± 1.2	5.1 ± 0.4	7.7 ± 0.6	2.7 ± 0.5
A2B	4.7 ± 0.9	3.0 ± 0.3	6.7 ± 0.8	6.2 ± 0.5	9.7 ± 0.8	3.4 ± 0.7
A3B	1.0 ± 0.1	1.2 ± 0.3	2.0 ± 0.3	2.1 ± 0.5	3.1 ± 0.2	3.1 ± 0.5
A4B	1.5 ± 0.2	1.3 ± 0.1	2.1 ± 0.5	5.6 ± 0.5	3.3 ± 0.7	3.6 ± 0.4
DDP	6.1 ± 0.7	2.7 ± 0.3	> 20	10.3 ± 1.0	9.5 ± 0.6	11.3 ± 0.8
QX	8.9 ± 0.6	10.3 ± 1.1	19.8 ± 1.3	9.3 ± 0.8	10.2 ± 0.9	13.5 ± 1.2
CuCl ₂	> 50	> 50	> 50	> 50	> 50	> 50
CuBr ₂	> 50	> 50	> 50	> 50	> 50	> 50

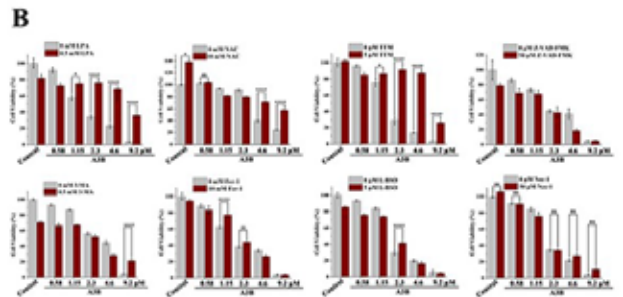


Figure 1: (A) The half-maximal lethal concentration (IC₅₀) of various drugs against five cancer cell lines and one normal liver line; (B) The mechanism of A3B-induced cell death in Huh-7 cells investigated using various cell death inhibitors: Copper-dependent and GSH-dependent modes of cell death.

Results: A series of novel copper(II) complexes were synthesized and evaluated for their anticancer activity. Among them, A3B exhibited the most potent cytotoxicity against Huh-7 cells, with an IC₅₀ value of 1.0 μM for 48h and an IC₅₀ value of

2.3 μM for 24h. Treatment with A3B resulted in the upregulation of DLAT and the downregulation of Lip-DLAT, LISA, and FDX1, indicating disruption of the lipoylation process involved in cuproptosis. EPR analysis demonstrated that the copper complexes could deplete intracellular glutathione (GSH) and catalyze the generation of hydroxyl radicals (•OH) from H₂O₂. This led to a reduction in GSH levels, an increase in oxidized glutathione (GSSG), and elevated reactive oxygen species (ROS), suggesting that GSH reduces Cu(II) to Cu(I), thereby initiating Fenton-like reactions. The resulting oxidative stress caused mitochondrial damage, as confirmed by JC-1 staining and TEM, ultimately inducing apoptosis. Flow cytometry revealed apoptosis rates of 1.55% in the control group, 73.2% in A3B-treated (4.6 μM) cells. Moreover, A3B induced the release of key damage-associated molecular patterns (DAMPs), including calreticulin (CRT), high-mobility group box 1 (HMGB1), and ATP, indicating the induction of ICD.

Conclusions: A3B can synergistic tumor immunotherapy in HCC by combining cuproptosis, apoptosis, and chemodynamic therapy.

Keywords: Immunogenic Cell Death, Cuproptosis, Copper (II) Complexes, Hepatocellular Carcinoma

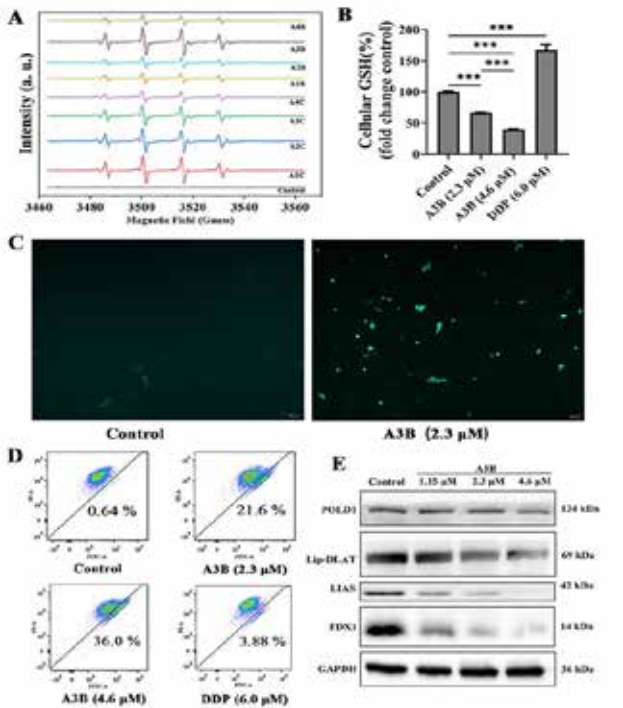


Figure 2: The A3B causes mitochondrial damage and induces cuproptosis in Huh-7 cells. (A) EPR spectra of •OH generated from H₂O₂ catalyzed by A1B-A4B. [DMPO] = 0.1 mM; [GSH] = 0.05 mM; [complex] = 0.05 mM; [H₂O₂] = 8 mM. After treating Huh-7 cells with A3B for 24 h, (B) GSH levels were detected; (C) Cellular ROS levels were observed by fluorescence microscopy (100×). (D) Changes in mitochondrial membrane potential were detected by FCM; (E) Changes in cuproptosis-related proteins were detected by Western blot. *p < 0.05, **p < 0.01, *p < 0.001.**

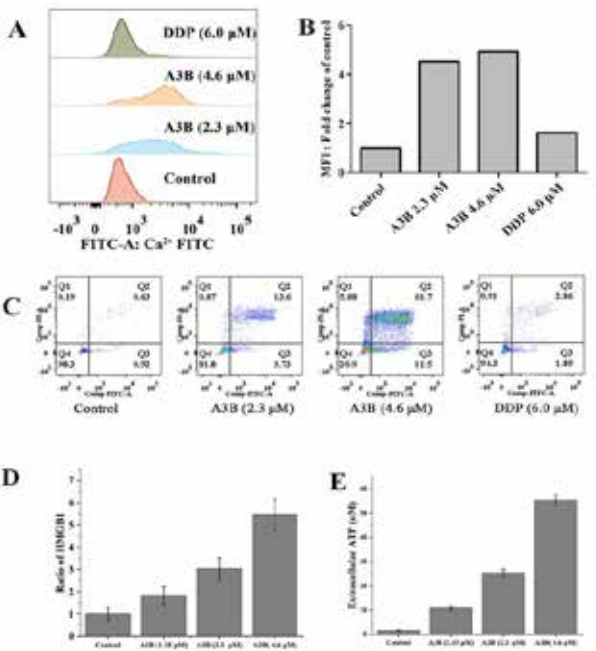


Figure 3: A3B induced apoptosis and immunogenic cell death in Huh-7 cells. (A, B) A3B increased the level of Ca²⁺, (C) induce apoptosis and (D) immunogenic cell death (release DAMPs).

PE-19

Multimomics Profiling of Plasma and Buffy Coat Reveals Predictive Biomarkers for Immunotherapy Response in Hepatocellular Carcinoma

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Aims: Immune checkpoint blockade (ICB) has become a standard treatment for advanced hepatocellular carcinoma (HCC). However, the lack of robust and reliable biomarkers for predicting immunotherapy response impedes effective patient stratification. We aimed to identify blood-based predictive biomarkers for ICB response in HCC.

Methods: We performed integrative blood multimomics profiling using targeted proteomics, methylome sequencing, and whole-transcriptome sequencing of plasma and buffy coat samples from HCC patients. Differential protein expression analysis was conducted to identify candidate predictive biomarkers. Methylome and transcriptome data were subsequently leveraged to support and validate the identified biomarkers using in-house and publicly available datasets.

Results: Differential expression and methylation analyses re-

vealed a distinct molecular landscape between responders and non-responders to ICB therapy. A machine learning-derived predictive signature demonstrated promising performance in distinguishing treatment response at the protein level. Validation using methylome and transcriptome data corroborated consistent dysregulation of candidate biomarkers across multiple omics layers, reinforcing their robustness and reproducibility.

Conclusions: Integrative blood-based multimomics profiling identifies promising predictive biomarkers for immunotherapy response in HCC. These findings may improve patient stratification for ICB treatment and inform future therapeutic strategies, pending further large-scale validation and standardization.

Keywords: Hepatocellular Carcinoma, Immunotherapy, Liquid Biopsy, Predictive Biomarker

PE-20

Matrix Stiffness-Induced AGRIN in Exomere Promotes Angiogenesis to Drive Hepatocellular Carcinoma

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Aims: The stiffening of the extracellular matrix is a key characteristic of the tumour microenvironment in hepatocellular carcinoma (HCC). The biomechanical properties of matrix rigidity due to excessive ECM deposition and cross-linking have a significant influence on tumour and neighbouring stromal cells. While small extracellular vesicles (sEVs) under stiffness have been associated with HCC progression, the role of a newly discovered, non-membranous nanoparticle, called exomere (EM), has yet to be investigated in this biophysical context. This study hypothesises that matrix stiffness reprograms the biogenesis and packaging of EM, allowing them to act as potential mediators that accelerate HCC development.

Methods: EM was isolated from several HCC cancer cell lines cultured with collagen-coated polyacrylamide gels with elastic moduli of 0.5 kPa ('soft') and 8 kPa ('stiff') using serial ultracentrifugation. The function of soft versus stiff EM was evaluated on HCC cancer cells using *in vitro* assays and *in vivo* mouse models. The effect of EM on angiogenic potential was also examined in HUVEC cells determined by comparative proteomics analysis between soft and stiff EM contents. The RNA interference technique was used to assess and validate the role of target candidates within the EM.

Results: EM derived from stiff HCC cells stimulated cell growth, motility and tumour development. Proteomics MS analysis showed that stiff EM converged into hypoxia-induced PI3K/

HIF-1 α /VEGF axis. HUVEC cells gained pro-angiogenic markers and phosphorylation of Akt, eNOS and GSK-3 β after treatment with stiff EM. The proteoglycan AGRIN was identified as a major cargo affected by matrix stiffness and responsible for enhanced angiogenesis. Silencing AGRIN eliminated the pro-angiogenic capability of EM and activation of signalling cascades in HUVEC cells.

Conclusions: This study elucidates a mechano-transduction stimulus through which matrix stiffness facilitates the incorporation of AGRIN into EM, thereby activating the endothelial PI3K/HIF-1 α /VEGF axis to enhance HCC angiogenesis and metastasis. This highlights the EM as a significant mediator of biomechanical signalling.

Keywords: Hepatocellular Carcinoma, Tumour Microenvironment (TME), Extracellular Vesicles and Nanoparticles, Angiogenesis

PE-21

PLD1-Mediated PERK Signaling Promotes Hepatocellular Carcinoma Progression under Glucose Deprivation

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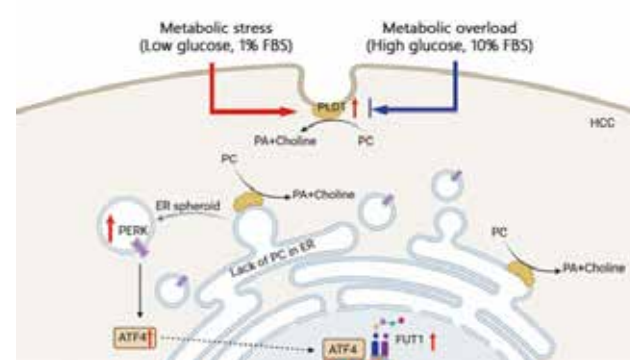
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Aims: Phospholipase D1 (PLD1) is a key enzyme that catalyzes the hydrolysis of phosphatidylcholine (PC) into choline and phosphatidic acid (PA). While PLD1 has been previously associated with liver pathologies such as fatty liver and cirrhosis, its specific functional role and underlying molecular mechanisms in hepatocellular carcinoma (HCC) progression remain to be fully elucidated.

Methods: To investigate the role of PLD1, multiple HCC cell lines (HepG2, Huh-7, SNU-398, and SNU-449) were utilized, with MIHA cells serving as a normal hepatocyte control. Cellular responses were analyzed under metabolic stress conditions, specifically 1% FBS and low-glucose environments.

Results: PLD1 expression was significantly upregulated in HCC cell lines, particularly in HepG2, compared to normal hepatocytes. Under metabolic stress, a concomitant increase in PLD1 and ATF4 expression was observed. Elevated PLD1 levels correlated with suppressed caspase-3 activity and enhanced ERK phosphorylation, indicating a strategic shift toward cell survival. Mechanistically, PLD1-mediated reduction of intracel-

lular PC content triggered the PERK signaling pathway, leading to ER stress responses, ER aggregate formation, and increased nuclear localization of ATF4. Furthermore, clinical data analysis from The Cancer Genome Atlas (TCGA) confirmed a significant positive correlation among PLD1, ATF4, and its downstream effector, FUT1.



Conclusions: Our findings demonstrate that PLD1 promotes HCC cell survival under nutrient-deprived conditions by modulating intracellular phosphatidylcholine levels. This metabolic adaptation activates the PERK-ATF4 signaling axis, identifying the PLD1-PERK pathway as a potential therapeutic target for HCC.

Keywords: Hepatocellular Carcinoma, Phospholipase D1, Metabolic Stress, Perk

PE-22

Regional Disparities in Liver Cancer Incidence in Mongolia: A Population-Based Analysis (2022–2024)

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Aims: Liver cancer remains one of the leading causes of cancer-related morbidity and mortality in Mongolia, largely driven by chronic hepatitis B and C infections, alcohol consumption, and metabolic disorders. Understanding regional disparities in liver cancer incidence is essential for developing targeted prevention and early detection strategies. This study aimed to analyze regional variations in liver cancer incidence across Mongolia using recent population-based data.

Methods: A retrospective descriptive analysis was conducted using national liver cancer incidence data from 2022 to 2024 across 21 provinces and the capital city of Ulaanbaatar. Provinces were grouped into four official geographic regions: Western, Khangai, Central, and Eastern. Population data were used to calculate incidence rates per 100,000 population. Re-

gional case totals, average annual incidence, and proportional contributions to the national burden were computed.

Results: Between 2022 and 2024, a total of 7,023 liver cancer cases were reported nationwide. The Central region, which includes the capital city, accounted for the largest share of cases (approximately 77–80% of the national burden), reflecting the higher population concentration. However, when adjusted for population size, the Eastern region showed the highest incidence rate, averaging approximately 103 cases per 100,000 population per year. The Western region demonstrated moderate incidence levels (approximately 68 cases per 100,000 population annually), while the Central region showed an average incidence of approximately 65 cases per 100,000 population annually. Substantial provincial variation was observed, with several provinces demonstrating notably higher incidence rates relative to their population sizes.

Conclusions: This analysis reveals significant regional disparities in liver cancer incidence in Mongolia. While the Central region contributes the largest absolute number of cases due to population density, the Eastern region demonstrates the highest population-adjusted incidence rate. These findings highlight the need for region-specific public health interventions, including targeted hepatitis screening, vaccination programs, and early cancer detection strategies in high-incidence areas.

Keywords: Liver Cancer, Regional Disparities, Cancer Incidence, Population-Based Analysis

PE-23

p53-Regulated tsRNA-6 Mediating DNA Homologous Recombination Repair Promotes Proliferation in HCC Cells

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Aims: Transfer RNA-derived small RNAs (tsRNAs) are fragments originating from tRNA and are recognized as a novel class of non-coding RNAs with distinct biogenesis pathways and high tissue specificity. Dysregulated tsRNAs have been implicated in promoting pathological processes in various human diseases, including cancer. However, the profile of tsRNAs and their roles in the initiation and progression of hepatocellular carcinoma (HCC) remain largely unexplored. Additionally, it is unclear whether the aberrant expression of tsRNAs is associated with somatic TP53 mutations in HCC.

Methods: To achieve a relatively comprehensive profiling of

tsRNAs in HCC patients, we employed the PANDORA-seq technology on tumor and adjacent tissues as well as serum samples from HCC patients. The expression levels of aberrantly expressed tsRNAs were further validated in HCC tissues, serum, and various HCC cell lines using qPCR. Subsequently, tsRNAs exhibiting significant differential expression in HCC were selected for functional analysis. Gain-of-function and loss-of-function experiments were performed in HCC cells to investigate the phenotypic effects and underlying functional mechanisms of these tsRNAs.

Results: Here, we demonstrated that tsRNA-6 was significantly upregulated in the serum and tissues of patients with HCC. Compared to normal liver cells (THLE-2), tsRNA-6 exhibited markedly higher expression levels in HCC cells, particularly in p53-mutant hepatocytes, where its expression was most profoundly upregulated. Knockdown of tsRNA-6 significantly suppressed the proliferation of TP53-mutant HCC cells. Mechanistically, the knockdown of tsRNA-6 led to a significant down-regulation of genes involved in homologous recombination, thereby predominantly affecting cell cycle progression and DNA repair processes.

Conclusions: This study demonstrated that the expression of certain tsRNAs can be negatively regulated by p53. Furthermore, the newly identified tsRNA-6 promotes the proliferation of TP53-mutant HCC cells via the homologous recombination pathway, thereby providing novel insights for early diagnosis and potential therapeutic targets in HCC.

Keywords: tsRNA, P53, Hepatocellular Carcinoma, Homologous Recombination

PE-24

An LTR Retrotransposon-Derived Microprotein PRMH1 Interacts with Rad51 to Promote Homologous Recombination Repair and Hepatocellular Carcinoma Progression

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Aims: At present, some long non-coding RNAs (lncRNAs) have been proved to be able to encode microproteins. However, whether these hidden microproteins participate in the p53-regulated homologous recombination (HR) repair pathway and play a significant biological role in the occurrence and development of hepatocellular carcinoma (HCC) is still unclear. Therefore, the search for functional microproteins that target HR repair may provide a potential biological target for HCC therapy.

Methods: By integrating the differentially expressed LTR-lncRNAs in TCGA HCC tissues, the lncRNAs in TCGA HCC samples with wild-type and mutant p53, and the Ribo-seq datasets of HuH-7 cells, we dedicated to mining LTR-lncRNAs that are regulated by p53 and can encode microproteins from these high-throughput sequencing data and confirmed the function of selected lncRNA-encoded microproteins in HCC cell lines.

Results: Here, we report that human LTR-derived lncRNA encoded a 119-amino acid microprotein, termed PRMH1 (p53-regulated microprotein for homologous recombination repair 1, PRMH1). The microprotein PRMH1 is highly expressed in p53 mutant HCC tissues and cells and promotes cell proliferation in p53-mutated HCC cells, and its transcription is promoted by NF-Y and suppressed by p53. Mechanistically, PRMH1 specifically binds to the 257-339aa domain of Rad51 to form a DNA repair complex that supplants 53BP1 at double-strand break (DSB) sites and then initiates Rad51-mediated homologous recombination repair. Notably, PRMH1 is essential for the stabilization of Rad51, acting as a microprotein platform to recruit and assemble HR protein factors.

Conclusions: This study reveals the important roles of lncRNA-encoded microproteins in p53-regulated HR repair pathway, and provide new biomarkers and targets for the diagnosis and treatment of HCC.

Keywords: Microprotein, Homologous Recombination Repair, LTR Retrotransposon, Hepatocellular Carcinoma

PE-25

Citrullinated Fibrinogen as a Potential Biomarker in Hepatocellular Carcinoma: Development of Monoclonal Antibodies

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Aims: Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality worldwide, highlighting the need for novel diagnostic biomarkers. Citrullination, a post-translational modification mediated by peptidylarginine deiminase (PAD), has emerged as an important process in inflammation and tumor biology. Our previous studies demonstrated increased PAD expression and accumulation of citrullinated proteins in liver fibrosis models, suggesting that protein citrullination may contribute to the fibrosis–cancer transition. Fibrinogen, a major plasma protein synthesized in the liver and an extracellular matrix-associated protein, may undergo citrullination under inflammatory conditions. This study aimed to develop monoclonal antibodies targeting citrullinated fibrinogen and to explore their potential application in HCC

biomarker research.

Methods: BALB/c mice were immunized with citrullinated fibrinogen peptides or citrullinated serum fibrinogen generated by PAD2. Monoclonal antibodies recognizing citrullinated fibrinogen were produced using hybridoma technology. Candidate clones were screened by enzyme-linked immunosorbent assay (ELISA) and further validated by Western blotting and immunohistochemistry. Antibody isotyping was performed, and the applicability of selected antibodies was evaluated in experimental models, including a bile duct ligation (BDL) mouse model of liver fibrosis. Preliminary immunohistochemical analyses were also conducted in human HCC tissues.

Results: Hybridoma screening identified several monoclonal antibodies that specifically recognized citrullinated fibrinogen. Western blot analysis confirmed selective binding of multiple clones to citrullinated fibrinogen compared with native fibrinogen. Antibody isotyping revealed subclasses including IgG1, IgG2a, IgG2b, and IgM. In the BDL mouse model, accumulation of citrullinated fibrinogen was observed in fibrotic liver tissues. Preliminary immunohistochemical analysis of human HCC tissues demonstrated detectable citrullinated fibrinogen signals. Furthermore, sandwich-ELISA suggested that citrullinated fibrinogen may be detectable in human serum samples.

Conclusions: Monoclonal antibodies recognizing citrullinated fibrinogen were successfully generated and validated in experimental liver disease models. These antibodies provide a novel tool for investigating extracellular matrix protein citrullination and may facilitate the development of diagnostic biomarkers for HCC.

Keywords: Citrullination, Fibrinogen, Hepatocellular Carcinoma, Monoclonal Antibody

PE-26

Integrated Proteomics and Metabolomics Analysis Reveals Molecular Signatures Associated with Liver Cancer in a Preclinical Model of Acute Hypoxia Stress

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Aims: Acute hypobaric hypoxia induces metabolic stress, disrupting redox homeostasis and promoting liver injury; however, the molecular mechanisms linking hypoxia to hepatic dysfunction remain poorly defined. This study aimed to char-

acterize time-dependent liver-specific proteomic and metabolomic alterations during acute hypoxic exposure.

Methods: Male SD rats (n=16/group) were exposed to simulated hypobaric hypoxia (25,000 ft) for 1, 3, or 7 days. Liver tissues were subjected to untargeted proteomic and metabolomic analyses to define temporal molecular perturbations associated with hepatic stress.

Results: Hypoxia induced significant liver injury, evidenced by elevated serum bilirubin, AST, and ALT levels and a reduced liver-to-body weight ratio ($P<0.05$). Liver metabolomics showed a time-dependent remodelling, of 341-up, 20-down at day-1, 316 up, 22-down at day-3, and 356 up, 10 down at day-7 ($FC>1.5$, $P<0.05$). These changes predominantly involved activation of inflammatory and mitochondrial redox pathways, including tryptophan (C00099, C00025), amino sugar metabolism (C00140), folate metabolism (C00576), and the TCA cycle (C00025), alongside suppression of nitrogen metabolism (C00262, C00086), indicating impaired detoxification ($>2FC$, $P<0.05$). Proteomic analysis showed extensive dysregulation of (1091-up, 586-down) proteins at day-1, 1104-up and 821 down at day-3, and 453-up and 606 down at day-7 ($FC>1.5$, $P<0.05$). Proteins associated with stress and lipid metabolism (FADS1, ACOX2, ACOT8), fatty acid metabolism (ACADVL, CPT1B), and calcium signalling (PTGS1) were enriched ($>2FC$, $P<0.05$). Integrated multi-omics showed strong correlations between increased TCA cycle activity and inflammatory signalling pathways ($R^2>0.7$, $P<0.05$). Network-level analysis further linked apoptotic (BAX, APAF1, CDH1, PRKCD), platelet activation (ATP2B3, PPP2R1B) and Eph–ephrin signalling (EPHA7, MYH9, LYN, EPHA3), angiotensinogen (ACE, CMA1) with altered nucleotide, amino acid, and antioxidant metabolism, identifying Eph–ephrin signalling as a key contributor to hypoxia-induced liver inflammation.

Conclusions: Acute hypobaric hypoxia induces early liver injury marked by redox imbalance, metabolic rewiring, and inflammatory activation, with coordinated proteomic–metabolomic disruptions highlighting Eph–ephrin signalling as a key driver of hypoxia-induced hepatic inflammation and a potential therapeutic target.

Keywords: Hypobaric Hypoxia, Proteomics Profile, Metabolomics Profile, Hepatic Stress

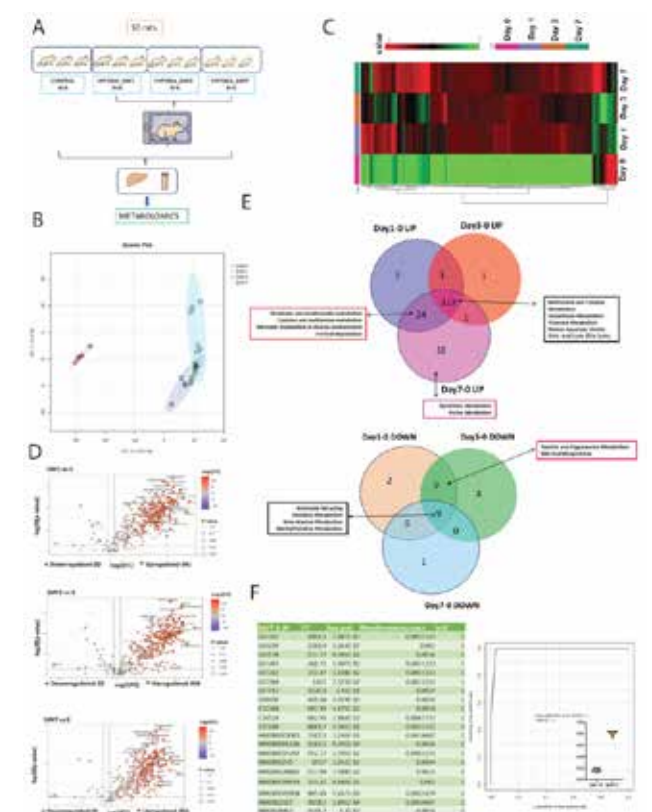


Figure 1.

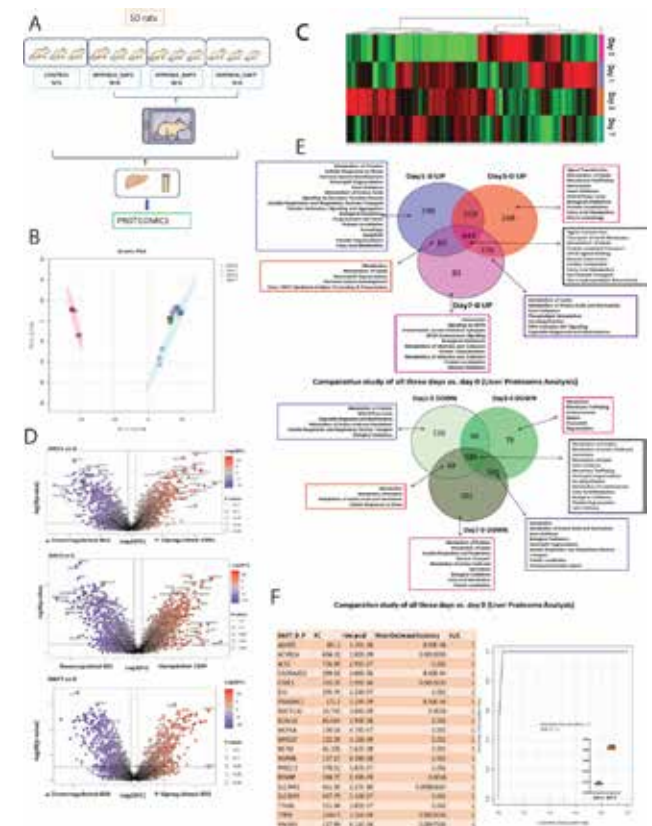


Figure 2.

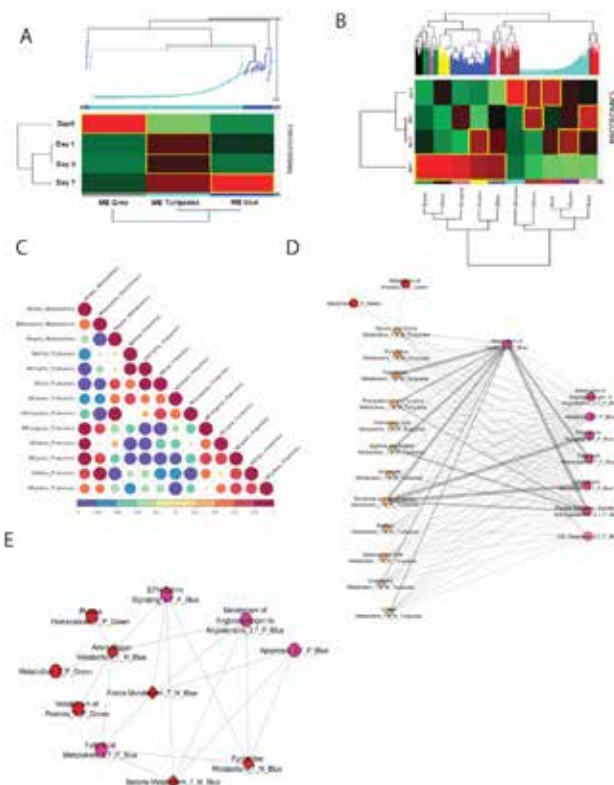


Figure 3.

PE-27

Does MBOAT7 rs641738 Polymorphism Influence Hepatocellular Carcinoma Susceptibility? A Meta-Analysis

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Aims: The MBOAT7 rs641738 single-nucleotide polymorphism (SNP) has been proven to influence various liver diseases, but its association with hepatocellular carcinoma (HCC) susceptibility has been debated. To address this discrepancy, we conducted the current meta-analysis.

Methods: We performed a systematic review in PubMed, Web of Science, Scopus, and EMBASE; applied specific inclusion and exclusion criteria; and extracted the data. Meta-analysis was conducted with the MetaGenyo tool. Sensitivity and subgroup analyses were also performed.

Results: Eight studies were included in the systematic review, and 12 cohorts from 6 studies were included in the meta-analysis. Our meta-analysis revealed an association between the MBOAT7 SNP and HCC susceptibility in both the dominant [odds ratio (OR): 1.14, 95% confidence interval (95%CI): 1.02-1.26, $P=0.020$] and recessive (OR: 1.21, 95%CI: 1.05-1.39,

$P=0.008$) models. Subgroup analysis revealed that stratification of the included patients by geographical origin showed a significant association in Asia (OR: 1.20, 95%CI: 1.03-1.39).

Conclusions: This meta-analysis underscores the contribution of the MBOAT7 rs641738 SNP to hepatocarcinogenesis, especially in Asian populations, which warrants further investigation.

Keywords: Hepatocellular carcinoma; MBOAT7; Meta-analysis; Single-nucleotide polymorphisms

PE-28

Spatial Architecture of POSTN-Expressing Fibroblasts and T Cells Shapes an Aggressive Notch-Active Niche in Combined Hepatocellular Carcinoma and Cholangiocarcinoma

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Aims: Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CCA) is a rare and heterogeneous primary liver malignancy with limited molecular stratification. Our previous study identified a subset of cHCC-CCA with high Notch signaling activity associated with aggressive tumor behavior. However, the spatial microenvironmental features that accompany and potentially sustain Notch activation remain poorly defined, particularly at the single-cell level and in relation to stromal-immune interactions.

Methods: Artificial intelligence-powered digital pathologic analysis of hematoxylin and eosin-stained whole-slide images was performed in nine cHCC-CCAs, along with three HCCs and three CCAs, using Lunit SCOPE IO to characterize the spatial cellular composition of the tumor microenvironment. Single-cell-level spatial transcriptomic analysis (Xenium In Situ) was conducted in all tumors along with three non-neoplastic liver tissues. All three previously defined cHCC-CCA subgroups (G1, G2, G3), classified according to Notch pathway activation status, were included in the analysis.

Results: Digital pathologic image analysis showed no significant differences in the proportion of stromal area within the tumor, fibroblast density in cancer stroma, or lymphoid cell density in either cancer areas or stromal areas among the subgroups. In contrast, spatial transcriptomic analysis revealed that POSTN was the most highly expressed potential Notch ligand in the Notch-high cHCC-CCA subgroup (G2). Among Notch receptors, NOTCH1 showed the highest expression in G2, while CD44, a downstream Notch-related molecule, was also markedly upregulated (Figure 1, upper). Spatial transcriptomic

mapping demonstrated selective POSTN and CD44 expression in tumor areas and intratumoral stroma (Figure 1, lower left). At single-cell resolution, CD44 expression was restricted to tumor cells, whereas POSTN expression was detected in fibroblasts and immune cells (Figure 1, lower left). Compared with other cHCC-CCA subtypes and HCC, G2 cHCC-CCA showed the highest proportion of CD8+ T cells, and POSTN expression was identified in this subset, supporting a potential role for both fibroblasts and T cells as sources of stromal POSTN in this aggressive subgroup.

Conclusions: These findings suggest that POSTN-rich stromal regions, composed of fibroblasts and immune cells including CD8+ T cells, are spatially adjacent to tumor cells and form a distinct Notch-active niche. POSTN-NOTCH1 interactions between fibroblasts/CD8+ T cells and tumor cells may induce CD44 expression in tumor cells, potentially contributing to cancer stemness and aggressive behavior (Figure 2). In addition, these results highlight that qualitative spatial organization, rather than simple differences in stromal abundance, may underlie biological aggressiveness in this subset. This niche may represent a therapeutic vulnerability in aggressive cHCC-CCA.

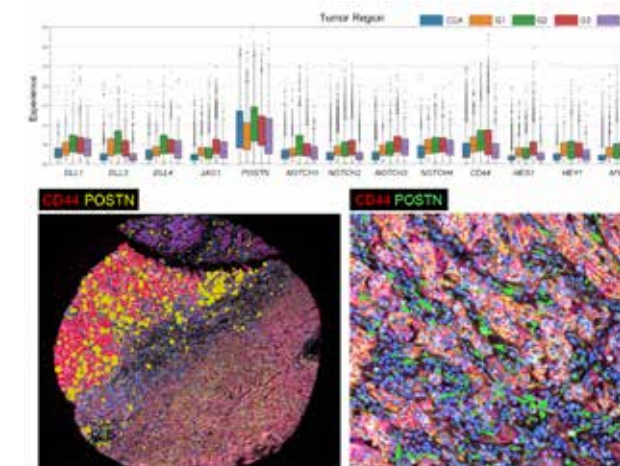


Figure 1.

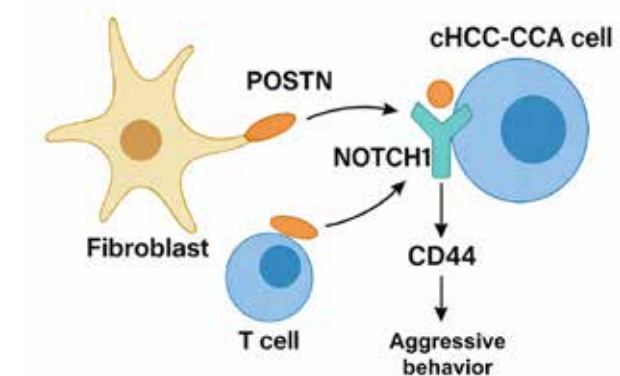


Figure 2.

PE-29

Circulating MIR-184 and MIR-206 as Predictive Biomarkers for Early Recurrence in HBV-Related Hepatocellular Carcinoma: A Prospective Study

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Aims: Early recurrence after curative resection remains a major challenge in hepatocellular carcinoma (HCC), particularly in hepatitis B virus (HBV)-related cases. Liquid biopsy using circulating microRNAs (miRNAs) offers a non-invasive approach to identify molecular markers predictive of recurrence.

Methods: We prospectively enrolled 30 individuals with HBV-related HCC presenting with a single tumor (<5 cm) and no vascular invasion or metastasis. Blood samples were collected preoperatively and on postoperative day 7. Expression of 20 selected miRNAs from circulating cell-free DNA/RNA and exosomes was analyzed. Participants were categorized into early recurrence (within 1 year, n=6) and non-recurrence (n=24) groups. Differentially expressed miRNAs were identified, and target genes of significant miRNAs were retrieved from miRtarBase. Protein-protein interaction (PPI) networks were constructed using STRING and visualized in Cytoscape. Enrichment analysis was performed using Gene Ontology and KEGG pathway databases.

Results: On postoperative day 7, expression of miR-184 and miR-206 was significantly lower in the early recurrence group than in the non-recurrence group ($P<0.05$). Other miRNAs showed no significant differences. Target gene analysis revealed 16 key hub proteins—CCND1, CCND2, KLF4, NOTCH3, BDNF, MET, CDK4, BCL2, AKT2, IGF1R, MYC, HDAC4, ESR1, KRAS, SMARCB1, and AGO2—enriched in cancer-related pathways and involved in HCC progression.

Conclusions: Reduced postoperative expression of miR-184 and miR-206 may predict early recurrence in individuals with HBV-related HCC. Their associated regulatory networks suggest possible mechanisms of recurrence and represent potential biomarkers for postoperative surveillance. Further studies are needed to validate their prognostic value.

Keywords: Liquid Biopsy, Hepatocellular Carcinoma, Early Recurrence

PE-30

Expression and Role of PD-L1 and SOX10 in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the fifth most common cancer and second leading cause of cancer-related mortality worldwide. This study aimed to investigate programmed death ligand-1 (PD-L1) and SRY-box transcription factor 10 (SOX10) expression in 191 HCC specimens and to analyze their association with clinicopathological features.

Methods: Formalin-fixed, paraffin-embedded HCC specimens were assessed for PD-L1 and SOX10 expression using immunohistochemical staining. Clinicopathological features were obtained from medical records and by reviewing hematoxylin and eosin-stained slides.

Results: The proportions of PD-L1-positive and SOX10-positive groups were 13.1% and 46.1%, respectively. PD-L1 positivity was significantly associated with higher T classification ($P<0.001$). SOX10 positivity was significantly associated with both higher T classification ($P<0.001$) and higher Edmondson-Steiner grade ($P<0.001$). In addition, PD-L1 expression showed a borderline correlation with SOX10 expression ($P=0.054$). In univariate analysis, both PD-L1 and SOX10 expression were associated with shorter overall survival (OS) and relapse-free survival (RFS) in patients with HCC.

Conclusions: PD-L1 and SOX10 expression were associated with unfavorable prognostic factors as well as shorter OS and RFS. Further investigation is warranted to elucidate the molecular pathways through which SOX10 may regulate PD-L1 expression and to explore implications for immunotherapy response in patients with HCC.

PE-31

C1QC-High Macrophages Define an Immune-Interactive Tumor Microenvironment Associated with Immunotherapy Response In Advanced Hepatocellular CarcinomaDooyeon Kim^{1,2}, Hye Ri Ahn¹, Sujin Kim^{1,2}, Soobeen Moon^{1,2}, Hui Gyeong Kim¹, Hyo Jung Cho¹

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Aims: Clinical responses to immune checkpoint inhibitors in advanced hepatocellular carcinoma (HCC) remain highly variable across patients, highlighting the need for biomarkers

that reflect the immune state of the tumor microenvironment (TME). Tumor-associated macrophages are key regulators of antitumor immunity and immune cell interactions.

Methods: Plasma proteomics (SOMAscan) was performed in responders ($n=5$) and non-responders ($n=5$) with advanced HCC treated with atezolizumab plus bevacizumab. Transcriptomic signatures associated with immunotherapy response were derived from a public RNA-seq cohort of 73 patients treated with atezolizumab plus bevacizumab. Candidate biomarkers were identified by directional concordance between plasma and tumor datasets and prioritized using ROC analysis. Their roles in the TME were evaluated using bulk and single-cell transcriptomic analyses in the Gepliver dataset.

Results: C1QC was identified as a biomarker associated with treatment response across plasma and tumor datasets. In both our cohort and an independent public RNA-seq dataset, C1QC expression was significantly higher in responders than in non-responders and showed strong discrimination of treatment response in both tumor transcriptomic (AUC=0.82) and plasma proteomic datasets (AUC=0.92). Tumors with high C1QC expression were enriched for an immunoregulatory myeloid program and showed increased immune cell-cell interaction activity. Consistently, higher C1QC expression was associated with improved survival in the TCGA HCC cohort. Single-cell transcriptomic analysis revealed that C1QC-expressing macrophages represent a distinct TAM population acting as interaction hubs within the tumor microenvironment, displaying enhanced signaling with T cells and an immune-interactive network.

Conclusions: C1QC-high macrophage programs define an immune-interactive TME and may serve as a predictive biomarker for immunotherapy response in advanced HCC.

Keywords: Hepatocellular Carcinoma, Immunotherapy, Tumor-Associated Macrophages, C1QC

PE-32

Comparison of a Generative Artificial Intelligence Model and a Hepatobiliary Multidisciplinary Team Recommendations in the Management of Hepatocellular Carcinoma: A Retrospective StudyCristina Ciulli¹, Emanuele Scarpa², Pasquale Chiacchio², Alessandro Fogliati¹, Mauro Alessandro Scotti¹, Antonio Ciaccio³, Antonio Rovere⁴, Christian Cotsoglu¹, Rita Niespolo³, Federica Elisei⁶, Michele Pietro Aprigliano⁷, Lorenzo Ripamonti¹, Mattia Garancini², Fabrizio Romano²

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Aims: The management of hepatocellular carcinoma (HCC) is based on decisions formulated by a multidisciplinary team (MDT) following evaluation of clinical history, imaging and prior therapies. Generative artificial intelligence (AI) tools are increasingly explored as decision-support systems in healthcare. This study aimed to compare treatment recommendations generated by a large language model with MDT decisions in patients with HCC.

Methods: Patients with HCC discussed at our hepatobiliary MDT between 01/2023 and 02/2025 were retrospectively included. Anonymized case summaries, excluding MDT conclusions, were submitted to ChatGPT-4 (OpenAI). Recommendations were categorized using a four-level progressive concordance scale: (1)treatment aim (curative vs palliative), (2)treatment extent (locoregional vs systemic), (3)treatment modality, and (4)specific technique. Concordance levels 1–2 were defined as Low Concordance (LC) and levels 3–4 as High Concordance (HC).

Results: 100 patients were included (median age 77 years). Liver function was Child–Pugh A in 76%, B in 13%, and normal in 11%. HCC was a first diagnosis in 53% of patients (43% multifocal) and a recurrence in 47%. HC between AI-generated and MDT recommendations was observed in 81% of cases, while 19% showed LC. In 78.9% of LC cases, discrepancies reflected the MDT's allocation for more aggressive interventions compared with AI. A significant difference in age distribution was observed between HC and LC groups ($P=0.001$), with other variables comparable.

Conclusions: Generative AI recommendations showed high agreement with expert MDT decisions in HCC management. While AI may support complex clinical decision-making, it appears less inclined to recommend aggressive or non-standard interventions, particularly in borderline scenarios.

Keywords: Hepatocellular Carcinoma, Artificial Intelligence, Multidisciplinary Team

PE-33

Identification of WDR54 as Novel Therapeutic Targets for Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the most prevalent primary liver malignancy, accounting for approximately 90% of all liver cancer cases. The primary etiologies of HCC include chronic hepatitis B or C infection, liver cirrhosis, alcohol consumption, obesity and exposure to aflatoxin. Notably, liver cirrhosis serves as a critical predisposing condition, present in

90% of HCC patients. Due to the lack of distinct early symptoms, most cases are diagnosed at an advanced stage, resulting in a poor prognosis. Current therapeutic modalities include surgical resection, liver transplantation, radiofrequency ablation (RFA) and the molecular targeted agent sorafenib. Despite these interventions, the overall average survival rate remains low at approximately 40%, highlighting significant therapeutic limitations and the urgent need for novel treatment strategies.

In this study, we utilized Gene Expression Profiling Interactive Analysis 3 (GEPIA3) to analyze 2,385 differentially expressed genes (DEGs) and 4,695 survival-related genes in liver cancer. By identifying the intersection of these datasets, we narrowed down potential gene candidates. Among them, we focused on WD repeat domain 54 (WDR54) to investigate its potential role as a therapeutic target or a prognostic biomarker.

Methods: *In-silico* Analysis

To investigate the differential expression of WDR54, we compared 160 normal liver samples with 371 HCC tissue samples using the GEPIA3 database. Furthermore, we leveraged three independent datasets from the Gene Expression Omnibus (GEO)—GSE144269, GSE77314, and GSE77276—to further validate the expression patterns of WDR54 in normal versus cancerous liver tissues. The prognostic significance of WDR54 expression on overall survival (OS) was subsequently evaluated using both GEPIA3 and the Kaplan-Meier plotter platforms.

In-vitro Analysis

To examine WDR54 expression levels across various liver cancer contexts, we cultured several HCC cell lines, including Hep3B, Huh7, SNU-449, HepG2, and PLC/PRF5. Total RNA was extracted from these cells then synthesized to cDNA. Subsequently, quantitative real-time PCR (qRT-PCR) was performed using a SYBR Green-based Master mix to quantify the transcriptional levels of WDR54 within each cell line.

Results: Comparative analysis of the GEPIA3 and GEO datasets confirmed that *WDR54* is significantly overexpressed in patients with HCC. Furthermore, Kaplan-Meier plotter analysis revealed that patients with high *WDR54* expression exhibited significantly lower OS rates compared to those with lower expression levels.

Consistent with these *in-silico* findings, qRT-PCR results showed that WDR54 expression was relatively low in Hep3B, whereas it was markedly elevated in Huh7. Given that Hep3B is characterized by a relatively less aggressive phenotype and Huh7 is known for its high aggressiveness, these results suggest a positive correlation between WDR54 expression levels and the clinical aggressiveness of HCC.

Conclusions: HCC accounts for 90% of all liver cancer cases and continues to present significant therapeutic challenges. To evaluate the potential of WDR54 as a therapeutic target, we initially performed an integrated *in-silico* analysis to assess

its expression levels and correlation with patient survival, followed by *in vitro* experimental validation. Our findings reveal a significant upregulation of WDR54 in both HCC patients and liver cancer cell lines, suggesting that WDR54 holds great potential as a diagnostic and prognostic biomarker.

Keywords: WD Repeat Domain 54 (WDR54), Hepatocellular Carcinoma (HCC), In Silico Analysis

PE-34

A Cancer-Associated Fibroblast Gene Signature Is Associated with Immune Microenvironment Features and Predicts Clinical Outcomes in Hepatocellular Carcinoma

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Aims: Cancer-associated fibroblasts (CAFs) are major components of the tumor microenvironment and contribute to tumor progression, immune regulation, and therapeutic resistance in hepatocellular carcinoma (HCC). However, the functional heterogeneity of CAF subtypes and their clinical relevance remain unclear in HCC. In this study, we aimed to characterize CAF-related gene signatures based on various public omics datasets and investigate their association with clinical outcomes in HCC.

Methods: Single-cell RNA sequencing datasets of HCC were analyzed to identify fibroblast populations and define CAF subtypes based on transcriptional profiles. Differential gene expression and pathway enrichment analyses were performed to characterize subtype-specific molecular functions. To evaluate the clinical relevance, CAF-related gene signatures derived from single-cell analysis were integrated with publicly available omics datasets. In addition, a CAF-associated risk score was constructed and its association with tumor stage and patient prognosis was examined.

Results: We identified multiple CAF subtypes with distinct transcriptional programs associated with extracellular matrix remodeling, inflammatory signaling, and tumor-stroma interactions. Integration of the CAF risk signatures with public omics datasets revealed that higher CAF-associated risk scores were significantly associated with advanced HCC stages and poorer survival outcomes. Functional analysis further demonstrated that stromal remodeling and immune-related pathways were significantly upregulated in tumors with high CAF-related signatures. In addition, the CAF risk signature showed a significant correlation with immune microenvironment remodeling.

Conclusions: CAF subtype-specific risk signatures were significantly associated with tumor progression and poor prognosis in HCC. These findings suggest that CAF-driven stromal programs represent potential therapeutic targets in hepatocellular carcinoma.

Keywords: Cancer-Associated Fibroblasts, Hepatocellular Carcinoma, Gene Signature, Bioinformatics

PE-35

Atezolizumab and Bevacizumab Therapy Combined with Expanded NK Cells Significantly Prolongs Survival in Vivo Hepatocellular Carcinoma Model

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Aims: Atezolizumab plus bevacizumab (Ate+Beva) proved better efficacy compared to sorafenib for advanced hepatocellular carcinoma (HCC) patients in IMbrave150 trial. However objective response rate of Ate+Beva therapy is around 30%, therefore several trials about combination protocol such as dual immune check point inhibitor plus bevacizumab etc. are ongoing to overcome this unmet need. Natural killer (NK) cell therapy is considered as promising tool that can enhance the efficacy of immunotherapy via several mechanism, however there are no studies about this issue. Therefore we performed preclinical study for efficacy of Ate+Beva therapy combined with expanded NK cell in HCC *in vivo* model.

Methods: SNU-398 cells were subcutaneously injected into the left flank (2.5×10^6) and right thigh (5×10^6) of SCID mice. Four days later, atezolizumab (10 mg/kg) and bevacizumab (5 mg/kg) were administered intraperitoneally, and NK cells (1×10^7) were injected via the tail vein. Tumor size (length $\times$ width) was measured twice weekly. Atezolizumab, bevacizumab, and NK cell treatments were repeated three times at 1-week intervals (Figure 1).

Results: Total 16 mice were categorized as four groups (Control, NK monotherapy, Ate+Beva, NK+Ate+Beva). The effect about shrinkage of tumor volume & survival rate were maximized in the NK+Ate+Beva therapy group compared to other three groups with significance statistically (Figure 2, 3). There were no meaningful toxicity in NK+Ate+Beva group compared to other three groups.

Conclusions: This study demonstrates that combination of NK cell with Ate+Beva can improve the efficacy of Ate+Beva therapy in HCC preclinical model. Further clinical prospective studies are needed for proving synergistic effect of NK cell and

Ate+Beva therapy to HCC patients.

Keywords: Atezolizumab, Bevacizumab, NK Cell, Hepatocellular Carcinoma

1. Mouse Treatment Scheme

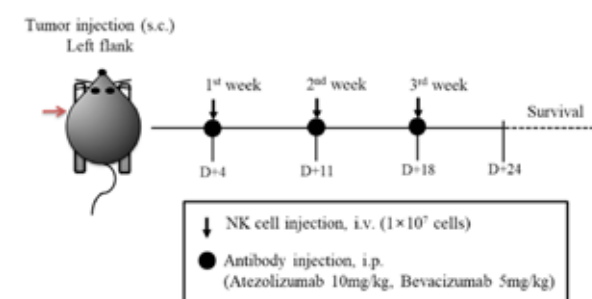


Figure 1.

2. Assessment of Tumor Size

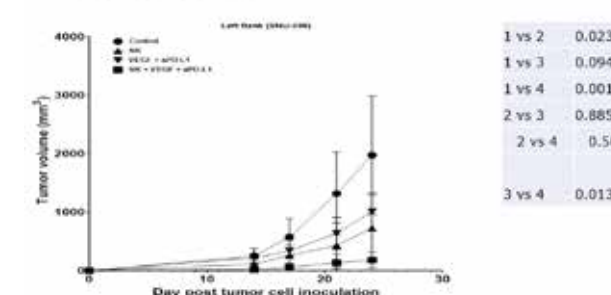


Figure 2.

3. Assessment of Survival Rate

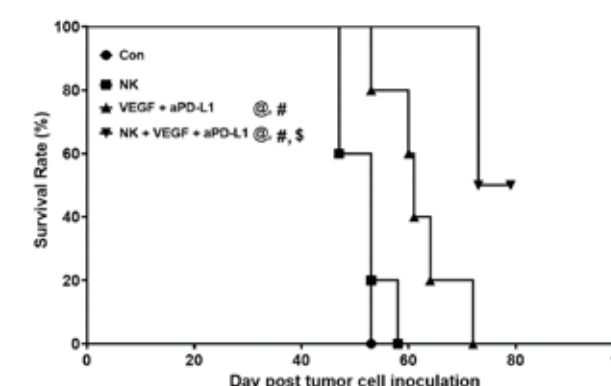


Figure 3.

PE-36

Comparative Feasibility of Liquid Biopsy Modalities for Immunotherapy Biomarker Discovery in Hepatocellular Carcinoma: Focus on Exosomal miRNA

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Aims: Reliable biomarkers for predicting response to immune checkpoint inhibitors in hepatocellular carcinoma (HCC) remain lacking. Liquid biopsy approaches, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomal microRNA (miRNA), have been explored; however, their comparative feasibility and biological relevance in this setting remain unclear.

Methods: Patients with advanced HCC treated with atezolizumab plus bevacizumab were prospectively enrolled. Peripheral blood samples were analyzed using three liquid biopsy modalities: CTC isolation (n=5), ctDNA methylation and genomic profiling (n=10), and exosomal miRNA sequencing (n=10, including healthy controls). Longitudinal samples were available in a subset of patients (n=3), allowing comparison between baseline and on-treatment profiles.

Results: CTC isolation demonstrated low yield and limited reproducibility across samples. Despite initial detection of CTCs with tumor-related markers, CD45 depletion resulted in reduced cell counts and inconsistent detection, limiting its applicability for downstream biomarker analysis.

ctDNA analysis was technically feasible in a subset of samples; however, frequent quality control failures and insufficient input material were encountered. Methylation profiling revealed heterogeneous patterns across patients, and tumor-specific signals were not consistently observed when compared with PBMC or tumor tissue, suggesting limited reliability as a biomarker in this setting.

In contrast, exosomal miRNA analysis showed higher technical stability with successful profiling in the majority of samples. In a subset of patients with paired samples (n=3), longitudinal analysis demonstrated dynamic changes in miRNA expression between baseline and on-treatment time points. Notably, several biologically relevant miRNAs, including miR-122 (liver-specific), miR-126 (angiogenesis-related), and miR-155 (immune modulation), exhibited treatment-associated variation. In addition, a marked increase in miR-4449, a potential immune-related candidate identified in our cohort, was observed, suggesting its possible involvement in tumor-immune interactions. These findings support the potential role of exosomal miRNA as a source of biologically meaningful signals.

Conclusions: Among the evaluated liquid biopsy modalities, exosomal miRNA demonstrated the most consistent and biologically relevant signals. These findings suggest that exosomal miRNAs, particularly those associated with immune regulation and angiogenesis, may serve as dynamic and non-invasive surrogates of tumor-immune interactions, warranting further investigation as biomarkers for immunotherapy in HCC.

Keywords: Hepatocellular Carcinoma, Liquid Biopsy, Exosomal MiRNA

PE-38

AMBRA1 Inhibits Hepatocellular Carcinoma Progression and Cancer Stemness by Regulating Nucleocytoplasmic Transport

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Aims: Hepatocellular carcinoma (HCC) is a highly aggressive malignancy driven by uncontrolled proliferation and the presence of cancer stem cells (CSCs). AMBRA1 has been implicated in cell cycle control and autophagy, but its role in regulating HCC stemness and its clinical significance remain unclear. This study aims to investigate the tumor-suppressive function of AMBRA1 and its regulatory mechanisms in HCC.

Methods: AMBRA1 expression was evaluated using bulk, single-cell, and spatial transcriptomics, with protein levels validated in a clinical HCC cohort. To investigate its function, we employed CRISPR/Cas9-mediated knockout (KO) using multiple guide RNAs in murine HCC cell lines. Functional impacts were assessed through proliferation and spheroid formation assays. *In vivo* tumorigenesis was evaluated using a somatic mutation-driven HCC mouse model. Mechanistically, tandem-affinity purification and mass spectrometry (TAP-MS) were performed to identify AMBRA1-interacting partners involved in its E3-ligase activity.

Results: Multi-omic and clinical analyses revealed that AMBRA1 is significantly downregulated in human HCC at both mRNA and protein levels. Low AMBRA1 expression was tightly associated with poor patient survival and exhibited a strong negative correlation with cancer stemness scores. *In vitro*, AMBRA1 deficiency in Hepa1.6 and RIL-175 cells significantly enhanced cell proliferation and increased spheroid formation capacity. *In vivo*, CRISPR-mediated KO of AMBRA1 accelerated liver tumor growth and reduced survival in mice. Mechanistically, TAP-MS analysis identified an enrichment of protein targets involved in nucleocytoplasmic transport, suggesting that AMBRA1 suppresses HCC progression and stemness by modulating nuclear–cytoplasmic trafficking.

Conclusions: Our findings establish AMBRA1 as a bona fide tumor suppressor that restricts HCC progression and CSC maintenance. By modulating nucleocytoplasmic transport, AMBRA1 serves as a critical regulator of liver oncogenesis and a potential target for therapeutic intervention.

Keywords: Hepatocellular Carcinoma (HCC), AMBRA1, Tumor Suppressor, Cancer Stemness

PE-39

INPP5B Regulates Lipid Metabolism and Cancer Stemness in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is characterized by marked heterogeneity and cancer stem cells (CSCs), which drive tumor progression and therapeutic resistance. Metabolic plasticity, particularly lipid metabolism remodeling, is critical for CSC maintenance, yet the underlying mechanisms remain unclear. We hypothesize that inositol polyphosphate-5-phosphatase B (INPP5B) regulates lipid metabolism to control CSC properties and tumorigenesis in HCC.

Methods: Public datasets (TCGA-LIHC and GSE14520) were analyzed to evaluate INPP5B expression and clinical associations. Functional studies were performed using INPP5B overexpression and knockdown HCC cell models. CSC-related phenotypes were evaluated by spheroid formation and stemness marker expression. Lipid metabolism was assessed by Oil Red O and BODIPY staining. Transcriptomic profiling and gene ontology analyses were performed to identify pathways associated with INPP5B. Tumorigenicity was assessed in subcutaneous and hydrodynamic tail vein mouse models. PI(4,5)P₂ supplementation and ATGL-related assays were included as preliminary analyses.

Results: INPP5B expression was reduced in poorly differentiated, CSC-enriched HCC tumors and correlated with worse survival. INPP5B overexpression suppressed spheroid formation and tumor-initiating capacity, whereas knockdown produced the opposite effects. INPP5B overexpression reduced lipid droplet accumulation without significantly affecting fatty acid uptake, suggesting altered lipid utilization. Transcriptomic analyses indicated that INPP5B regulates pathways involved in lipid droplet turnover and fatty acid metabolism. *In vivo*, INPP5B overexpression reduced tumor growth, while its loss promoted lipid accumulation and tumor progression. Preliminary analyses suggest a potential involvement of phosphoinositide signaling and ATGL-mediated lipolysis in these processes.

Conclusions: INPP5B is associated with regulation of lipid metabolism and CSC-related phenotypes in HCC. Reduced INPP5B expression correlates with lipid accumulation and enhanced tumorigenic potential. These findings support a role for INPP5B-linked metabolic pathways in HCC progression and suggest potential therapeutic relevance.

Keywords: Hepatocellular Carcinoma, Lipid Metabolism, Cancer Stem Cells

PE-40

An Investigation of GPATCH4 as a Potential Oncogene in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths worldwide. G-patch domain-containing 4 (GPATCH4) is known to regulate nucleolar structure and cell growth. However, its role in HCC remains unknown. This study aims to investigate the clinical significance and oncogenic potential of GPATCH4 in HCC.

Methods: We evaluated the tumor-promoting potential of GPATCH4 using public online cancer databases (TCGA, GEPIA2, UALCAN, TNMplot, and Kaplan-Meier plotter). These analyses compared GPATCH4 expression between normal and HCC tissues. Additionally, we assessed its correlation with cancer stage, tumor grade, survival, and metastasis rates. For *in vitro* validation, quantitative real-time PCR (qRT-PCR) was performed to measure GPATCH4 expression across five human HCC cell lines.

Results: Bioinformatic analyses revealed that GPATCH4 expression was significantly upregulated in HCC tissues compared to normal counterparts. This upregulation correlated with advanced stages, increased metastasis, and poorer clinical outcomes. Furthermore, *in vitro* analysis confirmed the basal expression of GPATCH4 across multiple HCC cell lines, establishing models for future functional studies.

Conclusions: Through comprehensive bioinformatic analysis, this study demonstrates the significant upregulation and clinical relevance of GPATCH4 in HCC, supported by its confirmed expression *in vitro*. These findings suggest its potential role in tumor progression. Ultimately, our results provide deeper insights into HCC pathogenesis and propose GPATCH4 as a promising prognostic biomarker.

Keywords: GPATCH4, Hepatocellular Carcinoma, Public Online Cancer Databases

14. Liver Cancer, Clinical

PE-1

Association of Tumor Location with Therapeutic Outcomes after Radical Resection for Hepatocellular Carcinoma: A Retrospective Study

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Aims: To assess the association between tumor distance to the main or first-order portal vein and prognosis in patients with HCC undergoing curative resection.

Methods: This retrospective cohort study evaluated patients with HCC who underwent curative resection between January, 2018, and September, 2024. Tumors were categorized according to anatomical location as central or peripheral. Central tumors were defined as those located within 2cm of the main portal vein trunk or its first-order branches, whereas all remaining tumors were classified as peripheral. RFS and OS were compared between the 2 groups.

Results: A total of 667 patients with HCC who underwent curative resection were initially included. After propensity score matching, 247 patients were retained in each group. In the matched cohort, the median recurrence-free survival was 23.0 months (95%CI, 18.08–28.0) among patients with centrally located tumors and 30.5 months (95%CI, 26.28–34.8) among those with peripherally located tumors ($P < 0.05$). The median overall survival was 56.0 months (95%CI, 52.18–59.9) in the central tumor group and 72.0 months (95%CI, 67.48–76.6) in the peripheral tumor group ($P < 0.05$). Multivariable Cox proportional hazards analysis demonstrated that a tumor located less than 2cm from the main trunk or first-order branch of the portal vein was independently associated with an increased risk of recurrence-free survival (HR=1.74) and overall survival (HR=1.73) following curative resection (all $P < 0.05$).

Conclusions: Among patients with hepatocellular carcinoma undergoing curative resection, a shorter tumor–portal vein distance was associated with poorer prognosis.

Keywords: HCC, Tumor Location, Radical Resection

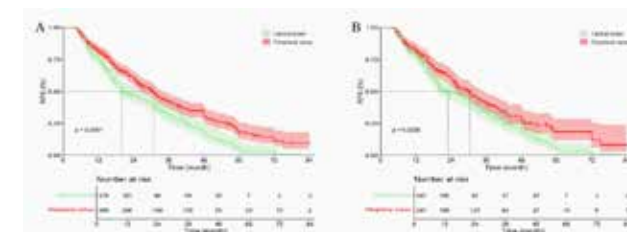


Figure 1.

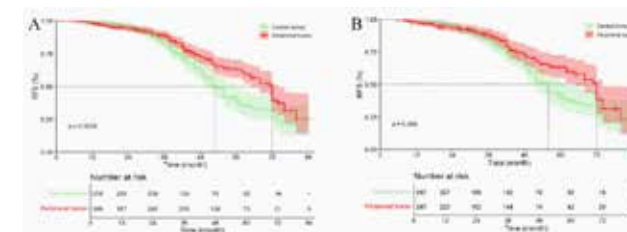


Figure 2.

PE-2

Early-Onset Liver Cancer Burden in Southeast Asia: Sex-Specific and Nutrition-Related Patterns from the Global Burden of Disease Study

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Department of Internal Medicine, Universitas Islam Indonesia, Indonesia

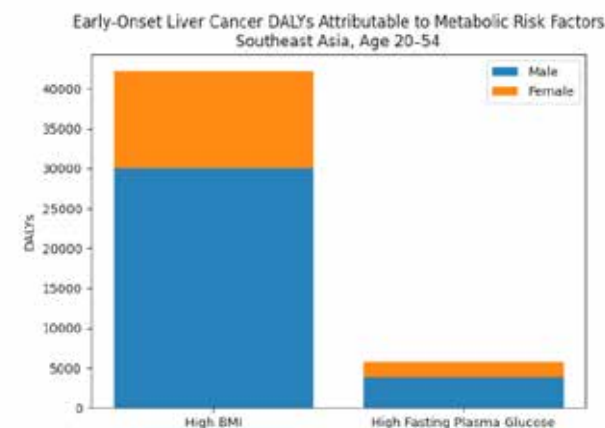
Aims: Liver cancer remains a leading cause of cancer-related mortality worldwide and represents a major burden within hepatobiliary surgical practice. Although traditionally regarded as a malignancy of older adults, early-onset liver cancer has emerged as a growing concern in Southeast Asia amid rapid nutritional and metabolic transitions. Rising prevalence of obesity and hyperglycemia may contribute to shifting age and sex patterns of disease burden alongside established etiologies. However, population-level evidence describing early-onset liver cancer in Southeast Asia from a sex-specific and nutrition-related perspective remains limited. This study aimed to quantify the burden of early-onset liver cancer in Southeast Asia and to examine sex-based disparities attributable to metabolic risk factors.

Methods: A secondary analysis of 2023 estimates from the Global Burden of Disease Study was conducted. Analyses were restricted to Southeast Asian countries. Early-onset liver cancer was defined as diagnosis occurring between 20 and 54 years of age. Outcomes included disability-adjusted life years (DALYs), years of life lost (YLL), and years lived with disability (YLD) attributable to high fasting plasma glucose and high body mass index (BMI). Estimates were stratified by sex.

Results: In 2023, early-onset liver cancer burden attributable to metabolic risk factors demonstrated pronounced sex-specific disparities. High BMI was the dominant contributor, accounting for 29,929 DALYs among males compared with 12,255 DALYs among females. High fasting plasma glucose contributed 3,863 DALYs in males and 1,947 DALYs in females. Across both risk factors, DALYs were overwhelmingly driven by YLL, indicating substantial premature mortality. High BMI accounted for 29,736 YLLs in males and 12,171 YLLs in females, while high fasting plasma glucose contributed 3,838 YLLs and 1,933 YLLs, respectively. In contrast, YLDs constituted a minimal proportion of the total burden, with high BMI contributing 193 YLDs in males and 83 YLDs in females, and high fasting plasma glucose contributing 25.58 YLDs and 13.68 YLDs, respectively.

Conclusions: Early-onset liver cancer in Southeast Asia imposes a substantial and predominantly fatal burden, disproportionately affecting males. Obesity and hyperglycemia emerged as key modifiable nutritional and metabolic risk factors, underscoring their relevance for prevention strategies.

Keywords: Early Onset Liver Cancer, Metabolic Risk Factor, DALYs, YLLS



PE-3

Prognostic Impact of Acute-on-Chronic Liver Failure in Hepatocellular Carcinoma with Acute Decompensation

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Aims: Acute-on-chronic liver failure (ACLF) strongly determines outcomes in cirrhosis; however, its role in patients with hepatocellular carcinoma (HCC) presenting with acute decompensation (AD) remains unclear. We aimed to evaluate the prognostic impact of ACLF and relevance of tumor-related precipitating events (PEs).

Methods: We retrospectively analyzed 256 patients with HCC and cirrhosis admitted for AD. ACLF was defined according to the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) criteria. PEs were classified as non-tumor, tumor-related, or unidentified. The primary endpoint was 28-day mortality. We used Cox proportional hazards models to identify independent prognostic factors.

Results: At admission, 66 patients (25.8%) were diagnosed with ACLF. The 28-day mortality rate was significantly higher in the ACLF group than in the non-ACLF group (63.6% vs. 15.8%, $P < 0.001$). Mortality increased progressively with ACLF grade (38.1%, 64.0%, and 90.0% for grades 1, 2, and 3, respectively). In multivariable analysis, ACLF was the strongest independent predictor of 28-day mortality (hazard ratio: 5.39; 95% confidence interval: 3.26–8.93; $P < 0.001$) and maintained its prognostic value across Barcelona Clinic Liver Cancer (BCLC) stages and PE types. Notably, patients with tumor-related PEs (31.6%) demonstrated 28-day mortality comparable with those with

non-tumor PEs (23.5% vs. 22.9%, $P = 1.000$).

Conclusions: The EASL-CLIF criteria provide robust risk stratification for short-term mortality in patients with HCC presenting with AD, independent of tumor stage. Tumor-related events confer mortality risks comparable with traditional insults, supporting their inclusion in the ACLF framework.



Figure 1.

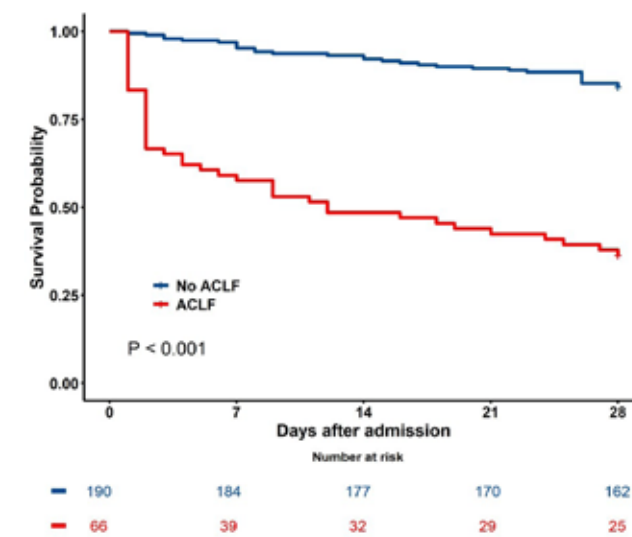


Figure 1. Kaplan-Meier survival estimates for 28-day mortality according to the presence of ACLF at admission.

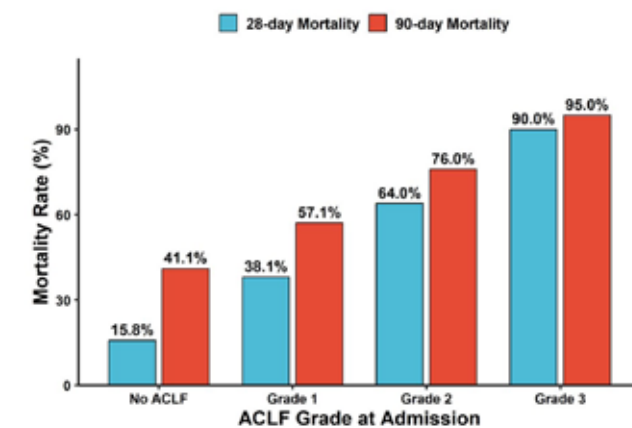


Figure 3. 28-day and 90-day mortality rates stratified by ACLF grade.

Keywords: Hepatocellular Carcinoma, Acute-On-Chronic Liver Failure, Acute Decompensation, Mortality

PE-4

Impact of Transitional-Phase Parenchymal Signal Intensity on LI-RADS Performance in Hepatocellular Carcinoma

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Aims: To compare the diagnostic performance of Liver Imaging Reporting and Data System (LI-RADS) according to different washout assessments incorporating TP liver parenchymal signal intensity on gadoxetate-enhanced MRI, and to identify factors associated with hyperintense TP liver parenchyma.

Methods: This retrospective study included patients who underwent gadoxetate-enhanced MRI and subsequent hepatic resection or liver transplantation between January 2019 and December 2020. Signal intensity of TP liver parenchyma was assessed relative to the portal vein and categorized as hypo, iso, or hyperintense. Washout was defined as: (a) confined to the portal venous-phase only, consistent with LI-RADS v2018 (PVP-only); (b) extending to the TP regardless of TP liver parenchymal signal intensity (TP-all); and (c) extending to the TP only when TP liver parenchymal signal was hypointense or isointense (TP-iso/hypo). Sensitivity and specificity of LR-5 were compared across these definitions using generalized estimating equations. Univariable and multivariable logistic regression analyses were performed to identify predictors of hyperintense TP parenchyma.

Results: A total of 438 patients (mean age $\pm$ SD: 60 $\pm$ 9.1 years; 345 men) with 558 hepatic observations were included. 25.6% (112/438) of patients showed hyperintense liver parenchyma in the TP, while 51.6% (226/438) showed isointense liver parenchyma and 22.8% (100/438) showed hypointense signal. Compared with PVP-only, TP-iso/hypo showed higher sensitivity (77.8% [332/427] versus 70.7% [302/427]; $P < .001$) without evidence of a reduction in specificity (96.2% [126/131] versus 96.9% [127/131]; $P = .95$). Low BMI (adjusted odds ratio [OR]: 0.89, $P = .003$), low bilirubin (adjusted OR: 0.62, $P = .03$), and high cardiac index (adjusted OR: 2.89, $P = .03$) were associated with hyperintense TP liver parenchyma.

Conclusions: Extending non-peripheral washout to the TP on gadoxetate-enhanced MRI while considering TP liver parenchymal signal intensity enhanced the diagnostic performance of LI-RADS for HCC.

Keywords: Hepatocellular Carcinoma, Liver Imaging Reporting And Data System (LI-RADS), Gadaxetate-Enhanced MRI, Transitional Phase, Washout

Table 1. Diagnostic performance of LI-RADS for the diagnosis of HCC according to the three different washout definitions.

Washout criteria	True-positive	False-positive	True-negative	False-negative	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
PVP-only*	302	4	127	125	70.7 [302/427] (66.5–74.9)	96.9 [127/131] (94.1–99.8)	76.9 [429/558] (73.2–80.2)
TP-all†	337	12	119	90	78.9 [337/427] (75.1–82.8)	90.8 [119/131] (85.8–95.9)	81.7 [456/558] (78.2–84.8)
TP+ iso/hypo‡	332	5	126	95	77.8 [332/427] (73.9–81.6)	96.2 [126/131] (93.0–99.4)	82.1 [458/558] (78.6–85.1)
P value (PVP-only vs. TP-all)					<.001	.02	<.001
P value (PVP-only vs. TP-iso/hypo)					<.001	.95	<.001
P value (TP-all vs. TP-iso/hypo)					.07	.02	>.99

Key findings: Compared with PVP-only washout, extending washout to TP-iso/hypo had a higher sensitivity for HCC diagnosis (77.8% vs 70.7%, $P<.001$), with no different specificity (96.2% vs 96.9%, $P=.95$).
Note—Unless otherwise mentioned, numbers are percentages with 95% confidence intervals in parentheses.
P-values were adjusted for multiple comparisons using the Bonferroni method. $P<.05$ was considered statistically significant.
*Washout was confined to the portal venous-phase only, consistent with LI-RADS v2018.
†Washout was extended to the transitional phase regardless of transitional-phase liver parenchyma signal intensity.
‡Washout was extended to the transitional phase only when transitional-phase liver parenchyma signal intensity was isointense or hypointense.
HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; PVP, portal venous-phase; TP, transitional phase

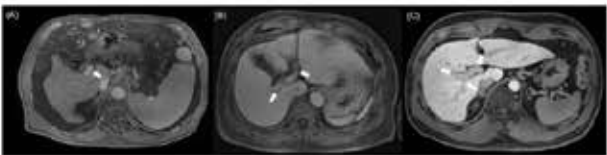


Figure 1. Transitional-phase liver parenchymal signal intensity relative to the portal vein (arrows) on gadolinium-enhanced MRI. Hypointense (A), isointense (B), and hyperintense (C) liver parenchyma. Hyperintense liver parenchyma may cause pseudowashout.

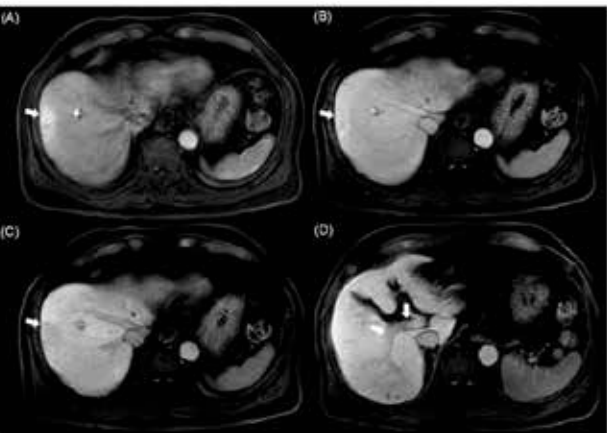


Figure 2. An 85-year-old man with chronic hepatitis B. (A–D) Gadolinium-enhanced MRI shows a 3.0-cm non-rim arterial-phase hyperenhancing mass (arrow) in segment 8 (A) without nonperipheral washout on portal venous-phase (B). The mass is hypointense on transitional phase (C). The lesion is categorized as LR-4 (probably HCC) according to LI-RADS v2018. If washout is extended to the transitional phase regardless of transitional-phase liver parenchymal signal intensity (TP-all), the lesion is categorized as LR-5 (definitely HCC). However, because the transitional-phase parenchyma is hyperintense relative to the portal vein (D, arrow), the lesion is categorized as LR-4 under the TP-adequate criteria. Pathology confirmed cholangiocarcinoma, indicating a true-negative result under the TP-adequate criteria under which LR-5 is considered positive for HCC.

PE-5

Unveiling Heterogeneous Sex Effects on Hepatocellular Carcinoma Survival: A Machine Learning-Based Individualized Analysis Using a Nationwide Registry

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Aims: While a male predominance in hepatocellular carcinoma (HCC) incidence is well-established, the individualized impact of biological sex on survival remains complex and heterogeneous. This study aimed to comprehensively analyze sex differences in HCC survival and quantify individualized sex effects using a machine learning-based approach.

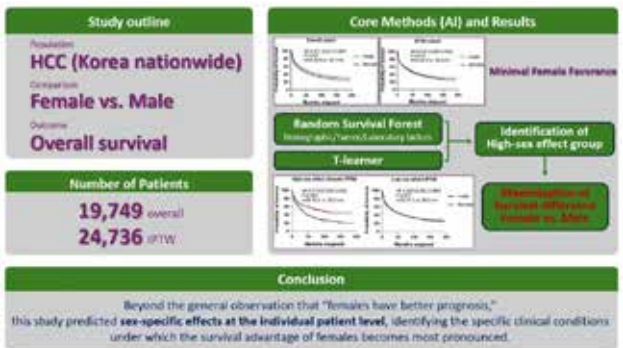
Methods: We analyzed a nationwide cohort of 19,749 patients diagnosed with HCC between 2000 and 2020. Survival outcomes were evaluated using multivariate Cox regression and Inverse Probability of Treatment Weighting (IPTW). To estimate the individualized effect of sex on survival, we developed a Random Survival Forest (RSF) model. A T-Learner approach was then applied to calculate the individual risk difference between assuming a female versus male sex for each patient, classifying them into high (female favorable) and low sex effect groups.

Results: The cohort comprised 15,608 males (79.0%) and 4,141 females (21.0%). Female sex was an independent favorable prognostic factor in the IPTW cohort (Hazard Ratio [HR] 0.883, $P<0.001$). This survival benefit was age-dependent, being most prominent in younger patients (<55 years) and entirely diminishing after age 75. Permutation importance analysis identified tumor stage and extrahepatic spread as the most critical survival predictors. Notably, the T-Learner identified a distinct “high sex effect” subgroup (16.3% of patients) characterized by younger age, severely impaired liver function, and advanced tumor stage (particularly stage IVB). Within this female favorable subgroup, females exhibited a profoundly longer median overall survival compared to males (IPTW, 95.5 vs. 31.2 months; HR 0.573, $P<0.001$). Conversely, the remaining 83.7% (“low sex effect” group) showed no significant sex-based survival difference after IPTW adjustment (HR 1.022, $P=0.477$).

Conclusions: The survival benefit of female sex in HCC is not uniform but highly heterogeneous. The protective effect of female sex is profoundly amplified in a specific subset of patients presenting with poor liver function and advanced-stage disease. Utilizing machine learning to assess individualized prognostic factors highlights the necessity for tailored therapeutic and prognostic strategies based on a patient’s unique

clinical and biological profile.

Keywords: Hepatocellular Carcinoma; Sex Difference; Machine Learning; Precision Medicine



PE-6

Sex Disparities in Hepatocellular Carcinoma: Epidemiologic Insights into Stage-Driven Survival and Treatment Inequality from a Nationwide Cohort

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Aims: Sex disparities in hepatocellular carcinoma (HCC) are well recognized; however, whether the observed female survival advantage reflects intrinsic tumor biology or stage distribution remains unclear. In addition, age-dependent treatment disparities have not been comprehensively evaluated.

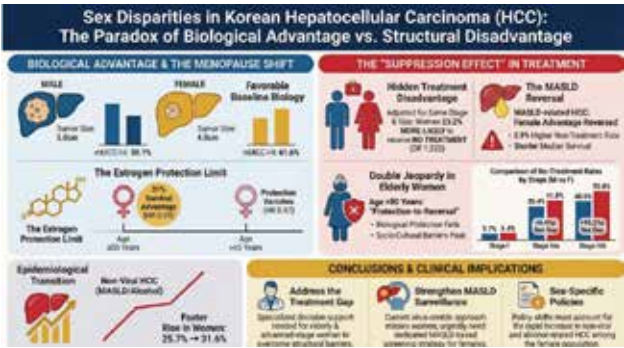
Methods: We analyzed 19,729 patients with HCC registered in the Korean Primary Liver Cancer Registry (2008–2020). Multivariable Cox regression, stage-stratified survival analyses, competing-risk sensitivity models, and logistic regression for no-treatment were performed. Age–sex interaction and etiologic subgroup analyses were conducted.

Results: Females were older at diagnosis but presented with smaller tumors, lower vascular invasion rates, and a higher proportion of early-stage disease. In unadjusted analysis, female sex was associated with superior overall survival (HR 0.830, 95% CI 0.784–0.879). After adjustment for stage and liver function, the association attenuated (HR 0.869), and stage-stratified analyses demonstrated nearly overlapping survival curves across all stages, indicating that the apparent survival advantage was largely mediated by stage distribution.

Although overall untreated rates were similar (~18%), multivariable logistic regression revealed a suppression effect: after adjusting for tumor burden and liver function, female sex was independently associated with a 23% higher likelihood of receiving no treatment (OR 1.232, 95% CI 1.059–1.433).

Age-stratified analyses demonstrated a protection-to-reversal pattern. The survival advantage of female sex was evident below age 65 but disappeared thereafter. Untreated proportions crossed over around age 80, with females aged ≥ 85 years exhibiting substantially higher untreated rates. Among etiologic subgroups, Other/MASLD was the only category showing reversal, with females experiencing higher untreated rates and shorter survival compared with males.

Conclusions: The apparent survival advantage associated with female sex in HCC is largely explained by favorable stage distribution rather than intrinsic within-stage biology. Structural treatment inequality becomes evident after clinical adjustment and is magnified in very elderly patients and in MASLD-related HCC. These findings underscore the need for age- and etiology-specific strategies to mitigate sex-based disparities in HCC care.



Keywords: Healthcare Disparities; Hepatocellular Carcinoma; Masld; Menopause; Sex Disparity

PE-7

Cytokeratin 19 Expression Stratifies Outcomes with Hepatic Arterial Infusion Chemotherapy but Not Atezolizumab plus Bevacizumab in Advanced Hepatocellular Carcinoma

Kwon Yong Tak¹, Keungmo Yang¹, Hee Sun Choi¹, Ji Won Han¹, Suho Kim², Jung Suk Oh², Jeong Won Jang¹, Pil Soo Sung¹

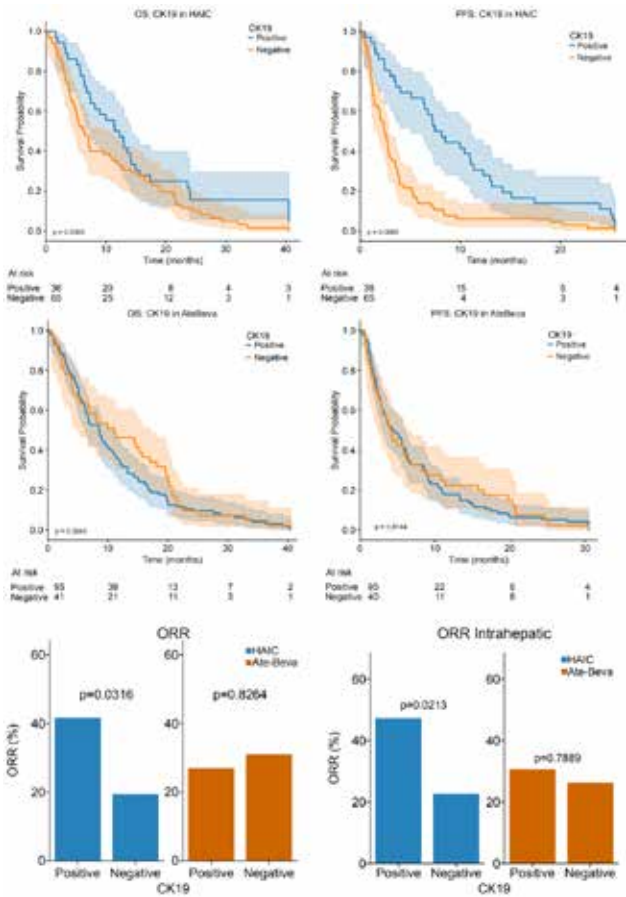
¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul St Mary’s Hospital, The Catholic University of Korea, Seoul, Republic of Korea; ²Department of Radiology, Seoul St Mary’s Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Cytokeratin 19 (CK19)-positive hepatocellular carcinoma (HCC) exhibits biliary/progenitor features and aggressive biology, raising uncertainty regarding the optimal therapeutic strategy for this subgroup. We evaluated the prognostic and predictive value of CK19 expression according to treatment modality in patients with advanced HCC treated with hepatic arterial infusion chemotherapy (HAIC) or atezolizumab plus bevacizumab.

Methods: We retrospectively analysed consecutive patients

with advanced HCC who received atezolizumab plus bevacizumab or HAIC between January 2020 and July 2025. Only patients with available tumour biopsy and immunohistochemical assessment of CK19 were included. Overall survival (OS) and progression-free survival (PFS) were compared by CK19 status within each treatment group using Kaplan-Meier analysis and log-rank testing. Objective response rate (ORR), including overall and intrahepatic responses, was evaluated by radiologic assessment, excluding non-evaluable cases. Categorical variables were compared using chi-square tests.

Results: We included 136 patients treated with atezolizumab plus bevacizumab (CK19-positive n=95; CK19-negative n=41; median follow-up 8.7 months) and 101 treated with HAIC (CK19-positive n=36; CK19-negative n=65; median follow-up 7.4 months). In the atezolizumab plus bevacizumab group, OS and PFS did not differ by CK19 status (OS $P=0.3643$; PFS $P=0.8144$), and ORR was similar for both overall ($P=0.8264$) and intrahepatic responses ($P=0.7889$). In contrast, in the HAIC group, CK19-positive tumours showed improved OS and PFS compared with CK19-negative tumours (OS $P=0.0365$; PFS $P<0.0001$). ORR was higher in CK19-positive than CK19-negative tumours after HAIC for both overall response (41.7% vs 19.4%, $P=0.0316$) and intrahepatic response (47.2% vs 22.6%, $P=0.0213$).



Conclusions: CK19 expression identifies a subgroup of advanced HCC with differential outcomes following HAIC, whereas outcomes with atezolizumab plus bevacizumab were not stratified by CK19 status. CK19 assessment may support biomarker-informed selection of HAIC in advanced HCC, warranting prospective validation.

Keywords: Hepatocellular Carcinoma, Combined Hepatocellular-Cholangiocarcinoma, Atezolizumab Plus Bevacizumab, Hepatic Arterial Infusion Chemotherapy

PE-8

Gaps in Essential Diagnostics for Early Detection of Hepatocellular Carcinoma in India

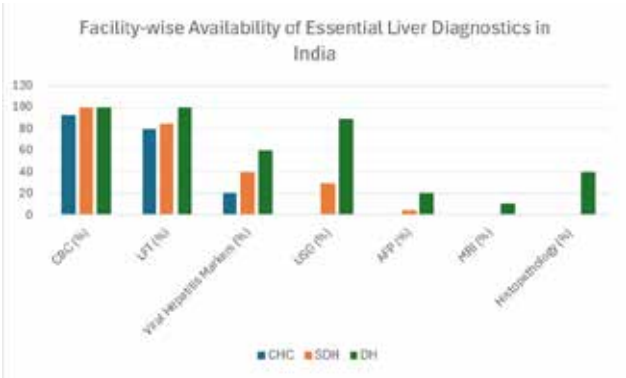
Sahil Arora¹, Pooja Gupta²

¹Department of Pathology Amity University Gurugram, ²Department of Basic Science Amity University Gurugram, India

Aims: Chronic liver diseases—including hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis, and metabolic dysfunction-associated steatotic liver disease (MASLD)—are major risk factors for hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality in India. Early diagnosis through laboratory testing, viral serology, imaging, and histopathology is critical to reduce progression to advanced liver disease and liver cancer. This study aimed to assess the availability of essential liver-related diagnostics across public healthcare facilities in India and identify systemic gaps affecting early detection.

Methods: A cross-sectional survey was conducted across 30 government healthcare facilities in four Indian states (Himachal Pradesh, Uttar Pradesh, Assam, and Tripura). Availability of liver-related diagnostics was assessed using benchmarks from the Essential Diagnostics List 2023 by the World Health Organization and the National Essential Diagnostics List 2019 by the Indian Council of Medical Research. Facilities included District Hospitals (DHs, n=9), Sub-District Hospitals (SDHs, n=7), and Community Health Centres (CHCs, n=14). Diagnostics evaluated included liver function tests (LFTs), viral hepatitis markers (HBsAg, Anti-HCV), alpha-fetoprotein (AFP), imaging (USG, CT, MRI), and histopathology.

Results: Overall availability of recommended diagnostics was 54% in DHs, 49% in SDHs, and 52% in CHCs. While LFTs and CBC were available in 100% of DHs, access to advanced diagnostics was limited: MRI (11%), bone marrow aspiration (22%), and AFP testing were inconsistently available. USG was present in 89% of DHs but nearly absent in CHCs (0.10%). Viral hepatitis testing was variable across facilities. Geographic disparities were observed, with availability ranging from 57% in Himachal Pradesh to 44% in Tripura. Remote facilities reported availability as low as 22% of recommended tests.



State	Surveyed	CBC	LFT	Viral Hep	USG	AFP	MRI	Histopathology
Assam	Cachar	43.75	17.19	80	0	62.50	67.50	7.50
	Goalpara	70	10	50	20	60	30	20
	Hailakandi	100	0	80	20	80	20	0
	Karimganj	96.05	10.53	31.58	7.89	40.79	10.53	2.63
Delhi	Kamrup M	100	33.33	100	33.33	100	33.33	33.33
	West Delhi	100	0	0	0	100	100	0
Haryana	New Delhi	100	25	75	50	100	100	0
	Faridabad	87.50	0	62.50	0	87.50	25	0
Himachal Pradesh	Srinagar	98.25	96.49	1.75	1.75	5.25	1.75	0
	East Imphal	55.56	11.11	25	25	77.78	0	0
Jharkhand	West Imphal	83.33	50	100	100	33.33	100	100
	Bishnupur	75.00	75	75	75	75	75	75
Kerala	Jaipur	100	0	14.29	0	92.86	35.71	0
	North Tripura	60	20	80	40	100	20	20
Madhya Pradesh	South Tripura	100	30	100	0	80	14.29	14.29
	Unakoti	100	40	80	40	80	20	0
Odisha	West Tripura	100	33.33	100	25	83.33	25	25
	Aligarh	100	8.33	100	33.33	100	75	8.33
Uttar Pradesh	Budaun	100	0	70	10	100	50	0
	Bulandshahr	100	0	100	0	100	100	12.50
West Bengal	Kasganj	100	0	100	20	100	40	0
	Gautam B	100	40	100	0	90	20	20
Total		84.34	29.22	40.36	8.13	57.23	25.30	5.72

Conclusions: Significant gaps exist in access to essential liver diagnostics across India's public health system, particularly at primary and secondary care levels. Limited availability of viral serology, imaging, and tumor markers may delay detection of cirrhosis and HCC. Strengthening laboratory infrastructure, expanding hepatitis screening, and improving imaging access are critical to enabling early diagnosis and reducing liver-related mortality.

Keywords: Hepatocellular Carcinoma, Essential Diagnostics, Health Systems Gaps, India

PE-9

Malignant Transformation of Infantile Hepatic Hemangioma to Angiosarcoma in a Four-Year Old Male

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Aims: Infantile hepatic hemangioma (IHH) is typically benign and responsive to beta-blockers and/or endovascular therapy. We report a rare case of suspected malignant transformation of IHH to hepatic angiosarcoma.

Methods: A 4.5-year-old boy had a cutaneous hemangioma on the right abdominal wall since birth, maximal at 6 months, with good response to propranolol and an asymptomatic interval for ~1.6 years. At ~2 years, he developed a painless right upper abdominal mass. Contrast CT suggested IHH. He received propranolol and transarterial embolization (TAE) with transient reduction followed by progression over 6 months. Two further transarterial chemoembolization (TACE) sessions produced poor response

Results: The child underwent left hepatectomy with R0 resection and postoperative imaging showed no residual hepatic lesion. Histology of the resection specimen showed atypical vascular areas suspicious for angiosarcoma. At 3-month review, recurrence was detected in the remnant lobe. PET-CT demonstrated a metabolically active hepatic lesion with peritoneal metastases. He is receiving systemic chemotherapy (bevacizumab, doxorubicin, vincristine), with consideration of liver transplantation after cytoreduction.

Conclusions: Refractory growth of presumed IHH despite appropriate beta-blocker therapy and repeated endovascular interventions, and early post-resection recurrence, should prompt reconsideration of diagnosis and early tissue confirmation. Hepatic angiosarcoma, though exceptionally rare in children, can mimic IHH and requires multidisciplinary oncologic management.

Keywords: Infantile Hepatic Hemangioma, Hepatic Angiosarcoma, Transarterial Embolization, Chemoembolization (TAE/TACE), Malignant Transformation, Recurrence

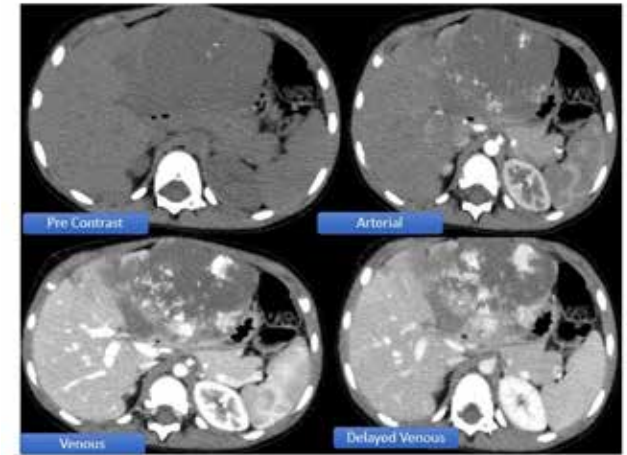


Fig2 : Baseline CT



Fig 3 Hepatectomy

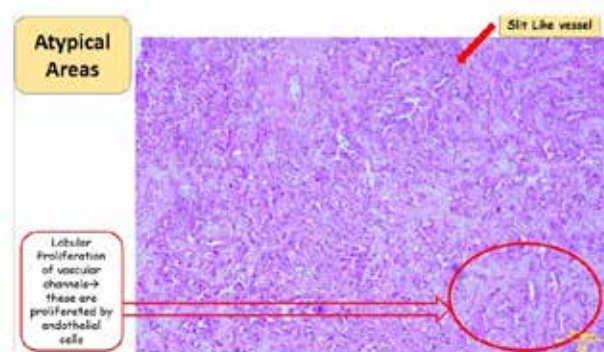


Fig 4 Histology suggestive of angiosarcoma

PE-10

A New Machine Learning-Based Algorithm to Identify Patients with Hepatocellular Carcinoma

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Aims: The aim of this study was to develop a machine learning model to identify, through the integration of clinical and laboratory data, patients with HCC from patients with liver cirrhosis (LC).

Methods: The population study (n=160) with available clinical and laboratory data, was classified in 2 subgroups of patients, prospectively followed up in our referral center: 72 patients with LC, 88 with HCC. The different groups of patients were used as training set. Using machine learning algorithms, classifiers were created using Random Forest analysis, Random Ferns classification and the Ensemble approach.

Results: Data from the 160 patients with LC and HCC were used to create a classifier using a Random Forest model. This model was then validated on the same dataset with an overall classification error of 0.23125, specifically 0.2778 for LC and 0.1932 for HCC. The same data were then analyzed with a Random Ferns model (accuracy: 0.7312, F1 score: 0.7190, kappa:

0.4632), and an ensemble approach method (accuracy 0.9938, kappa 0.9874). The SuperLearner was able to classify patients with high sensitivity and specificity.

Conclusions: This machine learning approach identified a potential new algorithm that could help clinicians identify patients with HCC.

Keywords: HCC, Machine Learning, Artificial Intelligence, Diagnosis

PE-11

Advanced Hepatocellular Carcinoma Achieving Complete Response to Atezolizumab and Bevacizumab: A Report of Two Cases

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Aims: Palliative systemic therapy is the mainstay of treatment for advanced hepatocellular carcinoma (HCC). The complete response (CR) rate to systemic therapy is very low, with the highest rate reported in the IMbrave150 trial at 7.7%. Here, we report two cases of advanced HCC achieving CR following treatment with Atezolizumab–Bevacizumab (Atezo–Beva), with durable disease stability.

Methods: For patients with HCC who achieve CR with immune checkpoint inhibitors (ICIs), how long should treatment be continued to optimize overall survival (OS) benefit, cost, and adverse events?

Results: Case Report 1

A 35-year-old male with a history of chronic hepatitis B. In December 2022, he was diagnosed with HCC and underwent hepatic resection. In August 2023, he was diagnosed with recurrent HCC-BCLC C (left adrenal metastasis) – HBV – CP A. The patient was treated with Lenvatinib. After 5 months, disease progression was observed, and he subsequently underwent left adrenalectomy. Two months postoperatively, the disease progressed with the development of pulmonary metastases. The patient was treated with Atezo–Beva and achieved CR. After 20 cycles of therapy, treatment was discontinued due to financial constraints. At present, one year after treatment discontinuation, there is no evidence of disease recurrence.

Case report 2

A 57-year-old male with a history of HBV and diabetes mellitus. In November 2021, he was diagnosed with HCC and underwent portal vein embolization (PVE) and transarterial chemoembolization (TACE). In January 2022, he subsequently underwent hepatic resection. In July 2022, he was diagnosed with recurrent HCC – BCLC C (pulmonary metastases) – HBV – CP A. The patient was treated with Atezo–Beva and achieved CR. After 37 cycles, he developed

an ischemic stroke, and treatment was discontinued. At present, 22 months after treatment cessation, there is no evidence of disease recurrence.

A post hoc analysis of the IMbrave150 trial and a multicenter study of first-line ICIs in HCC demonstrated that achieving CR was associated with prolonged OS and durable disease control, even after treatment discontinuation. Among patients who achieved CR, recurrence was rare in those who continued treatment for 24 months.

A study involving 3,933 patients with HCC treated with ICIs reported a CR rate of 2.5% according to RECIST criteria and 4.4% according to mRECIST criteria. Among patients who discontinued ICIs, those who continued ICIs for more than 6 months after achieving CR according to mRECIST had longer recurrence-free survival than those who discontinued treatment earlier.

Conclusions: Achieving CR with ICIs in patients with HCC is associated with prolonged OS and durable disease control. After achieving CR, treatment should be continued for at least an additional 6 months.

Keywords: Immune Checkpoint Inhibitors, Complete Response, Treatment Duration

PE-12

Impact of SGLT2 Inhibitors on Liver-Related Outcomes in Patients with Type 2 Diabetes and Viral Hepatitis: A Korean Nationwide Cohort Study

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Aims: Diabetes mellitus and chronic hepatitis B/C infection are risk factors for liver cirrhosis and hepatocellular carcinoma (HCC). This study aimed to evaluate whether sodium-glucose cotransporter-2 inhibitors (SGLT2i) improved liver-related outcomes in patients with chronic viral hepatitis and co-existing diabetes.

Methods: Using data from the Korean nationwide cohort, this study included 37,629 patients with concurrent diabetes and chronic hepatitis B/C infection, without prior HCC, who were treated with oral hypoglycemic agents. Patients who were treated with SGLT2is for over 90 days were allocated to the SGLT2i group, whereas those who never received SGLT2is comprised the non-SGLT2i group. The primary outcome was the occurrence of liver-related events, including HCC.

Results: After 1:2 propensity score matching, the SGLT2i group comprised 12,543 patients (chronic hepatitis B, CHB: n=9392; chronic hepatitis C, CHC: n=4300, CHB & CHC: n=1149),

while the non-SGLT2i group included 25,086 patients (CHB: n=18806; CHC: n=8553, CHB & CHC: 2273). The incidence rate of composite liver-related complications was lower in the SGLT2i group than that in the non-SGLT2i group (6.67 per 1,000 vs. 8.99 per 1,000). Moreover, SGLT2i therapy was associated with a reduced risk of HCC development (subdistribution hazard ratio [sHR]=0.77, 95% confidence interval [CI]=0.66–0.91; $P=0.002$) and developing cirrhosis (sHR=0.67, 95% CI=0.54–0.83; $P<0.001$).

Conclusions: SGLT2is should be considered a therapeutic option for controlling diabetes, reducing the metabolic burden, and improving liver outcomes in patients with concurrent diabetes and chronic viral hepatitis.

Keywords: SGLT2 Inhibitors, Type 2 Diabetes, Chronic Viral Hepatitis, Hepatocellular Carcinoma

PE-14

Real-World Effectiveness of Atezolizumab plus Bevacizumab in High-Risk Unresectable Hepatocellular Carcinoma: A Multicenter Propensity Score-Matched Cohort Study

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Aims: Atezolizumab plus bevacizumab (Ate/Bev) is the established first-line therapy for advanced hepatocellular carcinoma (HCC), but evidence in real-world high-risk populations

remains limited. Real-world cohorts often include high-risk patients, leading to less favorable outcomes compared with IMbrave150. This study aimed to evaluate survival outcomes in high-risk patients to help guide the need for more intensive treatment approaches.

Methods: We retrospectively analyzed 783 patients with advanced HCC who received Ate/Bev between 2022 and 2024 at multiple centers in South Korea. The high-risk group (n = 255, 32.6%) was defined as patients with main portal vein invasion (Vp4), tumor involvement $\geq 50\%$ of the liver volume, or bile duct invasion. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were performed to adjust for baseline imbalances between the high-risk and non-high-risk groups.

Results: In the entire cohort, the high-risk group had significantly shorter OS (median 10.5 months [95% CI, 9.3–11.8] vs. 17.8 months [95% CI, 16.3–19.2]; HR 1.97; 95% CI, 1.65–2.37; $P < 0.001$) and PFS (median 6.0 months [95% CI, 4.6–7.5] vs. 7.6 months [95% CI, 6.4–8.8]; HR 1.40; 95% CI, 1.19–1.65; $P < 0.001$) compared with the non-high-risk group. After PSM adjustment, the high-risk group maintained significantly worse OS (HR 1.37; 95% CI, 1.10–1.71; $P = 0.006$), while PFS did not reach statistical significance (HR 1.20; 95% CI, 0.98–1.46; $P = 0.083$). IPTW analysis yielded consistent results, with a significantly higher risk of death in the high-risk group (HR 1.48; 95% CI, 1.16–1.88; $P = 0.001$) and a non-significant difference in PFS (HR 1.15; 95% CI, 0.92–1.43; $P = 0.215$). High-risk patients experienced significantly more grade ≥ 3 adverse events (24.2% vs. 17.3%, $P = 0.020$), higher rates of temporary treatment interruption (11.7% vs. 4.6%, $P < 0.001$), and more frequent permanent treatment discontinuation (16.0% vs. 8.5%, $P = 0.004$). In contrast, the incidence of varix bleeding (7.4% vs. 4.4%, $P = 0.082$) and severe proteinuria ($\geq 3+$) (7.0% vs. 10.1%, $P = 0.177$) did not differ significantly between the two groups.

Conclusions: In this multicenter real-world cohort, high-risk patients treated with atezolizumab plus bevacizumab showed comparable tumor response and adjusted PFS to non-high-risk patients, yet OS remained significantly worse, suggesting poor post-progression survival as the main driver. These findings highlight the need for effective second-line and multimodal strategies to improve outcomes beyond first-line progression in this population.

Keywords: Hepatocellular Carcinoma, Atezolizumab Bevacizumab

PE-15

Prognostic Stratification in Real-World Patients with Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab

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Aims: Atezolizumab plus bevacizumab (Ate/Bev) is the established first-line therapy for advanced hepatocellular carcinoma (HCC). However, prognostic stratification based on simple baseline clinical factors in patients treated with Ate/Bev has not been well established in real-world practice.

Methods: We retrospectively analyzed 792 patients with advanced HCC who received Ate/Bev between 2022 and 2024 at multiple centers in South Korea.

Results: Six baseline variables—ALBI grade ≥ 2 , ECOG performance status ≥ 2 , infiltrative tumor type, bile duct invasion, neutrophil-to-lymphocyte ratio ≥ 3.0 , and alpha-fetoprotein ≥ 400 ng/mL—were independently associated with OS. A weighted score incorporating these variables stratified patients into low- (0–1), intermediate- (2–3), and high-risk (≥ 4) groups. Median OS was 20.5 months in the low-risk group, 12.5 months in the intermediate-risk group, and 8.4 months in the high-risk group (log-rank $P < 0.001$). Compared with the low-risk group, the hazard ratio for death was 1.94 (95% CI, 1.57–2.40) in the intermediate-risk group and 2.99 (95% CI, 2.39–3.74) in the high-risk group.

Conclusions: In this multicenter real-world cohort, a prognostic score based on routinely available baseline clinical parameters was associated with survival outcomes in patients with advanced HCC treated with Ate/Bev.

Keywords: Hepatocellular Carcinoma, Atezolizumab-Bevacizumab

PE-16

Efficacy and Safety of Hepatic Arterial Infusion Chemotherapy Sequential Therapy versus Atezolizumab and Bevacizumab in the First Line Treatment of Infiltrative Hepatocellular Carcinoma with Portal Vein Thrombosis: A Cohort Study with Propensity Score Matching

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Aims: Infiltrative hepatocellular carcinoma (HCC) is an aggressive and biologically distinct subtype that often carries a poor prognosis. Owing to its molecular characteristics—such as immunosuppressive signaling and low immune infiltrates—these tumors derive limited benefit from immunotherapy, highlighting the need for alternative treatment strategies. This study evaluates a HAIC-based sequential approach exclusively in patients with infiltrative HCC.

Methods: This cohort study included patients with infiltrative hepatocellular carcinoma treated with atezolizumab–bevacizumab (n=209) or HAIC plus sequential therapy (n=38). HAIC-based sequential approach consists of six HAIC cycles followed by tailored subsequent therapies. Only patients who were evaluable at the first radiologic response assessment were included. 1:1 Propensity score matching was applied to adjust for potential baseline imbalances.

Results: After propensity score matching, the median PFS was 8.05 months (95% CI, 5.63–10.47) in the Atezolizumab–Bevacizumab (Ate/Bev) group and 11.31 months (95% CI, 4.15–18.46) in the HAIC plus sequential therapy group (log-rank $P = 0.005$). The median OS was 15.01 months (95% CI, 11.41–18.62) in the Ate/Bev group compared with 20.27 months (95% CI, 11.97–28.59) in the HAIC plus sequential therapy group (log-rank $P < 0.001$). The objective response rate (ORR) was significantly higher in the HAIC plus sequential group compared with the Ate/Bev group (73.7% vs. 26.8%, $P < 0.001$). The disease control rate (DCR) was 94.7% in the HAIC plus sequential group vs. 75.1% in the Ate/Bev group ($P = 0.017$). Among the 38 patients treated with HAIC-based sequential therapy, grade ≥ 3 adverse events occurred in 12 patients (31.6%). This rate was not statistically significantly different from 50 of 209 patients observed in the Ate/Bev group ($P = 0.2415$). No treatment-related deaths were reported but HAIC plus sequential therapy should be considered in younger patients with good PS score due to potential toxicity.

Conclusions: In younger patients with preserved performance status, a HAIC-based sequential treatment strategy may serve as a viable alternative to atezolizumab–bevacizumab for infil-

trative HCC.

Keywords: Hepatocellular Carcinoma, HAIC, ATE/BEV

PE-17

Targeted Therapy Reversing Malignant Biliary Obstruction in Advanced Hepatocellular Carcinoma: A Mechanistic Clinical Observation Challenging the Bilirubin Contraindication Threshold for Lenvatinib

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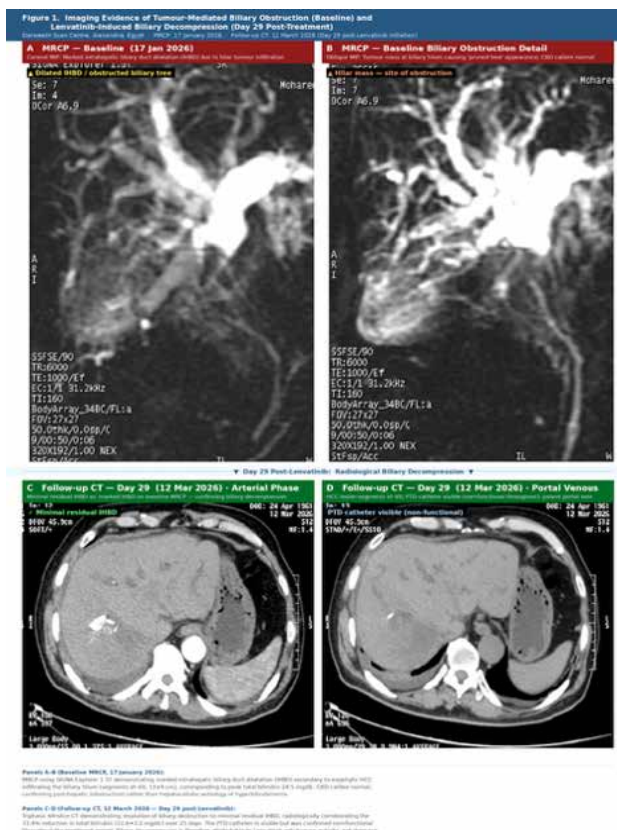
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Aims: Current prescribing guidelines restrict Lenvatinib to patients with serum bilirubin ≤ 3 mg/dL, a threshold derived from pharmacokinetic data in hepatocellular dysfunction. This restriction does not distinguish between hepatocellular decompensation and tumour-mediated biliary obstruction — a mechanistically distinct entity in which hepatic synthetic function and drug metabolism may remain fully preserved. No prospective study has evaluated the safety or feasibility of Lenvatinib in HCC-mediated obstructive hyperbilirubinemia.

Methods: We report a proof-of-concept clinical observation of a 65-year-old male with HCV-related cirrhosis and advanced HCC (BCLC Stage C, Child-Pugh A) presenting with severe obstructive jaundice caused by tumour infiltration of the biliary hilum (MRCP-confirmed; peak total bilirubin 24.5 mg/dL). Percutaneous transhepatic drainage (PTD) was placed but confirmed non-functional throughout. Given preserved hepatic synthetic function (Child-Pugh A, INR 1.36, albumin 3.1 g/dL) and CT-confirmed mechanical ductal obstruction as the sole mechanism of hyperbilirubinemia, Lenvatinib 10 mg once daily was initiated at total bilirubin 11.6 mg/dL — 3.9-fold above the approved threshold — following full informed consent.

Results: Over 25 days with the PTD confirmed non-functional throughout, total bilirubin declined 72.4% (11.6→3.2 mg/dL) and direct bilirubin declined 68.2% (7.23→2.3 mg/dL). Transaminases normalised in parallel (ALT: 123→71 U/L; AST: 84→56 U/L). Follow-up CT (Day 29) confirmed resolution of marked intrahepatic biliary duct dilatation (IHBD) to minimal residual dilatation, providing radiological corroboration of biliary decompression. No grade ≥ 2 adverse events, hepatotoxicity, or dose modification occurred. The non-functionality of the PTD throughout excludes mechanical drainage as a confounding explanation and implicates Lenvatinib-induced tumour regression as the mechanism.

Conclusions: This observation provides first clinical evidence that HCC-mediated obstructive hyperbilirubinemia is mechanistically distinct from hepatocellular dysfunction, and that the universal bilirubin ≤ 3 mg/dL contraindication may be inappropriately applied to Child-Pugh A patients with tumour-mediated biliary obstruction and intact drug metabolism. Lenvatinib may confer a dual benefit — anti-tumour efficacy and obstructive jaundice resolution — in this clinically identifiable subgroup. Prospective multi-centre evaluation with pharmacokinetic monitoring is warranted.



Keywords: Hepatocellular Carcinoma, Lenvatinib, Targeted Therapy, Obstructive Jaundice, Biliary Obstruction

PE-18

SeeLiver+: A Multi-Marker LC-MS/MS Platform for Improved Early HCC Detection and Liver Disease Stratification

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Aims: Diagnostic performance of current hepatocellular carcinoma (HCC) algorithms decreases in non-viral etiologies and early-stage disease, representing a major challenge for effective surveillance. We developed SeeLiver+, an upgraded LC-MS/MS-based multi-marker platform that expands the SeeLiver test (GAFAD model) with additional protein biomarkers to improve diagnostic accuracy and enable broader characterization of liver disease states.

Methods: Targeted LC-MS/MS quantification of AFP-Fuc% together with five complementary protein biomarkers was integrated into a multivariable algorithm. Study cohorts included healthy individuals and patients with hepatitis, cirrhosis, and HCC across viral and non-viral etiologies.

Results: Incorporation of the additional biomarker panel substantially improved discrimination of HCC from non-HCC in diagnostically challenging populations, increasing the area under the receiver operating characteristic curve (AUC) from 0.783 to 0.939 (p -value < 0.05). In early-stage HCC, SeeLiver+ achieved an AUC of 0.956 (p -value < 0.05), compared with 0.877 for the original SeeLiver (GAFAD) model, demonstrating markedly improved discrimination. The expanded marker panel also showed improved capability to distinguish among different liver disease states, including hepatitis, cirrhosis, and HCC, compared with the original model.

Conclusions: SeeLiver+ enhances early HCC detection while providing improved differentiation across liver disease stages. This LC-MS/MS-based multi-marker approach may support more precise surveillance and clinical assessment in patients with chronic liver disease.

Keywords: Hepatocellular Carcinoma, Non-Viral Etiologies, Early-Stage Disease, Liver Disease Stratification

PE-19

Clonorchis sinensis Infection and Preoperative Treatment Status: Influence on Recurrence and Survival after Curative Resection of Hepatocellular Carcinoma

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Aims: The impact of *Clonorchis sinensis* (Cs) infection combined with/without biliary dilation on prognosis after curative resection of hepatocellular carcinoma (HCC) remains unclear, and the necessity of preoperative anthelmintic treatment is controversial. This study evaluated the prognostic role of Cs infection and assessed the effects of biliary dilation (as assessed by imaging reports) and preoperative anthelmintic treatment (as defined by negative stool eggs for Cs) on recurrence-free survival (RFS) and overall survival (OS) of patients with HCC curative resection.

Methods: This retrospective study included patients treated at the First Affiliated Hospital of Guangxi Medical University (December 2018–December 2023). Among 10,600 screened patients with hepatobiliary tumors, 3,688 underwent hepatectomy for pathologically confirmed HCC. Of these, 335 Cs-infected patients were assigned to the Cs-infection group and 670 non-infected patients were randomly selected as controls (1:2 ratio). Propensity score matching (PSM) was used to adjust for covariates. Among Cs-infection group, Subgroup analyses were performed based on biliary dilation (n=94 vs. n=241) and preoperative anthelmintic treatment (stool egg-negative n=58 vs. egg-positive n=277).

Results: After PSM, Cs infection was independently associated with poorer OS (median 43 vs. 46 months; HR=1.29, $P=0.014$) and RFS (median 39 vs. 54 months; HR=1.36, $P=0.012$). Sub-group analyses showed that biliary dilation showed no significant impact on OS or RFS (all $P>0.05$) before and after PSM. Preoperative egg-negative patients had similar OS ($P=0.240$) but higher recurrence risk before PSM (median RFS: 25 vs. 40 months; HR=1.53, $P=0.023$); However, this difference disappeared after PSM (median RFS: 23 vs. 25 months; HR=1.17, $P=0.545$).

Conclusions: Cs infection is associated with poorer OS and RFS in HCC patients following curative resection. However, pre-operative biliary dilation and anthelmintic treatment had no significant impact on patient outcomes.

PE-20

Keywords: Clonorchis Sinensis, Hepatocellular Carcinoma, Recurrence-Free Survival, Overall Survival

Comparison of Treatment Efficacy and Safety Profile of Atezolizumab plus Bevacizumab in BCLC B and C Patients with Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) imposes a considerable global burden, and rigorous evidence to guide therapeutic stratification across BCLC B and C remains limited. Atezolizumab plus bevacizumab (ATE/BEV) is established as first line therapy for advanced HCC, yet effectiveness and safety between BCLC B and C in practice are undefined. Real world BCLC B cohorts are heterogeneous and include patients who are TACE non eligible, such as those with TACE refractoriness, huge HCC, multinodular HCC, or hypovascular HCC. We conducted a multicenter real world analysis comparing ATE/BEV across BCLC B and C, assessing overall and progression free survival, objective response, disease control, and treatment related adverse events.

Methods: A retrospective analysis was conducted on 828 HCC patients treated with ATE/BEV across nine academic tertiary hospitals. Finally, 91 patients with BCLC stage B and 737 patients with BCLC stage C were included in the analysis.

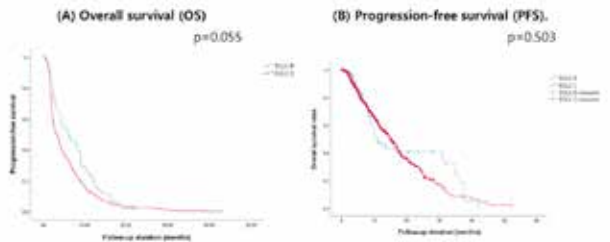
Results: Baseline characteristics were largely balanced between BCLC B and BCLC C, including gender distribution (85.7% vs 87.1%, $P=0.709$), etiology and maximum tumor diameter (6.57 vs 6.87 cm, $P=0.604$). Notably, BCLC B had a higher mean tumor count (2.99 vs 2.18, $P<0.001$). Disease control rates were comparable (75.9% vs 68.3%, $P=0.090$), whereas the objective response rate was numerically higher in BCLC C but did not reach statistical significance (15.7% vs 25.6%, $P=0.056$) (Table 1). Kaplan–Meier estimates showed no significant difference in overall survival between groups (median 11.13 vs 10.82 months; $P=0.799$) (Figure 1).

	BCLC B (n=91)	BCLC C (n=737)
TACE refractoriness	51 (56.0)	60 (8.1)
Infiltrative type HCC	4 (4.4)	22 (3.0)
Huge HCC	4 (4.4)	11 (1.5)
Multinodular HCC	10 (1.1)	13 (1.8)
Disseminated HCC	13 (1.4)	9 (1.2)
AP shunt	1 (1.1)	1 (0.1)
Hypovascular HCC	6 (6.6)	1 (0.1)
Macrovascular invasion	-	163 (22.1)
Extrahepatic metastasis	-	436 (59.2)
Bile duct invasion	-	15 (2.0)
Combined	-	49 (6.6)

Table 1. Indications for Atezolizumab + Bevacizumab Initiation

	BCLC B (n=91)	BCLC C (n=737)	P-value
Best overall response			0.028
Complete response	2 (2.6)	18 (2.8)	
Partial Response	10 (13.0)	143 (22.6)	
Stable disease	48 (62.3)	272 (42.9)	
Progressive disease	17 (22.1)	199 (31.4)	
Not assessable	14 (15.4)	103 (14.0)	0.873
Objective response rate	12 (15.6)	161 (25.4)	0.056
Disease control rate	60 (77.9)	433 (68.3)	0.090
Progression-free survival, months	7.45 ± 5.49	5.81 ± 6.05	0.067
Overall survival, months	11.13 ± 10.98	10.82 ± 8.04	0.799

Table 2. Clinical Response to Atezolizumab + Bevacizumab (RECIST 1.1)



Conclusions: ATE/BEV demonstrated comparable effectiveness in BCLC B and BCLC C in real world practice. BCLC B patients, particularly those unsuitable for TACE, achieved meaningful disease control and survival. Our findings support expanding the role of ATE/BEV as a viable first line option in intermediate stage HCC when TACE is limited or not appropriate. Further studies are needed to refine patient selection for ATE/BEV in BCLC B HCC.

Keywords: BCLC, Hepatocellular Carcinoma, Atezolizumab Plus Bevacizumab, Efficacy

PE-21

Comparative Efficacy and Safety of Subsequent Systemic Therapies Following Lenvatinib or Sorafenib Failure in HCC: A Meta-Survival Analysis

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Aims: While immune checkpoint inhibitors (ICI)-based regimens have emerged as the current standard of care of hepatocellular carcinoma (HCC), tyrosine kinase inhibitors (TKIs) continue to play a significant role, being frequently utilized in both first-line and subsequent treatment settings. However, evidence-based guidance for treatment selection following TKI failure remains limited.

Methods: Clinical studies investigating subsequent-line systemic treatments after lenvatinib or sorafenib failure were identified through a systematic review of PubMed, Embase, and the Cochrane library. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and grade 3–4 adverse events (AEs) were pooled using meta-analytic methods.

Results: Fifty-nine studies were included in the meta-analysis. Following lenvatinib failure, the pooled median OS was 14.98 months (95% CI, 9.57–20.38; I²=42%) for atezolizumab plus bevacizumab and 10.79 months (95% CI, 6.53–15.05; I²=98%) for sorafenib. The pooled median PFS was 5.78 months (95% CI, 3.19–8.37; I²=66%) for atezolizumab plus bevacizumab, 5.45 months (95% CI, 0.76–10.15; I²=87.2%) for regorafenib, and 2.95 months (95% CI, 1.73–4.17; I²=63.8%) for sorafenib. In patients who experienced sorafenib failure, the pooled median OS was highest with nivolumab plus ipilimumab (22.80 months; 95% CI, 9.40–36.20), followed by cabozantinib (14.25 months; 95% CI, 5.39–23.12; I²=88.3%), pembrolizumab (14.04 months; 95% CI, 12.68–15.41; I²=0.0%), and regorafenib (10.72 months; 95% CI, 8.95–12.50; I²=83.7%). The median PFS following sorafenib failure was most favorable with cabozantinib (5.56 months; 95% CI, 3.76–7.35; I²=65.9%) and lenvatinib plus PD-1 inhibitors (5.30 months; 95% CI, 4.68–5.92; I²=0.0%). In the comparative analysis, nivolumab monotherapy demonstrated comparable efficacy to regorafenib in both OS (HR=1.069; 95% CI, 0.752–1.519; P=0.711) and PFS (HR=1.060; 95% CI, 0.663–1.695; P=0.807).

Conclusions: Following first-line TKI failure in HCC, ICI-based combinations—specifically atezolizumab/bevacizumab af-

ter lenvatinib and nivolumab/ipilimumab after sorafenib—demonstrated superior survival benefits compared to other systemic options.

Keywords: Hepatocellular Carcinoma, Systemic Treatment, Lenvatinib, Sorafenib

PE-22

Surgery for Hepatocellular Carcinoma Patients with Portal Vein Main Trunk Thrombosis (VP4): Initial Experience of a Single Center

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Aims: Hepatocellular carcinoma with main portal vein trunk thrombosis is a very poor prognostic factor, with an overall survival time ranging from 2.7 – 4 months. Treatment methods are not uniform and include: surgery, radiotherapy, HAIC (Hepatic Arterial Infusion Chemotherapy), and systemic therapy. Surgery may restore portal vein patency, potentially improving the patient's overall survival.

Methods: From February 2023 to July 2025, we performed surgery on 12 cases of HCC with Vp4 Portal Vein Tumor Thrombosis (PVTT), including 2 cases with accompanying Biliary Duct Tumor Thrombosis (BDTT), and 1 case with Inferior Vena Cava (IVC) thrombosis.

Results: We performed: 1 case of isolated portal vein thrombectomy; 11 cases of major hepatectomy and thrombectomy, including 1 case combined with splenectomy, 2 cases of extrahepatic bile duct resection, and 1 case of IVC segment replacement. Postoperative mortality occurred in 1 case. Acute postoperative portal vein thrombosis was observed in 4 cases. The mean follow-up period was 8.6 months (3 months – 24 months) for 10 patients (1 case lost to follow-up). There were 3 deaths at 4 months and 23 months post-surgery due to advanced cancer.

Conclusions: Surgery may be a beneficial measure in multimodal treatment coordination, potentially improving the overall survival of HCC patients with main portal vein trunk thrombosis.

Keywords: Portal Vein Tumor Thrombosis, VP4, Thrombectomy

PE-23

Surgical Outcomes and Adherence to Quality Performance Indicators of Hepatectomy for Hepatocellular Carcinoma from the Up-Philippine General Hospital CancerSurg Study

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Aims: Hepatectomy remains the primary curative option for hepatocellular carcinoma (HCC) in the Philippines, where access to liver transplantation and ablation is limited. Quality Performance Indicators (QPIs) are standardized, evidence-based measures designed to assess fundamental aspects of patient care that relate to overall outcome. This study reviewed the outcomes of hepatectomy for HCC and adherence to quality performance indicators at the University of the Philippines–Philippine General Hospital (UP-PGH).

Methods: A retrospective analysis was conducted on patients who underwent hepatic resection between January and June 2024, evaluating clinical characteristics, operative outcomes, and compliance with established quality performance indicators.

Results: Twelve patients underwent curative resection with hepatectomy. All patients had preoperative liver function assessment done, and surgical planning with an abdominal CT scan. Only 1 patient (8.3%) was diagnosed through screening, and timely surgery was only performed on 2 patients (16.7%). The median interval from consultation to cancer diagnosis was 70.5 days, and initial consultation to surgical intervention was 127.5 days. All surgeries were done or supervised by a hepatobiliary surgeon. Morbidity occurred in 16.7% of patients, and no 30-day mortality was observed. R0 resection was achieved in 91.7%. All cases were managed by a multidisciplinary team, although only one-third were discussed in formal multidisciplinary conferences.

Conclusions: Overall, hepatectomy for HCC at UP-PGH demonstrated favorable short-term outcomes and high adherence to quality indicators. Strengthening multidisciplinary conferences and reducing treatment delays may further enhance surgical outcomes and optimize liver cancer care in the tertiary government setting.

Keywords: Hepatectomy, Quality Performance Indicators, Philippines

PE-24

Risk Factors and Prognosis of Primary Curative Hepatectomy in Hepatocellular Carcinoma Patients

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Aims: This retrospective study analyzed nearly a decade of clinical experience to identify prognostic factors associated with recurrence, disease-free survival (DFS), and overall survival (OS) in patients with newly diagnosed hepatocellular carcinoma

(HCC) treated with curative hepatectomy at Cho Ray Hospital.

Methods: A descriptive case series analysis was conducted involving 2,419 patients with hepatocellular carcinoma (HCC) who underwent primary curative hepatectomy between January 2015 and December 2022, with follow-up extending through December 2024.

Results: The overall recurrence rate was 64.57%, with 1-, 2-, and 3-year recurrence rates of 55.1%, 68.3%, and 77.4%, respectively. The mean disease-free survival (DFS) was 22.4 months (median, 9.8 months), while the mean overall survival (OS) was 40.9 months (median, 30.3 months). Univariate analysis demonstrated significant associations of recurrence, DFS, and OS with alpha-fetoprotein (AFP) level, vascular invasion, tumor number, tumor size, histological pattern, Edmondson–Steiner grade, tumor necrosis, resectable metastatic lesions, and extent of resection. Underlying liver disease was significantly associated with DFS only. Multivariate logistic regression identified AFP level, vascular invasion, tumor number, tumor size, and resectable metastatic lesions as independent predictors of recurrence and mortality. Multivariate Cox proportional hazards analysis further confirmed tumor number as an independent prognostic factor for both DFS and OS.

Conclusions: Despite the high 3-year recurrence rate, 3-year mortality outcomes were favorable. Tumor number was identified as an independent prognostic factor for hepatocellular carcinoma recurrence, disease-free survival (DFS), and overall survival (OS).

Keywords: Hepatocellular Carcinoma, Recurrence, Overall Survival

PE-25

Intrahepatic Cholangiocarcinoma in Cirrhotic versus Non-Cirrhotic Patients: Clinicopathologic, MRI, and Prognostic Features

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Aims: Intrahepatic cholangiocarcinomas (ICCAs) may differ in clinical, imaging, and prognostic features according to the presence of underlying liver cirrhosis, but evidence remains limited. This study aimed to compare the clinicopathologic features, MRI characteristics, and long-term survival outcomes of ICCA in patients with and without cirrhosis.

Methods: We retrospectively analyzed 322 consecutive patients with ICCA who underwent preoperative MRI and curative-intent resection between 2010 and 2018 at a tertiary referral center. Two abdominal radiologists independently reviewed MRI features. Clinical, pathologic, and MRI findings were compared

between cirrhotic and non-cirrhotic patients. Recurrence-free survival (RFS), overall survival (OS), and prognostic factors were assessed using Kaplan–Meier analysis, the log-rank test, and Cox proportional hazards regression.

Results: Among 322 patients (mean age, 62.5 ± 10.0 years; 198 men), 50 (15.5%) had histologic cirrhosis. Compared with non-cirrhotic patients, cirrhotic patients had smaller tumors (mean, 4.1 vs. 5.4 cm; $P=.002$), earlier-stage disease ($P=.010$), and more frequent purely mass-forming morphology (98.0% [49/50] vs. 86.8% [236/272]; $P=.022$). On MRI, ICCAs in cirrhotic livers were more often peripherally located (84.0% [42/50] vs. 58.8% [160/272]; $P=.001$) and showed higher rates of non-rim arterial-phase hyperenhancement (22.0% [11/50] vs. 4.4% [12/272]; $P<.001$) and non-peripheral washout (20.0% [10/50] vs. 4.0% [11/272]; $P<.001$). In contrast, bile duct invasion (14.0% [7/50] vs. 58.5% [159/272]; $P<.001$) and vascular invasion (14.0% [7/50] vs. 57.7% [157/272]; $P<.001$) were less frequent. Cirrhosis was not an independent predictor of RFS or OS. Instead, tumor size (hazard ratio [HR]=1.01 for RFS; HR=1.01 for OS), multiplicity (HR=1.80/1.84), arterial-phase enhancement pattern (HR=2.25/2.64), vascular invasion (HR=1.66/1.72), and resection margin status (HR=1.50/1.49) were significant prognostic factors (all $P<.05$).

Conclusions: ICCA shows distinct clinicopathologic and MRI features according to cirrhosis status. However, postoperative survival appears to be driven primarily by tumor-related factors rather than the presence of cirrhosis.

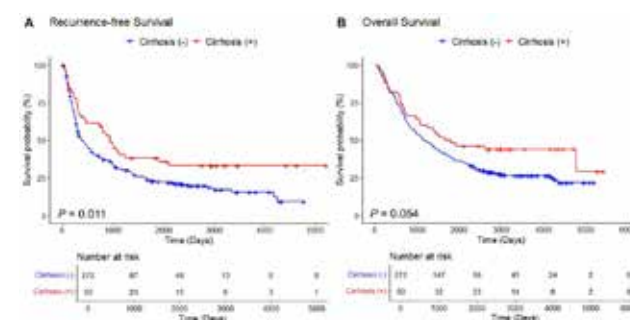


Figure 1.

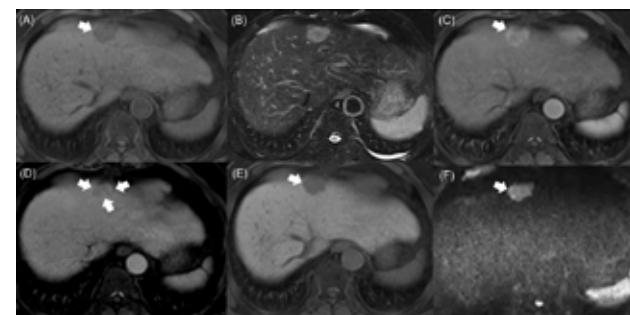


Figure 2.

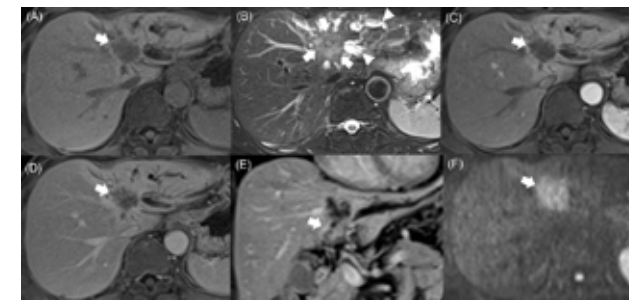


Figure 3.

Keywords: Liver Neoplasms; Cholangiocarcinoma; Cirrhosis; Magnetic Resonance Imaging; Prognosis

PE-26

Development and Validation of a Dynamic Prognostic Nomogram for Conditional Survival in Hepatocellular Carcinoma: An Analysis from the Korea Liver Cancer Registry

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Aims: Compared to overall survival, conditional survival is a more relevant measure of prognosis in surviving patients over time. This study developed and validated a nomogram-based dynamic prognostic model to predict the conditional survival estimates of patients with hepatocellular carcinoma (HCC) through an analysis of a nationwide cancer registry.

Methods: This retrospective cohort study included 2,492 patients with HCC registered in the Korea Liver Cancer Registry. Patients underwent hepatic resection (HR) from 2008 to 2017, were followed up until December 2019, and were divided into development and validation cohorts. Univariate and multivariate Cox regression analyses were conducted to determine the risk factors for conditional survival of patients who underwent HR. The patients were scored based on the Cox regression coefficients; the nomogram was predicted by calculating the survival probability with Cox model.

Results: Our dynamic prognostic model nomogram for predicting conditional overall survival demonstrated Harrell's C-index of 0.622 and 0.674 in the development and validation sets; for conditional disease-specific survival, it was 0.623 and 0.686 in the development and validation sets. The prediction power of

the model is applicable in clinical practice. Factors incorporated in our nomogram included age, albumin, the ADV score, lymph node metastasis, and T stage in American Joint Commission on Cancer staging system.

Conclusions: We developed and validated a nomogram to predict conditional survival estimates for overall survival and disease-specific survival. The proposed nomogram incorporating the ADV score presents a more accurate and useful prognostic prediction for patients with HCC who received HR.

Keywords: Hepatocellular Carcinoma, Conditional Survival Prognosis

PE-28

Combination of Radiotherapy and Durvalumab/Gemcitabine/Cisplatin Therapy Improve Survival in Biliary Tract Cancer (Especially Extrahepatic Bile Duct Cancer) Patients

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Aims: Durvalumab (Durva) plus gemcitabine/cisplatin (GP) proved better efficacy compared to GP for advanced biliary tract cancer (BTC) patients in TOPAZ-1 trial. Radiotherapy (RT) has immune-stimulatory effect through several mechanism such as releasing tumor associated antigen etc. However, there is no data about synergistic effect and clinical efficacy of RT plus Durva/GP therapy. Therefore we performed study for describing clinical efficacy of combination of RT plus Durva/GP therapy.

Methods: The clinical course of patients with advanced BTC who received Durva/GP therapy in single cancer center from April 2023 to July 2025 was assessed. Response rate (partial response [PR], stable disease [SD], progressive disease [PD]) per RECIST v1.1 and median progression free survival (PFS), overall survival (OS) were analyzed.

Results: Total 21 BTC patients were treated with Durva/GP therapy. Gallbladder cancer (GBC): Intrahepatic cholangiocarcinoma (IHCCC) : Extrahepatic CCC (EHCCC) patients were 6:8:7. Eight patients (RT group) received several types of RT (PULSAR in 6 patients, TARE in 1 patient, carbon beam therapy in 1 patient). The rate of PR:SD:PD in RT versus (vs) non-RT group were 37.5% vs 15.4% : 62.5% vs 61.5% : 0% vs 23.1%. Median PFS in RT vs non-RT group were 10 vs 5 months ($P=0.028$) and median OS were 13 vs 10 months ($P=0.012$). In only EHCCC patients, median PFS, OS of RT group were better than non-RT group with statistically significance (PFS 10 vs 5 months, $P=0.004$; OS

11 vs 6 months, $P=0.027$). Almost all patients complained only grade 1/2 nausea and there were no cases with Grade 3/4 adverse effects.

Conclusions: This study demonstrates that radiotherapy can improve clinical efficacy of Durva/GP therapy in advanced BTC, especially EHCCC patients. Further large scaled prospective studies are needed for proving synergistic effect of radiotherapy and Durva/GP therapy to BTC patients.

Keywords: Biliary Tract Cancer, Durvalumab, Radiotherapy, Combination Therapy

PE-29

Pretreatment Neutrophil-to-Lymphocyte Ratio as a Predictive Marker for Tumor Response to Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma: A Multicenter Retrospective Study

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Aims: Atezolizumab combined with bevacizumab has been used in the treatment of advanced hepatocellular carcinoma (HCC). However, reliable predictive biomarkers for evaluating tumor response to this therapy remain limited. This study aimed to identify predictive factors in patient with HCC undergoing treatment with atezolizumab and bevacizumab.

Methods: This multicenter retrospective study included 943 patients with HCC who received atezolizumab plus bevacizumab. Factors associated with tumor response were analyzed.

Results: According to the Response Evaluation Criteria in Solid Tumors, the rates of complete remission, partial response, stable disease, and progressive disease were 2.9 %, 22.9 %, 48.8 % and 25.5 %, respectively. The objective response rate

(ORR) and disease control rate (DCR) were 25.8 % and 74.6 %, respectively. Progression free survival and overall survival were significantly associated with best tumor response ($P<0.001$). Multivariate analysis identified BCLC stage (HR = 0.478, 95% CI = 0.278 – 0.821, $P=0.007$) and neutrophil-to-lymphocyte ratio (NLR) (HR = 0.670, 95% CI = 0.488 – 0.920, $P = 0.013$) as independent predictive factors for objective tumor response. The ORR and DCR were 31.2 % and 77.2 %, respectively, in the NLR <2 group, and 23.7 % and 73.5 %, respectively, in the NLR $\geq$ 2 group ($P<0.001$).

Conclusions: Pretreatment NLR was correlated with the tumor response, which was subsequently associated with survival outcomes. NLR may serve as a predictor of a lack of response to atezolizumab plus bevacizumab treatment. Therefore, NLR represents a readily measurable biomarker with the potential to support the timely identification of HCC patients who are more likely to benefit from atezolizumab and bevacizumab treatment.

Keywords: Hepatocellular Carcinoma, Neutrophil-To-Lymphocyte Ratio, Tumor Response

PE-30

Transarterial Radioembolization versus Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Aims: To evaluate and compare the safety and efficacy of transarterial radioembolization (TARE) and transarterial chemoembolization (TACE) in the treatment of patients with unresectable hepatocellular carcinoma (HCC).

Methods: A systematic search of MEDLINE/PubMed, EMBASE, and the Cochrane Library identified studies comparing TARE and TACE for unresectable HCC. Meta-analyses were conducted to evaluate hazard ratios (HRs) for overall survival (OS), progression-free survival (PFS), and time to progression (TTP); risk ratios (RRs) for treatment response, post-procedural pain, major complications, and mortality; and mean difference (MD) in hospital stay.

Results: Twenty-one studies were included. TARE was associated with a significantly higher complete response (CR) rate compared to TACE (RR = 1.23; 95% CI, 1.01–1.51; $P=0.045$). The pooled HR for OS was 0.93 (95% CI, 0.76–1.13; $P=0.443$), indicating comparable efficacy between TARE and TACE in terms of OS. The pooled HR for PFS was 0.68 (95% CI: 0.45–1.01; $P=0.055$), indicating a trend toward improved efficacy of TARE

compared to TACE in terms of PFS. TARE was associated with significantly less post-procedural pain (RR = 0.48; 95% CI, 0.27–0.83; $P=0.014$) and a shorter hospital stay (MD = –2.77 days; 95% CI, –4.33 to –1.22; $P=0.006$). No significant differences were observed in major complications or mortality.

Conclusions: TARE demonstrated a higher CR rate while providing survival outcomes comparable to those of TACE. In addition, TARE was associated with less post-procedural pain and a shorter hospital stay, indicating a more favorable tolerability profile.

Keywords: Radioembolization, Chemoembolization, HCC

PE-31

Improving Early Detection of Hepatocellular Carcinoma in the Modern Era: Evidence from a Population Registry

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Aims: Early detection of hepatocellular carcinoma (HCC) is critical for improving treatment eligibility and long-term outcomes. However, population-level temporal trends in stage at diagnosis remain incompletely characterized. This study aimed to evaluate stage migration patterns in HCC over nearly two decades using a large population-based registry.

Methods: We conducted a retrospective population-based analysis using registry data from 2004 to 2021. Cases were categorized according to summary stage at diagnosis. Temporal trends in stage distribution were assessed annually and across predefined diagnostic eras (2004–2009, 2010–2015, and 2016–2021). The primary outcome was the proportion of localized-stage diagnoses over time. Secondary analyses evaluated trends in regional and distant-stage disease.

Results: A total of 97,443 staged HCC cases were identified. The proportion of localized-stage diagnoses increased consistently over time, rising from 50.9% in 2004 to 55.5% in 2021. Era-based analysis demonstrated a stepwise improvement in early detection, with mean localized-stage proportions increasing from 52.3% in 2004–2009 to 55.2% in 2010–2015 and 56.7% in 2016–2021.

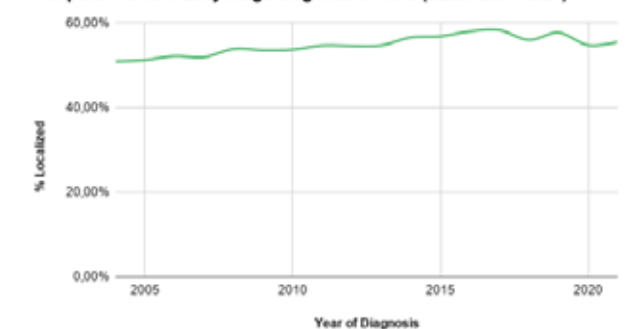
Conversely, distant-stage diagnoses declined modestly from 17.5% in the earliest era to 16.7% in the most recent period, while regional-stage disease showed minimal change. Over the same timeframe, the annual volume of staged HCC diagnoses nearly doubled, suggesting expanded surveillance engagement and improved diagnostic capture at the population level.

Conclusions: Over the past two decades, hepatocellular carcinoma has increasingly been diagnosed at earlier stages at the population level. This stage migration toward localized disease

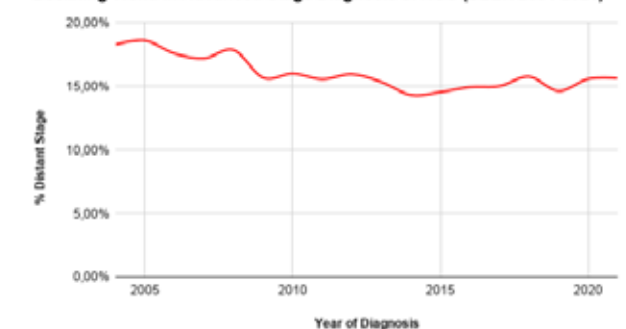
may reflect improvements in surveillance practices, imaging accessibility, and clinical awareness. These findings highlight meaningful progress in real-world HCC detection patterns and underscore the potential population impact of sustained screening initiatives. Continued efforts to enhance early detection strategies are essential to further shift the diagnostic spectrum and optimize treatment opportunities for patients with HCC.

Keywords: Hepatocellular Carcinoma, Stage Migration, Early Detection, Population-Based Study

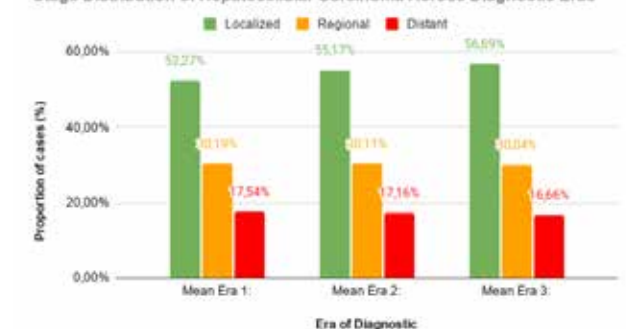
Temporal Trend in Early Stage Diagnosis of HCC (SEER 2004–2021)



Declining Trend in Advanced Stage Diagnosis of HCC (SEER 2004–2021)



Stage Distribution of Hepatocellular Carcinoma Across Diagnostic Eras



PE-32

Entecavir versus Tenofovir for Tertiary Prophylaxis in HBV-Related Hepatocellular Carcinoma: Evidence from a Nationwide Cohort

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Aims: While some reports indicate differential impacts of specific antiviral agents on the prognosis of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), these findings often lack generalizability due to their single-center nature. To address this gap, we utilized a nationwide cohort to investigate whether the choice between entecavir and tenofovir affects recurrence and survival in this patient population.

Methods: Utilizing the Korean Liver Cancer Registry database from 2014 to 2021, we identified a cohort of patients with HBV-related HCC. Subjects were stratified into entecavir and tenofovir users according to their initial therapy at diagnosis. To minimize potential selection bias and confounding, a propensity-score matching analysis was performed for intergroup comparison.

Results: The ETV and TDF groups comprised 1,806 and 2,429 patients, respectively. The mean age was significantly lower in the TDF group than in the ETV group (57.1 vs. 58.8 years, $P<0.001$). The proportion of male patients (80.6% vs. 76.7%, $P=0.002$), those with Child–Pugh class B or C (22.8% vs. 22.8%, $P=0.002$), and those with distant metastasis (13.3% vs. 10.7%) was significantly higher in the TDF group than in the ETV group. The proportion of patients who received curative treatment was 38.8% in the ETV group and 44.2% in the TDF group.

During a mean follow-up of 50 months in the overall cohort, 2,175 deaths were documented, and there was no statistically significant difference in overall survival between the TDF and ETV groups ($P=0.24$). In the subgroup analysis restricted to patients who received curative treatment (TDF 942, ETV 757), there was still no statistically significant difference in survival between the two groups ($P=0.99$). In this curative treatment subcohort, even after propensity score matching, in which 708 pairs were formed, no statistically significant difference in survival was observed between the two groups ($P=0.88$).

Conclusions: There was no significant difference in survival outcomes between the two antiviral agents in patients with HBV-related HCC. Further large-scale studies are warranted to validate these findings

Keywords: Hepatitis B, Hepatocellular Carcinoma, Antiviral Therapy, Survival

PE-34

Serum Proteomic Biomarkers for Predicting Immunotherapy and Targeted Therapy Response in Advanced Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, frequently presenting at advanced stages with a dismal prognosis. Although immune checkpoint inhibitor (ICI)-based combination regimens — such as atezolizumab plus bevacizumab — alongside targeted therapies including sorafenib and lenvatinib have become standard-of-care for advanced HCC, objective response rates continue to be modest. This study sought to identify serum proteomic biomarkers capable of predicting therapeutic efficacy, with the goal of informing personalized treatment strategies.

Methods: Serum samples were prospectively collected from 61 patients — 44 receiving immunotherapy and 17 undergoing targeted therapy — at both pre- and post-treatment time-points. Patients were stratified into “good responder” and “poor responder” groups based on clinical treatment duration. Mass spectrometry-based proteomics was applied to characterize protein expression profiles, yielding 565 proteins following rigorous quality filtering and batch effect correction. Differentially expressed proteins (DEPs) were identified using independent and paired t-tests.

Results: Pre-treatment proteomic profiling revealed distinct signatures between responder groups. In the immunotherapy cohort, poor responders demonstrated significantly elevated levels of Serum Amyloid A (SAA) and Neutrophil Defensin (DEFA), whereas good responders were characterized by higher expression of Kallistatin (SERPINA4), Apolipoprotein C-III (APOC3), and Antithrombin-III (SERPINC1). Functional enrichment analysis linked these proteins to biological processes including lipid localization, mucosal immune response, and lymphocyte chemotaxis. In the targeted therapy cohort, poor responders exhibited lower pre-treatment levels of Coagulation Factor IX (F9) and Kininogen-1 (KNG1). Longitudinal analysis further demonstrated that SAA levels remained persistently elevated in poor responders following immunotherapy, implicating sustained inflammatory signaling as a potential mechanism of treatment resistance.

Conclusions: Serum proteomics represents a robust and minimally invasive platform for the discovery of predictive bio-

markers in advanced HCC. The proteomic signatures identified for both immunotherapy and targeted therapy hold significant promise for forecasting patient outcomes and guiding individualized treatment selection in clinical practice.

Keywords: HCC, Proteomics, Immunotherapy, Target Therapy

PE-35

A Novel Prognostic Model Integrating the ASAP Score and Neutrophil-to-Lymphocyte Ratio in Advanced Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab: A Multicenter Cohort Study

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Aims: The ASAP score, comprising age, sex, alpha-fetoprotein, and protein induced by vitamin K absence-II, was originally developed for early hepatocellular carcinoma (HCC) detection and has recently shown potential prognostic relevance. Therefore, we aimed to evaluate the utility of the ASAP score for risk stratification in a multicenter cohort of patients with advanced HCC treated with atezolizumab plus bevacizumab.

Methods: Consecutive patients with unresectable HCC receiving first-line atezolizumab plus bevacizumab at Seoul National University Hospital (SNUH) were retrospectively analyzed, with external validation performed in an independent cohort from the Catholic Medical Center (CMC) of Korea. Cutoff values were determined using X-tile software. Associations between baseline variables, including the ASAP score, and overall survival (OS) and progression-free survival (PFS) were assessed using multivariable Cox models, and independently associated variables were integrated to derive a combined risk stratification model, which was evaluated using Kaplan–Meier estimates and Cox proportional hazards analyses.

Results: X-tile analysis identified 6.4 as the optimal cutoff for the ASAP score. In multivariable Cox analyses for OS and PFS the ASAP score and neutrophil-to-lymphocyte ratio (NLR) were the only baseline variables independently associated with both outcomes. Patients were therefore stratified using a combined ASAP–NLR model into a low-risk group (ASAP <6.4 and NLR <3.2) and a high-risk group (ASAP ≥6.4 and/or NLR

≥3.2). In the SNUH cohort, the median OS was 21.4 months in the low-risk group and 9.8 months in the high-risk group, with the high-risk group showing significantly worse OS (adjusted hazard ratio [aHR] 2.24; 95% confidence interval [CI] 1.54–3.25; $P<0.001$) and PFS (aHR 1.77; 95% CI 1.30–2.39; $P<0.001$). In the external CMC cohort, this risk stratification remained prognostically relevant, with a longer median OS in the low-risk group than in the high-risk group (23.6 vs. 13.4 months), and the high-risk group showing significantly worse OS (HR 1.34; 95% CI 1.34–3.28; $P<0.001$) as well as PFS (HR 1.66; 95% CI 1.16–2.38; $P=0.006$).

Conclusions: The combined ASAP–NLR model demonstrated effective risk stratification for survival outcomes in patients with advanced HCC receiving atezolizumab plus bevacizumab, with consistent findings in an external validation cohort, supporting its potential utility in real-world clinical practice.

Keywords: Liver Cancer, Immunotherapy, Risk Stratification

15. Liver Transplantation

PE-1

Use of Bariatric Surgery in Liver Donors before Surgery

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Aims: To evaluate the safety and efficacy of bariatric surgery in obese living liver donors prior to donor hepatectomy.

Methods: Our study included two potential living liver donors with a body mass index (BMI) greater than 34 kg/m², who were related donors for pediatric recipients with terminal liver disease. The recipients were 9 months, 7.3 kg old and 8 months old, 6.9 kg. Preoperative examination revealed hepatic steatosis in both donors, which contraindicated partial liver donation for transplantation. To reduce body weight and alleviate the severity of hepatic steatosis, both donors underwent bariatric surgery—laparoscopic gastric bypass grafting. Postoperative follow-up included assessment of BMI, biochemical liver function tests, and instrumental data. After 4 and 5 months, the donors underwent follow-up. Accordingly, after bariatric surgery, and after achieving target body weight indicators and stabilizing the general condition of the donors, both had liver steatosis resolved and a donor hemihepatectomy was performed.

Results: Both donors demonstrated a significant reduction in BMI, improved biochemical liver function, and no clinically significant steatosis based on instrumental studies. Bariatric surgery and subsequent donor hepatectomy were performed without intra- and postoperative complications. Liver trans-

plantation in pediatric recipients was successful, with satisfactory graft function in the early postoperative period.

Conclusions: The use of bariatric surgery, particularly gastric bypass, in potential living liver donors with obesity is a safe and effective method for preoperative optimization. This approach allows for an expanded donor pool and improved safety of living liver donation, particularly in pediatric transplantation.

This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan 2025-2027 (Grant No. AP26102345).

Keywords: Liver Donor, Bariatric Surgery, Obesity, Gastric Bypass

PE-2

Construction of an Imaging-Omics Machine Learning Prediction Model for Post-Liver Transplantation Recurrence of Liver Cancer Based on ECV

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Aims: This study aims to establish an imaging biomarker model related to the prognosis of liver transplant patients based on the extracellular volume (ECV) subtraction images obtained from abdominal enhanced CT scans before liver transplantation. This is intended to further clarify the predictive role of ECV subtraction images in liver cancer patients after liver transplantation.

Methods: A total of 145 patients with hepatocellular carcinoma who underwent liver transplantation were retrospectively included and randomly divided into a training set and a test set at a ratio of 7:3. The radiomics features of the tumors and the surrounding tissues of the patients' preoperative enhanced CT plain scan, delayed scan, and ECV subtraction images were extracted. After feature selection, the optimal machine learning algorithm was used to construct the ECV-ML model, and a combined model was established by combining clinical factors. The performance of the model was comprehensively evaluated using C-index, decision curve, calibration curve, and survival analysis.

Results: In the clinical model, the ratio of monocytes to lymphocytes and microvascular infiltration are independent risk factors for poor prognosis in liver cancer patients after liver transplantation. Using LASSO regression under ten-fold cross-validation, a total of 6 optimal features were selected, including 2 features of peri-tumor subtraction images, 2 features of peri-tumor plain scan images, and 2 features of tumor delayed images. In the ECV-ML model, the algorithm based on XGBoost has the best predictive effect for early recurrence after transplantation. The combined model and the ECV-ML model

both performed better than the clinical model in predicting early postoperative recurrence (the C-index of the training set was 0.86, 0.85, and 0.61 respectively, and the C-index of the test set was 0.83, 0.82, and 0.65 respectively), but there was no significant difference between the two models.

Conclusions: The ECV-ML model based on preoperative ECV parameter graphs and CT images demonstrates effective predictive performance in predicting the early recurrence of HCC patients after liver transplantation, and can significantly improve the predictive performance of the simple clinical parameter-based liver cancer liver transplantation recurrence prediction model.

Keywords: Radiomics, Hepatocellular Carcinoma, Liver Transplantation, Extracellular Volume

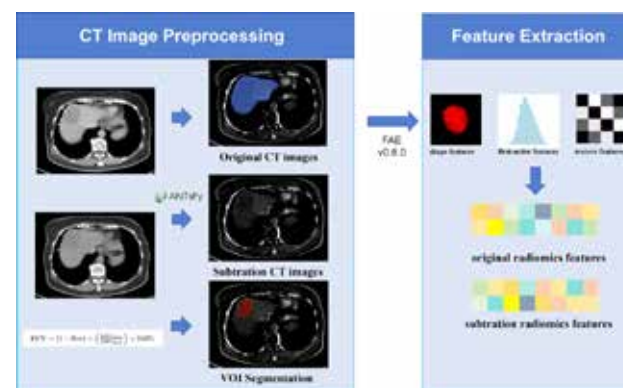


Figure 1. Feature Extraction.

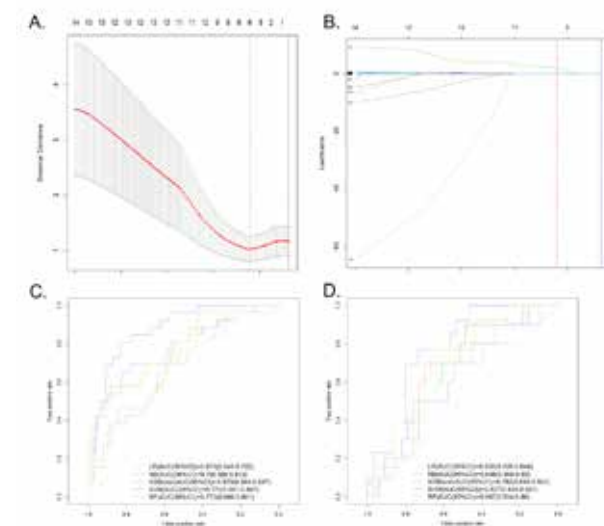


Figure 2. ECV-ML model building.

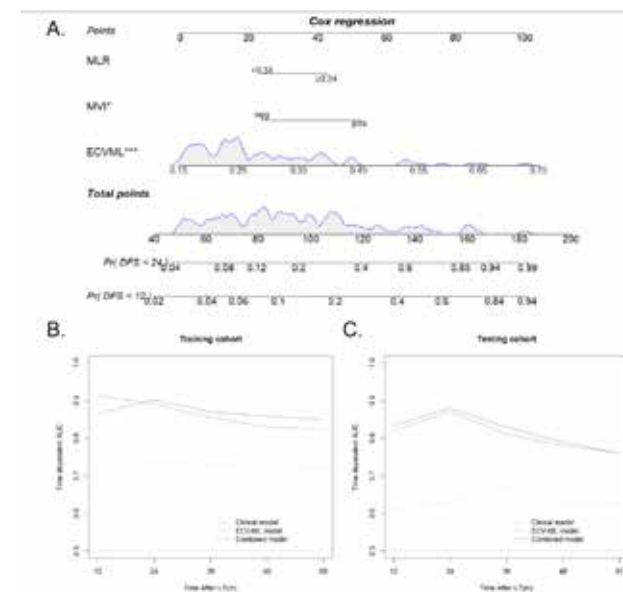


Figure 3. Model Comparison.

PE-3

The Fibrinogen-to-Albumin Ratio (FAR) Predicts Prognosis in Hepatocellular Carcinoma Patients after Liver Transplantation: Development and Validation of a Novel Nomogram

Kexin Wang, Xiaoyong Ye, Zhili Ji

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Aims: Hepatocellular carcinoma (HCC) is a common liver tumor. The fibrinogen-albumin ratio (FAR), as an indicator combining inflammatory status and nutritional status, may have significant value in the prognosis assessment of liver cancer patients undergoing liver transplantation. Hepatocellular carcinoma (HCC) is a common liver tumor. The fibrinogen-albumin ratio (FAR), as an indicator combining inflammatory status and nutritional status, may have significant value in the prognosis assessment of liver cancer patients undergoing liver transplantation.

Methods: This study retrospectively collected the clinical data of 239 HCC patients who underwent liver transplantation at Beijing Chaoyang Hospital from April 2013 to July 2023. The patients were randomly divided into a training set ($n = 168$) and a validation set ($n = 71$). The optimal cut-off value of FAR was determined by Maximally Selected Rank Statistics, and univariate and multivariate Cox regression analyses were conducted to evaluate the predictive value of FAR for overall survival (OS) and disease-free survival (DFS) in HCC patients after liver transplantation.

Results: The study results indicated that FAR had a non-linear

relationship with OS and DFS, with the optimal cut-off value being 6.23. Patients were divided into high FAR and low FAR groups based on FAR values. The results showed that patients in the high FAR group had significantly poorer prognosis ($P < 0.05$). Multivariate Cox regression analysis further demonstrated that microvascular invasion ($HR = 2.809$, $P = 0.006$) and $FAR \geq 6.23$ ($HR = 1.972$, $P = 0.031$) were independent risk factors for OS, while microvascular invasion ($HR = 2.892$, $P = 0.003$) and $FAR \geq 6.23$ ($HR = 2.176$, $P = 0.011$) were also independent risk factors for DFS. The prognostic prediction model based on FAR and microvascular invasion had good predictive performance and clinical utility.

Conclusions: This preoperative FAR is an independent prognostic factor for OS and DFS in HCC patients undergoing liver transplantation. The Nomogram model based on FAR has good predictive performance and is expected to serve as an auxiliary tool in clinical practice for preoperative risk assessment and postoperative prognosis judgment.

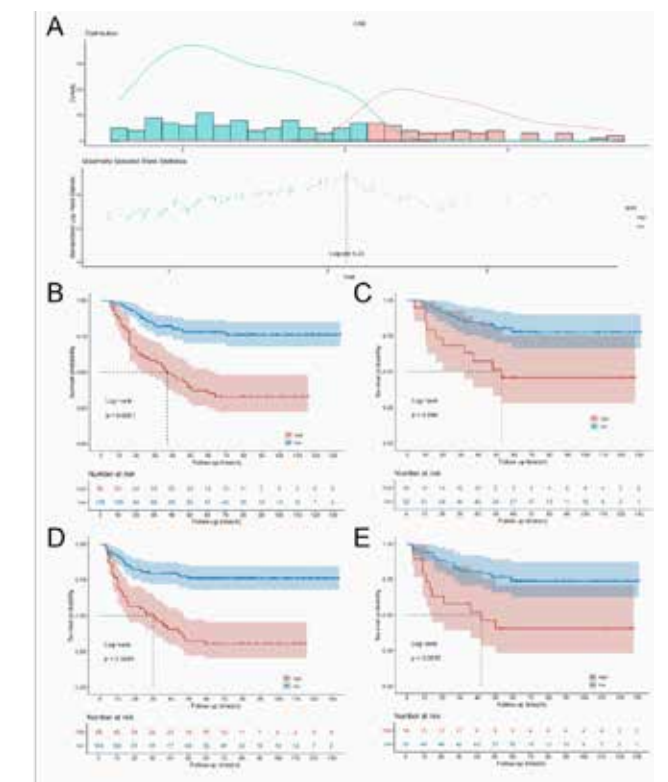


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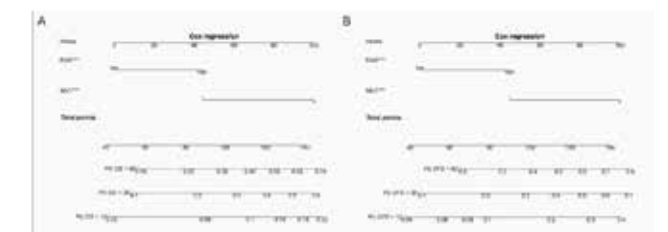


Figure 2.

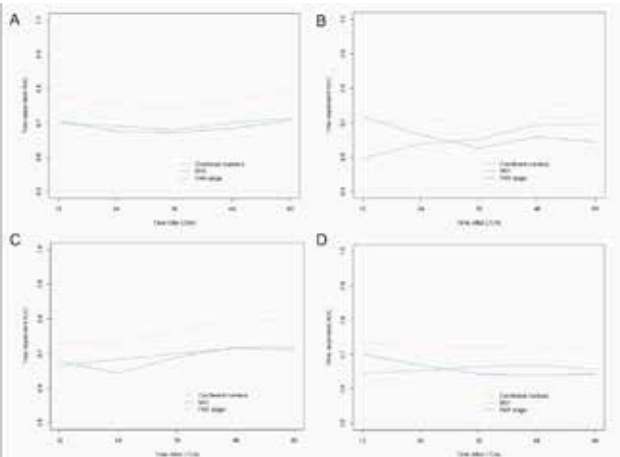


Figure 3.

Keywords: Liver Transplantation, Fibrinogenoalbumin Ratio, Hepatocellular Carcinoma, Prognosis

PE-4

Pediatric Liver Transplantation: Experience of a Single Center

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Aims: To evaluate the outcomes of liver transplantation in pediatric patients at a single specialized center, analyzing survival rates, complication frequency, and factors influencing clinical outcomes.

Methods: A retrospective analysis was conducted on medical records of patients under 18 years of age who underwent living donor liver transplantation at the center between 2014 and 2025. Demographic data, primary diagnosis, donor characteristics, surgical techniques, perioperative parameters, postoperative complications, and survival outcomes were studied.

Results: During the study period, 24 liver transplantations were performed in 24 children. Male recipients accounted for 57%, and female recipients for 43%. The median age of recipients was 9.5 months (range 7.75–15.5), with an average body weight of 16.8 kg. The most common indications for transplantation were biliary atresia (87%), metabolic disorders (8%), and autoimmune hepatitis (5%). All donors were relatives of the recipients. Surgical techniques included various anastomosis and vascular reconstruction methods, adapted to the age and anatomical characteristics of the child.

Complications occurred in 8 patients (33%) and included vascular thrombosis in 2 (25%), hemorrhage in 1 (12.5%), biliary complica-

tions in 2 (25%), and acute rejection in 3 (37.5%) cases. Postoperative mortality was 3 cases (12%). Factors associated with adverse outcomes included low body weight, young age (<1 year), comorbidities, and poor preoperative condition (high PELD scores).

Conclusions: Our center's experience confirms that liver transplantation in pediatric patients is a highly effective procedure with acceptable survival rates. The main challenges are managing perioperative complications and optimizing immunosuppression to reduce the risk of rejection.

Pediatric liver transplantation at our center demonstrates favorable survival outcomes and an acceptable complication rate. Future efforts should focus on improving the diagnosis and management of complications to further enhance clinical outcomes.

Keywords: Liver Transplantation, Pediatric Patients, Living Donor, Complications

PE-5

Splenic Artery Embolization Modulates Portal Hemodynamics and Improves Cytopenia after Living Donor Liver Transplantation

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Aims: Persistent hypersplenism with thrombocytopenia, leukopenia, and refractory ascites may occur after orthotopic liver transplantation (OLT) due to residual portal hypertension. While splenectomy is a traditional treatment option, splenic artery embolization (SAE) represents a less invasive alternative. We evaluated the safety and efficacy of SAE in OLT recipients with post-transplant hypersplenism.

Methods: Between January 2013 and June 2025, 74 OLT procedures were performed at the National Scientific Medical Research Center (Astana, Kazakhstan). Twelve recipients (16.2%) underwent SAE at 6–12 months post-transplant due to persistent hypersplenism. Indications included thrombocytopenia (platelet count < 60 × 10⁹/L), leukopenia (WBC < 2 × 10⁹/L), splenomegaly, and refractory ascites. SAE was performed via a percutaneous transfemoral approach under local anesthesia with selective occlusion of splenic artery branches. Clinical, laboratory, and radiological outcomes were analyzed.

Results: At 3 months following SAE, significant hematologic improvement was observed in all patients. Platelet counts increased from a median of 45 × 10⁹/L pre-procedure to 110 × 10⁹/L at 3 months. In patients with leukopenia, WBC counts

increased from 2,500 cells/μL to 7,000 cells/μL, with normalization achieved in all affected recipients. Ascites volume significantly decreased from a median of 1,800 mL to 700 mL at 3 months post-procedure, with marked clinical improvement in abdominal distension.

Post-embolization syndrome occurred in 8 patients (abdominal pain requiring analgesia), and transient fever was observed in 4 patients. Three patients developed perisplenic abscesses within 1 month, all was successfully managed with ultrasound-guided percutaneous drainage. No graft dysfunction or procedure-related mortality was observed.

Conclusions: Splenic artery embolization appears to be a safe and effective minimally invasive alternative to splenectomy for managing persistent hypersplenism and ascites after OLT.

Keywords: Liver Transplantation, Splenic Artery, Embolization, Hypersplenism

PE-6

Impact of Portal Vein Thrombosis on Waitlist and Post-Transplant Survival in Patients with End-Stage Liver Disease

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Aims: Portal vein thrombosis (PVT) is a frequent complication in patients with end-stage liver disease (ESLD) awaiting liver transplantation (LT). The presence of PVT may increase surgical complexity and has been associated with adverse post-transplant outcomes. However, its effect on waitlist mortality and overall transplant survival benefit remains unclear. This study aimed to evaluate the impact of PVT on waitlist mortality, post-transplant survival, and transplant survival benefit stratified by MELD score.

Methods: We retrospectively analyzed patients with ESLD who underwent evaluation and transplantation at Aktobe Medical Center between January 2015 and January 2025. Demographic characteristics (age, body mass index, smoking status), comorbidities, perioperative variables, postoperative complications, surgical infections, and follow-up duration were collected.

Patients were stratified according to the presence or absence of PVT. Waitlist mortality and post-transplant survival were assessed. Sequential stratification analysis was performed to estimate transplant survival benefit according to MELD score and PVT status. Appropriate statistical tests were applied for group comparisons.

Results: The presence of PVT was not associated with increased waitlist mortality. However, PVT was associated with significantly higher post-transplant mortality compared with patients without PVT.

Despite the increased post-transplant risk, the overall transplant survival benefit did not significantly differ between patients with and without PVT across MELD strata.

Conclusions: Portal vein thrombosis does not significantly affect waitlist mortality but is associated with increased post-transplant mortality. Nevertheless, liver transplantation continues to provide comparable overall survival benefits in patients with PVT. Careful perioperative assessment and surgical planning are essential when considering transplantation in clinically stable patients with PVT.

Keywords: Portal Vein Thrombosis, Waitlist, Liver Cirrhosis, Transplantation

PE-7

Impact of Adult Living Donor Liver Transplantation on Waitlist Mortality in Kazakhstan

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Aims: Living donor liver transplantation (LDLT) has significantly expanded access to life-saving treatment for patients with end-stage liver disease, particularly in regions where waitlist mortality is high and the availability of deceased donor organs is limited. Through a collaborative program with Seoul National University Hospital and several centers in Kazakhstan, LDLT has become an available therapeutic option for our population.

Methods: This collaboration has facilitated the development of national expertise while highlighting the inherent risks associated with living donation. LDLT carries potential risks for donors, including morbidity and, rarely, mortality, which must be carefully considered when establishing and expanding transplant programs.

Results: Over recent years, substantial improvements in surgical technique, perioperative management, and recipient outcomes have been observed across transplant centers in Kazakhstan. Nevertheless, LDLT remains a technically demanding procedure that requires experienced multidisciplinary teams. It is well established that higher-volume centers achieve superior outcomes.

Conclusions: Future investigations should focus on optimizing donor evaluation protocols, refining recipient selection criteria,

and further quantifying both donor risk and recipient outcomes. Continued research and structured program development will be essential to ensure the safe expansion and long-term sustainability of LDLT.

Keywords: Waiting List, Transplant Coordination, Living Donor

PE-8

A Novel Inflammatory and Nutrition-Based Risk Score for Predicting Overall Survival in Hepatocellular Carcinoma Patients after Liver Transplantation

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Aims: Hepatocellular carcinoma is a common malignant tumor in the liver. The prognostic predictive roles of inflammatory and nutrition-related markers in liver transplant patients with liver cancer remain unclear.

Methods: 239 patients with hepatocellular carcinoma undergoing liver transplantation were randomly divided into a training set and a validation at a 7:3 ratio. The optimal cut-off values for each indicator were determined using Maximally Selected Rank Statistics; a risk score (RS) was constructed using LASSO-Cox regression, and the optimal cut-off value of the RS was determined in the training set. A nomogram was further established and its predictive efficacy was evaluated.

Results: The risk score (RS) was ultimately included in three variables: FAR, GAR, and GPAR, with a cutoff value of 0.47. Patients in the high RS group had significantly poorer overall survival than those in the low RS group ($P < 0.05$), and this result was confirmed in the validation set and the subgroups meeting the Milan/Hangzhou criteria. Multivariate Cox analysis showed that high RS (HR = 2.174) and microvascular invasion (HR = 2.633) were independent risk factors. Based on these two factors, a nomogram was constructed, and the 1/3/5-year AUCs were 0.764/0.762/0.747 (training set) and 0.722/0.716/0.722 (validation set), and both calibration curves and decision curve analysis showed good consistency and clinical net benefit.

Conclusions: The preoperative risk score integrating FAR, GAR and GPAR can independently predict the overall survival of HCC patients after liver transplantation, providing a simple and practical new tool for clinical rapid prognosis assessment, individualized follow-up and adjuvant treatment strategy formulation.

Keywords: Hepatocellular Carcinoma, Liver Transplantation, Inflammatory-Nutritional Markers, Prognosis

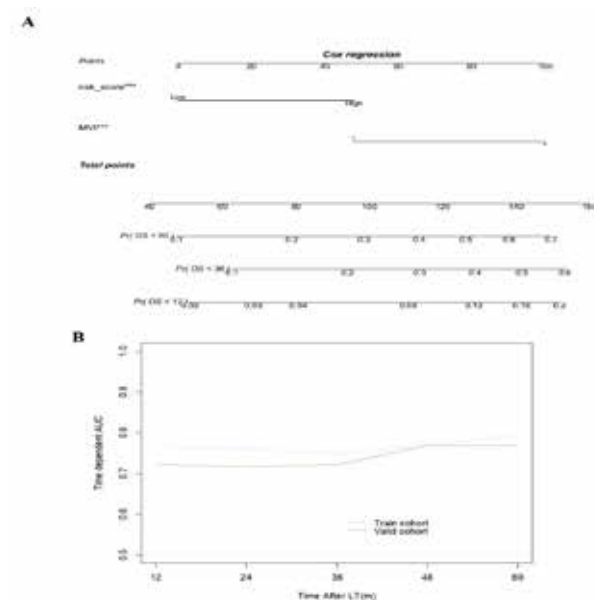


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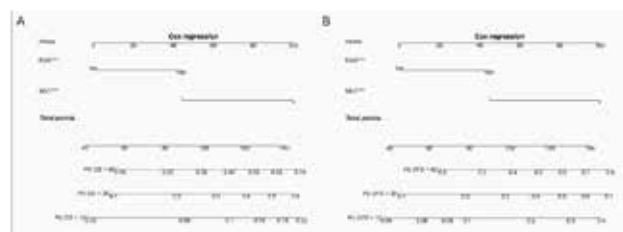


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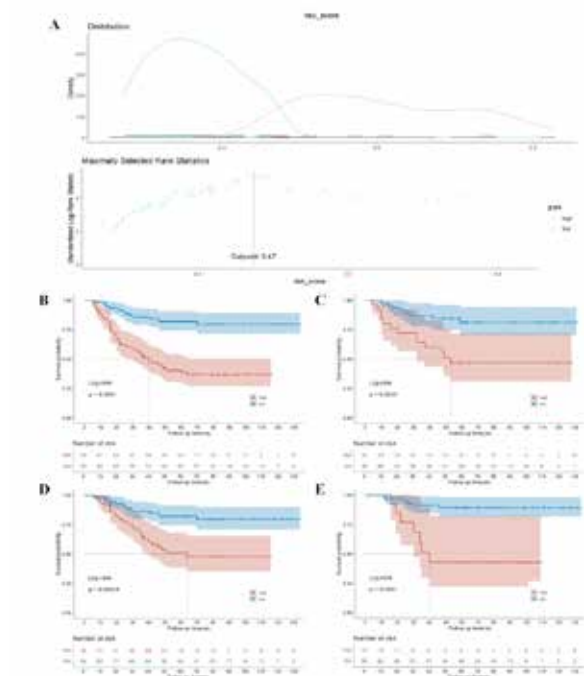


Figure 3.

PE-9

Liver Graft Rejection after Liver Transplantation in Kazakhstan: A Single-Center Experience

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Aims: Liver graft rejection remains a common and clinically relevant complication after liver transplantation (LT). Despite improvements in immunosuppressive therapy, the frequency and outcomes of rejection differ between centers, highlighting the value of single-center data. This study aimed to identify predisposing factors, determine the incidence and evaluate treatment response in patients with graft rejection after LT.

Methods: Clinical data of 124 patients who underwent LT at our center between January 2013 and November 2025 were retrospectively analyzed.

Results: Rejection was observed in 29 LT recipients (45 episodes), including 14 women and 15 men. Among these, 34 episodes were acute rejection (AR) and 11 were chronic rejection (CR). LDLT accounted for 71.4% of cases, while 28.6% underwent DDLT. The mean recipient age was 42 years (range 23–63). HBV/HDV coinfection (44.8%) was the most common cause of end-stage liver disease.

Subtherapeutic tacrolimus exposure or non-compliance (57.78%) and biliary complications (42.22%) were significantly associated with graft rejection. Late acute rejection (>90 days) predominated among AR episodes (n = 25). Liver biopsy according to the Banff criteria was performed in 24 AR cases, most frequently mild rejection (50%) based on the rejection activity index (RAI). In 10 cases, AR was diagnosed clinically.

Pulse corticosteroid therapy was administered in 24 AR cases and was successful in 66.7%. Among non-responders, antithymocyte globulin therapy was initiated in four patients and was effective in two. Response to escalation of immunosuppressive therapy was observed in 78% of nine AR cases. Significant improvement after treatment was observed in liver function parameters including ALT, AST, total bilirubin and ALP ($P < 0.05$).

Conclusions: Late AR predominated among AR episodes. The most common risk factors were biliary complications and non-compliance with immunosuppressive therapy. AR generally responded well to pulse corticosteroid therapy, whereas CR showed poor response to medical treatment and frequently required liver retransplantation.

Keywords: Acute Rejection, Chronic Rejection, Immunosuppression

PE-10

Turning Perfusate into Prognosis: AI-Enabled Real-Time Prediction of Early Liver Allograft Dysfunction

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ACS Medical College and Hospital, Dr. M.G.R. Educational and Research Institute, India

Aims: Early allograft dysfunction (EAD) remains a major determinant of morbidity and graft loss following liver transplantation. Conventional risk scores inadequately capture dynamic graft injury during preservation. We aimed to develop and prospectively validate an artificial intelligence (AI)-integrated predictive model combining normothermic machine perfusion (NMP)-derived biomarker signatures with clinical variables to accurately predict EAD.

Methods: In this prospective translational study, 96 donor livers undergoing NMP prior to transplantation were enrolled. Serial perfusate samples were collected at predefined intervals and analyzed for lactate kinetics, interleukin-6 (IL-6), high-mobility group box 1 (HMGB1), mitochondrial DNA (mtDNA), and bile composition indices.

A supervised machine learning framework incorporating gradient boosting and random forest algorithms was trained to predict EAD (defined by Olthoff criteria). Model performance was evaluated using 10-fold cross-validation and compared against conventional clinical predictors (Donor Risk Index, peak AST). Feature importance and Shapley additive explanations were used to delineate biomarker contributions.

Results: EAD occurred in 27% of recipients. The AI-integrated biomarker model demonstrated superior predictive performance compared with conventional metrics (AUROC 0.91 vs 0.68, $P < 0.001$). Incorporation of dynamic lactate clearance, mtDNA concentration, and IL-6 levels significantly enhanced discrimination.

Feature attribution analysis revealed mitochondrial injury markers and inflammatory cytokine burden as dominant predictors of graft dysfunction. The model maintained robust calibration across extended-criteria and donation-after-circulatory-death grafts. Decision curve analysis confirmed improved net clinical benefit for graft utilization strategies guided by the AI model.

Conclusions: AI-driven integration of perfusate biomarker dynamics during normothermic machine perfusion enables precise prediction of early allograft dysfunction beyond conventional clinical scores. This approach establishes a data-driven framework for real-time graft risk stratification, with potential to optimize organ allocation, reduce discard rates, and improve post-transplant outcomes. Prospective multicenter validation is warranted to facilitate clinical implementation.

Keywords: Early Allograft Dysfunction, Artificial Intelligence, Normothermic Machine Perfusion

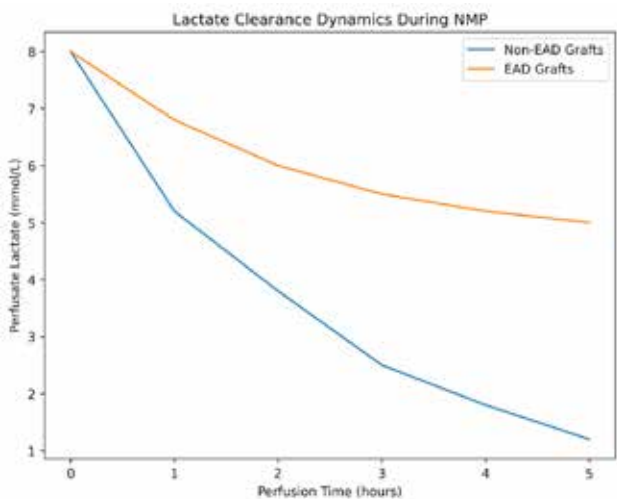


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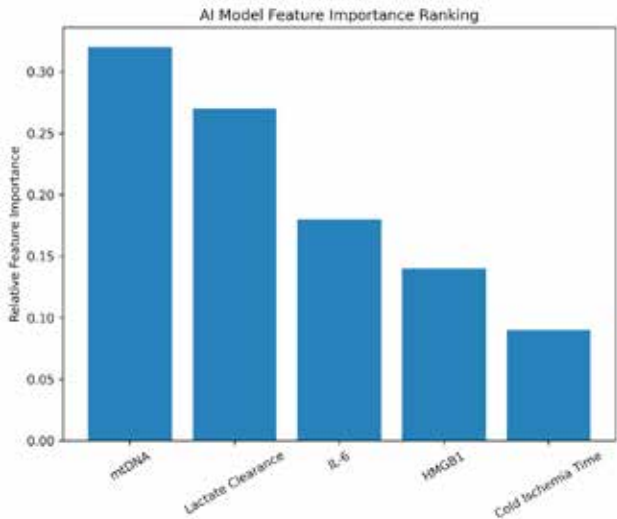


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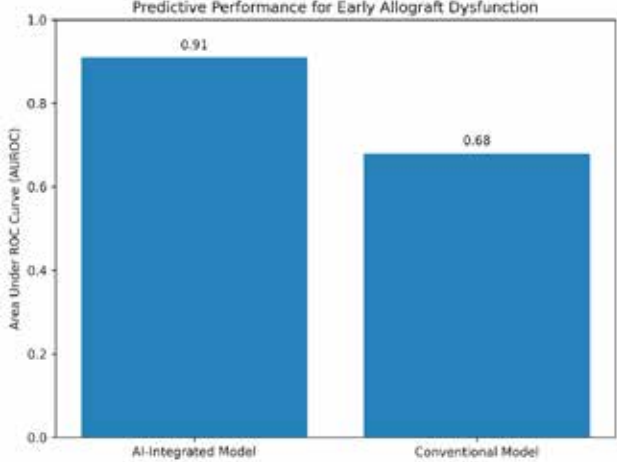


Figure 3.

PE-11

Intravenous Fetal Renal Stem Cell Therapy Is Associated With Reduction of Urinary Microalbumin in Post-Liver Transplant Nephropathy: A Prospective Pilot Study

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Aims: Acute and chronic kidney injury remain significant complications following living donor liver transplantation (LDLT). Novel regenerative approaches may offer therapeutic benefit. Fetal renal stem cells (FRSC) have demonstrated safety and renoprotective effects in preclinical models; however, their clinical impact in post-transplant nephropathy has not been evaluated. We aimed to assess the effect of FRSC infusion on urinary biomarkers of renal injury in LDLT recipients.

Methods: In this prospective pilot study, five adult LDLT recipients with evidence of nephropathy were followed for 9 months. Intravenous FRSC infusions were administered according to protocol at scheduled visits. Urinary microalbuminuria (MAU), urinary type IV collagen, and urinary neutrophil gelatinase-associated lipocalin (uNGAL) were measured longitudinally. Short-term changes in uNGAL were assessed before and 72 hours after infusion. Statistical comparisons were performed using paired analyses.

Results: The mean age was 41 years; three patients were male. A significant reduction in MAU was observed during follow-up (mean reduction -26.0%, $P=0.037$). Short-term decreases in uNGAL were noted 72 hours after infusion at the first visit (median 11.8 ng/mL, $P=0.027$) and second visit (median 9.3 ng/mL, $P=0.042$); however, this effect was not sustained at 6 months. Urinary type IV collagen levels did not demonstrate a significant change.

Conclusions: Intravenous FRSC therapy was associated with short-term reductions in urinary biomarkers of renal injury in LDLT recipients. These preliminary findings support further investigation in larger controlled studies to determine long-term efficacy and safety.

Keywords: Fetal Renal Stem Cell, Urinary Microalbumin, Liver Transplant, Nephropathy

PE-12

Integrative Machine Learning-Based Prediction of Primary Cilia Biomarkers to Mitigate Biliary Complications in Liver Transplant Patients

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Aims: Biliary complication remains a major cause of morbidity following liver transplantation. Manifestations such as biliary strictures and cholangiopathy often lead to graft failure. Primary cilia are highly specialized sensory organelles on cholangiocytes. However, the transcriptomic alterations related to primary cilia have not been systematically characterized. This study aimed to identify gene expression signatures associated with biliary complication compared to successful transplantation.

Methods: Transcriptomic data from the GSE220820 dataset were analyzed, including three liver transplant recipients who developed biliary complications and three with successful outcomes. Differentially expressed genes were identified, followed by protein-protein interaction network analysis using STRING to determine central hub genes based on network topology.

Results: Machine learning-based feature selection identified the top 96 transcripts based on adjusted p-values. Downregulated genes showed $\log_2$ fold changes from -2.02 to -0.04, while upregulated genes showed $\log_2$ fold changes between 0.02 and 0.08. Transcriptomic analysis highlighted Lgals3, Odc1, and Rbpj as significantly dysregulated genes involved in biliary homeostasis, epithelial integrity, and inflammatory signaling. Disruption of primary cilia may contribute to cholangiocyte dysfunction and biliary injury, particularly under conditions of ischemia-reperfusion and immune-mediated damage following transplantation.

Conclusions: These findings identify primary cilia-related gene signatures as potential biomarkers for biliary complications after liver transplantation. Key hub genes may serve as predictive markers and therapeutic targets, providing insight into mechanisms of cholangiocyte dysfunction and offering strategies to mitigate post-transplant biliary injury.

Keywords: Biliary, Cilia, Liver, Transplantation

PE-13

Management of Hepatic Hydrothorax in Cirrhosis: A Single-Center Experience in Patients Awaiting Liver Transplantation

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Aims: Hepatic hydrothorax is an uncommon but serious complication of advanced liver cirrhosis, occurring in approximately 5–10% of patients. It is typically associated with ascites and results from transdiaphragmatic migration of ascitic fluid. Optimal management remains challenging, particularly in patients

awaiting liver transplantation. This study aimed to evaluate treatment outcomes of hepatic hydrothorax in cirrhotic patients managed at a single center.

Methods: We retrospectively analyzed 28 patients with hepatic hydrothorax treated between March 2017 and October 2024. The mean age was 41 ± 4 years; 18 were male. Etiologies of cirrhosis included hepatitis B ($n=11$), hepatitis C ($n=9$), and primary biliary cholangitis ($n=8$). Disease severity was assessed using the Child-Pugh classification. Management strategies included therapeutic thoracentesis, pleural drainage, and medical therapy (diuretics). Recurrence and peri-procedural outcomes were evaluated.

Results: Most patients presented with right-sided hydrothorax. Recurrent pleural effusion occurred in 20 patients (66.7%) following thoracentesis. Fourteen patients required repeated thoracentesis, and five underwent pleural drainage due to massive hydrothorax. No procedure-related mortality was observed. All patients were evaluated as candidates for liver transplantation. In those who underwent transplantation, pleural drainage was successfully removed within 5–6 days postoperatively.

Conclusions: Hepatic hydrothorax remains a challenging complication of advanced cirrhosis with a high recurrence rate following thoracentesis. Pleural drainage appears to be a safe bridging strategy in selected patients awaiting liver transplantation. Definitive management requires treatment of the underlying liver disease, with transplantation representing the most effective curative option.

Keywords: Hepatic Hydrothorax, Liver Cirrhosis, Waiting List

PE-17

A Comprehensive Clinical Evaluation of Early Graft Function, Survival, and Postoperative Complications in Liver Transplantation

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Aims: Early identification of clinical predictors associated with graft performance and patient outcomes is essential for optimizing postoperative care and improving survival rates. Therefore, the present study aimed to evaluate early clinical outcomes, graft function, and complications associated with liver transplantation in a cohort of transplant recipients.

Methods: A prospective clinical evaluation was conducted on 120 patients undergoing liver transplantation at a tertiary transplant center. Recipient demographic characteristics, pre-operative clinical parameters including Model for End-Stage Liver Disease (MELD) score, donor characteristics, and intraoperative factors such as cold ischemia time and blood loss were recorded. Postoperative outcomes including liver function bio-

markers, graft survival, complications, and patient survival were monitored for 90 days following transplantation. Biochemical markers including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP) were measured to assess graft function. Statistical analysis was performed using multivariate regression to identify risk factors associated with early transplant outcomes.

Results: Among the 120 liver transplant recipients, the 90-day patient survival rate was 88.3%, while graft survival was 85.7%. Patients demonstrated significantly elevated liver enzymes immediately after surgery, with ALT levels reaching 356 ± 28 U/L and AST 421 ± 34 U/L within the first 24 hours, which gradually decreased to ALT 92 ± 14 U/L and AST 84 ± 11 U/L by day 7 ($P < 0.01$). Total bilirubin levels decreased from 9.2 ± 1.4 mg/dL preoperatively to 2.8 ± 0.7 mg/dL during postoperative recovery. Early postoperative complications were observed in 27.5% of patients, including acute rejection (11.7%), biliary complications (8.3%), and vascular thrombosis (7.5%). Multivariate analysis revealed that high MELD score (>30), prolonged cold ischemia time (>10 hours), and donor age >55 years were significant predictors of early graft dysfunction ($P < 0.05$). Patients with lower MELD scores and shorter ischemia times demonstrated significantly improved recovery and survival outcomes.

Conclusions: Identification of key risk factors such as MELD score, donor age, and ischemia duration may facilitate better perioperative management and improve graft survival. These findings emphasize the importance of comprehensive clinical assessment and optimized transplant strategies to enhance long-term outcomes in liver transplantation

Keywords: Clinical Evaluation, Liver Transplantation, Postoperative Complications

PE-18

ABO-Incompatible Living Donor Liver Retransplantation in a Pediatric Patient with Graft Failure due to Recurrent Progressive Familial Intrahepatic Cholestasis

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Aims: Cholestatic disorders are among the most severe liver diseases in infancy and childhood. Severe bile salt export pump (BSEP) deficiency, also referred to as progressive familial intrahepatic cholestasis type 2, is one such disorder. We present ABO incompatible living donor liver retransplantation in pediatric patient due to recurrent progressive familial intrahepatic cholestasis (PFIC) type 2.

Methods: A 9-year-old child who had undergone living donor liver transplantation at 6 months of age for hepatic failure due

to progressive familial intrahepatic cholestasis (PFIC) type 2 developed jaundice during outpatient follow-up. Anastomotic site stricture was initially suspected, and percutaneous transhepatic biliary drainage (PTBD) was performed. However, jaundice did not improve and progressively worsened despite 6 months of management. Liver biopsy subsequently confirmed recurrence of PFIC type 2. As part of treatment for recurrent PFIC and preparation for re-transplantation, rituximab therapy and plasmapheresis were initiated. A mild improvement in serum bilirubin levels was observed at 2 weeks after initiation of therapy; however, after approximately 4 weeks, bilirubin levels increased again, and ascites developed. Consequently, living donor liver re-transplantation was performed.

Results: The patient underwent living donor liver transplantation using a left lobe graft donated by the mother. On postoperative day 7, exploratory laparotomy was performed due to postoperative bleeding. Following surgical management, ascites resolved and laboratory parameters gradually improved, and the patient was discharged on postoperative day 25. The donor experienced no significant postoperative complications and was discharged on postoperative day 7.

Conclusions: Although experience with recurrent PFIC is limited, early recognition and prompt intervention are considered crucial when cholestasis develops in patients who have undergone liver transplantation for this condition. Further studies are needed to establish optimal treatment protocols and to determine appropriate timing for re-transplantation.

Keywords: PFIC Type 2, Living Donor Liver Retransplantation, Pediatric Patient

PE-19

Split Liver Transplantation: Two Adults Recipients

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Aims: Split liver transplantation (SLT) is an important tool to reduce the paucity of donor organ and waitlist mortality. However, a SLT is technically challenging, may cause increased perioperative complications, and has potential risk that transform an excellent deceased donor organ into two marginal grafts. Therefore, critical evaluation of deceased organs suitable for split transplantation and careful screening of potential SLT recipients is warranted. We introduce one case that split liver transplantation for two adult recipients.

Methods: A 28-year-old woman was waiting for deceased donor liver transplantation. Her MELD score was 40 point and stayed intensive care unit with renal replacement treatment. Her height was 150cm and weight was 52kg, blood type was O+. Deceased donor allocation was done, 52-year-old male,

175cm and 85kg. In preoperative volumetry, donor whole liver volume was about 1600g and the liver volume was too large for recipient. At that time, a 56-year-old woman hospitalized due to massive pleural effusion and ascites because of alcoholic liver cirrhosis. Her MELD score was 12 points and she had no living liver donor. Her blood type was O+ and body weight was 52kg. We decided split liver transplantation for two recipients, 28-year-old woman received modified right lobe with S1 graft, 56-year-old woman received extended left lobe graft.

Results: Modified right lobe graft with S1 graft was 1030g, extended left lobe graft was 670g. The recipient who received right lobe graft had postoperative bleeding, resolved with angioembolization. There was no postoperative complication except that event.

Conclusions: Donor organ shortage and donor pool expansion is conundrum in liver transplantation. Split liver transplantation is alternative for this problem, however, potential risk and ethical issue for graft quality because of split should be considered carefully. Experienced liver transplantation team is essential.

Keywords: Split Liver Transplantation, Donor Pool Expansion, Ethical Issue

PE-20

Exosomes from Chemically Derived Hepatic Progenitor Cells Protect Against Liver Ischemia Reperfusion Injury

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Aims: Hepatic ischemia-reperfusion injury (IRI) is a major complication in liver transplantation, trauma, and hemorrhagic shock, often leading to graft dysfunction. With the increasing use of extended-criteria donor livers, the development of effective and safe therapies is critical. Exosomes derived from progenitor cells have emerged as promising therapeutic agents due to their regenerative and immunomodulatory effects without the risks associated with stem cell therapy. This study investigates the protective potential of exosomes derived from human chemically derived hepatic progenitor cells (hCdHs) in an animal model of liver IRI.

Methods: Human chemically derived hepatic progenitor cells (hCdHs) were cultured from human liver tissue, and exosomes were isolated from the conditioned media via differential ultracentrifugation. Exosomes were characterized using nanoparticle tracking analysis, flow cytometry, and western blotting. *In vivo*, male SD rats underwent 70% partial hepatic ischemia for 60 minutes and were divided into four groups: Sham, IRI, IRI + Exosome, and IRI + Hydrocortisone. Blood samples and liver tissue were collected 24 hours post-reperfusion. Liver injury

was evaluated using serum biomarkers (AST, ALT, LDH), H&E staining, TUNEL assay, and qPCR.

Results: Exosomes averaged 200 nm in size and expressed exosomal surface markers. The IRI group showed elevated liver enzymes and histological damage. Both Exosome and Hydrocortisone groups exhibited reduced liver enzyme levels, improved histology, and decreased apoptosis. MicroRNA profiling of hCdH-derived exosomes identified several miRNAs with known IRI-protective effects based on the literature.

Conclusions: hCdH-derived exosomes attenuate liver IRI, showing similar protective effects to hydrocortisone. The presence of IRI-associated miRNAs suggests a potential mechanism. Future studies will include qPCR validation and mechanistic analysis focused on these miRNAs to further define the therapeutic potential of exosome-based interventions in liver transplantation.

Keywords: Hepatic Ischemic Reperfusion Injury, Extracellular Vesicles, Hepatic Progenitor Cells

PE-21

Liver Transplantation beyond Milan Criteria after Successful Downstaging for Hepatocellular Carcinoma: Early Experience from a Developing Transplant Center

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Aims: The Milan criteria remain the cornerstone for selecting patients with hepatocellular carcinoma (HCC) for liver transplantation (LT). However, expanding indications through effective downstaging has become increasingly important, particularly in regions where living donor liver transplantation (LDLT) predominates. Evidence from high-volume centers is growing, yet data from newly established transplant programs remain limited.

Methods: We retrospectively analyzed patients who underwent LT at a newly established transplant center. Recipient characteristics, tumor burden, downstaging strategies, and post-transplant outcomes were reviewed. Downstaging modalities included transarterial chemoembolization, radiofrequency ablation, hepatic artery infusion chemotherapy, and stereotactic body radiation therapy. Overall survival (OS) and recurrence-free survival (RFS) were assessed according to Milan criteria status.

Results: During the study period, 91 liver transplantations were performed, including 62 LDLT (68.1%) and 29 deceased donor LT (31.9%). Tumor-related indications accounted for 23 cases (25.3%), with 20 patients diagnosed with HCC. At initial evaluation, 13 patients were within Milan criteria and 7 exceeded Milan criteria. Selected patients beyond Milan criteria, includ-

ing those with portal vein tumor thrombosis, successfully underwent LT following multidisciplinary downstaging. The 1-, 3-, and 5-year OS rates for the overall cohort were 91.4%, 85.2%, and 82.7%, respectively. Among HCC patients, 5-year OS was 83.1% within Milan criteria and 53.3% beyond Milan criteria, with no significant difference in recurrence after successful downstaging.

Conclusions: Even in a developing transplant program, LT beyond Milan criteria can be safely performed with acceptable outcomes when supported by careful patient selection and effective downstaging. These findings suggest that expanded LT strategies are feasible through a multidisciplinary approach.

Keywords: Liver Transplantation, Hepatocellular Carcinoma, Downstaging

PE-22

Short-Course Maribavir as a Rapid Salvage Option in Preemptive CMV Management after Liver Transplantation: A Case Series Study

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Aims: Cytomegalovirus (CMV) infection after liver transplantation (LT) can lead to significant morbidity, and preemptive therapy is generally initiated based on CMV antigenemia. Ganciclovir is the first-line treatment for CMV antigenemia; however, treatment is sometimes discontinued because of adverse events. Maribavir can be used as an alternative in patients with refractory or resistant (R/R) CMV infection. Although several studies have evaluated the safety and efficacy of maribavir in solid organ transplant, real-world data in LT recipients remain limited. Therefore, we aimed to describe the clinical course of LT recipients treated with maribavir.

Methods: We retrospectively reviewed 7 adult liver transplant recipients (median age, 59 years; 5 males) who received maribavir 400 mg twice daily for CMV viremia after preemptive ganciclovir-based therapy.

Results: The main reason for switching to maribavir were hematologic toxicity, including neutropenia, or thrombocytopenia (n=5), and inadequate virological response despite over 2 weeks of ganciclovir therapy (n=3). Maribavir was administered for a median of 9 days (range, 2–12 days). At initiation, the median CMV PCR level was 3.6×10^4 IU/mL, which decreased by a median of approximately 97% by the end of maribavir treatment. CMV antigenemia became undetectable in six patients (86%), and decreased to a low level (1 positive cell) in one patient.

Conclusions: Maribavir provided a rapid salvage option for patients who could not continue ganciclovir because of toxicity or insufficient response. Short-term maribavir use led to prompt virological control without the need for prolonged therapy, suggesting a potential role as a targeted “rescue” strategy within preemptive CMV management after LT.

Keywords: MARIBAVIR, CMV, PREEMPTIVE

PE-23

Clinical Impact of Early Postoperative Tacrolimus Levels on Rejection and Biliary Complications in ABO-Incompatible Living Donor Liver Transplantation: A Comparative Study

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Aims: In ABO-incompatible living donor liver transplantation (ABOi LDLT), higher early tacrolimus (FK) exposure has traditionally been targeted to prevent rejection and biliary complications. This study aimed to investigate whether there were differences in rejection or biliary complications according to FK levels in the early postoperative period after LDLT.

Methods: We retrospectively analyzed 203 LDLT recipients transplanted up to 2025. Patients were categorized as ABO-compatible (ABOc, n=162) or ABO-incompatible (ABOi, n=41). ABOi recipients were divided into two groups based on a mean FK level cutoff of 7 ng/mL during the first postoperative month. Outcomes included acute cellular rejection (ACR), biliary complications, and graft survival.

Results: The median FK level during the first postoperative month was 6.4 (5.2–6.9) in the ABOi <7, 8.2 (7.0–10.4) in the ABOi ≥7, and 6.5 (4.6–13.8) in ABOc group ($P=0.951$). ACR rates did not differ among groups (0%, 5.6%, and 11.7%, respectively; $P=0.223$), nor did biliary complication rates (26.1%, 22.2%, and 22.8%; $P=0.951$). One- and 3-year graft survival were comparable across groups. In Cox regression analysis (using ABOc as the reference), neither ABOi <7 (HR 0.333; $P=0.282$), ABOi ≥7 (HR 1.186; $P=0.751$), nor mean FK level (HR 0.967; $P=0.967$) was associated with graft loss.

Conclusions: Early postoperative FK levels during the first month were not associated with rejection, biliary complications, or graft survival in either ABOi or ABOc LDLT. Although a relatively wide range of FK levels is currently used in practice, prospective studies are needed to define the optimal FK target that balances efficacy and safety in ABOi LDLT.

Keywords: ABO-Incompatible, Tacrolimus

PE-24

Chinese-Style Modified Piggyback Liver Transplantation

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Aims: The piggyback technique is widely used in orthotopic liver transplantation because it preserves the recipient inferior vena cava and maintains intraoperative hemodynamic stability. Classical piggyback liver transplantation may be complicated by hepatic venous outflow obstruction due to limited anastomotic size or unfavorable venous geometry. To overcome these limitations, a Chinese-style modified piggyback liver transplantation technique has been developed and increasingly applied in clinical practice.

Methods: The Chinese-style modified piggyback technique preserves the recipient IVC while optimizing hepatic venous outflow reconstruction. The recipient hepatic venous orifice is enlarged by longitudinal incision of the anterior IVC wall or by combining the right and middle hepatic veins to create a wide anastomotic opening. The donor hepatic vein cuff is anastomosed to the reconstructed outflow under partial IVC clamping, allowing continuous venous return. Portal vein, hepatic artery, and biliary reconstructions are performed using standard techniques. Perioperative outcomes, including hemodynamic stability, blood loss, postoperative complications, and graft function, are assessed.

Results: Compared with conventional OLT, the Chinese-style modified piggyback technique provides superior intraoperative hemodynamic stability, reduces the need for venovenous bypass, and decreases blood transfusion requirements. The widened venous outflow effectively lowers the incidence of hepatic venous outflow obstruction. Postoperative liver function recovery is favorable, with comparable or improved short-term graft survival and no increase in perioperative mortality.

Conclusions: Chinese-style modified piggyback liver transplantation is a safe and effective refinement of the piggyback technique, combining IVC preservation with optimized hepatic venous outflow reconstruction. It may be particularly beneficial for recipients with severe portal hypertension or compromised cardiopulmonary function.

Keywords: Modified Piggyback Liver Transplantation, Inferior Vena Cava Preservation, Hepatic Venous Outflow

PE-25

Prognostic Impact of COVID-19 Infection After Liver Transplantation: A Multicenter Analysis using the KOTRY Database

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Aims: Solid organ transplant recipients, including those undergoing liver transplantation (LT), are known to be highly vulnerable to viral infections due to lifelong immunosuppression. COVID-19 is considered a major risk factor that may exacerbate severe complications and mortality. However, comprehensive analyses based on large-scale multicenter registries are lacking in Asia. This study aims to evaluate the impact of COVID-19 infection on survival and post-transplant complications in Korean LT recipients using the Korean Organ Transplantation Registry (KOTRY) database.

Methods: A retrospective, multicenter cohort study was conducted using KOTRY data. A total of 2,289 adult LT recipients with available follow-up data were included and categorized into the COVID-19 infected group (n=541) and the non-infected group (n=1,748). The primary endpoints were overall patient and graft survival. The secondary endpoints included the incidence of post-transplant complications, particularly acute rejection and renal failure. Categorical variables were compared using the Chi-square test, and survival outcomes were assessed based on registry follow-up data.

Results: Among the 2,289 LT recipients analyzed, 541 patients (23.6%) experienced COVID-19 infection during the follow-up period. Overall patient survival rates were comparable between the COVID-19 infected and non-infected groups (89.1% vs. 88.3%, $P=0.6556$). Similarly, overall graft survival did not show a statistically significant difference (87.6% vs. 86.1%, $P=0.4069$). However, regarding secondary complications, the incidence of acute rejection was significantly higher in the COVID-19 infected group compared to the non-infected group (13.5% vs. 8.1%, $P=0.0002$). The rate of renal failure requiring management was slightly higher in the infected group, but the difference was not statistically significant (6.7% vs. 5.6%, $P=0.4223$).

Conclusions: In this Korean multicenter cohort, COVID-19 infection after liver transplantation did not significantly impair overall patient or graft survival, likely due to effective clinical management. However, COVID-19 infection was significantly associated with an increased risk of acute rejection. These findings suggest that COVID-19 presents a critical immunological challenge in LT recipients. Close monitoring of graft function and tailored immunosuppressive strategies are essential for

managing post-transplant patients who contract COVID-19.

Keywords: Liver Transplantation, COVID-19, Prognosis

PE-26

Clinical Value of Inflammatory Indexes in Predicting Post-Transplantation Prognosis in Hepatocellular Carcinoma

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Aims: This study aims to systematically evaluate the clinical value of various preoperative inflammatory indexes in predicting post-LT outcomes to optimize the stratification of suitable HCC patients that can benefit from LT.

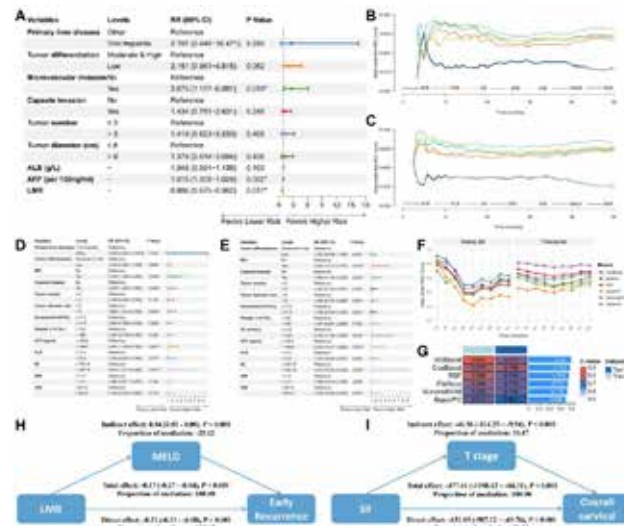
Methods: This retrospective study included 239 HCC patients who underwent LT. Preoperative general and laboratory data were collected to calculate various inflammatory biomarkers. Least absolute shrinkage and selection operator and logistic regression were used to identify independent risk factors for early tumor recurrence, while log-rank test and Cox regression were used to identify independent risk factors for postoperative survival. Subgroup analysis was used to evaluate the predictive value in different sub-populations. Prediction models were established using multiple machine-learning model and evaluated by concordance index, area under the ROC curve, calibration curve and decision curve analysis. Mediating effect analysis was utilized to elucidate potential mediating factors.

Results: Lymphocyte-to-monocyte ratio (LMR) served as an independent predictor for early tumor recurrence, with an optimal cut-off of 2.64. The systemic immune-inflammation index (SII) served as an independent risk factor for both overall survival (OS) and disease-free survival (DFS), with an optimal cut-off value of 155.19. The prognostic value of SII was robust across nearly all clinical subgroups while the predictive value of LMR was limited to certain subgroups. The CoxBoost model, incorporating alpha-fetoprotein (AFP) and SII as its most important variables, demonstrated the optimal predictive accuracy and clinical benefit in all established models. Additionally, mediating analysis indicated that tumor T stage significantly mediated the correlation between SII and postoperative survival outcomes, while liver function exerted significantly suppression effect on correlation between LMR and early tumor recurrence.

Conclusions: Preoperative LMR and SII are effective predictors for early tumor recurrence and long-term survival in HCC patients following LT, respectively. Integrating inflammatory indexes with other preoperative indexes into a CoxBoost model can further optimize post-transplantation prognostic predic-

tion and assist clinical decision-making.

Keywords: Hepatocellular Carcinoma, Liver Transplantation, Inflammatory Index, Prognosis



PE-27

External Validation and Clinical Refinement of the SNAPP Score for Predicting Hepatocellular Carcinoma Recurrence after Living Donor Liver Transplantation

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Aims: The SNAPP score integrates tumor size and number, alpha-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II), and FDG-PET/CT findings to predict hepatocellular carcinoma (HCC) recurrence before living donor liver transplantation (LDLT). We externally validated the SNAPP score in a multicenter cohort and proposed a simplified risk stratification approach for clinical use.

Methods: This retrospective study included 230 adults who underwent LDLT for HCC between 2007 and 2025. Patients without pretransplant PIVKA-II or PET/CT data were excluded. Predictive performance was assessed using Harrell's C-index, time-dependent area under the curve (AUC), calibration, and decision curve analysis (DCA).

Results: Among 230 patients, 49 (21.3%) developed recurrence. Cumulative recurrence rates were 17.6% at 3 year and 20.7% at 5 year. Patients with SNAPP scores ≥ 3 showed significantly lower recurrence-free survival than those with scores 0-2 (log-rank $P < 0.001$). The SNAPP score showed moderate discrimination (C-index 0.73; 95% CI 0.67–0.80) with time-dependent AUCs of 0.758, 0.746, and 0.753 at 1, 3, and 5 years, respectively. Calibration slopes of 1.33 at 3 years and 1.21 at 5 years indicat-

ed insufficient spread of predicted probabilities, and negative calibration-in-the-large values suggested overall underestimation of risk. DCA confirmed net clinical benefit of SNAPP-guided strategies over treat-all and treat-none approaches.

Conclusions: The SNAPP score demonstrated moderate discrimination, acceptable calibration, and clinical utility in this external multicenter cohort. A simplified binary stratification (SNAPP 0-2 vs ≥ 3) provided a pragmatic threshold for post-transplant risk stratification and surveillance.

Keywords: Living Donor Liver Transplantation, Hepatocellular Carcinoma, External Validation, Snapp Score

PE-28

Diagnostic Performance of Non-Invasive Steatosis Assessment Tools in Living Liver Donors

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Aims: Accurate assessment of hepatic macrosteatosis is critical for living donor liver transplantation (LDLT), as significant steatosis increases the risk of graft dysfunction. FibroScan controlled attenuation parameter (CAP) and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) are widely used non-invasive tools; however, their comparative diagnostic performance in the unique low-steatosis donor population has not been adequately characterized. We compared the diagnostic accuracy and concordance of CAP and MRI-PDFF for detecting macrovesicular steatosis in living liver donors, using intraoperative biopsy as the reference standard.

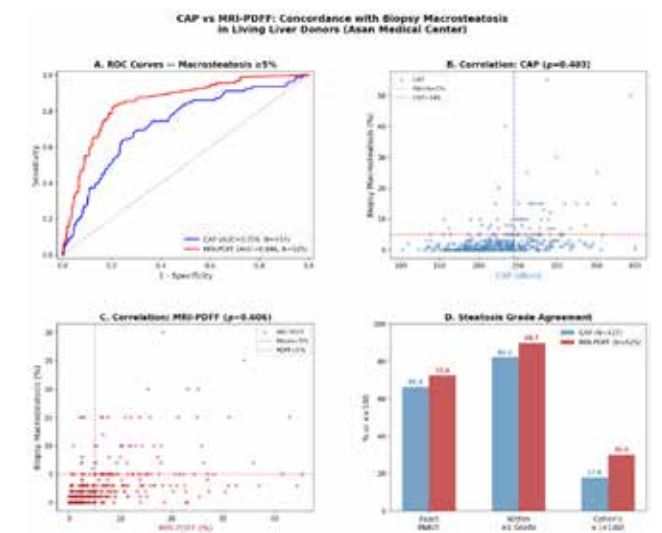
Methods: In this retrospective single-center study at Asan Medical Center, we identified right-lobe living liver donors who underwent intraoperative liver biopsy with macrosteatosis quantification. Donors who had preoperative FibroScan CAP ($n = 437$) and/or MRI-PDFF measurements ($n = 525$) were included. Diagnostic performance for macrosteatosis $\geq 5\%$ and $\geq 10\%$ was evaluated using the area under the receiver operating characteristic curve (AUROC). Optimal cutoff values were determined by Youden index. Grade-level concordance was assessed using Cohen's kappa (κ) and percent agreement.

Results: The prevalence of macrosteatosis $\geq 5\%$ was 17.8% (78/437) in the CAP cohort and 17.0% (89/525) in the MRI-PDFF cohort, with a median macrosteatosis of 1% (IQR 0–3%) in both groups. For detecting macrosteatosis $\geq 5\%$, MRI-PDFF demonstrated a significantly higher AUROC than CAP (0.846

vs 0.726), with superior sensitivity (82.0% vs 64.1%) and negative predictive value (95.3% vs 90.1%) at optimal cutoffs of 4.98% and 245 dB/m, respectively. For macrosteatosis $\geq 10\%$, MRI-PDFF maintained its advantage (AUROC 0.844 vs 0.763). MRI-PDFF also showed a stronger correlation with biopsy macrosteatosis (Spearman $\rho = 0.606$ vs 0.403). In steatosis grade concordance analysis, MRI-PDFF outperformed CAP in exact grade agreement (72.4% vs 66.4%), within ± 1 grade agreement (89.7% vs 82.2%), and Cohen's κ (0.300 vs 0.178). A preliminary analysis of 14 donors who underwent ultrasound-derived fat fraction (UDFF) measurement showed an AUROC of 0.762 for macrosteatosis $\geq 5\%$, warranting further investigation in a larger cohort.

Conclusions: In living liver donors, MRI-PDFF provides superior diagnostic accuracy and concordance with intraoperative biopsy compared to FibroScan CAP for assessing macrovesicular steatosis. Given the low prevalence and narrow distribution of steatosis in donors, MRI-PDFF's higher sensitivity and NPV support its preferential use as a non-invasive screening tool. However, both modalities showed only moderate agreement at the grade level, suggesting that biopsy remains indispensable for borderline cases. Novel quantitative ultrasound techniques such as UDFF may offer an additional accessible alternative and merit prospective validation in this population.

Keywords: Donor Selection, Hepatic Steatosis, Controlled Attenuation Parameter, Proton Density Fat Fraction



PE-29

Poor Outcomes of Living-Donor Liver Transplantation Using Grafts with a Graft-To-Recipient Weight Ratio below 0.7: A Large-Single Center Cohort Study

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Aims: To evaluate outcomes of living-donor liver transplantation (LDLT) using grafts with a graft-to-recipient weight ratio (GRWR) below 0.7. Although small-for-size grafts expand donor eligibility, their safety and long-term outcomes remain controversial.

Methods: A retrospective analysis of 5,435 adult LDLT recipients was conducted; 65 received grafts with GRWR <0.7, 258 with GRWR 0.7–0.8, and 5,112 with GRWR ≥0.8. Subgroup analysis regarding small-for-size syndrome (SFSS), portal inflow modulation (PIM), and MELD score and risk factor analysis were performed.

Results: Before and after propensity score matching, recipients with GRWR <0.7 had significantly higher 1-year graft failure and mortality than those with GRWR 0.7–0.8 or ≥0.8 ($P<0.05$); the incidences of SFSS and major vascular or biliary complications showed no significant differences among the groups. Overall survival (OS) and graft survival (GS) were significantly poorer in patients with GRWR <0.7 than in those with GRWR 0.7–0.8 or ≥0.8 ($P<0.001$). SFSS Grade B–C was associated with the poorest OS and GS across all GRWR categories. In recipients with GRWR 0.7–0.8, PIM and MELD scores <20 were associated with significantly better survival. In both entire and matched cohorts, multivariable Cox regression identified GRWR 0.7–0.8 and GRWR >0.8 as significant favorable prognostic factors; major vascular complications and SFSS Grade B–C were significant risk factors for GS ($P<0.05$).

Conclusions: LDLT with GRWR <0.7 showed poor survival, particularly in patients with MELD scores ≥20, whereas GRWR ≥0.7 was feasible with appropriate PIM and prevention of SFSS and vascular complications.

Keywords: Living-Donor Liver Transplantation, Small Graft, Survival

PE-30

GRWR 0.7% Is a Safe Threshold in Standard Living Donor Liver Transplantation: Outcome Analysis of 2,506 Cases

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Aims: Early evidence suggests that acceptable outcomes have been observed at GRWR below 0.6%, but only when portal pressure modulation is employed. However, the minimum safe GRWR achievable in standard practice without portal interventions remains undefined and the traditional 0.8% threshold may be unnecessarily restrictive.

Methods: This study analyzed 2,506 consecutive LDLT cases

at a single center, all performed without routine portal pressure modulation. GRWR and outcomes were assessed across all graft types (1,868 modified right, 308 extended right, 71 standard right, 111 left lobe, 114 left lateral). 1,892 grafts had complete follow-up data. The minimum safe GRWR was determined using survival-based inflection-point analysis and Kruskal-Wallis testing at 0.1% increments.

Results: Without portal pressure modulation, overall survival was 81.0%. A key survival inflection occurred at 0.7% GRWR: patients below 0.7% had 71.4% survival ($n=105$), while those at 0.7% or higher had 81.5% survival ($n=1,787$), a 10.1 percentage-point improvement ($P=0.010$). The traditional 0.8% threshold did not provide additional safety; survival below 0.8% was 77.6% ($n=272$) versus 81.5% at 0.8% or higher ($n=1,620$), a 4.0 percentage-point difference ($P=0.123$, not significant). The 0.7–0.8% GRWR range achieved 82.9% survival ($n=152$) without portal interventions.

Conclusions: For centers using standard techniques without portal pressure modulation, a GRWR of 0.7% is an evidence-based minimum threshold, offering a 10.1 percentage-point survival benefit over lower values ($P=0.010$). The 0.8% threshold is unnecessarily restrictive ($P=0.123$).

Keywords: GRWR

16. Biliary and Pancreatic Surgery

PE-1

Aging Shapes Immunosuppressive Niches in Gallbladder Cancer

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Aims: Aging profoundly reshapes the tumor microenvironment (TME) and critically influences therapeutic outcomes in hepato-biliary-pancreatic malignancies. Gallbladder cancer (GBC) predominantly affects elderly individuals, yet the mechanisms by which aging-associated TME remodeling drives tumor progression and immune escape remain poorly defined. Understanding age-dependent TME alterations is essential for optimizing treatment strategies in GBC.

Methods: Tumor samples from younger (<60 years, $n=5$) and older (>70 years, $n=5$) patients with GBC were analyzed using integrated single-cell RNA sequencing and spatial transcriptomics. Age-related differences in cellular composition, transcriptional programs, differentiation trajectories, and cell–cell communication were systematically assessed. Spatial analyses were performed to identify aging-associated immunosuppres-

sive niches and their underlying signaling pathways.

Results: Aging led to profound remodeling of both immune and stromal components in the GBC TME. Tumors from older patients exhibited increased infiltration of immunosuppressive cell populations, including regulatory T cells, M2-polarized tumor-associated macrophages, myeloid-derived suppressor cells, and exhausted CD8⁺ T cells, accompanied by impaired antitumor immune activity. Stromal fibroblasts displayed enhanced extracellular matrix remodeling programs, promoting a fibrotic and tumor-supportive microenvironment, while endothelial cells showed transcriptional features indicative of vascular dysfunction. Notably, the inflammatory signaling pathways NF- κ B and STAT3 were broadly activated in the aged TME. Spatial transcriptomics further revealed a distinct immunosuppressive niche enriched in older patients, characterized by heightened NF- κ B/STAT3 activity and clear spatial segregation from immune-active regions.

Conclusions: Aging drives the formation of spatially organized immunosuppressive niches in GBC through coordinated activation of NF- κ B, STAT3, and stromal remodeling pathways. These findings provide mechanistic insight into age-related immune evasion and underscore the need for age-adapted immunotherapeutic and combination treatment strategies in elderly GBC patients.

Keywords: Aging, Gallbladder Cancer, Tumor Microenvironment, Immunosuppressive Niche

PE-2

Spatial Fibroblast–NK Crosstalk Drives Immunosuppressive Niches in Gallbladder Cancer

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Aims: Gallbladder cancer (GBC) is a highly aggressive malignancy with poor responsiveness to immunotherapy. Natural killer (NK) cells are essential innate cytotoxic effectors; however, the mechanisms driving NK-cell dysfunction within the GBC tumor microenvironment (TME) remain largely undefined. Identifying stromal–immune regulatory pathways underlying NK-cell suppression may reveal actionable targets for overcoming immune escape and therapeutic resistance.

Methods: Single-cell RNA sequencing and spatial transcriptomics were integrated to characterize NK-cell heterogeneity and their regulatory interactions in GBC. Cell–cell communication was inferred using CellChat, complemented by spatial co-localization analysis and multiplex immunofluorescence. Spatial transcriptomics was further used to delineate immunosuppressive niches associated with impaired NK-cell cytotoxicity.

Results: We identified a tumor-associated NK (TaNK) cell subset

exhibiting reduced cytotoxic activity and elevated exhaustion signatures. Myofibroblastic cancer-associated fibroblasts (my-CAFs) emerged as dominant suppressors of NK-cell function, mediating inhibitory signaling through the COL1A1–LAIR1 ligand–receptor axis. This stromal–immune interaction mechanistically linked extracellular matrix remodeling to NK-cell dysfunction. Spatial profiling and histological validation revealed strong co-localization of myCAFs and TaNK cells within an immunosuppressive niche characterized by immune exclusion and dense matrix deposition. Tumors enriched for myCAF–TaNK co-infiltration displayed markedly diminished NK cytotoxic gene expression and were associated with unfavorable immunotherapy-related outcomes.

Conclusions: Our study identifies a myCAF-driven COL1A1–LAIR1 signaling axis that suppresses NK-cell cytotoxicity and shapes an immunosuppressive niche in GBC. These findings highlight a previously unrecognized stromal–NK regulatory mechanism and suggest potential therapeutic strategies targeting fibroblast remodeling or NK-cell reactivation to improve immunotherapy efficacy in GBC.

Keywords: Gallbladder Cancer, NK Cell Dysfunction, Cancer-Associated Fibroblasts, Immunosuppressive Spatial Niche

PE-3

Pylorus Resecting Pancreatoduodenectomy with or without Feeding Jejunostomy- A Randomized Controlled Trial

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Aims: Postoperative nutrition after pancreatoduodenectomy (PD) remains controversial. Although many centers routinely place a feeding jejunostomy tube (FJT) after PD, it is associated with morbidity. We conducted this study to compare the perioperative outcomes with and without FJT placement post-PD.

Methods: This was an open-label randomized controlled trial, in which the FJT was placed in one arm and the nasojejunal tube (NJT) in the other, conducted from March 2021 to February 2024. All patients with periampullary neoplasm who underwent pylorus resecting PD were included in this study. The primary outcome assessed was clinically relevant delayed gastric emptying (CR-DGE), and the secondary outcomes were clinically relevant postoperative pancreatic fistula (CR-POPF), postoperative complications, and hospital stay.

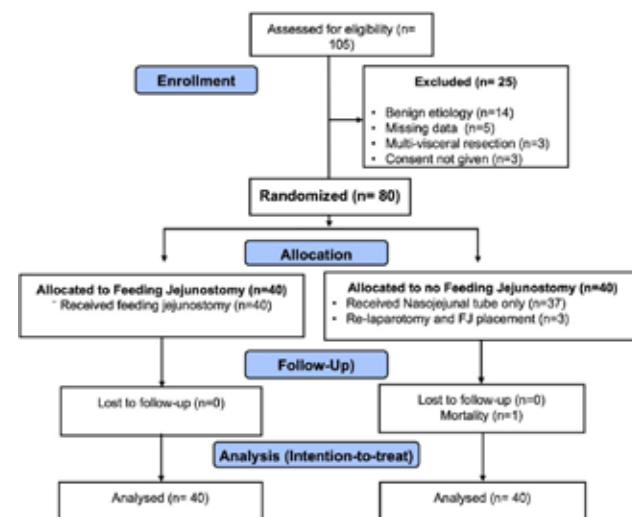
Results: Forty patients were allocated to the FJT and NJ groups, and the two groups were comparable in baseline demographics, disease characteristics, and perioperative outcomes, including CR-POPF rates. The FJT group had a significantly higher

CR-DGE rate (55% vs. 25%, $P=0.006$), required increased use of prokinetic drugs (77.5% vs. 45%, $P=0.003$), and had a longer median postoperative hospital stay (11 vs. 9 days, $P=0.007$). Both groups had similar tube-related complications. In the NJT group, 22.5% of the patients with CR-DGE required parenteral nutrition. On multivariate analysis, the presence of FJT [adjusted odds ratio (aOR)- 6.030(1.431-25.402), $P=0.014$] and intra-abdominal collection [aOR, 7.108 (1.026-49.224), $P=0.047$] were independent risk factors for CR-DGE.

Conclusions: Post-PD placement of FJT was an independent risk factor for CR-DGE. Hence, the routine use of the FJT can be omitted after PD without compromising postoperative morbidity and nutrition.

The trial was registered with the Clinical Trial Register with CTRI number: CTRI/2021/02/030942

Keywords: Pancreatoduodenectomy, Feeding Jejunostomy, Delayed Gastric Emptying, Nasojejunum Tube



PE-4

Outcomes of Reinforcement Patch around Pancreaticojejunostomy on Clinically Relevant Pancreatic Fistula after Pancreatoduodenectomy- A Randomized Controlled Trial

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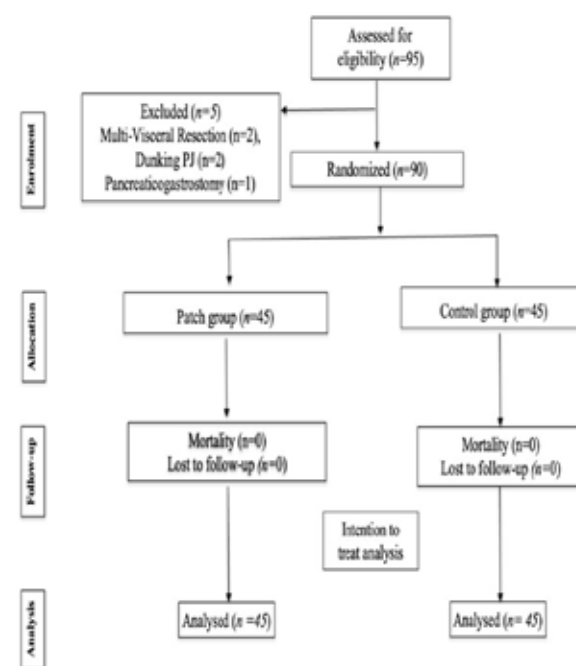
Aims: Clinically relevant postoperative pancreatic fistula (CR-POPF) is a major concern following pancreatoduodenectomy (PD). Various studies have evaluated sealant patches around pancreaticojejunostomy (PJ) for its prevention, with mixed results. This study evaluated a reinforcement patch (composed of oxidised regenerated cellulose, trylisine, and polyethylene

glycol) applied around PJ and compared it with a standard arm.

Methods: This was a single-centre, open-label, randomized controlled trial that included patients who underwent pylorus-resecting pancreatoduodenectomy from May 2024 to September 2025. A standard duct-to-mucosa PJ was performed in the control arm, whereas in the patch arm, the PJ was reinforced with a Veriset™ (Medtronic) patch. The primary outcome was the incidence of CR-POPF; secondary outcomes were perioperative outcomes, including Clavien–Dindo grade $\geq$ III complications.

Results: Ninety patients were randomised and analysed (45 in the patch group and 45 in the control group). The two groups were comparable in baseline demographics, disease characteristics, and perioperative outcomes. The incidence of CR-POPF was 17.7% (8/45) in the patch group and 31.1% (14/45) in the control group, although this difference was not statistically significant ($P=0.141$). It corresponds to an absolute risk reduction of 13.3%, a relative risk reduction of approximately 42.9%, and an odds ratio of 0.48 (95% CI 0.18–1.29; $P=0.220$). Major complications, defined as Clavien-Dindo Grade $\geq$ III ($P=0.803$) and postoperative hospital stay ($P=0.416$) were also comparable between the groups.

CONSORT Diagram



Conclusions: Although reinforcement patches around the PJ did not result in a statistically significant reduction in CR-POPF, the incidence was lower in the patch arm. A study with a larger sample size is required to further elucidate these findings.

Trial Registration: The trial was registered with CTRI with refer-

ence no. CTRI/2024/05/067014.

Keywords: Pancreatoduodenectomy, Pancreaticojejunostomy, Post-Operative Pancreatic Fistula, Reinforcement Patch

PE-5

Safety and Outcomes of Laparoscopic Echinococectomy for Hepatic Hydatid Cysts: A 10-Year Single-Center Experience

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Aims: Hepatic echinococcosis remains a significant challenge in surgical hepatology, particularly in endemic regions. Surgical intervention is considered the definitive treatment, whereas medical therapy alone has limited efficacy. Minimally invasive techniques, including laparoscopic echinococectomy, offer the potential to reduce operative trauma, postoperative complications, and recovery time. This study aimed to evaluate the safety and clinical outcomes of laparoscopic echinococectomy in patients with hepatic hydatid cysts.

Methods: Between 2015 and 2025, 54 patients with hepatic echinococcosis underwent laparoscopic surgery at our center. The cohort included 28 men and 24 women aged 19–52 years. A standard three-trocar technique was used. After trocar placement, the operative field was isolated with gauze soaked in povidone-iodine solution to prevent contamination. The cyst was punctured and aspirated, followed by instillation of 1% povidone-iodine solution into the cavity for scolical treatment. After repeated aspiration, the cyst wall was opened using electrocoagulation. The fibrous capsule was partially excised, and parasitic membranes were removed in an endoscopic retrieval bag. Bile duct openings, when identified, were coagulated using argon plasma coagulation. The residual cavity was treated with povidone-iodine and drained with silicone drains.

Results: Laparoscopic echinococectomy was successfully completed in all patients without conversion to open surgery. The mean operative time was 53 ± 10 minutes. No intraoperative complications were observed. The average hospital stay was 5–7 days. No early postoperative complications were recorded.

Conclusions: Laparoscopic echinococectomy is a safe and effective treatment option for selected patients with superficial hepatic hydatid cysts. The minimally invasive approach reduces surgical trauma and shortens postoperative recovery without compromising safety.

Keywords: Laparoscopic Echinococectomy, Hydatid Cysts, Hepatic Echinococcosis

PE-6

En Bloc Right Hepatic Trisectionectomy with Total Caudate Lobectomy and Portal Vein Resection for Hilar Cholangiocarcinoma: A Non-Touch Technique

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Aims: Advanced hilar cholangiocarcinoma (HCCA), particularly Bismuth–Corlette type IIIa and IV, often requires extended right-sided hepatectomy with total caudate lobectomy. A step-by-step non-touch strategy may facilitate radical resection, with portal vein resection (PVR) when indicated. We report perioperative and pathologic outcomes of a five-case series managed with this approach.

Methods: Five consecutive patients with advanced HCCA (Bismuth–Corlette IIIa: n=2, IV: n=3) underwent right hepatic trisectionectomy with total caudate lobectomy using a standardized non-touch workflow: early inflow control and lymphadenectomy, en bloc hilar plate handling with minimal tumor manipulation, complete caudate dissection along the inferior vena cava plane, vascular resection/reconstruction when required, and biliary reconstruction after specimen removal. Outcomes included operative metrics, lymph node yield/positivity, bile duct margin status, postoperative complications graded by Clavien–Dindo, length of stay, and mortality.

Results: Mean parenchymal transection time was 87.54 ± 33.79 min (40–200) and mean operative time 327.24 ± 73.49 min (200–448). Mean estimated blood loss was 230.29 ± 138.91 mL (100–700); transfusion (blood loss >500 mL) occurred in 2 cases. Mean lymph node yield was 14.71 ± 6.21 (9–24), with 1.8 ± 2.2 positive nodes (0–8). Bile duct margin R0 was achieved in 5/5 (100%). Postoperative complications included post-hepatectomy hemorrhage (n=2; Clavien–Dindo IVb), liver failure (n=2; II), bile leak (n=1; II), and surgical site infection (n=1; II). Mean hospital stay was 27 ± 13 days (10–63). There was one death following treatment withdrawal due to critical illness (Clavien–Dindo IVb).

Conclusions: In this five-case series of Bismuth IIIa/IV HCCA, a step-by-step non-touch right hepatic trisectionectomy with total caudate lobectomy and portal vein resection achieved consistent negative bile duct margins and adequate nodal yield, with acceptable operative parameters but substantial severe morbidity. Larger studies are needed to refine patient selection and validate oncologic benefit.

Keywords: Right Hepatic Trisectionectomy, Total Caudate Lobectomy, Portal Vein Resection, Non-Touch Technique

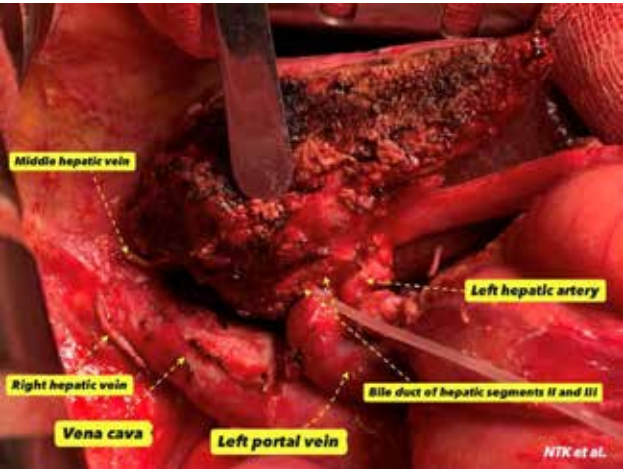


Figure 1.

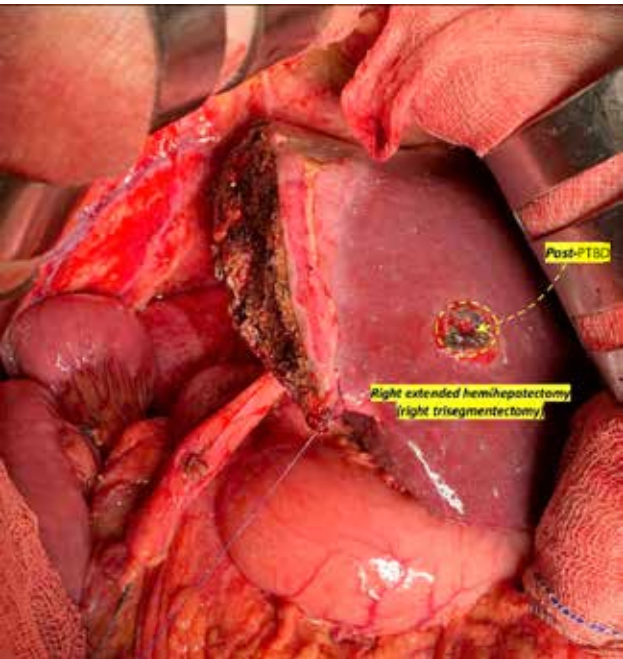


Figure 2.

PE-7

Clinical Significance of a Key Tumor Suppressor Gene as a Prognostic and Translational Biomarker in Periapillary Adenocarcinoma

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Aims: Periapillary adenocarcinoma (PAC) represents a heterogeneous group of malignancies arising from the ampulla, distal bile duct, duodenum, and pancreatic head, with variable

clinical outcomes. Reliable molecular prognostic biomarkers remain limited. While alterations in the tumor suppressor gene PTEN are recognized in gastrointestinal malignancies, the prognostic relevance of epigenetic PTEN silencing in PAC has not been comprehensively investigated.

Methods: This retrospective cohort study included 101 patients with resected PAC. PTEN genetic alterations were evaluated by Sanger sequencing. Promoter methylation status was assessed using methylation-specific polymerase chain reaction (MSP), and protein expression was determined by immunohistochemistry. Apoptotic activity was analyzed using the TUNEL assay. Clinicopathological parameters and survival outcomes were correlated with PTEN molecular findings.

Results: PTEN promoter hypermethylation was observed in 54.4% of cases and was significantly associated with advanced T stage ($P=0.017$), lymph node metastasis ($P=0.004$), perineural invasion ($P<0.001$), and tumor recurrence ($P=0.001$). Loss of PTEN protein expression was identified in 52% of tumors and correlated with inferior overall survival. Patients exhibiting both promoter hypermethylation and reduced protein expression demonstrated the poorest survival outcomes. In contrast, PTEN gene mutations were infrequent and lacked significant prognostic impact. Among tumor subtypes, ampullary carcinomas showed superior survival compared to duodenal, distal bile duct, and pancreatic head cancers ($P=0.001$). Early-stage disease and receipt of adjuvant chemoradiotherapy were associated with improved survival ($P=0.001$ and $P=0.010$, respectively). Interestingly, PTEN apoptosis negativity correlated with better clinical outcomes.

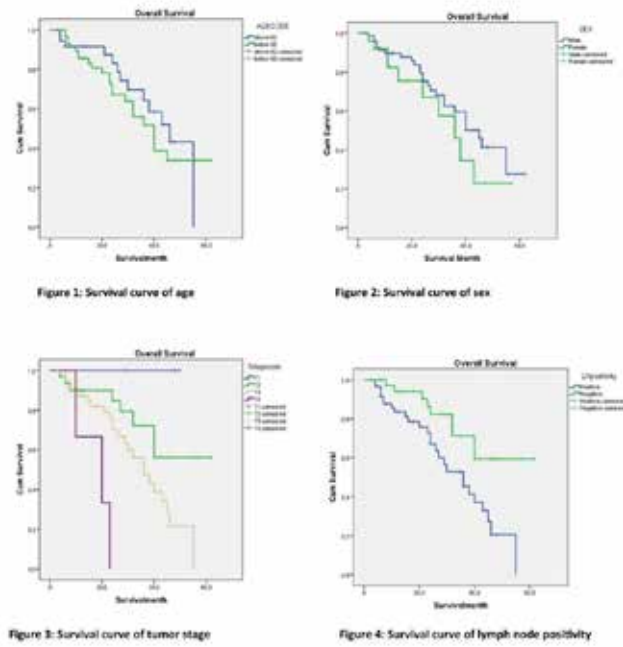


Figure 1.

PE-8

Total Laparoscopic Radical Antegrade Modular Pancreato-Splenectomy with Left-Posterior Artery First-Approach for Distal Pancreatic Cancer: Step-by-Step Technique

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Aims: The radical antegrade modular pancreato-splenectomy (RAMPS) has become a standard approach for achieving negative posterior margins and comprehensive lymphadenectomy in distal pancreatic ductal adenocarcinoma (PDAC). However, the laparoscopic RAMPS (lap-RAMPS) remains technically demanding, particularly in achieving early vascular control and complete left-sided mesopancreas dissection. This study describes the technical details and evaluates the safety, feasibility, and oncologic adequacy of lap-RAMPS using a left-posterior superior mesenteric artery (SMA) first-approach in patients with distal PDAC.

Methods: A prospective analysis was performed on patients with resectable or borderline resectable distal PDAC who underwent lap-RAMPS with a left-posterior SMA first-approach between January 2021 and December 2025. Operative outcomes, pathological findings, and short-term oncologic results were evaluated.

Results: A total of 32 patients (mean age 60.1 ± 9.2 years) underwent the procedure. The mean operative time was 378 ± 66 minutes, and estimated blood loss averaged 242 ± 115 mL. R0 resection was achieved in 93.8% of cases. The mean number of harvested lymph nodes was 29.3 ± 10.8 . Clavien–Dindo grade $\geq$ III complications occurred in 2 patients (6.3%), and there was no 90-day mortality. Histopathology revealed posterior margin invasion in 2 cases (6.3%) and lymph node metastasis in 43.8%. At a median follow-up of 18 months, 1-year disease-free survival and overall survival rates were 71.9% and 87.5%, respectively.

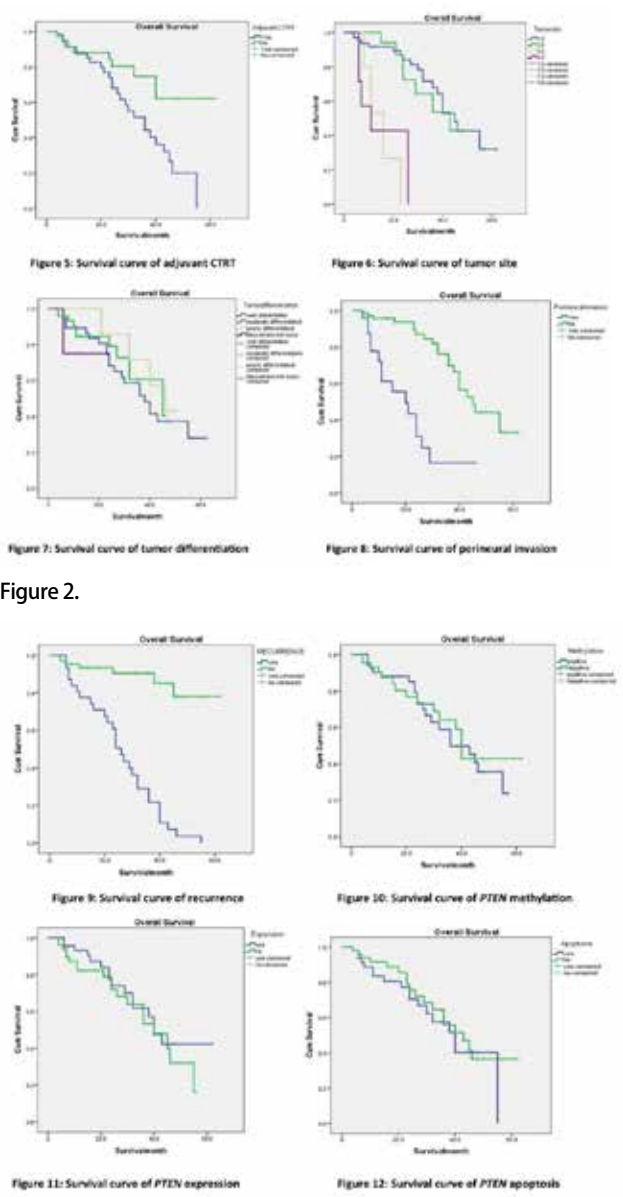


Figure 3.

Conclusions: This study highlights epigenetic silencing of PTEN, rather than genetic mutation, as a key prognostic determinant in periampullary adenocarcinoma. Combined assessment of PTEN promoter methylation and protein expression may provide clinically actionable biomarkers for risk stratification and postoperative management. Integration of PTEN-based molecular profiling could help identify high-risk patients who may benefit from intensified surveillance and targeted PI3K/AKT pathway therapies.

Keywords: Periapillary Adenocarcinoma, Epigenetic Silencing, PI3K/Akt Signaling Pathway, Adjuvant Chemoradiotherapy

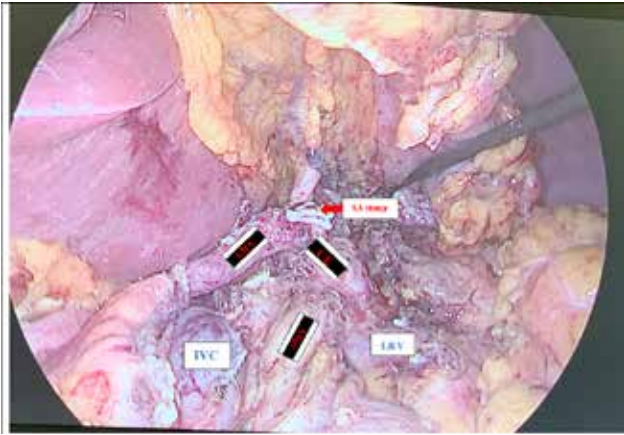


Figure 1.

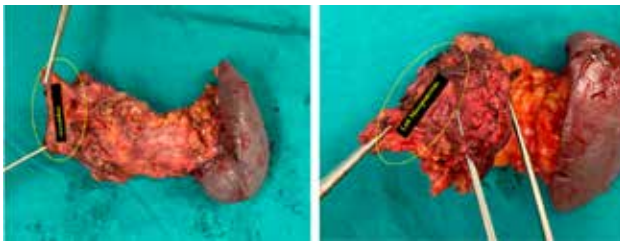


Figure 2.

Conclusions: Lap-RAMPS using a left-posterior SMA first-approach is safe, reproducible, and oncologically sound for distal pancreatic cancer. This technique provides a valuable minimally invasive alternative for radical distal pancreatectomy, even in centers without robotic platforms.

Keywords: Left Posterior Sma First-Approach, Adical Antegrade Modular Pancreato-Splenectomy, Laparoscopic

PE-9

Laparoscopic Total Pancreatectomy with En Bloc Total Mesopancreas Dissection Using a Tail-First, Counterclockwise Approach

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Aims: Total laparoscopic total pancreatectomy (LTP) is infrequently performed because retropancreatic exposure, vascular control, and complete mesopancreas clearance are technically demanding. We report a tail-first, counterclockwise approach designed to facilitate en bloc total mesopancreas dissection (TMD) with standard lymphadenectomy.

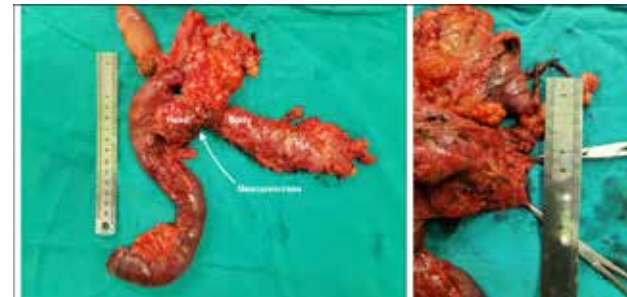
Methods: LTP begins with spleen-preserving retrograde mobilization of the pancreatic body and tail from the inferior border, progressing left-to-right, followed by a counterclockwise dissection to complete circumferential release. The splenic vessels are divided at the terminal tail while preserving the spleen, and the mobilized pancreas is retracted rightward to widen the retropancreatic working space. This maneuver improves laparoscopic angles for isolation and dissection of key arteries (including the splenic and gastroduodenal arteries) and supports SMA-oriented dissection within the TMD plane. We applied this technique in two patients: one with diffuse low-grade intraductal papillary mucinous neoplasm (IPMN) involving the pancreas from head to tail, and one with multifocal pancreatic neuroendocrine tumors (NETs).

Results: In the IPMN case, operative time was 490 minutes and estimated blood loss was 100 mL; pathology confirmed low-grade IPMN extending from the head to the tail. In the multifocal NET case, the same stepwise sequence enabled stable retropancreatic exposure and controlled vascular dissection, achieving en bloc clearance with standard lymphadenectomy.

No intraoperative conversions were required, and both procedures were completed laparoscopically.

Conclusions: Tail-first mobilization with counterclockwise dissection may enhance retropancreatic visualization and arterial control during LTP, providing a reproducible framework for TMD in selected patients with diffuse IPMN and multifocal NETs.

Keywords: Laparoscopic Total Pancreatectomy, Total Mesopancreas Dissection, Tail-First, Counterclockwise Approach



PE-12

Liver Capsule as a Preferable Site for Xenogeneic Islet Cell Implantation in Experimental Diabetes

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Aims: One of the key challenges in islet cell-based therapy is identifying an implantation site that ensures stable metabolic control. The liver is often considered a physiologically favorable environment for endocrine integration. We compared metabolic outcomes and survival following xenogeneic islet cell implantation into the liver capsule, round ligament of the liver, and subcutaneous tissue in rat models of diabetes.

Methods: Adult Wistar rats (180–220 g) (n=49) were rendered diabetic using pancreatectomy combined with alloxan administration. Animals were assigned to three groups: liver capsule (n=18), round ligament (n=15), and subcutaneous implantation (n=16). Fasting blood glucose (mean ± SD) was measured at baseline and on days 14, 28, and 60. Statistical analysis was performed using ANOVA with post-hoc testing; $P < 0.05$ was considered significant. Survival and adverse events were recorded.

Results: Baseline glucose levels were comparable across groups (liver capsule: 24.8 ± 2.6 mmol/L; round ligament: 23.7 ± 2.4 mmol/L; subcutaneous: 24.2 ± 2.5 mmol/L). At day 14, glucose decreased to 17.3 ± 2.1 mmol/L in the liver capsule group, compared with 19.5 ± 2.3 mmol/L in the round ligament group and 22.7 ± 2.8 mmol/L in the subcutaneous group.

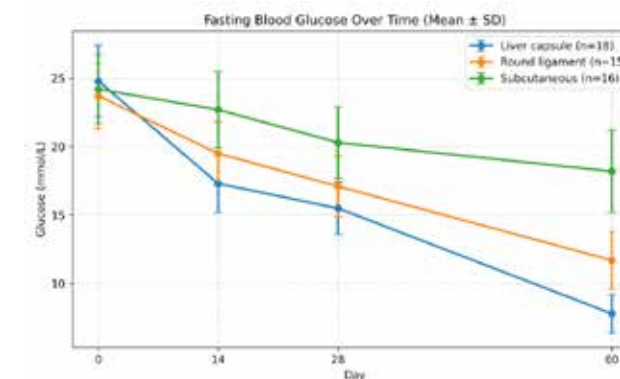
By day 28, further improvement was observed (15.5 ± 1.9 vs 17.1 ± 2.2 vs 20.3 ± 2.6 mmol/L, respectively).

At day 60, the liver capsule group demonstrated marked metabolic recovery (7.8 ± 1.4 mmol/L), whereas glucose remained elevated in the round ligament (11.7 ± 2.1 mmol/L) and subcutaneous groups (18.2 ± 3.0 mmol/L). Overall glycemic reduction was significantly greater in the liver capsule group compared with extrahepatic sites ($P < 0.05$). Mortality was lowest in the liver capsule group (2/18), compared with 5/15 and 8/16 in the round ligament and subcutaneous groups.

No severe hemorrhagic or infectious complications were documented.

Conclusions: Implantation under the liver capsule resulted in more sustained glycemic control and improved survival compared with extrahepatic sites. The hepatic microenvironment appears to support more effective engraftment, providing a rational basis for further preclinical optimization and future translational development.

Keywords: Xenotransplantation, Liver Capsule, ISLET Cells, Hepatic Implantation



PE-13

Intraoperative and Early Postoperative Complications After 2,645 Laparoscopic Cholecystectomies: A 15-Year Single-Center Experience

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Aims: Laparoscopic cholecystectomy (LC) is the gold standard treatment for gallbladder disease; however, intraoperative and early postoperative complications remain clinically significant. Identification of factors associated with adverse outcomes may improve perioperative management and surgical decision-making. This study aimed to analyze the incidence and causes of intraoperative and early postoperative complications following LC in a high-volume center.

Methods: A retrospective analysis was performed of 2,645 consecutive LC procedures conducted between April 2010 and September 2025. Patient demographics, indication for surgery, intraoperative findings, conversion rates, and postoperative complications were evaluated. Acute and chronic cholecystitis cases were analyzed. Complications were assessed during the early postoperative period.

Results: The mean age was 52.3 ± 0.7 years; 65.9% were female. Early postoperative and intraoperative complications occurred in 58 patients (3.5%). Conversion to open surgery was required in 51 cases (1.9%). The most common indication for conversion was dense inflammatory adhesions in the hepatoduodenal ligament (56.8%). Common bile duct injury occurred in 3 patients (0.11%).

Early postoperative complications included bile leakage (n=18), postoperative bleeding (n=2), subhepatic infiltrate (n=5), and choleperitonitis secondary to bile duct injury (n=4). Re-laparoscopy was required in 3 cases, and laparotomy in 4 cases. Surgical site infection occurred in 5–6% of patients. One patient (0.04%) died due to pulmonary embolism.

Conclusions: Laparoscopic cholecystectomy demonstrates a low overall complication and mortality rate in a high-volume center. Dense inflammatory adhesions represent the primary cause of conversion. Careful preoperative risk stratification and meticulous surgical technique are essential to minimize bile duct injury and severe postoperative complications.

Keywords: Postoperative Complications, Laparoscopic Cholecystectomy, Gallbladder Disease

PE-14

Hepatic Function Optimization in Malignant Obstructive Jaundice

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Aims: Malignant obstructive jaundice (MOJ) caused by biliopancreatoduodenal tumors leads to progressive hepatic dysfunction, impaired detoxification, and increased risk of postoperative liver failure in hepatopancreatobiliary surgery. Preoperative restoration of liver function is crucial to reduce perioperative complications and improve surgical outcomes.

To evaluate the effectiveness of percutaneous transhepatic cholangiostomy (PTCS) combined with bile sorption in improving hepatic function in patients with malignant obstructive jaundice before definitive surgery.

Methods: Eighty-four patients with MOJ underwent PTCS between 2023 and 2025. Patients were divided into a bile sorption group (n=51) and a control group (n=33). Liver function

was assessed by alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and serum creatinine before and after biliary decompression. Tumor staging followed AJCC criteria. Statistical analysis included Student's t-test and Pearson correlation ($P<0.05$ considered significant).

Results: At admission, ALT (1.8 ± 0.07 mmol/L) and AST (1.4 ± 0.08 mmol/L) significantly exceeded reference values ($P<0.01$), indicating hepatocellular injury. Total bilirubin reached 234.6 ± 8.2 μ mol/L ($P<0.001$), confirming severe cholestasis. Serum creatinine averaged 159.3 ± 7.6 μ mol/L ($P<0.05$), reflecting systemic metabolic stress.

Patients with obstruction >1 month had significantly greater hepatic dysfunction ($P<0.05$). After PTCS, the bile sorption group demonstrated a faster reduction in ALT, AST, and bilirubin compared to controls. By day 7, intergroup differences were significant ($P<0.05$), with more pronounced bilirubin decline in the bile sorption group ($P<0.01$). Enzyme normalization correlated with clinical stabilization and improved hepatic reserve before surgery ($P<0.05$).

Conclusions: MOJ causes severe hepatic dysfunction that increases surgical risk. Dynamic monitoring of liver enzymes provides objective assessment of hepatic recovery after biliary decompression. PTCS combined with bile sorption significantly enhances liver function restoration and may reduce perioperative hepatic complications ($P<0.05$).

Keywords: Obstructive Jaundice, Hepatit, Malignant Obstructive Jaundice, HPB Surgery

PE-15

Laparoscopic Left-Sided Hepatectomy Guided by Dilated Bile Ducts as Anatomical Landmarks for Hepatolithiasis: A Single-Center Preliminary Study

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Aims: Hepatolithiasis, prevalent in East and Southeast Asia, often leads to complications such as cholangitis, strictures, and cholangiocarcinoma. Conventional interventions frequently leave residual stones, requiring repeat treatments. We evaluated a modified laparoscopic left-sided hepatectomy guided by dilated bile ducts (DBDs) as anatomical landmarks [modified laparoscopic left-sided hepatectomy guided by dilated bile ducts as anatomical landmarks (MITNA) approach]—with reference to the middle hepatic vein (MHV) when necessary—to optimize stone clearance and preserve healthy liver.

Methods: In this prospective study, 32 consecutive patients undergoing laparoscopic left-sided hepatectomy for hepatolithiasis at 108 Military Central Hospital (January 2023–January 2025) were enrolled. Preoperative imaging identified the ex-

tent of DBDs. Patients with disease confined to the left lateral lobe underwent left lateral hepatectomy (LLH) with the transection line placed to the right of the falciform ligament. Those with disease extending to segment 4 or near the hilum underwent left hemihepatectomy (LHH), using a transection plane between DBDs and the MHV. Perioperative data (operative time, blood loss, complications, stone clearance) and follow-up outcomes were collected.

Results: All 32 patients completed laparoscopic hepatectomy without conversion, 22 underwent LLH and 10 had LHH. The mean operative time was 140.7 ± 46.8 min with the mean blood loss 111.5 ± 70.8 mL. Postoperative complications occurred in 12.5% of patients (Clavien-Dindo grade I–IIIa). The mean hospital stay was 7.7 ± 2.5 days. At a mean follow-up of 9.50 ± 4.08 months, only one patient (3.1%) had residual stones, which were successfully cleared through endoscopic intervention, resulting in a final stone clearance rate of 100%.

Conclusions: The MITNA approach is a feasible and promising approach for left-sided hepatolithiasis. This approach ensures complete resection of affected bile ducts and stones while sparing normal liver parenchyma, resulting in high stone clearance rates and low morbidity.

Keywords: Hepatolithiasis, Sectionectomy, Hepatectomy, Laparoscopy

Table 1 Baseline characteristics of patients (n=32)	
Characteristic	Value
Age (years)	54.8±9.9; 52.5 [49.0–60.8]
Sex	
Male	8 (25.0)
Female	24 (75.0)
Previous biliary surgery	5 (15.6)
Prior-ERCP	3 (9.4)
Comorbidities	
Hypertension	10 (31.3)
Diabetes mellitus	6 (18.8)
Imaging features	
Dilated left lobe bile ducts	32 (100.0)
Left lobe impacted stones	28 (87.5)
Stone in right intrahepatic duct	1 (3.1)
Stone in the common bile duct	10 (31.3)
Stone in the gallbladder	4 (12.5)
Huang's classification	
Type I	22 (68.8)
Type II	9 (28.1)
Type IV	1 (3.1)

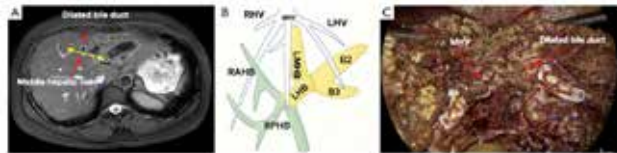


Figure 1.

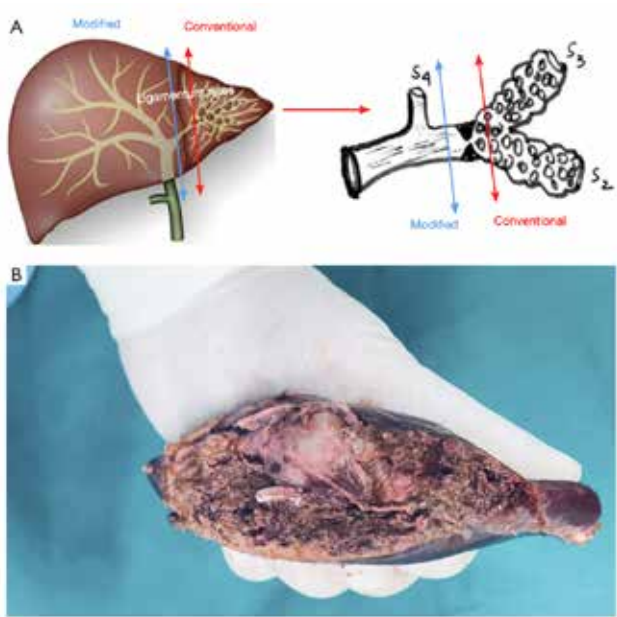


Figure 2.

PE-17

The Role of the Family in Supporting Gallstone Prevention through Dietary Compliance and Family-Based Education: Literature Review

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Aims: Gallstone disease (cholelithiasis) is a hepatobiliary system disorder whose prevalence continues to increase and is closely related to diet and lifestyle. Various studies have shown that consuming foods high in fat and low in fiber contributes to gallstone formation. The World Health Organization reports that gallstone disorders affect more than 20 million adults worldwide. Prevention efforts for this disease involve implementing a healthy diet, which in practice is greatly influenced by family support. This study aims to examine the role of families in supporting gallstone prevention through dietary adherence and family-based education.

Methods: The method used was a literature review of 15 relevant national and international journals, obtained from the PubMed, PMC, and accredited national journal databases.

Results: Research results indicate that diet is a major factor in the formation and prevention of gallstones. Diets high in saturated fat and cholesterol are associated with a 30–40% increased risk of gallstones, while low-fat, high-fiber diets have been shown to reduce the risk by 20–30%. Groups without

gallstones have higher daily fiber intakes compared to those with gallstones. The family support shows that individuals with family support have a 15–40% higher level of dietary adherence than those without family support.

Conclusions: The family plays a crucial role in preventing gallstones through dietary monitoring, emotional support, and health education. A family-based prevention approach has the potential to increase the success of sustainable gallstone risk management

Keywords: Gallstone, Family Support, Dietary

PE-20

Diagnostic Relevance of Neutrophil Gelatinase-Associated Lipocalin in Cholangiocarcinoma and Biliary Tract Cancers among Elderly Patients

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Aims: Cholangiocarcinoma and biliary tract cancers are aggressive hepatobiliary malignancies with poor prognosis, particularly in elderly patients where early diagnosis remains challenging. Neutrophil gelatinase-associated lipocalin (NGAL), a 24-kDa glycoprotein involved in inflammation and tumor progression, has emerged as a potential cancer biomarker. This study aimed to evaluate the diagnostic utility of NGAL in comparison with macrophage inhibitory cytokine-1 (MIC-1) and carbohydrate antigen 19-9 (CA19-9) in elderly patients with biliary malignancies.

Methods: Sixty-eight elderly patients aged 70–80 years were enrolled, including individuals diagnosed with cholangiocarcinoma or other biliary tract cancers and a non-malignant comparison group presenting with biliary-like symptoms but no evidence of cancer. Endoscopic pancreatic juice samples were collected following secretin stimulation. NGAL and MIC-1 levels were quantified using enzyme-linked immunosorbent assay, while CA19-9 concentrations were measured by radioimmunoassay.

Results: Pancreatic juice concentrations of NGAL, MIC-1, and CA19-9 were significantly elevated in patients with cholangiocarcinoma and biliary tract cancers compared with non-malignant controls. NGAL levels were consistently increased across all biliary malignancies, indicating broad diagnostic sensitivity. MIC-1 concentrations were significantly higher in cholangiocarcinoma compared with other biliary tract cancers and were most pronounced in elderly cholangiocarcinoma patients. In contrast, CA19-9 demonstrated limited discriminatory performance between patient groups.

Conclusions: NGAL demonstrates strong potential as a hepa-

tobiliary biomarker for the detection of cholangiocarcinoma and biliary tract cancers in elderly patients, outperforming CA19-9 in diagnostic differentiation. MIC-1 may further enhance tumor subtype discrimination. These findings support further evaluation of NGAL, including serum-based assessment, for integration into hepatobiliary oncology diagnostic strategies.

Keywords: Biliary Tract Cancers, Neutrophil Gelatinase-Associated Lipocalin, Immunosorbent Assay, Carbohydrate Antigen

PE-21

Early Prediction of Severe Acute Pancreatitis Using Initial Inflammatory Biomarkers: A Simple and Effective Risk Stratification Model

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Aims: Acute pancreatitis (AP) is a leading cause of gastrointestinal hospitalization worldwide. Although most cases are mild, approximately 15–20% progress to severe acute pancreatitis (SAP), characterized by persistent organ failure and substantial mortality. Early identification of high-risk patients remains a major clinical challenge. Simple, rapidly available biomarkers that predict disease severity at admission would be valuable for guiding early management.

Aim: To evaluate the predictive value of early inflammatory biomarkers and develop a simple admission-based model for early identification of severe acute pancreatitis.

Methods: We conducted a retrospective study including 88 patients diagnosed with AP between 5/2022 and 11/2025. Clinical and laboratory data obtained within the first 24 hours of admission were analyzed, including white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP). Disease severity was classified according to the Revised Atlanta Classification. Multivariate logistic regression analysis identified independent predictors of SAP. Receiver operating characteristic (ROC) curve analysis determined predictive accuracy and optimal cut-off values.

Results: Among the 88 patients, 40 (22.7%) developed severe acute pancreatitis. Admission levels of NLR, CRP, and PLR were significantly higher in the SAP group ($P<0.001$). Multivariate analysis demonstrated that $NLR > 8.5$ (OR 5.1; 95% CI: 2.4–10.6; $P<0.001$) and $CRP > 150$ mg/L (OR 4.2; 95% CI: 1.9–9.0; $P=0.001$) were independent predictors of SAP. The combined NLR–CRP model showed excellent predictive performance with an AUC of 0.93, sensitivity 88.1%, and specificity 84.3%, outperforming

individual biomarkers.

Conclusions: Admission NLR and CRP are strong independent predictors of severe acute pancreatitis. A combined NLR–CRP model provides a rapid, inexpensive, and clinically practical tool for early risk stratification. Implementation of this model may enable early identification of high-risk patients, optimize triage to intensive monitoring, and potentially reduce morbidity and mortality in acute pancreatitis.

Keywords: Acute Pancreatitis, Early Prediction, Severe Acute Pancreatitis, NLR, CRP, Inflammatory Biomarkers

PE-22

Bile Mycobiome Diversity Classifies Fungal Peptide Signature for Early Prediction of Gallbladder Carcinoma

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Aims: Carcinoma of Gallbladder (CAGB) has poor prognosis. While the bile microbiome and lipidome are associated with CAGB development, the contribution of fungal mycobiome is unexplored. Our study aims to investigate the fungal Mycobiome diversity and correlate it with the incidence of CAGB with classification of top fungal peptides to potentially stratify CAGB patients.

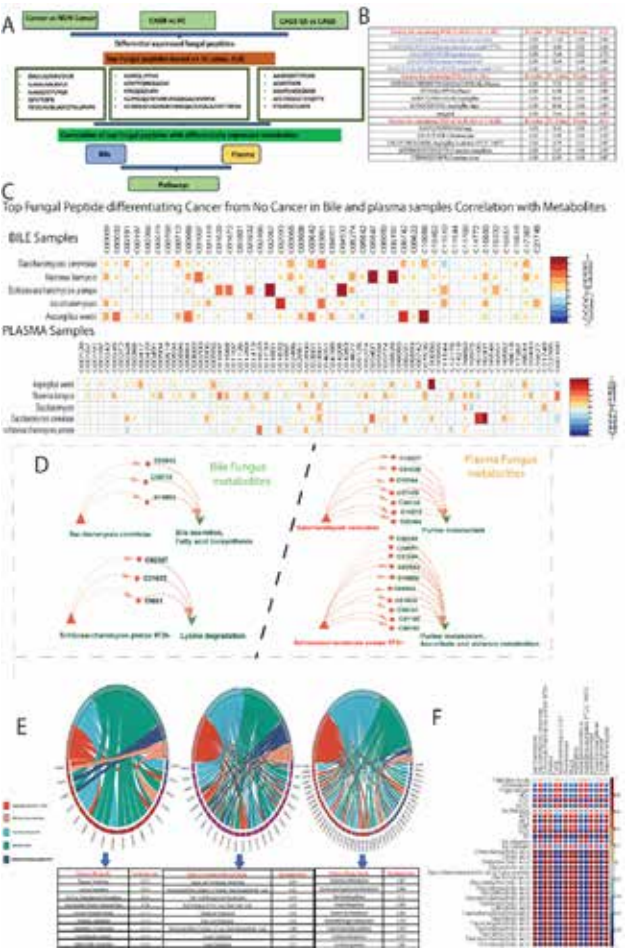
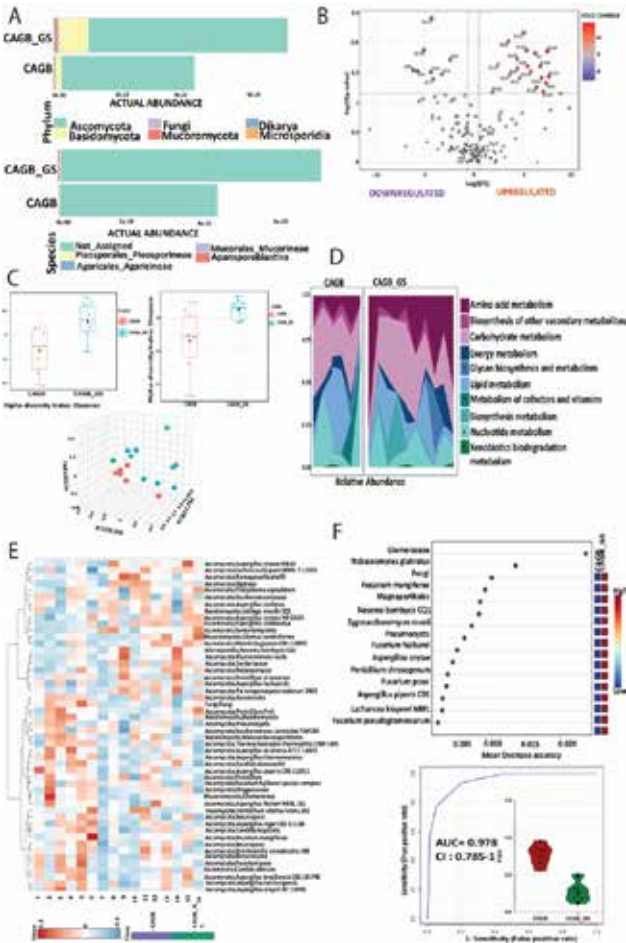
Methods: Bile samples were collected from patients undergoing cholecystectomy for Gallstone (GS) disease ($n=30$), patients undergoing surgery for CAGB ($n=30$), and healthy liver donors ($n=20$) were subjected to fungal peptide-based diversity analysis and metabolomics. Results were cross-validated in 80 patients on the plasma samples, correlated with clinical parameters, and subjected to machine learning analysis.

Results: Fungal peptide-based diversity analysis identified 6-Phyla and 24-Fungal species differentially regulated in the bile samples of the study cohort. Fungal diversity (alpha and beta diversity) was significantly higher in CAGB as compared to GS or HC ($P<0.05$). 93 fungal peptides were upregulated and 63 were downregulated in CAGB ($P<0.05$, $FC>1.5$). Linear discriminant analysis significantly segregated CAGB patients with marked increase in *Aspergillus wentii* ($\log_2FC-12.21$), *Nosema bombycis* ($\log_2FC-11.25$), *Saccharomyces* ($\log_2FC-10.89$), *Saccharomyces cerevisiae* ($\log_2FC-10.68$), and *Schizosaccharomyces pombe* ($\log_2FC-10.38$; $P<0.05$) in the

bile samples. Fungal-metabolite correlation analysis ($r^2>5$, $P<0.05$) identified *Aspergillus wentii*, *Nosema bombycis*, and others directly associated with lysine biosynthesis, taurine, and hypotaurine metabolism, fatty acid, and other in bile, and cysteine and methionine metabolism, ascorbate metabolism, purine metabolism, and others in plasma. Probability of detection (POD) calculated using fungal peptides showed a diagnostic efficiency of 96% for segregation of CAGB patients. The identified top 5 fungal peptides were validated using Single Reaction Monitoring analysis that predicted early mortality $>90\%$ accuracy/sensitivity, and specificity in a Machine Learning model.

Conclusions: CAGB patients showcase a distinct fungal diversity and identifies fungal peptide panel capable of segregation and early diagnosis of CAGB patients.

Keywords: Gall Bladder Carcinoma, Gallstone, Metabolomics Profile, Proteomics Profile



PE-23

How We Perform Laparoscopic Total Pancreatectomy: Tail-First Mobilization, Counterclockwise Total Mesopancreas Dissection

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Aims: Despite advances in minimally invasive HPB surgery, total pancreatectomy is rarely performed laparoscopically because it requires meticulous vascular control and comprehensive retropancreatic dissection. We present a reproducible technique of laparoscopic total pancreatectomy (LTP) integrating a tail-first pancreatic mobilization with a counterclockwise dissection sequence to facilitate en bloc total mesopancreas dissection and nodal clearance.

Methods: Technique description: After establishing laparoscopic access, the pancreatic tail and body are mobilized retrogradely with spleen preservation. Dissection is initiated at the inferior margin of the pancreatic body, advancing from the

left toward the right, and then extended in a counterclockwise direction to complete circumferential release of the body–tail segment. The splenic vessels are controlled and divided at the terminal portion of the tail while maintaining splenic perfusion. The mobilized pancreas is then gently tractioned to the right, which widens the retropancreatic working space and improves laparoscopic angles for arterial identification and dissection, including the splenic artery, gastroduodenal artery, and arteries within the retropancreatic plane. This setup also supports a right SMA-first step by providing earlier and clearer exposure of the SMA-related dissection field.

Results: Case 1 underwent laparoscopic total pancreatectomy with a tail-first, counterclockwise total mesopancreas dissection; operative time was 490 minutes and blood loss was 100 mL, and pathology confirmed a low-grade IPMN involving the pancreas from head to tail. Case 2 underwent the same laparoscopic strategy for multifocal pancreatic neuroendocrine tumors (NETs). In both cases, the tail-first mobilization with rightward traction improved retropancreatic exposure and facilitated en bloc total mesopancreas dissection with standard lymphadenectomy. This approach appears feasible for diffuse or multifocal pancreatic neoplasms such as IPMN and multifocal NETs.

Conclusions: The combination of tail-first retrograde mobilization and counterclockwise progression may simplify the most technically challenging phase of LTP—retropancreatic vascular dissection—while maintaining oncologic principles of en bloc mesopancreas removal and lymphadenectomy.

Keywords: Laparoscopic Total Pancreatectomy, Total Mesopancreas Dissection, Tail-First Approach, Counterclockwise Technique



PE-24

Estimated Time Frame for Malignant Progression of High-Grade Dysplasia in the Ampulla of Vater: Three Clinical Cases

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Aims: Ampullary high-grade dysplasia (HGD) is considered a premalignant lesion in the adenoma-carcinoma sequence; however, the timing of progression to invasive carcinoma remains poorly defined because most lesions are treated at an early stage. We aimed to describe the long-term clinical course of ampullary HGD and to estimate the time frame of malignant progression through three clinical cases.

Methods: We retrospectively reviewed three patients with ampullary adenomas initially diagnosed as HGD who subsequently progressed to invasive adenocarcinoma after prolonged follow-up. Clinical presentation, endoscopic and surgical treatment history, pathological findings, and oncologic outcomes were analyzed.

Results: All three patients developed invasive adenocarcinoma after prolonged intervals, demonstrating substantial biological heterogeneity. One untreated patient progressed to early-stage well-differentiated ampullary adenocarcinoma more than 10 years after the initial diagnosis and underwent curative resection with no nodal metastasis. A second patient developed adenocarcinoma 17 years after the initial endoscopic papillectomy despite repeated endoscopic treatment and a long period of apparent histologic remission; final pathology showed pT1N1 disease. In contrast, the third patient showed persistent/recurrent dysplasia despite repeated endoscopic papillectomy and argon plasma coagulation, and ultimately progressed to advanced carcinoma with nodal and para-aortic metastases, followed by recurrence and death. These cases indicate that malignant transformation may occur much later than expected and that apparent local control does not necessarily guarantee long-term oncologic safety.

Conclusions: Ampullary HGD can progress to invasive adenocarcinoma after exceptionally long intervals. These cases highlight the marked heterogeneity of ampullary neoplasms and suggest that long-term, possibly lifelong, surveillance should be considered even after endoscopic treatment. Further studies are needed to identify reliable predictors of malignant transformation.

Keywords: Ampulla of Vater, High-Grade Dysplasia, Surveillance, Case Series

PE-25

Modeling Pancreatic Cancer Initiation Using Normal Human Pancreatic Organoids with Crispr-Induced TP53 Loss

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Aims: Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest malignancies, with a two-year survival rate below 5%. A major barrier to understanding disease initiation and developing effective therapies is the lack of relevant human models that faithfully capture early tumorigenic events. Human pancreatic ductal organoids closely recapitulate native epithelial architecture and have emerged as powerful platforms for modeling pancreatic cancer development. Recent advances in CRISPR–Cas9 genome editing enable precise introduction of cancer-associated mutations into these organoid systems, facilitating mechanistic studies of tumor initiation.

Methods: Normal human pancreatic ductal organoids were successfully established, transcriptionally and structurally validated, and maintained long-term viability during extended culture and cryopreservation. To model early pancreatic tumorigenesis, a loss-of-function mutation in TP53 was introduced using CRISPR–Cas9, generating TP53-knockout (KO) organoids. Edited organoids were subsequently transplanted into immunodeficient NSG mice to assess *in vivo* tumor-initiating potential.

Results: TP53-KO organoids exhibited significantly increased proliferative capacity, loss of epithelial polarity, and pronounced structural abnormalities consistent with early neoplastic transformation. Upon transplantation into NSG mice, TP53-KO organoids formed premalignant lesions characterized by dysplastic glandular architecture. These findings indicate that TP53 loss alone is sufficient to confer early oncogenic properties in human pancreatic ductal cells, even in the absence of additional driver mutations.

Conclusions: This study establishes a human pancreatic cancer initiation model through CRISPR-mediated TP53 knockout in normal pancreatic ductal organoids. The ability of TP53-deficient organoids to initiate premalignant lesions both *in vitro* and *in vivo* provides a robust foundation for stepwise modeling of pancreatic cancer progression and for evaluating early therapeutic interventions.

Keywords: Pancreatic Adenocarcinoma, Crispr-Cas9, Human Pancreatic Organoids

PE-26

Impact of Sarcopenia on Surgical Outcomes in Patients Undergoing Pancreaticoduodenectomy (PD): A Tertiary Care Center Experience in Odisha- India

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Aims: Sarcopenia is common in pancreatic cancer and influence postoperative outcomes. Studies show perioperative complications, mortality, worse survival increase with sarcopenia. Aim: To study association of preoperative Sarcopenia with

immediate & delayed postoperative complications & surgical outcome in patients undergoing Pancreaticoduodenectomy(PD).

Methods: Area(SMA) at L3 vertebrae & L3 SMI (skeletal muscle index). Cut off for sarcopenia: <36.5 cm²/m²(males) and <30.2 cm²/m²(Females) taken. All patients underwent PD, postoperative outcomes were assessed.

Results: Underwent PD, postoperative outcomes were assessed. Total 57 patients underwent PD, 40.3% are females, and 59.6% males. 26 (45.6%) [12(46.1%) female, 14 (53.8%) male] have sarcopenia. The mean age was 58.59. The mean SMI Index in sarcopenia group (30.86 ± 3.39)(P value <0.001), SMI values [(33.78 ± 3.28) vs(43.2 ± 1.49)]male and [(27.45 ± 1.84) vs (36.92 ± 0.96)]female. Sarcopenic patients are associated with significantly low albumin levels ,mid-arm circumference [24.86 ± 4.9cm(p value <0.001)], Handgrip strength values [32.21 ± 9.3(p value 0.011)]. In sarcopenia group (n=26), 10(38.46%)pancreatic leak(CR-POPF), 6(23%)bile leak, 10(38.46%)DGE, total 15(57.69%) cases had late complications. ICU & hospital stay, Infective complications[10(45.45%)(p value 0.019)] higher in sarcopenia group.

Conclusions: Sarcopenia is associated with adverse postoperative outcomes and represent independent risk factor for clinically relavent and infectious complications after PD. Identifying sarcopenia patients before surgery enable to implement prehabilitation and targeted interventions to optimize and enhance surgical outcomes.

Keywords: Sarcopenia, Pancreaticoduodenectomy, POPF

PE-27

Afferent Loop Decompression and Outcomes after Pancreaticoduodenectomy: A Prospective Cohort with Propensity Matched Controls

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Aims: Clinically relevant postoperative pancreatic fistula (CRPOPF) remains a key driver of morbidity after pancreaticoduodenectomy (PD). Afferent loop decompression (ALD) has been proposed to lower intraluminal pressure and protect pancreatojejunostomy.

Methods: We conducted a prospective cohort at a single HPB unit (August 2024–July 2025) with 20 consecutive ALD cases compared to 60 historical controls without ALD, selected after 1:3 propensity matching. Primary outcome was CRPOPF (ISGPS Grade B/C). Secondary outcomes included delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), and bile leak.

Results: Baseline differences persisted in jaundice, preop-

erative stenting, and cholestatic indices. Biochemical leaks were more frequent with ALD, while CRPOPF did not differ significantly. Notably, DGE occurred in 0% of ALD vs 46.7% of nonALD patients, with Grade B DGE significantly lower in ALD. PPH and bile leak were observed only among nonALD patients, though rare. On univariate analysis, higher CA199 (logtransformed), BMI, and COPD/bronchial asthma were associated with increased odds of CRPOPF.

Conclusions: In this preliminary matched analysis, ALD was associated with markedly lower DGE and no signal of harm for CRPOPF, although biochemical leaks were more common. Larger prospective series with standardized protocols are warranted to clarify ALD's effect on clinically relevant fistula and to address baseline imbalances.

Keywords: Pancreaticoduodenectomy, Afferent Loop Decompression, POPF

PE-28

Review of Multivariate Logistic Regression Analysis of Serum CA 19-9 and Hematological Profiles in Distinguishing Pancreatic Malignancy from Chronic Pancreatitis

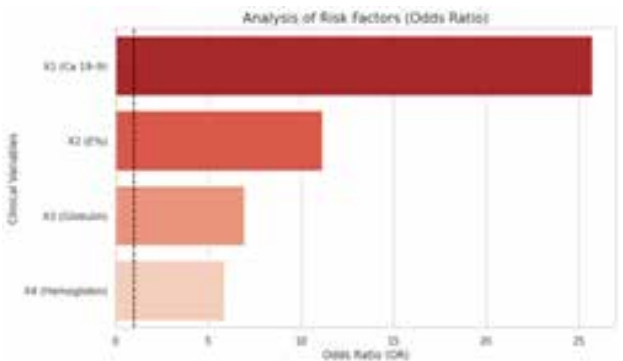
Devi Yulia Rahmi

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Aims: Differential diagnosis between pancreatic cancer and chronic pancreatitis remains a significant clinical challenge due to overlapping clinical presentations. While various biomarkers exist, their independent predictive value in a multivariate context requires precise quantification to improve diagnostic accuracy and clinical decision-making. This study aims to review the existing literature on independent clinical predictors that can effectively distinguish pancreatic malignancy from inflammatory pancreatic conditions through a multivariate computational approach.

Method: This study using review literatury collected articles from journal databases. Several literature found that serum CA 19-9, E%, globulin, and hemoglobin were used to differentiate pancreatic malignancy from chronic pancreatitis analyzed using a multivariate logistic regression model. Based on the findings of Yan et al. (2017), this study further developed the analysis by showing the Odds Ratio (OR).

Result: The multivariate analysis identified four significant independent predictors (Yan et al., 2017) ($P < 0.05$). Serum Ca 19-9 demonstrated the highest diagnostic impact with an Odds Ratio (OR) of 25.72 (95% CI: 2.858–231.43, $P=0.004$). This was followed by E% (OR: 11.15, $P=0.001$) and Globulin (OR: 6.95, $P=0.005$). van Heerde et al. (2014) also found that patients with autoimmune pancreatic have lower levels of Ca 19-9 than those patients with pancreatic carcinoma.



Odds Ratio (OR) (Developed from Yan et al., 2017)

Conclusion: Several review articles indicate that researchers use multivariate analysis to differentiate pancreatic malignancy from chronic pancreatitis. A data-driven, multivariate analytical approach can be considered a valuable tool for supporting decision-making.

Keyword: Pancreatic Cancer, Chronic Pancreatitis, CA 19-9, Multivariate Analysis, Logistic Regression

PE-30

Computational Analysis of BMI SDS as a Predictive Marker For Choledocholithiasis : A Literature Review

Muhammad Irzaq

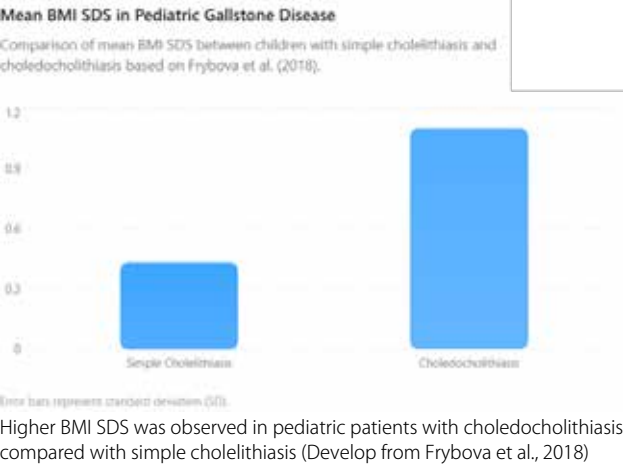
Art and Language, Alumnus of Padang State University, Indonesia

Aims: Choledocholithiasis is a significant complication of pediatric cholelithiasis and may lead to biliary obstruction and pancreatitis. The increasing prevalence of childhood obesity has been associated with a rising incidence of gallstone disease. Body Mass Index Standard Deviation Score (BMI SDS) is widely used to assess obesity in children and may help identify patients at increased risk of choledocholithiasis. This literature review aimed to evaluate the potential role of BMI SDS as a predictive marker for choledocholithiasis in pediatric patients.

Method: This literature review was conducted using articles retrieved from the National Library of Medicine (PubMed) database. Literature studies investigating the association between BMI SDS and pediatric gallstone disease were reviewed and analyzed descriptively.

Result: Among the reviewed studies, Frybova et al. (2018) do a retrospectively analyzed 147 pediatric patients. Complete anthropometric data were available for 98 patients, including 75 with simple cholelithiasis and 23 with choledocholithiasis. Patients with simple cholelithiasis had a mean BMI SDS of 0.43 ± 1.43 , while those with choledocholithiasis had a significantly higher BMI SDS of 1.10 ± 1.26 ($p = 0.001$). These findings suggest a strong association between elevated BMI SDS and choledocholithiasis (Frybova et al., 2018). Jatana et al. (2025)

also found that children with a high BMI have a greater risk of developing complicated biliary disease (such as choledocholithiasis and gallstone pancreatitis).



Conclusions: The incidence of para-aortic lymph node (PALN) metastasis in non-pancreatic periampullary cancer is 15.5%. It correlates with high pre-operative CA 19-9, lymphovascular invasion, higher lymph node ratio, advanced tumor stage, and poor survival, though adjuvant therapy improves outcomes. Routine PALN sampling with frozen section and dissection if positive is recommended for high-risk patients.

Keywords: Paraaortic Lymphnode Metastases, Non- Pancreatic Periampullary Tumor, Pancreaticoduodenectomy

PE-31

Incidence, Predictive Factors and Post-Operative Outcomes of Patients Undergoing Pancreatoduodenectomy for Non-Pancreatic Periampullary Cancer with Para-Aortic Lymph Node Metastases

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Aims: Pancreatoduodenectomy (PD) remains the mainstay of treatment for non-pancreatic periampullary cancers. The prognostic impact of para-aortic lymph node (PALN) metastasis in such cases is not universally established, with contradictory international guidelines and unreliability of current preoperative imaging modalities. There are scant data from Indian populations.

Methods: This prospective and retrospective cohort study was conducted at a tertiary centre in South India including all patients undergoing PD for non-pancreatic periampullary cancer. PALNs were dissected and sampled during surgery (minimum

2–3 nodes). Data collected included preoperative CA 19-9, intraoperative findings, postoperative complications, mortality, and overall survival.

Results: Among 58 patients, PALN metastasis was found in 15.5%, mostly with ampullary tumors. PALN positivity was linked to higher CA 19-9, advanced T/N stage, higher lymph node ratio, and strong lymphovascular invasion. Postoperative morbidity and mortality did not differ significantly with PALN status. However, patients with PALN metastasis had much poorer survival (median 12.1 vs 34.8 months), but those who received adjuvant therapy showed improved outcomes.

Conclusions: The incidence of para-aortic lymph node (PALN) metastasis in non-pancreatic periampullary cancer is 15.5%. It correlates with high pre-operative CA 19-9, lymphovascular invasion, higher lymph node ratio, advanced tumor stage, and poor survival, though adjuvant therapy improves outcomes. Routine PALN sampling with frozen section and dissection if positive is recommended for high-risk patients.

Keywords: Paraaortic Lymphnode Metastases, Non- Pancreatic Periampullary Tumor, Pancreaticoduodenectomy

PE-32

From Hands to Ports: A Comparative Outcome Analysis of Minimally Invasive and Open Distal/Central Pancreatectomy

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Aims: Open surgery was considered standard surgery for pancreatic body and tail pathology. With the development of advanced technology, minimally invasive techniques have increasingly been used in pancreatic surgery. Our study aims to evaluate the outcome of minimally invasive pancreatic surgery, postoperative morbidities, clinically significant postoperative pancreatic fistula (CR-POPF) and histopathological outcomes in patients undergoing central or distal pancreatectomy.

Methods: This retrospective audit includes all patients who underwent distal pancreatectomy with or without splenectomy and central pancreatectomy from 2015 to 2025 at tertiary care centre. Variables analyzed included patient demographics, clinical presentation, operative procedure (open, laparoscopic, robotic), pancreatic transection and closure techniques, hospital length of stay, morbidity (Clavien-Dindo grade), pancreatic fistula rate (ISGPS grade B/C), re-exploration, mortality, and histopathology.

Results: Among 42 patients, 69% were female. 17 patients underwent minimally invasive surgery, and 25 patients underwent open surgery. Indication included cystic and solid neoplasms, neuroendocrine tumors, splenic SOL, persistent

external pancreatic fistula. Spleen-preserving procedures comprised 40% of distal resections. Major postoperative morbidity (CD $\geq$ 3a) occurred more in open surgery (40%) vs MIS (17%), with a clinically significant postoperative pancreatic fistula rate of 68% in open surgery and 47% in MIS. Conversion rate of MIS was 29%. CR- POPF rate was more commonly seen in patient in whom stapler was used for pancreatic transection. On histopathology, solid pseudopapillary neoplasm and serous cystadenoma were most frequent lesions.

Conclusions: Central and distal pancreatectomy, including minimally invasive approaches, are safe with low morbidity in high-volume settings. Major morbidity and pancreatic fistula remain significant, correlating with both technical and patient factors. Robotic and laparoscopic techniques are feasible and increasingly prevalent, with equivalent safety to open surgery.

Keywords: Distal Pancreatectomy, Central Pancreatectomy, Laparoscopic

PE-34

Early Surgery vs. Delayed Surgery in Chronic Pancreatitis: Does Timing Influence the Outcomes?: A Comprehensive Analysis of Clinical Outcomes from a Tertiary Care Center, India

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Aims: Chronic pancreatitis is progressive inflammatory disease with recurrent pain, pancreatic insufficiency, increased risk of pancreatic cancer. The conventional approach is multidisciplinary step-up approach. Surgical intervention is traditionally sought late in course of disease. The existing guidelines lack clear recommendations regarding timing of surgery.

Methods: To compare the clinical outcomes of early surgery (<3 years) with traditional delayed surgery, effect of early surgery on pain control, opioid dependency, endocrine, exocrine function, and morbidity. Methods: Single-center prospective observational study from 2022--2024 at IMS SUM Hospital, Bhubaneswar, Odisha, India.

Results: The delayed surgery group more frequently had jaundice (14.5% vs 1.81%), head masses (25.45% vs 7.27%), benign biliary strictures (53.84 vs 23.64%), Exocrine insufficiency (12.72% vs 1.81%), had more interventions preoperatively - NJ placement, ERCP + CBD Stenting and required additional procedures like HJ & GJ. Early surgery resulted in better pain relief, complete relief - 72.73% vs 27.27%, lower preoperative, follow-up Izbicki pain scores (47.41 to 10.35) than delayed surgery patients (56.41 to 26.40). Diabetes incidence was lower in the early group (27.27% preop, 14.54% postop) than indelayed group (52.73% preop, 52.73% postop) and had lower average insulin requirement post-surgery. ($P=0.049$). Intraop param-

eters like operative time, blood loss were all significantly more in delayed group. Delayed surgery was associated with greater CR-POPFs (29.09% vs 5.45%). A preop Izbicki score cutoff of 52.5 was noted for complete pain relief.

Conclusions: This study support early surgery(<3years) for chronic pancreatitis for better pain relief, reduced risk of pancreatic insufficiency, reduced insulin requirements, low reintervention rates.

Keywords: Chronic Pancreatitis, Freys Procedure, Izbicki Pain Score

PE-35

Precision Medicine Approaches to Chronic Pancreatitis: Integrating Machine Learning with Clinical Data for Early Detection of Disease Progression

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Aims: Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas with a high risk of complications and malignant transformation. Early detection of CP progression is difficult to achieve with conventional methods. Precision medicine offers opportunities through biomarkers and clinical data to understand patient heterogeneity. The integration of machine learning has been shown to recognise biomarker patterns that distinguish CP from healthy individuals and pancreatic cancer, supporting more accurate and personalised early detection efforts.

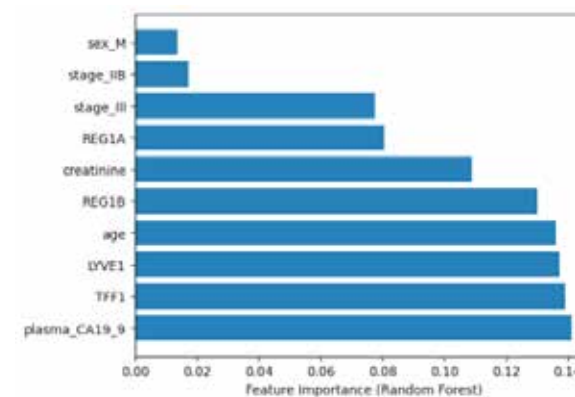
Methods: This study using secondary data from Kaggle about A urine biomarker dataset (Davis, 2020) from healthy, chronic pancreatitis (CP), and pancreatic cancer patients was analysed using Google Colab. The data were cleaned, coded, normalised, then categorised into CP and non-CP groups. Machine learning models (Logistic Regression, Random Forest) were trained on the processed data with cross-validation. Performance was evaluated using a while the contribution of key biomarkers was analysed through feature importance.

Results: A total of 590 samples were analysed, consisting of 208 CP patients and 382 non-CP patients. The machine learning model achieved promising classification performance with an AUC >0.80. The confusion matrix demonstrated good sensitivity in detecting CP, while feature importance analysis confirmed the role of key biomarkers in prediction.

Conclusions: Integrating machine learning with biomarker and clinical data can improve early detection of chronic pancreatitis progression. This approach supports the concept of precision medicine by identifying key biomarkers and providing more accurate predictive models, potentially enhancing per-

sonalised diagnostic and therapeutic strategies in CP patients. However, these findings require further validation through clinical trials.

Keywords: Precision Medicine Approaches, Chronic Pancreatitis, Disease Progression



PE-36

Clinico-Pathological Profile, Surgical Outcome and Survival Analysis after Pancreaticoduodenectomy: 7-Year Experience from Tertiary Care Teaching Hospital in Odisha

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Aims: Despite advances in multimodality treatment, morbidity after pancreaticoduodenectomy (PD) remains high. This study aimed to analyze the clinico-pathological profile, surgical outcomes, and survival of patients undergoing PD in a single tertiary care center.

Methods: Retrospective analysis was conducted using prospectively compiled data from 2016 to 2022. Patients who underwent PD and completed one year of follow-up were included. Survival analysis was performed using Kaplan-Meier analysis.

Results: Of 104 patients who underwent PD, age range was 15 to 77 years (median: 53), with most being male (61.5%) and having CCI score - 0 (77.9%). Jaundice was the common presenting complaint. Preoperative stenting was performed in 47% of patients mainly for cholangitis. Most patients underwent pancreaticojejunostomy (92%). Total morbidity was 77.1%, with pancreatic fistula (62.5%) as most common complication, followed by delayed gastric emptying (35.6%). Postoperative hemorrhage (7%), bile leak (5.8%), and surgical site infection (18%) were also observed. The 30-day and 90-day mortality rates were 3.8% and 9.6%, respectively. Adenocarcinoma was the most common histopathological finding (79.8%), followed by benign disease. Most adenocarcinomas were T3 stage (49.3%) with no lymph node involvement (62%)

(N1: 26.5%). Only 66.2% of adenocarcinoma patients received or were on chemotherapy. The median survival for adenocarcinoma was 45 months, with no significant difference among subtypes. However, significant survival improvement was observed in patients who received chemotherapy. The one-year, three-year, and five-year survival rates were 79.4%, 51.2%, and 35.7%, respectively.

Conclusions: Pancreaticoduodenectomy remains a high-risk surgery with significant morbidity and mortality. Adenocarcinoma was the most common diagnosis, and chemotherapy showed a significant survival benefit.

Keywords: Pancreaticoduodenectomy, 5 Yr Survival, POPF

PE-37

Hepatobiliary Tuberculosis Presenting with Biliary Tree Alterations: A Case Report and Literature Review

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Aims: Tuberculosis (TB) is a chronic infectious disease that predominantly affects the lungs, though extrapulmonary manifestations are also prevalent. Preoperative diagnosis of HBTB remains a significant clinical challenge due to its non-specific clinical and paraclinical features. Tuberculous obstructive jaundice is an exceedingly rare condition. The etiology involves primary biliary involvement leading to strictures, cholangitis secondary to the rupture of caseating granulomas into the bile ducts, or extrinsic compression by tuberculous lymphadenopathy in the periportal, pericholedochal, or peripancreatic regions.

Methods: We report the case of a 15-year-old female with a history of hepatic tuberculosis treated for six months, who presented with progressive jaundice. Magnetic resonance imaging revealed diffuse bilateral intrahepatic ductal dilation and a cystic dilation of the common hepatic duct measuring 43 mm in diameter.

Results: The patient underwent two surgical interventions. The initial procedure involved cyst excision and hepaticojejunostomy. Postoperatively, the patient developed concurrent biliary fistula and obstructive jaundice. A re-operation was performed eight days later, revealing a primary intraoperative misinterpretation of the biliary anatomy. Consequently, a segment 4b-5 hepatectomy and revision of the hepaticocenteric anastomosis were performed. Following the second procedure, the patient's condition stabilized, and she was discharged after 14 days.

Conclusions: Hepatobiliary tuberculosis is a rare condition that remains diagnostically challenging, often leading to misdiagnosis with other pathologies. In patients presenting with ob-

structive jaundice secondary to biliary tract alterations, a meticulous preoperative and intraoperative evaluation is essential given the complexity of the lesions. Partial hepatic resection may be indicated to facilitate the effective repair of biliary tract injuries.

Keywords: Hepatobiliary Tuberculosis, Tuberculous Obstructive Jaundice

PE-38

A Machine Learning–Driven Model for Predicting Biliary Drainage Success in Malignant Biliary Obstruction Using Endoscopic Ultrasound Data

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Aims: Malignant biliary obstruction (MBO) is a frequent complication of hepatopancreatobiliary malignancies and is associated with significant morbidity. Endoscopic ultrasound–guided biliary drainage (EUS-BD) has emerged as an effective therapeutic modality; however, predicting drainage success remains challenging. This study aimed to evaluate the performance of machine learning (ML) models integrated with clinical and EUS-derived variables in predicting biliary drainage outcomes in patients with MBO.

Methods: A retrospective secondary analysis was conducted on 90 patients treated between 2021 and 2023 from data set. Clinical, imaging, and procedural data were collected and analyzed using logistic regression, random forest, and neural network models. Data were split into training (70%) and validation (30%) sets. Successful drainage was defined as a reduction of serum bilirubin greater than 50% within seven days post-procedure. Model performance was assessed using the area under the receiver operating characteristic curve (AUC).

Results: The random forest model demonstrated the highest predictive accuracy (AUC 0.89, 95% CI 0.82–0.95), outperforming logistic regression (AUC 0.79, $P=0.002$) and neural networks (AUC 0.84, $P<0.001$). Successful biliary drainage was achieved in 72 of 90 patients (80%). Significant predictors of success included tumor size (OR 1.45, $P=0.004$), stent placement (OR 2.12, $P<0.001$), and baseline bilirubin level (OR 1.28, $P=0.01$). Complication rates were significantly lower in successful cases compared with unsuccessful ones (15% vs. 32%, $P=0.03$).

Conclusions: These findings indicate that integrating ML—particularly random forest models—with EUS and clinical data can substantially enhance prediction of biliary drainage success, supporting its potential role in clinical decision-making for MBO management.

Keywords: Malignant Biliary Obstruction, Endoscopic Ultrasound–Guided Biliary Drainage, Machine Learning

PE-39

Early Detection and Resectability in Pancreatic Head Adenocarcinoma: A Contemporary Overview

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Aims: Adenocarcinoma is the most common histological type of malignant tumor of the pancreas head. Its diagnosis is often delayed due to clinical latency. Imaging plays a vital role in the diagnostic process, enabling both a positive diagnosis and an assessment of extension.

Methods: This is a retrospective descriptive study including 36 cases of adenocarcinoma of the head of the pancreas collected in the Radiology Department of Mohammed VI University Hospital of Oujda over a two-year period from January 2023 to December 2024, in patients admitted to the Visceral Surgery A and Gastroenterology departments of the same hospital center.

Results: Our patients included 22 men and 14 women, whose average age at diagnosis was 54.4 years, ranging from 33 to 78 years. A thoracoabdominal-pelvic CT scan was performed in all our patients, allowing the detection of adenocarcinoma of the pancreatic head and the assessment of local and distant spread in 100% of cases. In our series, the tumor was considered resectable in 25.1% of cases, borderline in 36.1% of cases, and unresectable in 38.8% of cases. Pancreatic MRI was performed in 47.2% of cases to confirm and measure isodense lesions visible on CT scan and to rule out hepatic micrometastases in cases of resectable tumors.

Conclusions: Screening efforts are therefore focused on early detection in high-risk individuals. Emerging technologies and nanotechnologies could improve the detection of precursor lesions and early-stage cancers. Future strategies will likely use multiparametric risk models integrating clinical data, imaging, and artificial intelligence to identify resectable pancreatic adenocarcinomas at an early stage.

Keywords: Pancreatic Adenocarcinoma, Early Detection, Resectability

PE-40

Improving Outcomes in Bile Duct Injuries: A Contemporary Surgical Perspective

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Aims: Biliary surgery is frequently associated with a range of complications, some of which maybe severe, such as bile duct injuries.

Methods: The objective of this study is to report on our experience with biliary injuries that occurred or were treated by the General Surgery A Department at Mohammed VI University Hospital in Oujda. We also wish to compare our data with the conclusions drawn from the literature in order to establish an appropriate diagnostic strategy and an effective therapeutic approach.

Results: The diagnosis was made intraoperatively in 3% of cases, based on the observation of bile leakage. However, 97% of lesions were identified postoperatively. Clinical manifestations included jaundice in 67% of cases, cholangitis in 12%, biliary peritonitis in 9%, abdominal pain in 6%, and peritoneal effusion or pruritus in 3% of cases. To study these clinical manifestations, the following imaging modalities were used: abdominal computed tomography angiography in 79% of cases and magnetic resonance cholangiopancreatography in 88% of cases. Surgical repair ranged from simple lavage and drainage with end-to-end suturing to biliary-digestive anastomosis, depending on the nature and extent of the lesion. Postoperative complications included biliary fistula in one patient, anastomotic dehiscence leading to peritonitis in another, and one case of cholangitis. Two deaths were recorded in this series, corresponding to a mortality rate of 6%.

Conclusions: Prevention relies on a thorough understanding of biliary anatomy and its variations, as well as the surgeon's technical expertise.

Keywords: Biles Duct Injuries, Management

PE-41

Multimodal Strategy in Duodenum-Preserving Pancreatic Head Resection for an Inflammatory Pancreatic Head Tumor

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Aims: Chronic biliary pancreatitis rarely present as pancreatic head mass as a complication in 6% in one study of cases on imaging resembling malignancy. This poses a particular diagnostic dilemma, often leading to unnecessary extensive surgery.

Methods: A case of chronic pancreatitis presenting as a pancreatic head malignancy due to enhancing pancreatic head mass with peripancreatic (head) lymphadenopathy.

Results: During surgery, a solid 4 x 3 cm pancreatic head mass is seen adjacent to a 3-cm cyst at the level of pancreatic neck with dilated main pancreatic duct and nondilated distal common bile duct on intraoperative ultrasound. Frozen section

biopsy along with fine needle aspiration of the pancreatic mass revealed a pseudocyst with chronic inflammation and acute on chronic pancreatitis with no identified malignant cells. A cholecystectomy was done followed by ICG fluorescence-guided resection of the pancreatic head preserving the duodenum and a roux en y pancreaticojejunostomy. Integrity of the distal bile duct and vascularity of the duodenum were also examined and confirmed by ICG fluorescence. Patient was discharged after three weeks due to delayed gastric emptying.

Conclusions: This case illustrates the approach to diagnostic and therapeutic dilemma posed by tumor-like inflammatory lesion in the pancreatic head and the indispensable use of intraoperative ICG- fluorescence imaging, ultrasound, and frozen section biopsy with fine needle aspiration that helped managed the case. Integrating these strategies to de-escalate and simplify surgery from a possible Whipple surgery to a duodenum-preserving pancreatic head resection, enhances surgical accuracy, reduced operative morbidity, and improve patient outcomes.

Keywords: Indocyanine Green, Duodenum-Preserving Pancreatic Head Resection, Chronic Biliary Pancreatitis

PE-42

Hepatobiliary Outcomes in the Era of GLP-1 Therapy: Insights from a Large Randomized Evidence Base

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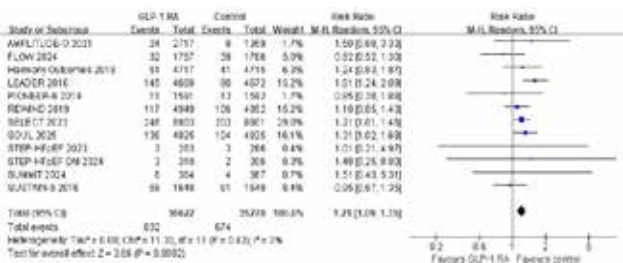
Aims: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly used for diabetes and obesity management, with emerging evidence suggesting potential hepatobiliary benefits. However, the overall impact of GLP-1 RAs on hepatobiliary outcomes across diverse populations remains incompletely defined. We conducted a meta-analysis of randomized controlled trials to evaluate the effect of GLP-1 RAs on hepatobiliary outcomes compared with placebo.

Methods: A systematic search identified randomized controlled trials comparing GLP-1 RAs with placebo that reported hepatobiliary outcomes. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Prespecified subgroup analyses were performed according to diabetes status, obesity status, and heart failure (HF) status. Heterogeneity was assessed using the I^2 statistic.

Results: Twelve randomized controlled trials including 71,892 participants were analyzed. Seven trials evaluated semaglutide, while five evaluated other GLP-1 RAs. Overall, GLP-1 RA thera-

py was associated with a significant increase in hepatobiliary outcomes compared with placebo (RR 1.21, 95% CI 1.09–1.35; $P=0.0002$), with minimal heterogeneity ($I^2 = 3\%$). Subgroup analyses demonstrated consistent findings across clinical populations. Among patients with diabetes, the risk remained elevated (RR 1.19, 95% CI 1.02–1.39; $P=0.03$; $I^2 = 28\%$), similar to those without diabetes (RR 1.21, 95% CI 1.01–1.45; $P=0.03$; $I^2 = 0\%$; P interaction = 0.89). Comparable effects were observed in patients with obesity (RR 1.22, 95% CI 1.02–1.46; $P=0.03$; $I^2 = 0\%$) and without obesity (RR 1.19, 95% CI 1.01–1.40; $P=0.04$; $I^2 = 37\%$; P interaction = 0.84). In patients with heart failure, no statistically significant difference was observed (RR 1.34, 95% CI 0.56–3.17; $P=0.51$; $I^2 = 0\%$), whereas a significant increase was observed in those without HF (RR 1.20, 95% CI 1.06–1.37; $P=0.005$; $I^2 = 28\%$; P interaction = 0.81).

Conclusions: In this large meta-analysis of randomized trials involving more than 70,000 participants, GLP-1 RA therapy was associated with a modestly increased risk of hepatobiliary events compared with placebo. This effect was consistent across diabetes and obesity subgroups, with no significant interaction between clinical populations. These findings highlight the importance of monitoring hepatobiliary complications during GLP-1 RA therapy while balancing their well-established cardiometabolic benefits.



Keywords: Glucagon-Like Peptide-1 Receptor Agonists, Hepatobiliary Outcomes, Obesity, Type 2 Diabetes Mellitus

PE-43

Laparoscopic En-Bloc Lymphadenectomy for Biliary Malignancies

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Aims: To describe the technical feasibility, perioperative outcomes, and oncologic rationale of laparoscopic en-bloc lymphadenectomy as a standardized component of radical resection for biliary malignancies.

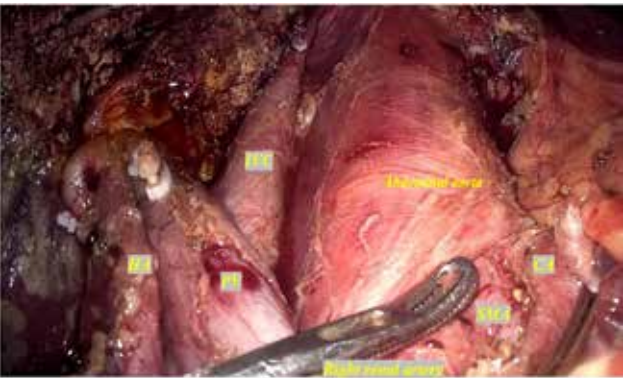
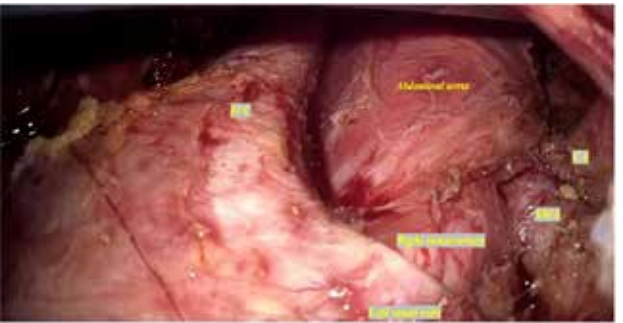
Methods: We conducted 32 patients with pathologically con-

firmed biliary malignancies. Dissection followed a reproducible, anatomy-based en-bloc protocol: (1) Right posterior dissection 1: Kocher incision to achieve duodenal mobilization, exposing the posterior surface of the pancreatic head; systematic clearance of lymph node 16a2, 14a, and 9, to expose the root of superior mesenteric artery and celiac trunk artery; (2) Right posterior dissection 2: Excision of lymph node 13a and right lateral nodes of 12b and 12p, followed by circumferential dissection and push them to the left under the duodenal ligament with lymph node 14a, 9, and 16a2; (3) Anterior hepatoduodenal ligament dissection: clearance of lymph node 5, free the gastroduodenal artery (GDA), and bilateral nodal dissection lymph node 12a, and left lateral of 12p, 12b; (4) Left-sided dissection: Clearance of lymph node 8a and 8p along the common hepatic artery, integrated with right-sided specimen at the celiac trunk artery, and subsequent clearance of lymph node 7 reserve or remove the left gastric artery and vein; (5) Distal and superior extension: dissection of lymph node 3 and 1 along The lesser curvature of the stomach and the left side of cardia, respectively; exposure of the diaphragmatic crus; and clearance of lymph node 19. And then completing the en-bloc resection of all designated regional lymph nodes.

Results: The median number of retrieved lymph nodes was 13 ± 2.14 ; Median operative time was 35 ± 17.19 minutes; Median intraoperative blood loss of 25.5 ± 32.7 ml. There were no postoperative complications related to lymph node dissection.

Conclusions: Laparoscopic en-bloc lymphadenectomy represents a technically refined and oncologically principled strategy for biliary malignancies. Its adoption aligns with contemporary understanding of lymphatic spread patterns and supports accurate nodal staging—a prerequisite for prognostication and adjuvant therapy decisions. The en-bloc technique offers distinct advantages over sequential dissection: improved specimen integrity, reduced risk of nodal capsule violation, shorter dissection time, and enhanced reproducibility across experienced surgical teams.

Keywords: En-Bloc Lymphadenectomy, Biliary Malignancies, Laparoscopy



PE-44

Near-Infrared Fluorescence Cholangiography Using Indocyanine Green in Laparoscopic Cholecystectomy: A Meta-Analysis of Visualization Rates and Complications

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Aims: Laparoscopic cholecystectomy (LC) is one of the most performed surgeries worldwide. Biliary tract injuries are among the most feared complications after LC. The primary cause of biliary injuries during LC is the incorrect identification of the biliary tract anatomy. Near-infrared fluorescence (NIRF) imaging, following intravenous (IV) injection of indocyanine green (ICG), shows promise for simplifying the intraoperative visualization of biliary anatomy. This technique enables real-time identification of the cystic duct and common bile duct, potentially enhancing the outcomes of LC. This systematic review and meta-analysis aimed to investigate the effects of NIRF-ICG on LC outcomes.

Methods: This meta-analysis followed the Cochrane Handbook for Systematic Reviews of Interventions guidelines. We searched PubMed, Embase, Cochrane Library, Web of Science, and Scopus until Jan 3, 2026. We included randomized-controlled trials and retrospective studies comparing NIRF-ICG LC and conventional LC. Statistical analysis was performed using Review Manager 5.3 software.

Results: Fifteen studies with 1581 patients (41.1%) in the NIRF-ICG group and 2264 (58.9%) in the control group were included. The NIRF-ICG was associated with statistically significant reduced overall complications, bile leakage, and duct drainage (risk ratio (RR) = 0.62, 95% CI: [0.40, 0.95], $P=0.03$; Fig 1), (RR = 0.34, 95% CI: [0.14, 0.83], $P=0.02$; Fig 2), and (RR = 0.64, 95% CI: [0.44, 0.91], $P=0.01$; Fig 3), respectively. Common bile duct (CBD), cystic duct- CBD junction, and common hepatic duct visual-

ization rates were better with the NIRF-ICG, (RR= 3.67, 95% CI: [2.62, 5.15], $P<0.001$), (RR = 3.00, 95% CI: [2.03, 4.43], $P<0.001$), and (RR = 2.87, 95% CI: [1.94, 4.25], $P<0.001$), respectively. There was no significant difference in cystic duct visualization rate (RR = 1.40, 95% CI: [0.71, 2.78], $P=0.33$).

Conclusions: NIRF following administration of ICG in LC offers better visualization of biliary tract anatomy and is associated with reduced overall complications, bile leakage, and bile duct drainage.

Keywords: Nearinfrared Fluorescence Cholangiography, Indocyanine Green Keyword, Cholecystectomy

PE-45

Long-Term Outcomes of Endobiliary Radiofrequency Ablation plus Stenting in Malignant Biliary Obstruction: A Patient-Level Meta-Analysis of Randomized Trials

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Aims: Endobiliary radiofrequency ablation (RFA) has been explored as an adjunct to stenting for malignant biliary obstruction (MBO), yet evidence remains mixed, particularly regarding long-term outcomes. Prior meta-analyses have been limited by short follow-up periods and reliance on aggregated data.

Objective: To assess the long-term efficacy and safety of RFA combined with stenting compared to stenting alone in patients with MBO using reconstructed individual patient data (IPD) from randomized controlled trials (RCTs).

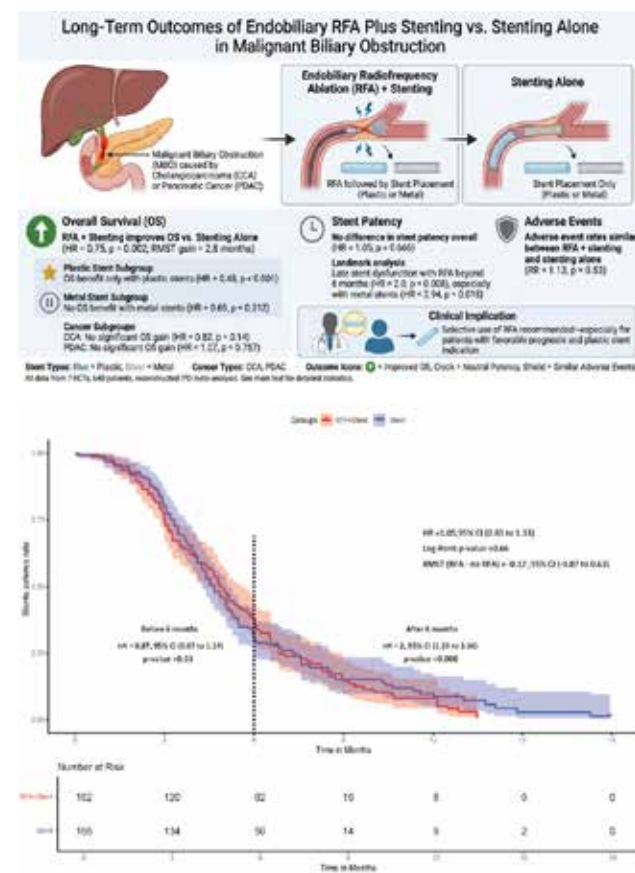
Methods: We searched Pubmed, Scopus, Web of Science, and Cochrane CENTRAL through December 15th, 2025 for RCTs comparing RFA plus stenting versus stenting alone in MBO. IPD were reconstructed from Kaplan–Meier curves using the tow-step approach. Time-to-event outcomes were analyzed using Cox proportional hazards models, with subgroup analyses by cancer and stent type. Restricted mean survival time (RMST) and landmark analyses were also performed. Pairwise meta-analysis was also performed.

Results: Seven RCTs involving 640 patients were included. RFA significantly improved overall survival (OS) compared to stenting alone (HR = 0.75, 95% CI: 0.63–0.91; $P=0.002$; RMST difference = 2.8 months). Subgroup analysis showed no OS benefit in cholangiocarcinoma (HR = 0.82; $P=0.14$) or pancreatic cancer (HR = 1.07; $P=0.757$). OS improvement was observed only with plastic stents (HR = 0.48; $P<0.001$), not metal stents (HR = 0.69; $P=0.312$). No overall difference was found in stent patency (HR = 1.05; $P=0.666$), but landmark analysis revealed worse patency beyond 6 months with RFA (HR = 2.00; $P=0.008$),

particularly in metal stents (HR = 2.94; $P=0.018$). The rate of adverse events was similar between groups (risk ratio = 1.13; $P=0.53$).

Conclusions: RFA combined with stenting improves long-term OS in MBO, especially with plastic stents, but offers no overall benefit in stent patency and may increase the risk of late dysfunction in metal stents. The safety profile was comparable to stenting alone. These findings support the selective use of RFA, particularly in patients with favorable prognosis and plastic stent indication.

Keywords: Malignant Biliary Obstruction, Radiofrequency Ablation, Stent Patency, Cholangiocarcinoma



PE-46

Assessment of G10 Intraoperative Scoring System for Conversion in Patients Undergoing Laparoscopic Cholecystectomy: A Cross-Sectional Study from Nepal

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Aims: Though, preoperative risk factors for conversion in laparoscopic cholecystectomy (LC) have been well studied, the

assessment of intraoperative factors for conversion in patients with cholecystitis is unclear. We aimed to assess the utility of the G10 scoring system among patients presenting for LC for symptomatic cholelithiasis in the clinical setting of a low- and middle-income country.

Methods: All the patients undergoing LC were assigned a G10 value. Gallbladder surgery was considered easy if the G10 score was <2, moderate ($2 \leq 4$), difficult ($5 \leq 7$), and extreme ($8 \leq 10$). All 10 risk factors were analyzed into a binary logistics model, and statistically significant risk factors were assessed.

Results: Among 177 patients, there were 36 males and 141 females. The median age of the patient was 42 years (range 11-79). There were 70 easy, 89 moderate, and 18 difficult cases. The overall mean G10 score was 2.32 ± 1.5 , which significantly increased as the severity progressed, with a mean value of 5.5 ± 0.51 for difficult cases ($P=0.0001$). The mean G10 score for surgeries completed laparoscopically was 2.1 ± 1.4 , while it was 3.71 ± 1.4 for open conversions [$P=0.0001$, AUC=0.79, CI=0.70-0.87]. There were 18 patients with G10 ≥ 5 with a conversion rate of 27.7%, while the overall conversion rate was 13.6%. Multivariate analysis showed free bile or pus outside the gallbladder [$P=0.02$, OR=5.1, CI=1.2-21.1] and fistula [$P=0.01$, OR=15.8, CI=1.9-129.8] as significant risk factors for conversion.

Conclusions: Intraoperative risk factors for the prediction of conversion included the presence of free bile or pus outside the gallbladder and cholecystoenteric fistula. Based on the F1 score analysis, complemented with the Youden Index, the optimal cutoff value for conversion, based on the G10 score, lies around 4. Broader application and validation of the G10 scoring system are mandated to assess the utilization of this novel intraoperative scoring system.

Keywords: Cholecystitis, Conversion Surgery, G10 Protocol, Lap Cholecystectomy, Laparoscopic Conversion

17. Liver Surgery

PE-1

Analysis of the Correlation between Surgical Team Coordination Quality and Perioperative Complications in Laparoscopic Anatomical Hepatectomy and Development of a Risk Prediction Model

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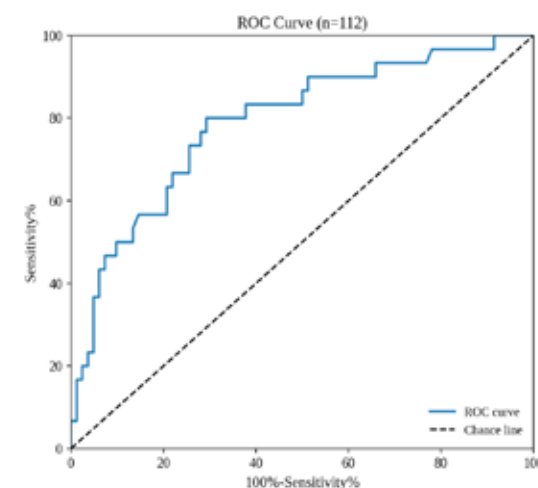
Aims: This study aimed to analyze the correlation between surgical team coordination quality and perioperative complications in laparoscopic anatomical hepatectomy and to develop a predictive model.

Methods: A retrospective study was conducted on patients who underwent laparoscopic anatomical hepatectomy at Jiangsu Provincial People's Hospital, Chongqing Hospital, from June 2023 to May 2025. Based on the surgical coordination quality scores divided by the tertile method, patients were categorized into high coordination quality group ($n=38$), medium coordination quality group ($n=37$), and low coordination quality group ($n=37$).

Results: A total of 112 patients were included in this study, with an average age of 57.1 ± 10.7 years. Males accounted for 61.6% (69/112) and females for 38.4% (43/112). Perioperative complications occurred in 29.5% (33/112) of cases. The complication rates in the high, medium, and low surgical coordination quality groups were 13.2% (5/38), 29.7% (11/37), and 45.9% (17/37) respectively, with statistically significant differences among the three groups ($P<0.05$). Multivariate logistic regression analysis revealed that improved surgical coordination quality [aOR=0.83 (95% CI 0.77-0.90), $P=0.01$] was an independent protective factor for perioperative complications in laparoscopic anatomical hepatectomy, whereas increased surgical difficulty [aOR=1.36 (95% CI 1.09-1.70), $P=0.02$] and intraoperative blood loss ≥ 400 mL [aOR=2.41 (95% CI 1.01-5.75), $P=0.04$] were independent risk factors. The combined prediction model demonstrated good performance [AUC=0.79 (95% CI 0.70-0.88)].

Conclusions: High-quality surgical team coordination was associated with a significantly lower incidence of perioperative complications in laparoscopic anatomical hepatectomy.

Keywords: Laparoscopic Anatomical Hepatectomy, Surgical Team Coordination Quality, Perioperative Period



PE-2

The Impact of Bariatric Surgery on the Development of Liver Fibrosis: A Single-Center Experience

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Aims: To evaluate the impact of bariatric surgery on the degree of liver fibrosis in patients with morbid obesity, based on the experience of a single center.

Methods: The study included 18 patients with morbid obesity who underwent bariatric surgery at a specialized center. All patients underwent a comprehensive clinical and laboratory examination preoperatively and dynamically after surgery. The degree of liver fibrosis was assessed using non-invasive methods (liver elastography, biochemical markers of fibrosis). Changes in body weight, body mass index, liver function tests, and the degree of fibrosis in the postoperative period were analyzed.

Results: Following bariatric surgery, most patients experienced significant weight loss and body mass index. Along with weight loss, improved liver function tests (ALT, AST) and a trend toward regression of liver fibrosis were observed. Some patients also experienced a decrease in the stage of fibrosis, demonstrating the potential reversibility of fibrotic changes with correction of metabolic disorders.

Conclusions: Bariatric surgery in patients with morbid obesity has a positive effect on the course of liver fibrosis, improving liver function and reducing the severity of fibrotic changes. These data support the use of bariatric surgery as a method for preventing the progression of non-alcoholic fatty liver disease and liver fibrosis. Further studies with a larger number of patients and a longer follow-up period are needed to definitively assess its effectiveness.

This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan 2025-2027 (Grant No. AP26102345).

Keywords: Liver Fibrosis, Bariatric Surgery, Obesity, Weight Loss

PE-3

Impact of Bariatric Surgery on the Development of Liver Fibrosis

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Aims: Morbid obesity is a significant risk factor for the development of non-alcoholic fatty liver disease (NAFLD) and the progression of liver fibrosis, potentially leading to cirrhosis.

Bariatric surgery is considered an effective treatment for obesity and associated metabolic disorders; however, the impact of different bariatric procedures on liver fibrosis dynamics requires further investigation.

Objective: To evaluate the effect of bariatric surgery on the degree of liver fibrosis in patients with morbid obesity based on single-center experience.

Methods: The study included 38 patients with morbid obesity who underwent bariatric surgery at a specialized center. All patients underwent comprehensive clinical and laboratory assessments before surgery and during postoperative follow-up. Liver fibrosis was assessed using non-invasive methods, including liver elastography and biochemical fibrosis markers. Changes in body weight, body mass index (BMI), liver function parameters, and fibrosis stage were analyzed in the postoperative period.

Results: Following bariatric surgery, the majority of patients experienced significant reductions in body weight and BMI. Weight loss was associated with improvements in liver function tests (ALT, AST) and a trend toward regression of liver fibrosis. In some patients, a decrease in fibrosis stage was observed, indicating the potentially reversible nature of fibrotic changes when metabolic disturbances are corrected.

Conclusions: Bariatric surgery in patients with morbid obesity has a positive effect on the course of liver fibrosis, contributing to improved liver function and reduced fibrotic changes. These findings support the use of bariatric procedures as a preventive strategy against the progression of NAFLD and liver fibrosis. Further studies with larger cohorts and longer follow-up periods are needed to definitively assess efficacy.

This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan 2025-2027 (Grant No. AP26102345).

Keywords: Liver Fibrosis, Bariatric Surgery, Obesity, Liver Disease

PE-5

In Vivo Monitoring of Hepatic Ischemia Using a Dual-Enzyme Activated Near-Infrared Fluorescence Probe

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Aims: Hepatic ischemia–reperfusion injury (HIRI) is a major complication of liver transplantation. After ischemia, reperfusion-induced reactive oxygen species (ROS) bursts cause acute hepatic injury, underscoring an unmet need for real-time intraoperative ischemia detection. This study presents a dual-enzyme-activated near-infrared (NIR) fluorescence probe, QN-NIR, which could rapidly identify hepatic ischemia to enable

early and effective monitoring before severe damage occurs.

Methods: Hypoxic conditions were induced in AML12 cells using CoCl_2 , and QN-NIR fluorescence activation was assessed. NAD(P)H quinone oxidoreductase 1 (*Nqo1*) or xanthine dehydrogenase (*Xdh*) knockdown cell lines were produced using CRISPRi-mediated knockdown system. For *in vivo* validation, partial hepatic ischemia was surgically induced in wild type male C57BL/6J mice for 1 h, followed by fluorescence imaging to measure QN-NIR activation. Fluorescence intensity was additionally compared with mice subjected to 6 h of reperfusion after ischemia.

Results: QN-NIR was robustly activated in AML12 cells under CoCl_2 -induced hypoxia via both activating enzymes, NQO1 and XDH. This supports improved specificity and reduced nonspecific activation *in vitro*. Consistently, QN-NIR generated strong ischemia-associated fluorescence in a partial hepatic ischemia mouse model, supporting ischemia-specific detection *in vivo*.

Conclusions: This study identifies dual-enzyme activated NIR imaging with QN-NIR as a practical approach for real-time *in vivo* detection of hepatic ischemia. QN-NIR activation enabled early recognition of ischemia prior to reperfusion, supporting its potential to guide timely intraoperative intervention and mitigate subsequent hepatic injury.

Keywords: Hepatic Ischemia–Reperfusion Injury (HIRI), *In Vivo* Imaging, NAD(P)H Quinone Oxidoreductase 1 (*Nqo1*), Nitroreductase (NTR)

PE-6

Laparoscopic Anatomical Left Hepatectomy Guided by the Dilated Bile Duct and Middle Hepatic Vein for Hepaticolithiasis in a Patient with Situs Inversus Totalis: How I Do It

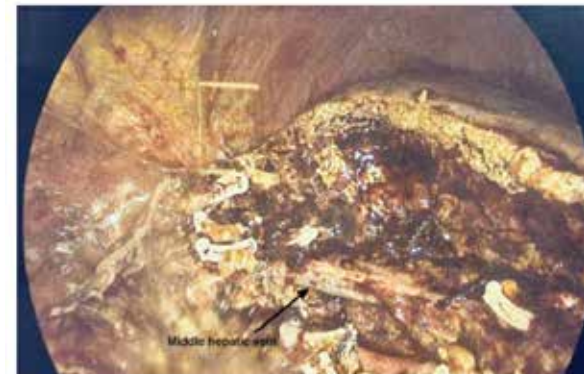
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Aims: Situs inversus totalis (SIT) is a rare congenital anomaly in which thoracic and abdominal organs are mirrored from normal positions. Hepaticolithiasis, common in East and Southeast Asia, often requires hepatectomy for localized disease with parenchymal atrophy. Laparoscopic approaches in SIT patients are challenging due to reversed anatomy and ergonomics. This report presents the first case of laparoscopic anatomical left hepatectomy for hepaticolithiasis in a SIT patient, guided by the dilated bile duct and middle hepatic vein.

Methods: A 57-year-old woman with SIT presented with recurrent cholangitis. Imaging showed multiple intrahepatic stones, strictures, and severe left liver atrophy, indicating localized disease. Laparoscopic left hepatectomy was performed with adaptations: mirrored trocar placement, French positioning,

and dissection using the dilated bile duct and middle hepatic vein as anatomical landmarks. The procedure ensured safe navigation of mirror-image anatomy.



Results: The surgery was completed with minimal blood loss and no complications; the patient was discharged on postoperative day six and remained asymptomatic at follow-up.

Conclusions: This case highlights that meticulous preoperative planning, ergonomic adjustments, and bile duct–oriented resection enable safe laparoscopic hepatectomy in SIT, achieving complete stone clearance and reducing recurrence risk in complex hepatolithiasis scenarios.

Keywords: Situs Inversus Totalis, Laparoscopic Anatomical Left Hepatectomy

PE-7

Deep Learning–Based Prognostic Prediction in Hepatocellular Carcinoma: Implications for Minimally Invasive Liver Surgery

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Aims: Hepatocellular carcinoma (HCC) is a biologically heterogeneous malignancy with variable outcomes following surgical treatment. Accurate prognostic stratification is essential to optimize treatment selection, surgical planning, and postoperative surveillance, particularly in the era of minimally invasive liver surgery, including robotic and endoscopic approaches. Conventional prognostic systems based on clinical staging and histopathology often fail to capture intra-tumoral heterogeneity and microenvironmental complexity. Recent advances in artificial intelligence, especially deep learning convolutional neural networks (CNNs), have demonstrated promising capability in prognostic prediction by extracting high-dimensional features from imaging and pathological data. This literature review synthesizes contemporary evidence on CNN-based prognostic models in HCC and discusses their relevance to modern liver surgery.

Methods: A narrative literature review was conducted focusing on randomized controlled trials and high-quality prospective or controlled studies published within the last five years. Eligible studies were identified through structured searches of PubMed, Scopus, and Web of Science. Included studies evaluated deep learning–based or supervised machine-learning models, with emphasis on CNN architectures, for prognostic prediction in adult patients with HCC. Prognostic endpoints included overall survival, disease-free survival, early recurrence, and microvascular invasion. Studies were selected based on methodological rigor, validation strategies, and clinical relevance. Evidence was synthesized qualitatively, with attention to study design, model performance, and potential surgical applicability.

Results: Across the reviewed studies, CNN-based prognostic models demonstrated improved predictive performance compared with conventional clinical, radiologic, or stag-

ing-based assessments. Imaging-based CNN approaches applied to preoperative CT and MRI enabled automated tumor segmentation and extraction of prognostically relevant features, supporting accurate prediction of recurrence and survival outcomes. Several studies reported reliable preoperative prediction of microvascular invasion, a key determinant of surgical margin planning and recurrence risk. Histopathology-based CNN analyses further enhanced prognostic accuracy by capturing spatial tumor and microenvironmental patterns beyond human visual assessment. Multimodal models integrating imaging-derived features with clinical variables consistently outperformed single-modality approaches. Key strengths of CNN-based methods include automated feature learning, reduced interobserver variability, and the ability to uncover latent prognostic biomarkers. Nonetheless, heterogeneity in model architecture, datasets, and outcome definitions remains a limitation.

Conclusions: CNN-based prognostic prediction holds significant potential to support robotic and endoscopic liver surgery by enabling risk-adapted patient selection, individualized resection strategies, and tailored postoperative surveillance. Future research should prioritize standardized reporting, prospective validation, and integration of explainable deep learning tools into surgical workflows. Contemporary evidence supports the prognostic utility of CNN-based deep learning models in hepatocellular carcinoma, although further validation is required prior to routine clinical implementation.

Keywords: Hepatocellular Carcinoma, Deep Learning Models, Prognostic Systems

PE-9

Digital and Intelligent Liver Surgery: A Systematic Review of Precision, Visualization, and Decision-Support Technologies

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Aims: Liver surgery remains technically challenging due to complex vascular anatomy, interindividual variability, and intraoperative deformation. Digital and intelligent technologies have increasingly been introduced to improve surgical precision, visualization, and intraoperative decision-making; however, the available evidence remains fragmented across technological domains. This systematic review synthesized current evidence on digital and intelligent technologies in liver surgery, with emphasis on precision planning, visualization, and artificial intelligence (AI)-based decision-support systems.

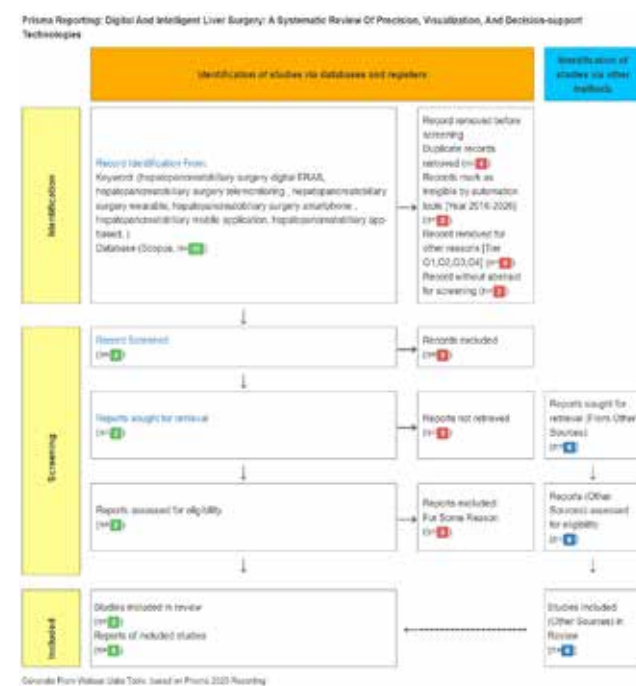
Methods: A qualitative systematic review was conducted in

accordance with PRISMA 2020 guidelines. Literature searches were conducted in Scopus (via Wataase Uake Tools) as the primary database, with PubMed included as an additional source. Studies published within the past 10 years were screened according to predefined eligibility criteria. Included studies were synthesized using a structured narrative synthesis due to heterogeneity in study design and reported outcomes.

Results: Eight studies met the inclusion criteria. Preoperative three-dimensional reconstruction and automated anatomical segmentation emerged as the most mature applications, enabling standardized and data-driven surgical planning. Visualization technologies, particularly augmented reality, demonstrated potential to enhance intraoperative spatial orientation but remained limited by challenges related to image registration, organ deformation, and system latency. Artificial intelligence–based decision-support systems enabled real-time intraoperative monitoring and safety evaluation; however, current validation primarily focuses on technical feasibility rather than patient-centered outcomes.

Conclusions: Digital and intelligent liver surgery is evolving as an integrated ecosystem combining precision planning, visualization, and decision support. While preoperative applications show advanced readiness, intraoperative technologies require further development to ensure robustness and clinical reliability. This review provides an evidence-based framework to guide future research, technological development, and clinical translation in hepatobiliary surgery.

Keywords: Digital Liver Surgery, Intelligent Surgery, Surgical Decision Support, Precision Hepatectomy



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PE-10

Early Diagnosis of Liver Impairment Based on Biochemical Markers: A Random Forest Predictive Modeling Approach

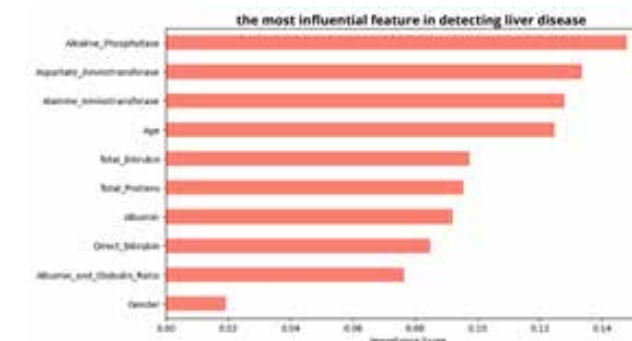
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Thaha Saifuddin, Indonesia

Aims: Liver impairment is a serious global health problem often called a “silent killer” due to its late clinical presentation. Early detection is crucial, but manual analysis of biochemical tests is complex and subjective. This study develops a Random Forest-based Machine Learning model to detect liver impairment using routine biochemical markers as a reliable tool for early clinical screening.

Methods: The research utilized the Indian Liver Patient Dataset (ILPD), consisting of 583 clinical records encompassing ten biochemical features, including liver enzymes and protein levels. Data preprocessing was performed using Python, which involved handling missing values through mean imputation and encoding categorical variables. A Random Forest (RF) classifier was implemented using an 80:20 train-test split. The model's performance was rigorously evaluated using accuracy metrics and feature importance rankings to identify the most significant biological indicators of liver dysfunction.

Results: The developed Random Forest model achieved a classification accuracy of 74.36%. Analysis of the model's internal decision-making process revealed that Alkaline Phosphatase and Aspartate Aminotransferase (SGOT) were the most influential biochemical markers in predicting liver status. These findings suggest that the algorithm can effectively capture non-linear relationships between enzymatic elevations and hepatic health, offering a consistent method for identifying at-risk patients who might be overlooked during standard manual reviews.



Conclusions: This study demonstrates that a Random Forest-based approach provides a robust framework for the early diagnosis of liver impairment. By transforming raw laboratory data into predictive insights, the model serves as an objective

"second opinion" for medical practitioners. While it does not replace clinical expertise, this automated screening tool can significantly streamline the diagnostic workflow and facilitate earlier medical intervention, ultimately contributing to better management of hepatic diseases.

Keywords: Early Diagnosis, Liver Impairment, Biochemical Markers

PE-11

Introducing Robot-Assisted Liver Resection in a Single-Surgeon Program: A Team-Based Approach and Early Outcomes

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Aims: Robot-assisted liver resection (RLR) has been increasingly adopted at high-volume centers with multiple specialized surgeons. However, evidence regarding the safe implementation of RLR in regional hospitals operating under a single-surgeon-led hepatobiliary program remains limited. We initiated an RLR program in October 2024 at a regional referral center staffed by only one hepatobiliary surgeon. This study aimed to evaluate team-building strategies designed to compensate for this structural limitation and to assess short-term outcomes during the introductory phase.

Methods: A structured, stepwise implementation strategy was employed to support a single-surgeon-led RLR program. This included (1) shared review of surgical videos among assistants, operating room nurses, and clinical engineers; (2) standardized preoperative simulation and postoperative feedback; (3) optimization of equipment, instrument, and cable layouts; and (4) supervised introduction under external proctoring. Consecutive patients undergoing RLR between October 2024 and December 2025 were retrospectively analyzed.

Results: A total of 27 patients were included (18 men and 9 women), with a median age of 72 years (range, 53–88). Procedures consisted of lobectomy (n=4), sectionectomy (n=8), subsegmentectomy (n=8), and partial hepatectomy (n=7). The median operative time was 372 minutes (range, 202–670), and the median blood loss was 59 mL (range, 3–507). The median postoperative hospital stay was 8 days (range, 5–21). No Clavien–Dindo grade $\geq$ III postoperative complications, including bile leakage, were observed.

Conclusions: By identifying RLR-specific challenges and addressing them through team-based improvements, RLR can be safely introduced even in a regional general hospital setting.

Keywords: Liver, Hepatectomy, Robot-Assisted Liver Resection

PE-13

Diaphragmatic Hernia after Living Donor Hepatectomy: Clinical Burden, Risk Factors, and Exploratory Biomarker Associations

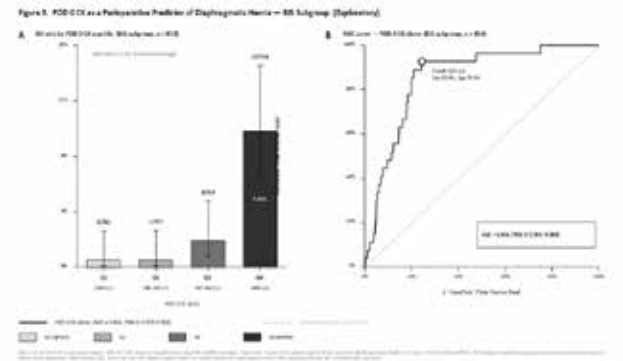
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Aims: Acquired diaphragmatic hernia (DH) after living donor hepatectomy (LDH) is an uncommon but clinically relevant late complication. The bipolar irrigated sealer (BIS) has been identified as a risk factor, yet the mechanism remains hypothetical and no perioperative biomarker has been evaluated.

Methods: We conducted a retrospective cohort study of 7,620 consecutive living liver donors who underwent LDH at a single high-volume center (2008–2024). The primary endpoint was CT-confirmed DH requiring surgical repair. Logistic regression was performed in the full cohort and a BIS-user subgroup (n = 854). Same-day postoperative creatine kinase (POD 0 CK) was evaluated as an exploratory perioperative marker.

Results: Among 7,620 donors, 39 (0.51%) developed DH. DH rates were higher in BIS users (27/854; 3.16%) than non-BIS users (12/6,766; 0.18%). Of 39 cases, 10 (25.6%) were emergencies; strangulation occurred in 3 (7.7%) and bowel resection in 2 (5.1%). BIS use was the strongest independent risk factor (adjusted OR, 15.92; 95% CI, 8.00–31.69; $P < 0.001$). In the pre-BIS era, CK showed no association with DH ($P = 0.69$). In BIS users, POD 0 CK demonstrated a dose-response gradient across quartiles (P -for-trend < 0.001) and strong discriminative ability (AUC, 0.854; 95% CI, 0.783–0.908).



Conclusions: Donor DH is uncommon but clinically significant. BIS use was the strongest independent risk factor, although temporal overlap with calendar year precludes definitive attribution. POD 0 CK showed a dose-response association with

DH in BIS users absent in the pre-BIS era; these findings are hypothesis-generating and require prospective validation.

Keywords: Diaphragmatic Hernia, Living Donor Hepatectomy, Bipolar Irrigated Sealer, Creatine Kinase

18. Others, Surgical

PE-5

Management Patterns and Outcomes of Liver Abscess in a Tertiary Care Center: Experience from 108 Patients

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Aims: Liver abscess continues to be a common surgical infection in tropical regions, with varied clinical severity and outcomes. This study analyzes the clinical profile, management strategies, and outcomes of patients treated for liver abscess at a tertiary care center.

Methods: A retrospective analysis of 108 consecutive patients with liver abscess was performed, evaluating demographics, treatment modality, and clinical outcomes.

Results: Among 108 patients, 97 (89.8%) were male and 11 (10.2%) were female. The majority belonged to the 50–69 year age group (58.3%). Interventional management was required in most cases, with 96 patients (88.9%) requiring antibiotics combined with percutaneous aspiration and/or catheter drainage. Conservative management with antibiotics alone was successful in 6 patients (5.6%). Emergency laparotomy was required in 7 patients (6.5%), predominantly for complicated or ruptured abscesses. Residual abscess on follow-up imaging was the most common outcome, observed in 61 patients (56.5%). Abscess rupture occurred in 25 patients (23.1%). Recurrence was documented in 3 patients (2.8%). Overall mortality was 7.4% (n = 8), largely associated with complicated disease at presentation.

Conclusions: Most liver abscesses require image-guided intervention in addition to antibiotics. Residual abscess and rupture remain frequent despite contemporary management, and mortality remains substantial in complicated cases, emphasizing the importance of early diagnosis and timely intervention.

Keywords: Liver Abscess, Management, Outcomes

PE-6

Mapping Cellular Proportion Shifts Using Imaging Biomarkers to Develop a Cell Composition-Based Staging System That Informs Actionable Surgical and Device Guidelines for the Prevention of POPF

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Aims: We present a conceptual model that will be empirically validated in the next phase of research. Microscopic changes in cellular composition alter tissue physics, which becomes detectable on imaging before gross disease. Disease-specific cellular proportion shifts, including reductions in acinar cells and increase in Duct-like cells via acinar-to-ductal metaplasia (ADM) and Stromal cells (Desmoplasia), are already established in PDAC. It begins as a shift in lineage proportion, not tumor. Similarly, there is an increase in Stellate cells, Extracellular matrix, and Immune cells noted in Chronic Pancreatitis. On the other hand, PNETs arise from the clonal expansion of a single endocrine subtype, disrupting Islet cellular ratios. Hence, the earliest controllable variable is “Cellular proportion,” which can serve as a perfect target for Pre-emptive intervention.

Methods: Microscopic cellular shifts produce reproducible macroscopic imaging signatures before overt disease. High-value composite markers like Pancreatic Volume/Density Index (PVDI), Duct-to-Parenchyma ratio, and Regional stiffness heterogeneity can be studied. Artificial Intelligence-based morphometry can be used to identify biological tipping points and delineate reversible and irreversible thresholds in the pancreas, including acinar cell loss, Fibrosis, ADM, etc. A cell-composition-based staging system specific to various anatomic regions of the pancreas can aid in Surgical strategies. Even a micron-scale, region-specific intervention can alter the disease trajectory.

Results: The framework is designed to 1) Target zones of proportion shift, not whole organ; 2) Intervene before fibrosis locks architecture; 3) Design for enzyme-rich vs enzyme-poor regions; 4) Respect microvascular density of islets.

Conclusions: Pancreatic disease begins when cellular ratios drift, becomes irreversible when thresholds are crossed, and is best treated when interventions are guided by cell-composition-aware imaging and strategy.

Keywords: Cellular-Proportion, PVDI-Pancreatic Volume/Density Index, Duct-To-Parenchyma Ratio

PE-7

A Case Report: Intraoperative Discovery of a Left-Sided Gallbladder: The Role of Preoperative Imaging

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Aims: A left-sided gallbladder (LSG), or sinistroposition of the gallbladder, is a rare anatomical variant in which the gallbladder is located to the left of the falciform ligament beneath the left hepatic lobe. It is usually discovered intraoperatively and may present surgical challenges.

Methods: We report the case of a 59-year-old female with known asymptomatic cholelithiasis who developed biliary colic and underwent laparoscopic cholecystectomy. Intraoperatively the gallbladder was found to be located to the left of the falciform ligament beneath segment III of the left lobe of the liver, consistent with true left-sided gallbladder. Port placement was modified, the gallbladder was safely dissected and removed via the umbilical port without complication.

Results: The anomaly’s rare nature, its difficulty in preoperative diagnosis, and its potential for associated biliovascular anomalies underscore the need for operative awareness and adaptability.

Conclusions: Awareness of LSG is important for surgeons performing cholecystectomy. Safe laparoscopic removal is feasible with appropriate modifications and careful dissection.

Keywords: Left-Sided Gallbladder, Laparoscopic Cholecystectomy, Sinistroposition

THE LIVER WEEK 2026

Turning Evidence into New Standards in Liver Disease Care
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AUTHOR INDEX



A	
Abdelmoety, Amr Aly	909
Abdelmoety, Hoda	909
Abdillah, Falakh	833
Abdu, Fuad A.	853, 855
Abdulbasit, Omira	953
Abdurrahman, Naufal	862
Abdykadyrov, Mazhit	818
Abe, Kazumichi	795
Abe, Masanori	795
Abou-Alfa, Ghassan K.	666
Abramov, Frida	692, 732
Abrashev, Erlan	818
Adame, Lilian	731
Adelipour, Maryam	918
Adisasmitha, Michael	695
Afroz, Shaikh Muna	936
Aftab, Soyeb	864
Agarwal, Kosh	731, 732
Ahmed, Mohamed Sherif Ali	768, 819, 955
Ahn, Chang Ho	892
Ahn, Chul-Soo	742, 933, 962
Ahn, Hye Ri	697, 894, 896
Ahn, Jhii-Hyun	672
Ahn, Sang Bong	794
Ahn, Sang Hoon	732, 748, 756, 778
Ahn, Sung Ho	685
Ahn, Young Hyeon	862
Aidar, Zulkharnay	923
Aigerim, Nurgaliyeva	923
Aita, Ada	767
Akil, Fardah	835
Alam, Seema	905
Al-Hinai, Raja	796
Ali, Asgar	938
Alifu, Jiasuer	853, 855
Alkhoury, Naim	746
Al-Nasseri, Amira	796
Alves, Gustavo Vasconcelos	666
Amare, Eden Demere	946
A, Mehndiratta	870
Am, Metwally	856
Anderson, Mark	731
Anekawati	866
Ang, Dante	913
An, Jihyun	680, 729
Anjum, Baby	872
Anmol, Anmol	905
An, Nayoung	811, 824, 880
Anouti, Ahmad	807
Anstee, Quentin M.	746
Aprigliano, Michele Pietro	894
Arab, Juan Pablo	807
Arailym, Nurzhanova	761
Arai, Yasuaki	666
Arcilla, Crisostomo	963
Aripova, Tamara	940
Ariyachet, Chaibaboot	848, 882

Arora, Sahil	904
Arslan, Nurgaliyev	871, 923
Arulalan, Surendar	925
Askarov, Takhir A.	805
Askarov, Tohir	940
Assainova, Arailym	922
Auttapricha, Thanida	807
Awalekar, Mrunal	741
Ayu, Putri	943
Ayush, Enkh-Amar	873
B	
Babboni, Serena	741
Bachtiar, Rini	835
Badamjav, Tegshjargal	788, 858
Bae, Chan joong	909
Bae, Chan Joong	907, 908
Bae, Eun Ju	775
Bae, Jun Seo	759, 895, 899
Baek, Geum Ok	811, 824, 880
Baek, Je-Hyun	718, 910
Baek, Yang Hyun	711, 715, 907, 908, 911
Bae, Seo Eun	778
Bae, Si Hyun	676, 686, 691, 694, 712, 717, 723, 751, 771, 772, 791, 804, 811
Bae, Songmee	749
Bae, Sun Hyun	816
Bagdat, Alatayev	919, 957
Baig, Asma	840
Baik, Jiyoung	762, 931
Baik, Soon Koo	758, 800, 828
Bair, Ming-Jong	844
Bajaj, Jasmohan	834
Balakrishnan, Dinesh	741
Ballena-Caicedo, Jhosmer	851
Balzano, Emanuele	741
Banh, Hieu	913
Bao, Yuntao	725, 750, 763, 885
Baral, Shankar	863
Baral, Suman	956
Basta, Giuseppina	741
Batbaatar, Lkhagvasuren	864
Batbold, Chuluunbileg	788
Batdelger, Dulguun	786, 788, 873
Batsaikhan, Batbold	788, 858
Batsaikhan, Chuluunbileg	858
Bayarnyam, T.	845
Baymakhanov, Bolatbek	677, 818
Ba, Yuntao	699
Bedossa, Pierre	746
Bhadoria, Ajeet Singh	870, 874
Bhadoria, Pooja	874
Bhatt5, Rajendra Dev	786
Bhattad, Utkarsh	834
Bhattarai, Anand	956
Bhattarai, Ganga Sagar	878
Bhattarai, Sushant	753

Biasiolo, Alessandra	767, 906
Bindal, Vasundhra	944
Biswas, Sayak	864
Biziya, Nyam	785, 829, 864, 888
Blatt, Lawrence	731
Blatt, Lawrence M.	731
Bong, Yunseo	758
Bouattour, Mohamed	666
Bowlus, Christopher L.	675
Bronzoni, Jessica	741
Bugianesi, Elisabetta	685, 746
Bui, Loc Quang	813
Burk, Caroline	799
Buti, Maria	732
Byrne, Christopher D.	708
Byrzhanaev, Nurzhan	677
Byun, Jihyo	737, 875
Byun, Jun Ho	875
Byun, Mi Young	712, 717

C	
Cagnin, Silvia	767, 906
Cai, Jinzhen	931
Cai, Zixin	856
Cali, Anna	685
Carrai, Paola	741
Carroll, Susheela	675
Catalano, Gabriele	741
Catameo, Elizabeth	963
Chae, Seung-Hoon	736
Chae, Yoon Gi	810
Chaiyakunapruk, Nathorn	688
Cha, Jinhye	866
Cha, Jung Hoon	712, 717, 751
Chakrabarti, Sarthak	834
Cha, Min Su	752
Chan, Cody	827
Chand, Arun Bahadur	786, 843
Chanda, Sushmita	731
Chang, Chun-Chao	844
Chang, Hye-Sook	792
Chang, Kai-Chi	708
Chang, Te-Sheng	844
Chang, U Im	675, 694, 738, 791
Chang, Yoosoo	708
Chang, Young	713, 739, 815, 866, 912
Chan, Kristy	799
Cha, Ra Ra	900
Chaudhari, Archana	749
Cha, Yeonwoo	840
Chen, Chi-Yi	844
Chen, Chun-Ting	844
Cheng, Chien-Yu	844
Cheng, Feng	776
Cheng, Pin-Nan	844
Chen, Guanzi	889
Chen, Guei-Ying	844

Cheng, Yu	677, 954
Cheng, Zuobin	677, 954
Chen, Jun-Ze	714
Chen, Li	694
Chen, Shilian	750
Chen, Xianxiang	699, 725
Chen, Yuying	730
Cheong, Jae Youn	673, 718, 780, 811, 824, 880, 910
Cheon, Young-Hoon	789
Cheuk, Veronica	799
Che, Wenliang	853, 855
Chiacchio, Pasquale	894
Chien, Shih-Chieh	708
Chlabicz, Matgorzata	868
Cho, Byungchul	710
Choe, Jaewon	792
Cho, Eun Ju	681, 682, 698, 711, 716, 734, 736, 737, 743, 772, 919
Cho, Eun Young	757
Cho, Hee Sun	673, 691, 712, 717, 723, 751, 766, 771, 805, 811
Cho, Hyeon-Yeol	749
Cho, Hyo Jung	673, 697, 780, 887, 894, 896
Cho, Hyun Chin	907, 908
Choi, Dongho	695, 752, 763, 803, 929, 946
Choi, Eunho	701, 702, 765, 810, 918
Choi, Eun-Kyoung	890
Choi, Eun-Woo	697
Choi, Gwang Hyeon	660, 675, 689, 691, 735, 736, 789, 918
Choi, Gwang Hyun	721
Choi, Gyu-Seong	679, 683, 762, 931
Choi, Hee Sun	903
Choi, Hei Gwon	696, 766, 888
Choi, Ho Joong	667, 696, 808
Choi, Hwa Young	721, 790
Choi, Hyeonho	800
Choi, In Woo	909
Choi, Jaehyun	689, 703
Choi, Jieun	793
Choi, Jimi	866
Choi, Ji-Mi	907
Choi, Jonggi	667, 689, 710
Choi, Jong Young	661, 694, 808
Choi, Jung Woo	900
Choi, Man Ho	737
Choi, Minha	933, 962
Choi, Miyoung	691, 815, 829, 912
Choi, Moon Seok	698
Choi, Murim	754
Choi, Myeung Gi	853
Choi, Na Ryung	687
Choi, Sang Hyun	729, 901, 914
Choi, Seo Hee	816
Choi, Sung Chul	792
Choi, Sung Eun	737, 875
Choi, Won-Il	704
Choi, Won-Mook	660, 667, 672, 689, 691, 710, 722
Choi, Yoo Jin	930

Choi, Yoonsun	762
Choi, Youngrok	667
Choi, Young Rok	678, 728, 930
Choi, YoungRok	674, 697, 729, 736
Choi, Yun Mi	804
Cho, Jai Young	679, 719
Cho, Jeong-Yeon	688
Cho, Jinhong	746
Cho, Juhee	692
Cho, Ju-Yeon	787
Cho, Kyung Joo	880
Cho, Mi-La	661, 808
Chong, Lee-Won	844
Chon, Hye Yeon	675
Chon, Young Eun	691, 722, 735, 860
Cho, Seok Keun	712, 717
Cho, Seon	794
Cho, Seong Hyeon	901
Cho, Sung Bum	841, 909
Cho, Sung-Bum	715, 907, 908, 911, 916
Cho, Sung Woo	751
Cho, Yong Kyun	708
Cho, Young Youn	660, 687, 688, 690, 720, 795
Cho, Yuri	682, 815, 880, 912
Chuang, Wan-Long	844
Chung, Clive	799
Chung, Clive Yik Sum	879
Chung, Katherine Po Sin	737, 875
Chung, Sung Won	680, 681, 710, 734, 739
Chun, Ho Jong	771
Chun, Sung Won	728
Chun, Sun Young	907, 908, 911
Ciaccio, Antonio	894
Cirillo, Giulia	741
Ciulli, Cristina	894
Cloherly, Gavin	731
Cotsoglu, Christian	894
Cotter, Thomas G.	807
Crittenden, Daria B.	675, 799
Cruz, Earnest Caizer Dela	740
Cruz, Meynard Keynes Dela	740
Cui, Le	883, 887
Cuy, Stevan	953

D

Dai, Chia-Yen	788, 844
Damayanti, Anindya Amanda	926
Dang, Quoc	951
Danpanichkul, Pojsakorn	807
Daramjav, Dolgion	858
Dashjamts, Gantogtokh	788, 858
Dato, Fabiola Di	798, 827
Daud, Nu'man AS	835
Dave, Vimal	666
Da Young Lee	877
Dechaphunkul, Arunee	666
Deng, Mingming	830, 831

Deng, Pengzhan	889
Derizal	843
Devi, Anjla	840
Díaz, Luis Antonio	807
Diep, Luu Thi Minh	812
Dimitri, Tzoi	919, 957
Diwedi, Ved Prakash	890
Do, Dinh Toi	820, 937
Do, Hayeon	762, 931
Dondov, Ganchimeg	788
Dong, Chun-Qiang	714
Donghia, Rossella	767
Dong, Kun	714
Doshanov, Maksat	677
Doszhan, Ainur	926
Do, Viet Anh	820, 937
Duan, Shuangdi	796
Dubatówka, Marlena	868
Dubey, Harshita	829, 864
Du, Xinyao	784

E

Elbeshbeshy, Hany	799
Elmesov, Aset	806
Elisei, Federica	894
Elkasaby, Mohamed Hamouda	768, 819, 955
Elston, Robert	666
Enkhbayar, Doljinsuren	785, 829, 864, 888
Erdenechuluun1, Munkh-Uyanga	873
Erinjeri, Joseph P.	666
Eun, Hyuk Soo	696, 737, 766, 770, 888
Eun, Jung Woo	811, 824, 880

F

Fan, Jia	666
Fan, Yin	911
Fauzan, Rahmat	843, 943
Feng, Gangping	796
Fogliati, Alessandro	894
Fortney, Tiffany	731
Fraessdorf, Mandy	746
Frenette, Catherine	675, 732
Fujii, Hideki	756, 829
Fujishiro, Mitsuhiko	814
Funahashi, Nobuaki	882
Fung, Scott K.	732

G

Gaini, Zulkharnay	871
Ganbayar, Oyunbold	786, 788
Gane, Edward	692, 731
Gani, Kuttymuratov	957
Gao, Bowen	798, 827
Gao-Feng, Zha	764
Gao, Wei	750, 885

Garancini, Mattia	894
Geissler, Rene	731
George, Dalene Ephme Ben	860
George, E. Ben	796
Ghimire, Asmita	842
Ghinolfi, Davide	741
Ghoshal, Uday Chand	834
Gi-Ae	691
Giang, Nguyen Truong	778
Giannelli, Gianluigi	767
Goenka, Mahesh Kumar	834
Gofton, Cameron	840
Goh, Myung Ji	698
González-Carmona, Maria A.	666
Gopalakrishnan, Unnikrishnan	741
Go, Yunjin	885
Grammatikopoulos, Tassos	798, 827
Gregori, Dario	906
Guellil, Abdelali	952
Guerra, Pietro	767, 906
Gu, Jun	934, 935
Gu, Minkyung	758
Guo, Qingping	817
Guo, Yabing	666
Guo, Zhenya	750
Gupta, Pooja	904
Gupta, Rohit	870
Gupta, Santosh Kumar	747
Gupta, Subash	806
Gupta, Subhash	740
Gu, Shengxin	934, 935
Gwak, Geum-Youn	692, 698, 792
Gwon, Suk Min	762, 931

H

Habibah, Ulil Albab	776, 878
Haceatrean, Alexei	731
Ha, Doan Thi Ngoc	812
H, Al Sabbah	856
Hamal, Deependra	878
Hamano, Ikumi	961
Hamdani, Irwan Deputra	953
Ham, Hoi Nguyen	939, 945
Hammad, Noha	868
Han, Chang In	804
Han, Chang Yeob	746, 775
Han, Da-Min	779
Han, Eui Soo	696
Han, Ga Won	673
Han, Ho-Seong	679, 719
Han, Hyein	711
Han, Jae Min	875
Han, Jae Mo	691, 723, 811
Han, Jaryung	928
Han, Ji Eun	673, 780
Han, Ji Hee	900
Han, Ji Su	847

Han, Ji Won	667, 673, 691, 694, 712, 715, 723, 729, 738, 743, 766, 769, 771, 772, 774, 787, 791, 805, 808, 811, 902, 903, 919
Han, Ji-Won	660
Han, Sangbin	667
Han, Seul Ki	672, 719, 739, 758, 800, 801, 828, 833
Han, Seungbong	709
Han, Yong-Hyun	704, 779
Han, Yong Kwon	703
Han, Young Seok	674, 928
Han, Yujin	730
Ha, Sang Yun	683
Hassan, Atef A.	768, 819, 955
Ha, Tae-Yong	742, 933, 962
Ha, Yeon Jeong	801
Ha, Yeonjung	739, 804, 860
He, Huifen	856
Helmizar, Roland	952
Hendrianus, Hendrianus	953
Heng, Xia	764
Heo, Jeong	666, 692, 715, 721, 799, 907, 908, 911
Heo, Mun Haeng	801
Heo, Nae-Yun	865
Heo, So Mi	892
Heo, Subin	672, 729, 901
He, Qiang	920
Herbert, Steven	953
He, Songqing	725, 750, 763, 796, 817, 885, 889, 911
He, Yimiao	898
Hieu, Le Trung	858, 874
Hieu, LE Trung	942, 958
Hieu, Nguyen Van	812
Hirschfield, Gideon M.	799
Ho, Gwo Fuang	666
Hong, Charmgil	673, 718, 780
Hong, Doo Pyo	824
Hong, Geun	674
Hong, Hyeyeon	689
Hong, Jiwon	697, 885, 887
Hong, Jung Yong	683
Hong, Suk Kyun	667, 697, 728, 736, 930
Hong, Su young	697
Hong, Su Young	678, 728, 930
Hong, You-Jung	775
Hong, Young Mi	715, 907, 908, 911, 916
Hosseini-Tabatabaei, Azadeh	746
Hou, Baohua	765
Hou, Jinlin	666, 732
Hsieh, Tsai-Yuan	844
Hsu, Yao-Chun	733
Hsu, Yu-Ting	847
Huang, Chia-Sheng	844
Huang, Chienwei	844
Huang, Chung-Feng	844
Huang, Jee-Fu	708, 844

Huang, Kai-Yong	714	Jang, Heejoon	660, 754
Huang, Mingrong	859	Jang, Jae Young	713, 733
Huang, Qiongguang	796	Jang, Jeong Won	673, 691, 694, 696, 712, 723, 724, 738, 743, 766, 771, 772, 774, 787, 791, 808, 811, 903, 919
Huang, Shang-Chin	708		
huang, Shanzhou	765	Jang, Jinah	763
Huang, Xiaohong	798, 827	Jang, Jung Eun	691, 723, 811
Huang, Xiaolun	881	Jang, Og-Jin	789
Huang, Yi-Hsiang	844	Jang, Se Young	703
Hudugur, Swamy Rajesh	947, 950, 951	Jang, Sungjun	810
Hu, Haoran	776	Jang, Young	801
Hu, Hong-Tao	666	Janssen, Harry L.A.	732
Hu, Jui-Ting	844	Jaroszewicz, Jerzy	868
Hung, Chao-Hung	844	Jekle, Andreas	731
Hung, Nguyen Kieu	778	Jeong, Byung-Kwan	704
Hur, Junho	695	Jeong, Heeseo	718
Hur, Moon Haeng	660, 667, 681, 682, 691, 698, 711, 716, 720, 734, 736, 739, 772, 815, 912	Jeong, Heo	675
		Jeong, Hyobin	689, 703
Hu, Yu	692	Jeong, I-Ji	836
Hwang, Hyojin	918	Jeong, Jaehong	667, 690, 748
Hwang, Inseok	686	Jeong, Jae-Uk	909
Hwang, Jae Seok	852	Jeong, Jae Yoon	687, 791
Hwang, Jun Seong	865	Jeong, Jin Gyo	672
Hwang, Sang Youn	715, 896, 907, 908, 911, 915, 916	Jeong, Joonho	907, 908, 911, 916
Hwang, Shin	742, 915, 933, 962	Jeong, Joon Ho	715
Hwang, Woochang	689	Jeong, Sook-Hyang	675, 721, 789, 918
Hwang, Yeongseok	729	Jeong, Soung Won	713
Hwang, Youngwon	674	Jeong, Su Jin	663
Hyun, Dongho	916	Jeong, Won-Il	737, 875
Hyun, Shin Ji	929	Jeong, Woo Kyoung	683
		Jeong, Yewon	701
		Jeong, Yujin	720
		Jeong, Yunju	661, 808
		Jeon, Hankyu	900
		Jeon, Jangsu	737
		Jeon, Ki Jung	915
		Jeon, Sae-Bom	885
		Jeon, So Young	685
		Jeon, Sumin	930
		Jeon, Sun Kyung	857
		Jeon, Wan	896, 915
		Jhun, Joo Yeon	661
		Jia, Guang	924
		Jia, Liu	764
		Jiang, Yuanxi	825
		Jian, Yong-Yuan	714
		Jie, Yusheng	889
		Jin5, Ju young	703
		Jin, Byung Chul	840
		Jin, Songwan	763
		Jin, Young-Joo	675, 839, 841
		Ji, Piyou	677
		Ji, Zhili	921, 924
		Jo, Ae Jeong	686
		Jo, Hye Jin	746
		Jo, Hyeonbin	698
		Jo, Hye-Sung	678, 930
		Jo, Min Kyoung	701
		Joo, Dong Jin	663, 809

I

Ibekenov, Onlasyn	677, 818
Idilman, Ramazan	660
Ilfa, Farah Miftakhul	865
Ilyasov, Nurbek	926, 927
Imai, Norihiro	708
Imajo, Kento	829
Im, Jung Woo	915
Investigators	668
Irzaq, Muhammad	948
Ishii, Isao	703
Ishikawa, Ozora	882

J

Jacobson, Ira M.	732
Jad, Beena	864
Jae, Won	907, 908
Ja Hyun Koo	877
Jang9, Eun Sun	815, 912
Jang, Byoung Kuk	852
Jang, Byungki	890
Jang, Byung Kuk	791
Jang, Eun Sun	680, 721, 736, 789, 918
Jang, Gibong	703
Jang, Hayoung	703

Jang, Heejoon	660, 754
Jang, Jae Young	713, 733
Jang, Jeong Won	673, 691, 694, 696, 712, 723, 724, 738, 743, 766, 771, 772, 774, 787, 791, 808, 811, 903, 919
Jang, Jinah	763
Jang, Jung Eun	691, 723, 811
Jang, Og-Jin	789
Jang, Se Young	703
Jang, Sungjun	810
Jang, Young	801
Janssen, Harry L.A.	732
Jaroszewicz, Jerzy	868
Jekle, Andreas	731
Jeong, Byung-Kwan	704
Jeong, Heeseo	718
Jeong, Heo	675
Jeong, Hyobin	689, 703
Jeong, I-Ji	836
Jeong, Jaehong	667, 690, 748
Jeong, Jae-Uk	909
Jeong, Jae Yoon	687, 791
Jeong, Jin Gyo	672
Jeong, Joonho	907, 908, 911, 916
Jeong, Joon Ho	715
Jeong, Sook-Hyang	675, 721, 789, 918
Jeong, Soung Won	713
Jeong, Su Jin	663
Jeong, Won-Il	737, 875
Jeong, Woo Kyoung	683
Jeong, Yewon	701
Jeong, Yujin	720
Jeong, Yunju	661, 808
Jeon, Hankyu	900
Jeon, Jangsu	737
Jeon, Ki Jung	915
Jeon, Sae-Bom	885
Jeon, So Young	685
Jeon, Sumin	930
Jeon, Sun Kyung	857
Jeon, Wan	896, 915
Jhun, Joo Yeon	661
Jia, Guang	924
Jia, Liu	764
Jiang, Yuanxi	825
Jian, Yong-Yuan	714
Jie, Yusheng	889
Jin5, Ju young	703
Jin, Byung Chul	840
Jin, Songwan	763
Jin, Young-Joo	675, 839, 841
Ji, Piyou	677
Ji, Zhili	921, 924
Jo, Ae Jeong	686
Jo, Hye Jin	746
Jo, Hyeonbin	698
Jo, Hye-Sung	678, 930
Jo, Min Kyoung	701
Joo, Dong Jin	663, 809

Joo, Ijin	857
Joo, Sae Kyung	754
Joo, Young-Eun	909
Jo, Seo Jeong	746
Jo, Sung Nam	789
Jothimani, Dinesh	760
Joung, Hyunchae	793
Ju, Cho Eun	667
Jucov, Alina	731
Jun, Dae Won	685, 686, 688, 689, 690, 703, 708, 756, 794, 795, 829
Jung, Chung Hyun	758, 828
Jung, Dong-Hwan	674, 742, 762, 933, 962
Jung, Hyun Sun	811, 824, 880
Jung, Jinhong	681
Jung, Jooyi	709
Jung, Jung Hyun	800
Jung, Jung hyung	672
Jung, Kyung Yun	695
Jung, Narae	880
Jung, Seong Won	801
Jung, Sungbin	689
Jung, Wonju	701
Jung, Yong Jin	720
Jung, Yong Jun	901, 914
Jung, Young Kul	701, 702, 739, 765, 801, 810, 907
Jung, Young-Kul	787, 793
Jung, Yun Kyung	946
Ju, Young Seok	697, 704
Jwa, Eun-Kyoung	836, 915

K

Kakenov, Erken	922
Kaliaskarova, Kulpash	761
Kalra, Rupinder	890
Kamada, Yoshihiro	756
Kamiński, Karol	868
Kane, Pauline	827
Kang, Danbee	692, 792
Kang, Dayoon	763
Kang, Hyun-Cheol	681, 816
Kang, Keon Wook	754
Kang, Minseok	929
Kang, Seong Hee	701, 702, 739, 765, 801, 810, 907
Kang, Seul-Ki	736, 781
Kang, Sungchan	802
Kang, Wonseok	698, 791
Kang, Woo-Hyoung	933, 962
Kang, Yeo Wool	711, 715, 907, 908, 911, 916
Kaniev, Shokan	677, 818
Kant, Ravi	874
Kao, Chien-Neng	844
Kao, Jia-Horng	732, 844
Kawaguchi, Takumi	708
Ke, Kai	796
Keldiyorova, Robiya	941
Keyal, Shruti	834

Khakoo, Salim I	667
Khandelwal, Rajat	834
Khanna, Rajeev	905
Khassenova, Malika	925
Khorolgarav, G.	845
Kim, A-Reum	929
Kim, Aryoung	792
Kim, Beom Kyung	748
Kim, Bo Hyun	660, 675, 680, 682, 691, 815, 912
Kim, Byung Ik	708
Kim, Byung-Woo	845
Kim, Chang Wook	694, 738, 771, 791
Kim, Changyeon	667, 734
Kim, Daekeun	763
Kim, Deok Gie	809
Kim, Deok-Gie	663, 667
Kim, Donghee	807
Kim, Donghwan	763
Kim, Dong Hwan	914
Kim, Dong-Sik	678, 773, 930
Kim, Dong Yun	748, 756
Kim, Dooyeon	697, 894, 896
Kim, Do Young	748, 756, 815, 912
Kim, Eunjeong	759, 895, 899
Kim, Ga-young	758
Kim, Gayoung	728, 930
Kim, Gi-Ae	660, 689, 709, 722, 739
Kim, Gil Hwan	775
Kim, Gun Ha	916
Kim, Haeryoung	815, 912
Kim, Hae Young	710
Kim, Hail	704
Kim, Ha Neul	696, 766, 888
Kim, Heeju	752
Kim, Hee Ju	763
Kim, Hee Yeon	738, 771, 787, 791
Kim, Hong Soo	713
Kim, Hui Gyeong	697, 894, 896
Kim, Hwi Young	687
Kim, Hye-Lin	688
Kim, Hyemi	880
Kim, Hye Seon	691, 723, 811
Kim, Hyeyoung	862
Kim, Hyobin	702, 765, 810
Kim, Hyo-Cheol	916
Kim, Hyojin	718, 910
Kim, Hyung-Don	815, 912
Kim, Hyung Joon	687, 688, 690, 720, 733, 795, 815, 912
Kim, Hyung Jun	915
Kim, Hyung Seok	880
Kim, Hyungsung	946
Kim, Hyun Je	703
Kim, Hyun Jin	900
Kim, Hyun Sung	703
Kim, In Hee	691, 722, 736, 781, 787, 840
Kim, In Soo	696, 766
Kim, Jae Eun	900
Kim, Jae-Yoon	728, 930

Kim, Jae Young	693	Kim, Seokhwi	892
Kim, Jae-Young	747	Kim, Seong Hun	840
Kim, Ja Kyung	675	Kim, Seong Je	865
Kim, Jeong Han	802	Kim, Seryoung	747
Kim, Jeongkwon	918	Kim, Seunghee	803
Kim, Jeong Min	849	Kim, Seung Up	688, 690, 708, 717, 748, 756, 791, 795, 880
Kim, Ji Hoon	701, 702, 733, 765, 810, 907, 918	Kim, Soon Sun	673, 718, 780, 811, 815, 824, 880, 910, 912
Kim, Jin	703	Kim, Soon-Young	674
Kim, Jin Dong	787	Kim, Su A	849
Kim, Jin Seoub	811	Kim, Suho	771, 903
Kim, Jin Sook	880	Kim, Sujin	697, 894, 896
Kim, Jin-Wook	918	Kim, Sung Eun	793
Kim, Jonghyun	685, 756	Kim, Sung-Eun	833, 890
Kim, Jongman	674, 679, 762, 931	Kim, Sung Hyun	812
Kim, Jong Man	667	Kim, Sung Min	836
Kim, Ju Hyun	803, 804, 810	Kim, Sung-Min	742, 933, 962
Kim, Jung Hee	675, 737, 793	Kim, Suyeon	849
Kim, Kang Mo	675, 710	Kim, Taehan	865
Kim, Ki Ae	801	Kim, Tae Hyun	816
Kim, Ki-Hun	661, 742, 893, 933, 962	Kim, Tae Hyung	691, 701, 702, 765, 810
Kim, Ki-Hun Kim	933	Kim, Won	685, 720, 746, 754
Kim, Ki-Hyun	909	Kim, W. Ray	708, 732, 827
Kim, Kungsik	695	Kim, Yeongshin	728
Kim, Kyeong Sik	763, 929	Kim, Yohan	695
Kim, Kyunga	674	Kim, Yoon Jun	660, 667, 675, 681, 682, 699, 711, 716, 720, 733, 734, 736, 743, 772, 919
Kim, Kyung-Ah	675, 721	Kim, Young Seok	675, 693, 713, 747, 757
Kim, Kyung Moon	668	Kim, Youngsoo	728
Kim, Kyung Sik	812	Kim, Young Suk	696, 766, 888
Kim, Kyurae	737, 875	Kim, Yujin	673, 780
Kim, Miji	946	Kim, Yun Jung	667
Kim, Mi-Kyung	852	Kim, Yun Soo	803, 804, 810
Kim, Mimi	688, 829	Kjær, Mette Skalslø	685
Kim, Mi Na	660, 748, 778, 815, 912	Kliers, Iris	685
Kim, Min Gu	701, 749	Koh, DaeHyun	781
Kim, Min Jeong	737, 875	Koh, Yang Seok	909
Kim, Min Kyoung	728, 930	Ko, Hyo Jung	933, 962
Kim, Min Kyung	810	Koh, Youngil	736
Kim, Min Na	754	Ko, Juhyeong	661
Kim, Minseob	678, 728, 930	Ko, Kyoung A	708
Kim, Min Seong	867	Kondo, Mayuko	814
Kim, Minsu	849	Kong, Gyeong Woon	763
Kim, Minsuk David	667, 716, 734	Kong, Lei	934, 935
Kim, Moon Young	672, 739, 740, 758, 787, 791, 800, 801, 828, 833	Koo, Ja Hyun	738, 779, 847, 853, 958
Kim, Myoung Soo	809	Korean Liver Cancer Study Group	915
Kim, Myung-gyu	758	Koshikawa., Naohiko	882
Kim, Nalee	683, 816	Kowdley, Kris V.	799
Kim, Namkug	729	Kown, Ye Ji	756
Ki, Moran	721, 790, 845	Ko, Yunmi	682, 720, 772, 839
Kim, Sang gyune	672	Kremer, Andreas E.	799
Kim, Sang Gyune	688, 690, 693, 708, 713, 740, 747, 757, 791, 795	Kudo, Masatoshi	666
Kim, Sang Hoon	933, 962	Kulkarni, Anand	834
Kim, Sang-Hoon	661, 773, 893, 933	Kulmaganbetov, Aidos	927, 937, 941
Kim, Sang Jin	674	Kumar, Ankush	943
Kim, Sang Kyum	737	Kumar, Hemanth	861
Kim, Sang Wook	840	Kumar, Maanasa Bhaskar Raj	962
Kim, Sejung	686		
Kim, Seok-Hwan	742, 773, 787, 791, 932		

Kumar, Mukesh	740	Lee, Hyejung	698, 734
Kumar, Pardeep	943	Lee, Hye Sun	685
Kumar, Ram	874	Lee, Hye Won	661, 667, 691, 748, 756, 778
Kumar, Rishav	949	Lee, Hyomin	695
Kuo, Hsing-Tao	844	Lee, Hyo Young	685, 686, 689, 691, 703, 735, 756, 794, 829
Kurash, Svetlana	761	Lee, Hyungmin	736, 781
Kustra, Robert	675	Lee, Hyun Woong	691, 723, 884
Kusuma, Susanto	835	Lee, Inho	762
Kuttymuratov, Gani	806, 919	Lee, In Joon	916
Kwak, Ji Yoon	900	Lee, In Seok	729
Kwon, Do Hoon	789	Lee, Jae Geun	663, 809
Kwon, Eunjoo	794	Lee, Jae-Geun	667
Kwon, Hyemi	708	Lee, Jaejun	676, 686, 694, 712, 713, 717, 724, 738, 771, 772, 774, 791, 794, 804
Kwon, Hyeon Uk	900	Lee, Jae Kyeong	701
Kwon, Jae Hyun	762, 915	Lee, Jae Min	900
Kwon, Jung Hyun	661, 675, 676, 680, 686, 691, 694, 722, 723, 787, 791	Lee, Jae Seung	739, 748, 791, 800, 801
Kwon, Kyung Min	799	Lee, Jae Young	763
Kwon, Mi Hyun	673, 751	Lee, Jeehye	802
Kwon, Minjeong	702, 765, 810	Lee, Jeong Ha	683
Kwon, Oh Sang	803, 804, 810	Lee, Jeong-Hoon	660, 667, 681, 682, 697, 711, 716, 720, 728, 734, 736, 743, 772, 919
Kwon, Seunghyun Lewis	736, 781	Lee, Jeong Min	857
Kyran, Eirini	798, 827	Lee, Jeong Seok	734
Kyzhyrov, Daulet	677, 818	Lee, Jin Suk	758, 828

L

Laia, Darius	833	Lee, Jin-Woo	839
Lai, Charlotte Jiaqi	887	Lee, Jisoo	747
Lal, Bikrant B	905	Lee, Jiwoo	804
Lampertico, Pietro	660	Lee, Ji Young	792
Lam, Sissi Yam Yuet	879	Lee, Jonghyun	685, 689, 756, 829
Lang, Ren	932	Lee, Jong Hyun	686
Lan, Yi	856	Lee, Jong Woo	915
Lapitan, Marie Carmela	913	Lee, Joo Ho	860
Lawitz, Eric J.	746	Lee, Joon Hyeok	698, 699, 733, 815, 912
Lee, Aejin	885	Lee, Jooyeon	866
Lee, Ahlim	675, 738, 791, 804	Lee, June Sung	733
Lee, Boram	679, 719	Lee, Jung Ho	703
Lee, Chae Eun	752, 763	Lee, Jung Il	884
Lee, Chang Hun	691, 736, 775, 781, 840	Lee, Jungkuk	841
Lee, Danbi	710	Lee, Jungnam	841
Lee, Dong Ho	716, 729, 755	Lee, Jun Hyuk	685
Lee, Dong Hyeon	720, 754	Lee, Jun-Hyuk	794
Lee, Do Yup	793	Lee, Kangin	763
Lee, Eui Jin	738	Lee, Kwangwoo	737
Lee, Eunjin	762, 931	Lee, Kwang Woo	875
Lee, Eunmi	875	Lee, Kwang-Woong	667, 678, 697, 728, 729, 736, 930
Lee, Gil Won	805	Lee, Kwan Sik	860
Lee, Hae Lim	675, 691, 723, 738, 771, 791	Lee, Kyeong Geun	695
Lee, Hae Won	679, 719	Lee, MeiHsuan	844
Lee, Hae-Won	773	Lee, Minjong	815, 912
Lee, Han Ah	660, 687, 688, 690, 691, 708, 720, 722, 735, 739, 756, 795, 800, 801, 815, 912	Lee, Min Woo	683
Lee, Han Chu	710	Lee, Mi Ra	758, 828
Lee, Hanna	704	Lee, Mi Rin	894
Lee, Hoseo	958	Lee, Moonhyung	852
		Lee, Moonki	687
		Lee, Myeongcheol	692
		Lee, Na Young	847
		Lee, Pei-Lun	844

Lee, Ryunjin	893	Lim, Seng Gee	732
Lee, Sae Hwan	713, 862	Lim, Seng-Gee	666
Lee, Saeyoung	718, 910	Lim, Su Bin	697, 885, 887
Lee, Sang Soo	900	Lim, Yaeji	687
Lee, Seo Jin	778	Lim, Young-Suk	660, 689, 710, 722, 732
Lee, Seongjun	689, 703	Lim, Yueh Ni	666
Lee, Seung Ok	840	Lin, Chih-Lang	844
Lee, Seung Soo	672, 710	Lin, Chih-Lin	844
Lee, Seung Tae	663	Lin, Han-Chieh	844
Lee, Soon Kyu	661, 675, 676, 680, 686, 691, 722, 723, 724, 791, 808	Lin, Hong-Yi	667
		Lin, Su	667
Lee, Sung-Gyu	661, 742, 762, 933, 962	Lin, Tse-I	731
Lee, Sunghee	793	Lin, Zhiyong	699, 750, 885
Lee, Sung Won	691, 694, 723, 738, 771, 787, 791	Lin, Zhi-Yong	714
Lee, Taebum	892	Li, Shiqi	830
Lee, Tae Hee	770, 791	Li, Siyang	817
Lee, Terence Kin Wah	884	Li, Siyuan	846
Lee, TzongHsi	844	Liu7, Jie	799
Lee, Wan-sik	909	Liu, Chun-Jen	844
Lee, Won Hee	704	Liu, Liang	819
Lee, Wonjae	759, 899	Liu, Linglin	898
Lee, Won Jae	895	Liu, Liping	825
Lee, Yongseop	663	Liu, Lu	855
Lee, Yoonseok	803, 804, 897	Liu, Mingjiang	699, 750
Lee, Yoon Seok	810	Liu, Zhongshun	911
Lee, Young-Sun	702, 708, 719, 765, 810, 815, 907, 912, 918	Li, Yan	889
Lee, Young-Sun Lee1 Ha Seok	701	Li, Yulan	750
Lee, Youn Jae	754, 757, 801	Li, Yu - Lan	763
Lee, Yugyeong	888	Li, Yu-Lan	885
Lee, Yu Gyeong	766	L, Jeong-Hoon	699
Lee, Yujin	759, 895, 899	Lkhagva-Ochir, Oyungerel	786, 788
Lee, Yun Bin	660, 667, 681, 682, 689, 691, 698, 711, 716, 720, 734, 736, 743, 772, 919	Lkhagvasuren, Batbaatar	829
		Lo, Ching-Chu	844
Lee, Yun Chae	840	Long, Michelle T.	685
Lee, Yun Kyu	754	Long, Nguyen Cong	812, 834
Lee, Yu Rim	715, 719, 907, 908, 911, 916	Lonjid, Tulgaa	788, 858
Le, Kha	731	Lopez, Andrew	692
Lencioni, Riccardo	666	Lo, Regina	799
Lens, Sabela	660	Lorenzoni, Giulia	906
Le, Van Duy	820, 937, 939, 940, 945	Lou, Wenhui	819
Levy, Cynthia	799	LTH, Thu	944
Lewis, Dylan	827	Luong, Tuan Hiep	820, 937, 940
Liang, Aijun	879, 887	Luo, Xuan	798, 827
Liangpunsakul, Suthat	807	Lu, Xia	764
Liang, Yuan	776	Lv, Yongshuang	899
Liao, Jingyuan	830, 831		
Liao, Lijuan	889		
Li, Chunfeng	692		
Li, Jiani	692		
Li, Melody Yu Song	884		
Lim, Gyungsun	716		
Lim, Gyung Sun	667, 681, 734		
Lim, Jaehong	892		
Lim, Jihye	791, 833		
Lim, Jin Hong	884		
Lim, Joo-Hyun	779		
Lim, Joonoh	697		

M

Ma, Guangtao	699, 750
Mahanta, Prathyusha	861
Mahapatra, Chitaranjan	825
Maher, Salim	840
Maiorova, Evguenia	692
Mak, Lung-Yi	731
Mallick, Shweta	741
Mamo, Michael Girma	695
Manhas, Savrina	692
Manivannan, Gnaneshvar	949, 962

Mannobjonov, Pulatbek	941	Na, Hoyoung	866
Mantawil, Ameerah	953	Nair, Krishnanunni	741
Ma, Nuo	855	Nam, Gihhoon	702, 765, 810
Mao, Linfeng	911	Nam, Gi-Hoon	701
Mao, Xiaowen	694	Nam, Heechul	675, 722, 735, 738, 787, 791
Maras, Jaswinder Singh	890, 944	Nam, Hee Chul	691, 771
Marceau, Caleb	692	Nam, Hyeyoon	702, 765, 810
Marcellin, Patrick	732	Nam, Hyo Jin	710
Marpaung, Andra Zuhri	833	Nam, Soon Woo	661, 676, 680, 686, 694, 722, 791
Marsyanda, Rani	950	Narayanamenon, Ramachandran	741
Martinelli, Caterina	741	Nayar, Raghav	935
Martini, Andrea	767, 906	Nazerke, Seidakhmetova	923
Martin, Ross	692	Naz, Qulsoom	872
Maruf, Md Abdullah Al	892	Neff7, Guy W.	746
Ma, Shuoshuo	881	Neupane, Promish	842
Masuzaki, Ryota	814	Newsome, Philip N.	685, 746
Matas, David	872	Ng, Irene Oi-Lin	809
Mathew1, Babu	944	Ng, Jestlin	885
Mayo, Marlyn J.	799	Ng, Kwan Ming	887
Ma, Yun	798, 827	Ngoc, Nguyen Minh	812
McNally, Bridgette B.	827	Ng, Tung Him	879, 887
Meena, Kuldeep	864	Nguyen-Dinh, Song Huy	913
Meeral, Rahmath	861	Nguyen, Giang	777, 913
Mehndiratta, Amrita	870	Nguyen, Ham Hoi	820, 937
Merla, Sathya V	864	Nguyen, Hoa	906
Merla, Sathya Veera	829	Nguyen, Hung	913
Miao, Xiaolong	931	Nguyen, Thanh Khiem	820, 937
Min, Eun-Ki	663, 809	Nguyen, Trong	777, 913
Ming, Xuemei	869	Nguyet, Dinh Anh	944
M, Jamil	870	Niespolo, Rita	894
Mohammed, Abdul-Quddus	855	Ning, Qin	730, 784
Mo, Hongmei	692	N, Luhmann	870
Mo, Lien-Ray	844	Nokkeaw, Archittapon	882
Montagnana, Martina	767	Nomin, B.	845
Montoya, Fiorella E. Zuzunaga	851	Noureddin, Mazen	746
Monzonís, Xavier	666	Nundy, Samiran	870
Moon, Deok-Bog	661, 742, 762, 836, 933, 962	Nuraini, Chairun Nisa’	862
Moon, Sang Yi	711	Nurgaliyev, Arslan	922
Moon, Soobeen	697, 894, 896	Nurgaliyev, Yerlan	927
Mo, Zhaohong	796	Nur, Lyazzat	925
Mueller, Sebastian	825	Nurzhan, Bikhonov	919, 957
Muhan, Lü	859	Nyamaa, Bayarmaa	785, 888
Munkhtuvshin, Oyundelger	785, 829, 864, 888	Nyamtsengel1, V.	845
Murat, Sultan	922		
Musakhodjaeva, Diloram	873		
Musakhodjaeva, Diloram A.	805		
Musin, Nadiyar	806		
Muthiah, Mark D.	667		
Myltykbay, Rysmakhanov	923		
Myung, Eun	909		

N

Nabila	862
Na, Byeong-Gon	933, 962
Naganathan, Selvakumar	724, 740, 806, 934
Nagarajan, Raj Kumar	949, 962
Nahm, Ji Hae	884

O

Obi, Shuntaro	814
O, Diana Chui-Yee	809
Oh, Hyeonseung	849
Oh, Hyunwoo	708
Ohira, Hiromasa	795
Oh, Jaewoo	875
Oh, Joo Hyun	686, 794, 829
Oh, Jung Suk	771, 903
Oh, Myeong Hun	820, 946
Oh, Namkee	679, 762, 931
Oh, Rak-Kyun	932
Oh, Wonseok	718, 910

Okamoto, Takeshi 814
Oktasari, Silvi 833
on behalf of the Innovative Target Exploration of NAFLD (ITEN) consortium 754
on behalf of The Korean Acute onChronic Liver Failure (KACLiF) Study Group 833
on behalf of the SYNCHRONIZETM™-MASLD Committees 668
on behalf of the VCTE-based Liver Investigation Network (V-LINK) Study group 688, 690, 795
Østergaard, Laura Harms 685
Ov, Sudheer 741
Oyungerel, M. 845

P

Paik, Yong-Han 683, 698
Pamecha, Viniyendra 944
Pandey, Sushmita 944
Pang, Yanfang 807
Papatheodoridis, George 660
Parewangi, Muhammad Luthfi 835
Parikh, Kush S 949
Park, Boram 674
Park, Byung-Hyun 775
Park, Chan 909
Park, Chang Wook 918
Park, Chan Hee 686, 689
Park, Cheon-Soo 929
Park, Geon Woo 703
Park, Gil-Chun 742, 933, 962
Park, Hana 756, 792, 802
Park, Han Sang 679, 762
Park, Hanul 781
Park, Hee Chul 681, 683, 816
Park, Hee Jin 849
Park, Huiyul 686, 688
Park, Hye Jung 880
Park, Hye Won 792
Park, Jeayeon 680, 682, 720, 737, 743, 772, 919
Park, Jeong Hwan 754
Park, Jimin 685
Park, Ji-Won 675, 890
Park, Ji Yeon 852
Park, Jong-Eun 737
Park, Joo-Young 699, 734
Park, Jung-Bun 674
Park, Junghoan 857
Park, Junho 728
Park, Jun Yong 660, 667, 674, 685, 704, 748, 756, 880

Park, Juri 718, 910
Park, Kwon Moo 703
Park, Minae 757
Park, Minjeong 737
Park, Min Kyung 660, 721, 789, 918
Park, Min Seo 766, 805
Park, Mi-So 698
Park, Sang Hun 754

Park, Sang Hyuk 728, 930
Park, Seoeun 673, 780
Park, Seol Hee 758
Park, Seongyeol 697
Park, Seung Shin 737
Park, Soo Jin 708
Park, Soo Young 660, 688, 690, 708, 715, 791, 795, 907, 908, 911

Park, Soyeon 718, 737
Park, Sung Jae 754, 757, 801
Park, Sung Jun 860
Park, Sungwon 792
Park, Tae Jun 697
Park, Yeshong 679, 719
Park, Yewan 709
Park, Yewon 795
Park, Yong Kwang 749
Park, Yoon 845
Park, Young Joo 715, 721
Park, Young Joon 736
Park, Young Min 837, 838
Park, Youngsu 682, 698
Park, You Ri 703
Park, Yu Jin 663
Park, Yu Su 896
Parmar, Daxa 837
Patel, Saumya K. 837
Peinovich, Nadine 692
Peng, Binbin 832
Peng, Bo 714
Peng, Cheng-Yuan 844
Pernebayeva, Gulbanu 761
Petagna, Lorenzo 741
Petrucelli, Stefania 741
Pezzati, Daniele 741
Pham, Manh Duy 813
Piotrowski, Damian 868
Pokhrel, Saroj 863
Pontisso, Patrizia 767, 906
Poudel, Dipendra Nath 878
Poudel, Rekha 753
Pradhan, A 825
Praja, Rian Ka 826
Purevsod, L. 845
Purnamasari, Indri 917
Putriana, Nadira 960

Q

Qian, Chaosi 825, 846
Qi, Xin 675
Qi, Xingshun 667
Quang, VU Van 942, 958
Quarta, Santana 767

R

Rahmah, Zulfania 900, 959

Rahmawati, Mirza Aulia 833
Rahmi, Devi Yulia 948
Rai, Ankit 935
Rai, Shiba Kumar 786
Rajagopal, Siddharthan 963
Raja, Kalayarasan 949
Rajendiran, Theakarajan 962
Ranjan, Amar 829, 864
Rathore, Kaushal 935
Ratziu, Vlad 685, 746
Rawal, Rakesh M. 837
Reddy, Rajender 834
Rela, Mohamed 760
Ren, Zhenggang 666
R, Gairola 870
Rho, Hyunsoo 775
Rhu, Jinsoo 679, 762, 931
Richards, Christopher 692
Rifai, Amelia 835
Rinella, Mary 685
Ripamonti, Lorenzo 894
Rito, Jen 731
Rodén, Michael 685
Romancap, Faisal 953
Romano, Fabrizio 894
Romeiro, Fernando Gomes 667
Ronot, Maxime 672
Roose, Heleen 731
Rosalina, Reny 826
Roszkowska, Urszula 868
Rou, Woo Sun 907, 908
Rovere, Antonio 894
Roy, Akash 834
Roy, Sourish 834
R, Qasrawi 856
R, Somvanshi 870
Ru, JangHoon 672
Rusman, Resha Dermawansyah 835
Rustamova, Nazokat B. 805
Rustemov, Dastan 922
Ruvoletto, Mariagrazia 767
Ruzimurodov, Nodirjon 940
Rysmakhanov, Myltykbay 777, 806, 922, 927
Ryu, Gangpyo 736
Ryu, Ho Jae 779
Ryu, Jae Eun 689, 703
Ryu, Jae Yong 696
Ryu, Seunggho 708
Ryu, Tom 713, 794, 862
Ryu, Youngju 762, 931

S

Saadah, Aminatus 865
Saadah, Asniah Asniah 866
Sachdeva, Aakash 874
Sadykova, Aikorkem 937
Sadykov, Chingiz 677

Sahni, Peush 740
Sakamoto6, Seisuke 678
Salam, Nasir 890
Salas-Silva, Soraya 695, 929, 946
Salsabila, Zavia Putri 900, 959
Saluja, Sundeep Singh 938
Santos, Rocelyn 953
Sanyal, Arun J. 685, 746
Saravnan, Gayathri 925
Sari, Novita 866
Satthawiwat, Nantawat 848
Scarpa, Emanuele 894
Schattenberg, Jörn M. 746
Schoelch, Corinna 746
Scotti, Mauro Alessandro 894
Seidakhmetov, Akhmet 922, 926, 927
Sen, Bindu 786, 843
Seo, Deok Hwa 696, 749
Seo, Deok Wha 751
Seo, Hyeewon 703
Seo, Hye-Young 852
Seo, Hyung Il 820, 946
Seo, Kwang Il 787
Seo, Sang Hyun 880
Seo, Seung Young 840
Seo, Wonhyo 758
Seo, Yeon Seok 688, 690, 701, 702, 765, 795, 801, 810, 907

Seo, Young Eun 841, 907, 908, 909, 911
Serik, Zharikov 871, 923
Seto, Wai-Kay 732
Shah, Aashal Bhavesh 749
Shaheen, Saad Shams Bin 840
Shankar, Sadhana 678
Shao, Qing 798, 827
Sharma, Hemant 806
Sharma, Narendra Kumar 890
Sharma, Neha 944
Sharma, Nupur 944
Sharma, Sadhana 938
Sharma, Vipul 944
Sharma, Yam prasad 863
Shim, Ju Hyun 680, 710, 729, 815, 912
Shim, Sungryul 735
Shin, Beom Jin 915
Shin, Chang Hun 793
Shin, Dongyoon 728
Shin, Du Yeon 824
Shin, Hangsik 730
Shin, Hyunjae 660, 667, 681, 682, 698, 711, 716, 720, 734, 736, 772

Shin, Hyun Phil 852
Shin, Ji Hyun 695, 752, 763, 803, 946
Shin, Saeam 663
Shin, Seung Kak 675, 739, 801, 803, 804, 810
Shin, Yoon E 693
Shi, Tingting 855
Shi, Xiaomin 830, 831
Shrestha, Nishma 753

Silva, Soraya Salas	763
Sim, Hyungtai	754
Simonetto, Douglas A.	807
Sim, Sooyeon	683
Singh, Manvendra	927
Singh, Meenu	870
Sinn, Dong Hyun	660, 667, 682, 684, 691, 692, 698, 722, 733, 792, 815
Sinn, Dong Hyunn	689
Si, Tengfei	798, 827
Smagulov, Aibolat	927, 937, 941
Sohn, Won	708
Sohn, Woo Chang	896
Soliman, Aly	909
Song, Byeong Geun	660, 667, 680, 681, 682, 684, 691, 692, 698, 815, 912
Song, Do Seon	694, 738, 739, 743, 791, 800, 801, 815, 902, 903, 912, 919
Song, Gi-Won	729, 742, 933, 962
Song, Hyun Ho	793
Song, Jeong Eun	739, 787, 801
Song, Jung Eun	715, 907, 908, 911, 916
Song, Myeong Jun	694, 787, 791
Song, Sang Hwa	909
Song, Xiaoling	934, 935
Son, Min kook	711
Sonthalia, Nikhil	834
Son, Youngju	763
Sood, Vikrant	905
Soraya, Salas-Silva	803
Souza, Matheus D.	807
Sowa, Paweł	868
Sreekumar, Sreejith	740
Srinivasan, Madhu	741
Startseva, Elena	746
St, Binoj	741
Stefanelli, Davide	906
Stefani, Annalisa	767
Sudiarto, Hilmi Ardian	960
Suen, Alfred	799
Sugianto, Violetta Meitrie	959
Suh, Kyung-Suk	736
Su, Huizhao	750
Suk, Ki Tae	793, 801, 849
Sultan, Murat	957
Sumiyabazar, Tsogdulam	788, 858
Sun, Chao	832, 850
Sung, Pil Soo	673, 683, 691, 694, 696, 701, 712, 717, 723, 724, 738, 743, 749, 751, 752, 766, 771, 772, 774, 791, 804, 805, 808, 811, 903, 919
Sun, Hung-Yu	847
Sun, Yandong	931
Surendran, Sudhindran	741
Su, Ruiling	714
Sutiadi, Deni Adam	865
Su, Wei-Wen	844
Syafriyon	843

T

Tai, Chi-Ming	844
Tajitsu, Noa	882
Tak, Eunyoung	893, 915
Tak, Kwon Yong	673, 683, 691, 694, 696, 701, 712, 723, 724, 737, 751, 752, 766, 771, 805, 811, 903
Tak, Won Young	675, 715, 907, 908, 911
Tam, Can Thi Thanh	858, 874
Tam, Claudia Wing Lam	879
Tanaka, Atsushi	795
Tan, Eunice Xiang-Xuan	667
Tang, Xiaowei	830, 831, 859
Tan, Xue-Lin	714
Tateishi, Ryosuke	814
Tavabie, Oliver	667
Tekumalla, Sri Harsha	666
Tewari, Awanish	834
Thang, Nguyen Duc	778
Thanh, Chu Thi	834
Thanh, Khiem Nguyen	939, 940, 945
Thanh, LE Van	942, 958
Tien, Dao Duc	858
Timilsina, Krishna	863
Timur, Suleimenov	919, 957
Tincani, Giovanni	741
Tingmao, Xue	764
Tiwari, Milan	863
Tong, Man	898
Torres, Ivi Patrice	913
Toshima, Takeo	678
T, Ramya	874
Tran, Anh Dinh	813
Tran, Thang	906
Tretti3, Giovanna	767
Trinh, Huy Le	813
Tripathi, Gaurav	944
Trizzino, Arianna	741
Trong, Nguyen Minh	778
Tsai, Pei-Chien	844
Tsai, Ying-Nan	733
Tsedendorj, Yumchinsuren	788, 858
Tseng, Cheng-Hao	733
Tseng, Kuo-Chih	844
Tseng, Shang-Chen	733
Tsui, Yu Man	809
Tuan, Hiep Luong	939, 945
Tuan, Le Quoc	944
Tucker, Bethany	798, 827
Tung, Nguyen Thanh	812
Tv, Christi	741

U

Uesugi, Aki	885
Ulyanova, Olga	926
Ulziitsogt, Bolor	788, 858
Usman, Kauser	872

Utebaliev, Ruslan	922

V

Van, Le Anh	858, 874
Van, LE Anh	942, 958
Varshney, Vaibhav	935
Varshney, Vaibhav Kumar	936
Venkatakrishnan, Guhan	741
Venugopal, Radhika	760
Vera-Ponce, Víctor Juan	851
Verma, Sagar	943
Vij, Mukul	760
Viray, Brent Andrew	953
Vukotic, Ranka	741

W

Wang, Chia-Chi	844
Wang, Haitao	954
Wang, Han-xuan	932
Wang, Hao	776
Wang, Hongyuan	732
Wang, Jing	667
Wang, Jingyi	883
Wang, Kexin	921
Wang, Mingyang	934, 935
Wang, Rensheng	750
Wang, Shan	846
Wang, Stanley	731
Wang, Wei	819
Wang, Wenquan	819
Wang, Xiaohong	830, 831
Wang, Xin	931
Wang, Yinzhu	840
wang, Yuechen	759
Wang, Yuechen	797
Watanabe10, Toshio	756
Wei Gao	699
Wei, Jinhui	765
Wei, Yingjian	911
Wei, Yong	954
Wei, Zaiwa	750
W, Hafez	856
Wibisana, Louis Widyatma	865
Wijarnpreecha, Karn	807
Wijerathna, Thilini Madushanka	824
Wild, Sarah H.	708
Won, Dae Hyeon	836, 933, 962
Won, Dae-Hyeon	730
Wong, Grace Lai-Hung	660, 732
Wongrujipairoj5, Patrawadee	807
Wong, Samuel Wan Ki	879
Won, Hong-Hee	698
Won, Kyoung Jae	701
Won, Sungho	711
Woo, Hyun Young	715, 721, 907, 908, 911, 916
Wu, Bin	931

Wu, Di	730
Wu, Jia-Ling	733
Wu, Min	731
Wu, Ting	730
Wu, Wenchih	844
Wu, Xue Qian	884

X

Xia, Hongping	768
Xiao, Fang	725
Xiaowen, Mao	764
Xie, Qiuli	889
Xie, Shengjie	817
Xing, Hao	725, 750
Xin, Yang	931
Xu, Ai-Bing	666
Xuan, Linh Nguyen Thi	858
Xu, Jia	830, 831
Xu, Jian	759, 797
Xu, Tingfeng	889
Xu, Wenli	889
Xu, Yaolin	819
Xu, Yaqi	694

Y

Yadav, Manisha	944
Yadav, Sanju	890, 944
Yamada, Tomoharu	814
Yam, Judy Wai Ping	694, 879, 883, 887
Yam, JWP	883
Yang, Chan Mo	892
Yang, Chi-Chieh	844
Yang, Dan	830, 831
Yang, Haiqing	817
Yang, Hye Won	737
Yang, Hyun	676, 686, 694, 712, 717, 771, 772, 791, 804
Yang, Jae Do	894
Yang, Jiwon	680, 710
Yang, Ju Dong	660, 667
Yang, Keungmo	713, 737, 738, 751, 772, 774, 791, 794, 804, 903
Yang, Sejung	672
Yang, Seong Wook	717
Yang, Sheng-Shun	844
Yang, Shihao	956
Yang, Won Suk	718, 910
Yang, Yiling	859
Yang, Ziyi	850
Yankannavar, Basavaraj Shankar	874
Yan, Lilian	660
Yan, Qiong	830, 831
Yan, Weiming	730, 784
Yao, Mei	714
Yao, Xu	830, 831, 859
Yee, Leland J.	732

Yeh, Ming-Lun	844
Yemaneberhan, Kidus Haile	929
Yen, Le Thi Hoang	944
Yeon, Jong Eun	701, 702, 765, 810, 907
Yeon Soo Jang	778
Yerzhanov, Zhalgas	941
Yeung, Cherlie Lot Sum	887
Ye, Xiao-yong	932
Ye, Xiaoyong	920, 921, 924
Yi, Hahn	729
Yl, Ki Yeon	715
Yl, Kiyoun	721
Yilmaz, Tonguc Utku	678
Yim, Hyung Joon	675, 701, 702, 765, 791, 810, 907
Yim, Sun Young	701, 702, 765, 810, 907
Yi, Nam-Joon	674, 736
Yin, Guoqing	855
Yip, Terry Cheuk-Fung	660
Yi, Shiming	954
Yi, Xinghuang	796
Yoneda, Masato	829
Yoo, Jae-Sung	771
Yoo, Jeongin	857
Yoo, Jeong Ju	693, 739
Yoo, Jeong-Ju	660, 667, 675, 691, 713, 722, 735, 747, 757
Yoo, Jung Ju	801
Yoon, Eileen L	685, 794
Yoon, Eileen L.	686, 688, 689, 756, 829
Yoon, Eileen Laurel	703
Yoon, Ho Yeong	849
Yoon, Jae Hyun	715, 719, 739, 800, 801, 841, 907, 908, 909, 911, 916
Yoon, Jae Woong	667, 716
Yoon, Jai Hoon	703
Yoon, Jiwoon	676, 686
Yoon, Jung-Hwan	660, 667, 681, 682, 699, 711, 716, 720, 734, 736, 743, 772, 919
Yoon, Jun Sik	675, 715, 754, 757, 801, 907, 908, 911, 916
Yoon, Ki Tae	791
Yoon, Moon Gyeong	811, 824, 880
Yoon, Sang Min	816
Yoon, Seung Kew	694
Yoon, Seung Yong	892
Yoon, Yoo-Seok	679, 719
Yoon, Young-In	667, 730, 742, 762, 933, 962
Yoo, Sung Hwan	756, 884
Yoo, Sun Hong	676, 686
Yoo, Yang Jae	701, 702, 719, 765, 810
Yoo, Young Jin	809
Youjung, Lee	756
Younes, Ramy	746
You, Young Kyoung	696, 808
Yuan, Fangfang	831
Yuan, Guandou	725, 750, 763, 796, 817, 885, 911
Yuan, Zhize	784
Yuen, Man-Fung	731
Yu, Hee Chul	894

Yu, Huihong	798, 827
Yu, Jeong Il	681, 683, 816
Yu, Jiyoung	736
Yu, Jung Hwan	839
Yulianda, Rara	950
Yu, Ming-Lung	844
Yun, Yeochan	749
Yu, Sehyeon	930
Yu, Shuiping	699
Yu, Su Jong	667, 680, 681, 682, 698, 711, 716, 717, 720, 734, 736, 737, 743, 772, 815, 912, 919
Yuxin, Hao	746
Yu, Young-Dong	930

Z

Zakaria, Abdelrahman	909
Zaki, Soad	909
Zeng, Yonglian	699, 750, 885
Zhanasbayeva, Marzhan	761, 925
Zhang, Cheng	714
Zhang, Hui	931
Zhang, Jie	889
Zhang, Wen	855
Zhang, Yong	931
Zhang, Yueming	819
Zhao, Ran	784
Zhao, Shanyu	796
Zhao, Yiwei	856
Zheng, Chaowen	825, 846
Zheng, Jinpeng	817
Zhijie, Xiao	764
Zhong, Jiaxin	856
Zhong, Mingbei	796
Zhou, Haoming	759, 776, 797
Zhou, Lin	920
Zhou, Yongheng	911
Zhuo, Chenyi	750
Zmudka, Karol	868
Zulkharnay, Aidar	937
Zulkharnay, Gaini	926

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