CMH
Clinical and Molecular Hepatology

The Liver Week 2021

LIVE VIRTUAL CONFERENCE

May 13-15, 2021

www.theliverweek.org

The Korean Association for the Study of the Liver
THE KOREAN ASSOCIATION OF HBP SURGERY
THE KOREAN LIVER CANCER ASSOCIATION
The Korean Liver Transplantation Society

PROGRAM AT A GLANCE

DAY 1 Thursday, May 13, 2021

K Session in Korean

	ROOM 1	ROOM 2	ROOM 3
08:00	* Postgraduate Course: Multidisciplinary Team Approach: from Updated Guidelines to Bedside Practice		
09:00	K Postgraduate Course 1 (09:00-10:30)	K Research Workshop 1 (09:00-10:30)	K US Education for Trainer 1 (09:00-10:30)
10:00			
	Break (10:30-10:40)		
11:00	K Postgraduate Course 2 (10:40-12:10)	Basic Research Symposium 1 (10:40-12:10)	K US Education for Trainer 2 (10:40-12:10)
12:00			
	Luncheon Symposium 1 [Yuhan] (12:10-13:10)	Luncheon Symposium 2 [Roche] (12:10-13:10)	Luncheon Symposium 3 [Abbvie] (12:10-13:10)
13:00			
14:00	K Postgraduate Course 3 (13:10-14:40)	K Research Workshop 2 (13:10-14:40)	K Health Insurance Forum (13:10-14:40)
	Break (14:40-14:50)		
15:00	K Postgraduate Course 4 (14:50-16:20)	Basic Research Symposium 2 (14:50-16:20)	Health Policy Forum Hepatitis C Virus Elimination: Lesson from Worldwide Progress (14:50-16:30)
16:00			

SCIENTIFIC PROGRAM

Room 1

DAY 1 Thursday, May 13, 2021

(*K): Session in Korean

09:00-10:30	**Postgraduate Course1. What's New for Viral Hepatitis in 2021?** (*K)	*Sang Uk Lee (Kosin Univ.), Ju Hyun Kim (Gachon Univ.)*
09:00-09:20	New Indications and New Endpoints of Hepatitis B Virus Treatment: When to Start, Change, and Stop?	*Hyung Joon Yim (Korea Univ.)*
09:20-09:40	Hepatitis C Virus Simplified Algorithm for Treatment: Who Is Eligible for Simplified Treatment?	*In Hee Kim (Jeonbuk National Univ.)*
09:40-10:00	Individualized Treatment of Viral Hepatitis B and C Based on Comorbidities	*Young-Joo Jin (Inha Univ.)*
10:00-10:20	The Recent Updates in HAV, HDV, and HEV	*Sae Hwan Lee (Soonchunhyang Univ.)*
10:20-10:30	Discussion	
10:30-10:40	Break	
10:40-12:10	**Postgraduate Course2. The New Normal Era for Hepatologists after COVID-19** (*K)	*Hee Bok Chae (Chungbuk National Univ.), Byung Seok Lee (Chungnam National Univ.)*
10:40-11:00	The Epidemiology and Virology of COVID-19 Infection	*Won-Suk Choi (Korea Univ.)*
11:00-11:20	Practice Guidance for Patients with Liver Disease in the Era of COVID-19	*Jeong-Hoon Lee (Seoul National Univ.)*
11:20-11:40	The Relationship between COVID-19 and Liver Disease	*Woo Jin Chung (Keimyung Univ.)*
11:40-12:00	The Challenges and Achievements in COVID-19 Treatment and Vaccines	*Pyoeng Gyun Choe (Seoul National Univ.)*
12:00-12:10	Discussion	
12:10-13:10	Luncheon Symposium 1 [Yuhan]	
13:10-14:40	**Postgraduate Course3. Optimizing Management of Alcohol-Related Liver Disease and Nonalcoholic Fatty Liver Disease** (*K)	*Soon Koo Baik (Yonsei Univ. Wonju), Soon Woo Nam (The Catholic Univ. of Korea)*
13:10-13:30	How to Identify High-Risk Individuals in Alcoholic Liver Disease	*Do Seon Song (The Catholic Univ. of Korea)*
13:30-13:50	How to Predict Rapid Progression of Fibrosis in Nonalcoholic Fatty Liver Disease	*Byoung Kuk Jang (Keimyung Univ.)*
13:50-14:10	Metabolism-Based Medical and Surgical Interventions for Nonalcoholic Fatty Liver Disease	*Eun-Jung Rhee (Sungkyunkwan Univ.)*
14:10-14:30	Liver Transplantation and beyond for Alcohol-Related Liver Failure	*Ho Joong Choi (The Catholic Univ. of Korea)*
14:30-14:40	Discussion	
14:40-14:50	Break	
14:50-16:20	**Postgraduate Course4. Upcoming Diagnostic and Therapeutic Approaches in Liver Cirrhosis** (*K)	*Yong Moon Shin (Univ. of Ulsan), Gab Jin Cheon (Univ. of Ulsan)*
14:50-15:10	Recent Advances in Noninvasive Diagnostic Approaches to Portal Hypertension	*Seong Hee Kang (Yonsei Univ. Wonju)*
15:10-15:30	Challenges in Cirrhosis Management Focused on Acute Kidney Injury and Refractory Ascites	*Yeon Seok Seo (Korea Univ.)*
15:30-15:50	Pharmacological Treatment of Portal Hypertension: A 2021 Update and Revisit	*Jae Young Jang (Soonchunhyang Univ.)*
15:50-16:10	Interventional Management of Portal Hypertension: A 2021 Update and Revisit	*Hyo Cheol Kim (Seoul National Univ.)*
16:10-16:20	Discussion	

(*K): Session in Korean

09:00-10:30	**Research Workshop 1. Indispensable Novel Techniques for the Study of Liver Disease** (*K)	*So-Young Jin (Soonchunhyang Univ.), Youngmi Jung (Pusan National Univ.)*
09:00-09:20	Single-Cell Multi-Omics Approaches to Understand Human Development and Aging	*Jong-Eun Park (Korea Advanced Institute of Science and Technology)*
09:20-09:40	Transplantation of Bioengineered Livers into Immunosuppressed Pigs	*Dong Jin Joo (Yonsei Univ.)*
09:40-10:00	Three Dimensional Human Liver-Chip	*Yoon-Kyoung Cho (Ulsan National Institute of Science and Technology)*
10:00-10:20	Fecal Microbiota Transplantation: Its Application to Nonalcoholic Steatohepatitis	*Sowon Park (Yonsei Univ.)*
10:20-10:30	Discussion	
10:30-10:40	Break	
10:40-12:10	**Basic Research Symposium 1. Stress-Induced Fates of Hepatocyte in Nonalcoholic Steatohepatitis and Alcoholic Steatohepatitis**	*Jong Eun Yeon (Korea Univ.), Wonhyo Seo (Ewha Womans Univ.)*
10:40-11:00	Reprograming Hepatocytes in Severe Alcoholic Hepatitis	*Jeongeun Hyun (Dankook Univ.)*
11:00-11:20	Sphingomyelin Synthase 1 Mediates Hepatocyte Pyroptosis to Trigger Nonalcoholic Steatohepatitis	*Eun Hee Koh (Univ. of Ulsan)*
11:20-11:40	Role of Intestine-Derived HDL on LPS Action in Gut-Liver Axis	*Yong-Hyun Han (Kangwon National Univ.)*
11:40-12:00	Neutrophils in Alcohol-Associated Liver Disease	*Bin Gao (National Institute on Alcohol Abuse and Alcoholism, USA)*
12:00-12:10	Discussion	
12:10-13:10	Luncheon Symposium 2 [Roche]	
13:10-14:40	**Research Workshop 2. Established Translational Techniques for the Study of Liver Disease** (*K)	*Neung Hwa Park (Univ. of Ulsan), Eun Hee Koh (Univ. of Ulsan)*
13:10-13:30	In Vivo and In Vitro Models for Alcoholic and Nonalcoholic Liver Disease	*Hyo-Jung Kwon (Chungnam National Univ.)*
13:30-13:50	Expandable and Functional Human Pluripotent Stem Cell-Derived Hepatic Organoids	*Myung Jin Son (Korea Research Institute of Bioscience and Biotechnology)*
13:50-14:10	Hepatic Immune Cell Isolation and Analysis in Mice and Humans	*Young-Sun Lee (Korea Univ.)*
14:10-14:30	Exosome Isolation Technique and Its Application to Liver Disease	*Wonhyo Seo (Ewha Womans Univ.)*
14:30-14:40	Discussion	
14:40-14:50	Break	
14:50-16:20	**Basic Research Symposium 2. Intrinsic and Multifactorial Contribution to Cirrhosis and Hepatocellular Carcinoma**	*Yong-Han Paik (Sungkyunkwan Univ.), Hyo-Jung Kwon (Chungnam National Univ.)*
14:50-15:10	Glutamine and Immune Checkpoint in Cancer Cells	*Keun-Gyu Park (Kyungpook National Univ.)*
15:10-15:30	Hippo Signaling in HCC Development	*Wantae Kim (Chungnam National Univ.)*
15:30-15:50	Mesenchymal Stem Cell-Derived Factors Regulate Liver Fibrosis	*Youngmi Jung (Pusan National Univ.)*
15:50-16:10	Non-Invasive Stool-Based Microbiome Profiling Predicts Liver Cirrhosis	*Tae Gyu Oh (Salk Institute for Biological Studies, USA)*
16:10-16:20	Discussion	

[*K]: Session in Korean

09:00-10:30	**Education for Ultrasonography Training Specialists Session 1** [*K]	*Soon Koo Baik (Yonsei Univ. Wonju), Won Young Tak (Kyungpook National Univ.)*
09:00-09:20	Questionnaire Analysis on Education and Management for Abdominal Ultrasonography Training Specialists	*Seung Kak Shin (Gachon Univ.)*
09:20-09:40	Role and Ethics of Abdominal Ultrasonography Training Specialists	*Young-Seok Cho (The Catholic Univ. of Korea)*
09:40-10:00	Artificial Intelligence-Based Medical Image Analysis	*Hwiyoung Kim (Yonsei Univ.)*
10:00-10:20	How To Write a Report of Abdominal Ultrasonography: Focusing on Cases	*Han Ah Lee (Inje Univ.)*
10:20-10:30	Discussion	
10:30-10:40	Break	
10:40-12:10	**Education for Ultrasonography Training Specialists Session 2** [*K]	*Yun Soo Kim (Gachon Univ.), Hyung Joon Yim (Korea Univ.)*
10:40-11:00	Settings and Practice of Contrast-Enhanced Ultrasonography	*Soo Young Park (Kyungpook National Univ.)*
11:00-11:20	Ultrasonography Cases of Various Atypical Hepatic Tumors	*Ki Tae Suk (Hallym Univ.)*
11:20-11:40	Non-Invasive Methods for Diagnosis of Nonalcoholic Fatty Liver Disease	*Hye Won Lee (Yonsei Univ.)*
11:40-12:00	Various Cases of Liver Disease Applying Doppler Ultrasonography	*Jeong Eun Song (Daegu Catholic Univ.)*
12:00-12:10	Discussion	
12:10-13:10	Luncheon Symposium 3 [Abbvie]	
13:10-14:40	**Health Insurance Forum** [*K]	*Hong Soo Kim (Soonchunhyang Univ.), Hyung Joon Kim (Chung-Ang Univ.)*
13:10-13:30	Role and Mission of Patient Classification System TFT in KASL	*Hyun Woong Lee (Yonsei Univ.)*
13:30-13:50	Expanding Reimbursement Policy on Non-Reimbursable Services in Hepatology	*Soon Sun Kim (Ajou Univ.)*
13:50-14:10	Unmet Need of National Reimbursement Policy for Hepatocellular Carcinoma	*Eun Sun Jang (Seoul National Univ.)*
14:10-14:30	Future Policy Direction of Pharmaceutical Benefit in National Health Insurance	*Yoon Suk Yang (Ministry of Health and Welfare)*
14:30-14:40	Discussion	
14:40-14:50	Break	
14:50-16:30	**Health Policy Forum. Hepatitis C Virus Elimination: Lesson from Worldwide Progress**	*Dong Jin Suh (Daehang Hospital), Han Chu Lee (Univ. of Ulsan)*
14:50-15:10	The Political and Clinical Progress for Hepatitis C Virus Elimination in Taiwan: From Beginning to Present	*Jia-Horng Kao (National Taiwan Univ., Taiwan)*
15:10-15:30	The Political and Clinical Progress for Hepatitis C Virus Elimination in Egypt: From Beginning to Present	*Imam Waked (National Liver Institute, Egypt)*
15:30-15:50	The Political and Clinical Progress for Hepatitis C Virus Elimination in Australia: From Beginning to Present	*Gregory Dore (Kirby Institute, Australia)*
15:50-16:10	The Critical Appraisal for Policy Progress to Date: What Is Needed and How Should It Proceed?	*Young-Suk Lim (Univ. of Ulsan)*
16:10-16:30	Discussion	

PROGRAM AT A GLANCE

DAY 2 Friday, May 14, 2021

K Session in Korean and English

	ROOM 1	ROOM 2	ROOM 3	ROOM 4	ROOM 5	ROOM 6
07:30	Breakfast Symposium 1 [Samil] (07:30-08:10)	Breakfast Symposium 2 [Chong Kun Dang] (07:30-08:10)	Breakfast Symposium 3 [Celltrion] (07:30-08:10)			
08:00	Break (08:10-08:20)					
09:00	KASL Symposium 1 (08:20-09:40)	KLCA Symposium 1 (08:20-09:40)	KLTS Symposium 1 (08:20-09:40)	SIG Forum 1 (08:20-09:40)	Free Paper Presentation 1 [Basic] (08:40-09:40)	
10:00	Opening Ceremony (09:40-10:00)					
	Plenary Presentation 1 (10:00-11:00)					
11:00	Break (11:00-11:10)					
12:00	K Young Investigators of the Year Session (11:10-12:30)	KLCA Symposium 2 (11:10-12:30)	KLTS Special Lecture (11:10-12:30)	SIG Forum 2 (11:10-12:30)	Free Paper Presentation 2 [Viral Hepatitis] (11:10-12:30)	
13:00	Luncheon Symposium 4 [Abbvie] (12:30-13:30)	Luncheon Symposium 5 [Bayer] (12:30-13:30)	Luncheon Symposium 6 [Yuhan] (12:30-13:30)	Luncheon Symposium 7 [Ipsen] (12:30-13:30)	Luncheon Symposium 8 [BMS] (12:30-13:30)	
14:00	KASL Symposium 2 (13:30-14:50)	KLCA Symposium 3 (13:30-14:50)	KAHBPS-KLTS Joint Symposium (13:30-14:50)	SIG Forum 3 (13:30-14:50)	Free Paper Presentation 3 [NAFLD, AIH, Others] (13:30-14:50)	
15:00	Break (14:50-15:00)					
	Distinguished Lectures (15:00-16:20)	KLTS-KLCA Joint Symposium (15:00-16:20)		SIG Forum 4 (15:00-16:20)	Free Paper Presentation 4 [Liver Cancer, Basic] (15:00-16:20)	K Press Conference (15:00-16:00)
16:00	Break (16:20-16:30)					
17:00	KASL Symposium 3 (16:30-17:50)	Free Paper Presentation 5 [Liver Cancer, Clinical] (16:30-17:50)	Free Paper Presentation 6 [Liver Transplantation] (16:30-17:50)	SIG Forum 5 (16:30-17:50)	K KLTS Coordinator Session (16:30-18:00)	
18:00						

07:30-08:10	Breakfast Symposium 1 [Samil]	
08:10-08:20	Break	
08:20-09:40	**KASL Symposium 1. Personalized Medicine in Liver Diseases: "Present and Future"**	*Seung Kew Yoon (The Catholic Univ. of Korea), Young Oh Kweon (Kyungpook National Univ.)*
08:20-08:40	Clinical Implication of Personalized Medicine in Hepatic and Biliary Cancer	*Yeul Hong Kim (Korea Univ.)*
08:40-09:00	Personalized Medicine in Nonalcoholic Fatty Liver Disease: From Genetics and Systems Biology	*Silvia Sookoian (Univ. of Buenos Aires, Argentina)*
09:00-09:20	Personalized Medicine in Liver Disease via Modulating the Gut Microbiota	*Ki Tae Suk (Hallym Univ.)*
09:20-09:40	Personalized Medicine in Autoimmune Hepatitis	*Atsumasa Komori (Nagasaki Univ., Japan)*
09:40-10:00	Opening Ceremony	
10:00-11:00	**Plenary Presentation 1**	*Byung Ik Kim (Sungkyunkwan Univ.), Han Chu Lee (Univ. of Ulsan), Chul Soo Ahn (Univ. of Ulsan)*
10:00-10:15	Nucleos(t)ide Analogue Treatment Is Associated with Lower Risk of Extrahepatic Malignancy in Chronic Hepatitis B Patients: A Landmark Study Using Nationwide Claim Data	*Sung Won Chung (Seoul National Univ.)*
10:15-10:30	Cost-Effectiveness and Health-Related Outcomes of One-Time Screening and Treatment for Hepatitis C in Korean Population: A Pilot Project for Hepatitis C Screening	*Young Chang (Soonchunhyang Univ.)*
10:30-10:45	Minimally Invasive Living Donor Liver Transplantation: Pure Laparoscopic Explant Hepatectomy and Graft Implantation Using Upper Midline Incision	*Kyung-Suk Suh (Seoul National Univ.)*
10:45-11:00	Roles of Intrahepatic Inflammation-induced IgA+PD-L1-High Macrophages in Development and Immunotherapy of Hepatocellular Carcinoma	*Pil Soo Sung (The Catholic Univ. of Korea)*
11:00-11:10	Break	
11:10-12:30	**Young Investigators of the Year Session** [*K&E]	*Jeong Ill Suh (Dongguk Univ.), So Young Kwon (Konkuk Univ.)*
11:10-11:35	My Research Interests in the Field of Hepatology and Gastroenterology	*Jeong-Hoon Lee (Seoul National Univ.)*
11:35-12:00	Optimizing the Secondary Prevention of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B: A Lesson from Real-World Evidence	*Jonggi Choi (Univ. of Ulsan)*
12:00-12:30	Recent Epidemiology of Hepatocellular Carcinoma in the USA	*Ju Dong Yang (Univ. of California, Los Angeles, USA)*
12:30-13:30	Luncheon Symposium 4 [Abbvie]	
13:30-14:50	**KASL Symposium 2. Current Issues and Future Therapy for Chronic Hepatitis B**	*Jung-Hwan Yoon (Seoul National Univ.), Kyun-Hwan Kim (Sungkyunkwan Univ.)*
13:30-13:50	Advancing Age and Comorbidity in Patients with Chronic Hepatitis B	*Yun Bin Lee (Seoul National Univ.)*
13:50-14:10	Hepatocellular Carcinoma Prediction Model for Antiviral-Treated Chronic Hepatitis B Patients	*Hwi Young Kim (Ewha Womans Univ.)*
14:10-14:30	Clinical Implications of Novel Biomarkers of Hepatitis B Virus	*Man-Fung Yuen (The Univ. of Hong Kong, Hong Kong)*
14:30-14:50	HBV-Host Genome Integration: How Can We Detect It and What Is Its Impact?	*Thomas Tu (The Univ. of Sydney, Australia)*
14:50-15:00	Break	

15:00-16:20	**Distinguished Lectures**	*Masao Omata (Yamanashi Central and Kita Hospitals, Japan), Jin Mo Yang (The Catholic Univ. of Korea)*
15:00-15:40	Progress and Challenges in Achieving Hepatitis B Virus Cure	*Fabien Zoulim (Lyon Univ., France)*
15:40-16:20	Acute-on-Chronic Liver Failure: Achievements and Future Perspectives	*Shiv Kumar Sarin (Institute of Liver & Biliary Science, India)*
16:20-16:30	Break	
16:30-17:50	**KASL Symposium 3. Updates on Management of Cirrhosis and Related Complications**	*June Sung Lee (Inje Univ.), Si Hyun Bae (The Catholic Univ. of Korea)*
16:30-16:50	Individualized Risk Stratification of Compensated Advanced Chronic Liver Disease (cACLD)	*Annalisa Berzigotti (Univ. of Bern, Switzerland)*
16:50-17:10	How to Prevent Decompensation in Compensated Cirrhosis	*Moon Young Kim (Yonsei Univ. Wonju)*
17:10-17:30	Current and Novel Treatment Strategies of Hepatic Encephalopathy	*Rajiv Jalan (Univ. College London, UK)*
17:30-17:50	Understanding Coagulation and Hemostasis in Cirrhosis	*Jung Il Lee (Yonsei Univ.)*

07:30-08:10	Breakfast Symposium 2 [Chong Kun Dang]	
08:10-08:20	Break	
08:20-09:40	**KLCA Symposium 1. Diagnosis and Surveillance in Hepatocellular Carcinoma**	*Seung Woon Paik (Sungkyunkwan Univ.), Yong Moon Shin (Univ. of Ulsan)*
08:20-08:40	LI-RADS Classification and Its Impact on the Prognosis of Primary Liver Cancer	*Sang Hyun Choi (Univ. of Ulsan)*
08:40-09:00	Imaging Phenotype of Hepatocellular Carcinoma Subtypes	*Jin-Young Choi (Yonsei Univ.)*
09:00-09:20	Different Hepatocellular Carcinoma Risk and Surveillance Strategies According to Situations: Young Age	*Nae-Yun Heo (Inje Univ.)*
09:20-09:40	Different Hepatocellular Carcinoma Risk and Surveillance Strategies According to Situations: After Virologic Cure	*Jung Hyun Kwon (The Catholic Univ. of Korea)*
09:40-10:00	Opening Ceremony	
10:00-11:00	**Plenary Presentation 1**	*Byung Ik Kim (Sungkyunkwan Univ.), Han Chu Lee (Univ. of Ulsan), Chul Soo Ahn (Univ. of Ulsan)*
11:00-11:10	Break	
11:10-12:30	**KLCA Symposium 2. Evolving Trends in Management of Hepatocellular Carcinoma**	*Jinsil Seong (Yonsei Univ.), Seung Kew Yoon (The Catholic Univ. of Korea)*
11:10-11:30	Role of Systemic Therapy in Intermediate-Stage Hepatocellular Carcinoma	*Masatoshi Kudo (Kindai Univ., Japan)*
11:30-11:50	Role of Loco-Regional Treatment in Advanced-Stage Hepatocellular Carcinoma	*Ju Hyun Shim (Univ. of Ulsan)*
11:50-12:10	Optimizing Radiotherapy with Immune Checkpoint Blockade in Hepatocellular Carcinoma	*Jeong Il Yu (Sungkyunkwan Univ.)*
12:10-12:30	Treatment of Advanced Hepatocellular Carcinoma with Child-Pugh B Cirrhosis	*Chang Wook Kim (The Catholic Univ. of Korea)*
12:30-13:30	Luncheon Symposium 5 [Bayer]	
13:30-14:50	**KLCA Symposium 3. Changing Landscape of Systemic Therapy in Advanced Hepatocellular Carcinoma**	*Soon Ho Um (Korea Univ.), Joong-Won Park (National Cancer Center Korea)*
13:30-13:50	Selecting First-Line Therapy for Advanced Hepatocellular Carcinoma: TKI vs. ICI	*Kyung-Hun Lee (Seoul National Univ.)*
13:50-14:10	How to Optimize Sequence of Systemic Treatment in Advanced Hepatocellular Carcinoma	*Ann-Lii Cheng (National Taiwan Univ., Taiwan)*
14:10-14:30	Hepatocellular Carcinoma Patients on Systemic Therapy: Prediction of Prognosis	*Beom Kyung Kim (Yonsei Univ.)*
14:30-14:50	Assessment of Tumor Response in Patients Receiving Systemic Therapy: RECIST 1.1, Modified RECIST, or Other Options	*Min-Hee Ryu (Univ. of Ulsan)*
14:50-15:00	Break	
15:00-16:20	**KLTS-KLCA Joint Symposium. Updates on Liver Transplantation for Hepatocellular Carcinoma**	*Kyung-Suk Suh (Seoul National Univ.), Jong Young Choi (The Catholic Univ. of Korea)*
15:00-15:20	Expanding Criteria for Liver Transplantation: Sero-Positive Donors	*Hae Won Lee (Seoul National Univ.)*
15:20-15:40	Hepatocellular Carcinoma Recurrence after Liver Transplantation: Risk Factors	*Wonseok Kang (Sungkyunkwan Univ.)*
15:40-16:00	Management of Hepatocellular Carcinoma Recurrence after Liver Transplantation: Surgery and Locoregional Therapy	*Dong-Hwan Jung (Univ. of Ulsan)*
16:00-16:20	Management of Hepatocellular Carcinoma Recurrence after Liver Transplantation: Systemic Therapy	*Bo Hyun Kim (National Cancer Center Korea)*
16:20-16:30	Break	

16:30-17:50	**Free Paper Presentation 5 [Liver Cancer, Clinical]**	*Jaeseok Hwang (Keimyung Univ.), Moon Seok Choi (Sungkyunkwan Univ.)*
16:30-16:40	Changes in General and Central Obesity Are Associated with Hepatocellular Carcinoma: A Nationwide Longitudinal Study	*Mi Na Kim (CHA Univ.)*
16:40-16:50	Incidence Rates of Hepatocellular Carcinoma Does Not Increase in Patients with Old Age or Medicare Group: A Nationwide 10-Year Analysis and Projection	*Young Eun Chon (CHA Univ.)*
16:50-17:00	Controlled Attenuation Parameter Value and the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients under Antiviral Therapy	*Joo Hyun Oh (Eulji Univ.)*
17:00-17:10	Imaging Findings of Liver MRI with Liver-Specific Contrast and the Risk of Hepatocellular Carcinoma	*Jong-In Chang (Sungkyunkwan Univ.)*
17:10-17:20	Whole Blood Viscosity Is a Biomarker for the Extrahepatic Metastases and Survival in Patients with Treatment-Naïve Hepatocellular Carcinoma	*Ji Won Han (The Catholic Univ. of Korea)*
17:20-17:30	Biomarkers for Locally Advanced Hepatocellular Carcinoma Patients Treated with Liver-Directed Combined Radiotherapy	*Seung Yeun Chung (Ajou Univ.)*
17:30-17:40	Machine Learning based Pattern Recognition Software to Predict 5-Year Recurrence Risk after Surgical Resection in Hepatocellular Carcinoma Patients: A Multicenter Study	*Youn I Choi (Gachon Univ.)*
17:40-17:50	Kinetics of the Neutrophil-Lymphocyte Ratio during PD-1 Inhibition as a Prognostic Factor in Advanced Hepatocellular Carcinoma	*Won-Mook Choi (Univ. of Ulsan)*

07:30-08:10	Breakfast Symposium 3 [Celltrion]	
08:10-08:20	Break	
08:20-09:40	**KLTS Symposium** **How to Overcome Hurdles of ABO-Incompatible Living Donor Liver Transplantation**	*Jae-Won Joh (Sungkyunkwan Univ.), Young Kyoung You (The Catholic Univ. of Korea)*
08:20-08:40	ABO-Incompatible Living Donor Liver Transplantation and Biliary Complications	*Gi-Won Song (Univ. of Ulsan)*
08:40-09:10	ABO-Incompatible Living Donor Liver Transplantation in High-Risk Patients: Hepatocellular Carcinoma and Infection	*Dong-Jin Joo (Yonsei Univ.)*
09:10-09:30	An Optimal Protocol to Overcome Weak Points of ABO-Incompatible Living Donor Liver Transplantation	*Nam-Joon Yi (Seoul National Univ.)*
09:30-09:40	Discussion	
09:40-10:00	Opening Ceremony	
10:00-11:00	**Plenary Presentation 1**	*Byung Ki Kim (Sungkyunkwan Univ.), Han Chu Lee (Univ. of Ulsan), Chul Soo Ahn (Univ. of Ulsan)*
11:00-11:10	Break	
11:10-12:30	**KLTS Special Lecture**	*Myoung Soo Kim (Yonsei Univ.), Shin Hwang (Univ. of Ulsan)*
11:10-11:40	Post-Transplant Lymphoproliferative Disorder after Liver Transplantation	*Olivia Martinez (Stanford Univ., USA)*
11:40-11:50	Discussion	
11:50-12:20	Outcome of Liver Retransplantation Using Living Donor Grafts	*Kaori Kuramitsu (Kobe Univ., Japan)*
12:20-12:30	Discussion	
12:30-13:30	Luncheon Symposium 6 [Yuhan]	
13:30-14:50	**KAHBPS-KLTS Joint Symposium.** **Strategies for Posthepatectomy Liver Failure: From Prevention to Treatment**	*In Seok Choi (Konyang Univ.), Kwang-Woong Lee (Seoul National Univ.)*
13:30-13:50	Preoperative Assessment of Liver Function in Patients Requiring Hepatectomy	*Young Seok Han (Kyungpook National Univ.)*
13:50-14:10	Prevention of Post Hepatectomy Liver Failure (PHLF): Where Are We? (PVE, ALPPS, HVE, Ischemic Preconditioning)	*Albert Chan (The Univ. of Hong Kong, Hong Kong)*
14:10-14:30	Early Detection of PHLF and Non-Surgical Management for PHLF	*Dong-Sik Kim (Korea Univ.)*
14:30-14:50	Timing and Results of Liver Transplantation for PHLF	*Pål-Dag Line (Univ. of Oslo, Norway)*
14:50-15:00	Break	
15:00-16:20	**KLTS-KLCA Joint Symposium. Updates on Liver Transplantation for Hepatocellular Carcinoma**	
16:20-16:30	Break	

16:30-17:50	**Free Paper Presentation 6 [Liver Transplantation]**	*Deok-Bog Moon (Univ. of Ulsan), Bong-Wan Kim (Ajou Univ.)*
16:30-16:40	Stepwise Development of Robotic Donor Right Hepatectomy According to the Anatomical Variations in the Hilum and the Graft Volume	*Hye Yeon Yang (Yonsei Univ.)*
16:40-16:50	Pre-Transplant Functional Status Predicts Postoperative Morbidity and Mortality after Liver Transplantation in Patients with Cirrhosis	*Jihye Kim (Sungkyunkwan Univ.)*
16:50-17:00	Preoperative Prediction Score of Hepatocellular Carcinoma Recurrence in Living Donor Liver Transplantation: Validation of SNAPP SCORE Developed at Asan Medical Center	*Seok-Hwan Kim (Chungnam National Univ.)*
17:00-17:10	Cross-match as an Immuno-Oncological Risk Factor for Hepatocellular Carcinoma Recurrence and Inferior Survival after Living Donor Liver Transplantation: A Call for Further Investigation	*Cheng-Maw Ho (National Taiwan Univ., Taiwan)*
17:10-17:20	Performance of Artificial Intelligence in Predicting Survival Following Deceased Donor Liver Transplantation: Retrospective Study Using Multi-Center Data from the Korean Organ Transplant Registry (KOTRY)	*Young-Dong Yu (Korea Univ.)*
17:20-17:30	Modified Charlson Comorbidity Index as a Pre-Operative Selection Tool for Liver Transplantation in Elderly Patients	*Jiho Choi (Seoul National Univ.)*
17:30-17:40	Salvage Living Donor Liver Transplantation for Hepatocellular Carcinoma Recurrence after Hepatectomy: Quantitative Prediction Using α-fetoprotein – des-γ-carboxyprothrombin – Tumor Volume (ADV) Score	*Shin Hwang (Univ. of Ulsan)*
17:40-17:50	The Impact of Immunosuppressants on Gut Microbiome of Long-Term Stable Patients after Liver Transplantation	*Soon Kyu Lee (The Catholic Univ. of Korea)*

08:20-09:40	**Special Interest Group Forum 1. Viral Hepatitis: Unresolved Issue for Chronic Hepatitis B Virus Infection**	*Seong Gyu Hwang (CHA Univ.), Jin-Wook Kim (Seoul National Univ.)*
08:20-08:40	Targeting cccDNA for Cure of Hepatitis B Virus Infection	*Kyun-Hwan Kim (Sungkyunkwan Univ.)*
08:40-09:00	Unresolved Issues of Immune Tolerance in Chronic Hepatitis B: Earlier Treatment the Better?	*Hye Won Lee (Yonsei Univ.)*
09:00-09:20	Prognostic Impact of Concurrent Hepatic Steatosis in Chronic Hepatitis B: Can Lifestyle Modification Reduce Hepatocellular Carcinoma Risk?	*Yun Bin Lee (Seoul National Univ.)*
09:20-09:40	Chemopreventive Strategies of HBV-Related Hepatocellular Carcinoma: The Emerging Role of Non-Viral Risk Factors	*Jonggi Choi (Univ. of Ulsan)*
09:40-10:00	Opening Ceremony	
10:00-11:00	**Plenary Presentation 1**	*Byung Ki Kim (Sungkyunkwan Univ.), Han Chu Lee (Univ. of Ulsan), Chul Soo Ahn (Univ. of Ulsan)*
11:00-11:10	Break	
11:10-12:30	**Special Interest Group Forum 2. Korea Nonalcoholic Fatty Liver Study Group: Advanced Knowledge in Nonalcoholic Fatty Liver Disease**	*Jin-Woo Lee (Inha Univ.), Yoon Jun Kim (Seoul National Univ.)*
11:10-11:30	Introduction of the Useful Big Database for Researchers in Nonalcoholic Fatty Liver Disease	*Donghee Kim (Stanford Univ., USA)*
11:30-11:50	Metabolic Associated Fatty Liver Disease and Cardiovascular Disease	*Jian-Gao Fan (Shanghai Jiao Tong Univ., China)*
11:50-12:10	From Nonalcoholic Steatohepatitis to Diabetes vs. from Diabetes to Nonalcoholic Steatohepatitis: Different or Similar in Treatment?	*Yongho Lee (Yonsei Univ.)*
12:10-12:30	How Nonalcoholic Fatty Liver Disease Patients Die: Heart, Liver, or Other Cancers?	*Jeong-Ju Yoo (Soonchunhyang Univ.)*
12:30-13:30	Luncheon Symposium 7 [Ipsen]	
13:30-14:50	**Special Interest Group Forum 3. Korean Autoimmune Liver Disease Study Group: Recent Update on Autoimmune Liver Disease**	*Sook-Hyang Jeong (Seoul National Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.)*
13:30-13:50	Update on Histopathology of Autoimmune Hepatitis	*Haeryoung Kim (Seoul National Univ.)*
13:50-14:10	Interpretation of Autoantibody Tests for Autoimmune Liver Diseases	*Yun-Jong Lee (Seoul National Univ.)*
14:10-14:30	Management of Difficult Cases of Autoimmune Hepatitis and New Therapeutics	*Atsumasa Komori (Nagasaki Univ., Japan)*
14:30-14:50	Update on Management of Primary Biliary Cholangitis	*Kyung-Ah Kim (Inje Univ.)*
14:50-15:00	Break	
15:00-16:20	**Special Interest Group Forum 4. Korean Study Group of Portal Hypertension: Application of Hepatic Venous Pressure Gradient to Clinical Practice**	*Soon Ho Um (Korea Univ.), Young Seok Kim (Soonchunhyang Univ.)*
15:00-15:20	Measurement of Hepatic Venous Pressure Gradient and Its Clinical Significance during TIPS or BRTO/PARTO: Tips and Pitfalls	*Hitoshi Maruyama (Juntendo Univ., Japan)*
15:20-15:40	Application of Hepatic Venous Pressure Gradient for Predicting Prognosis in Liver Cirrhosis	*Young Chang (Soonchunhyang Univ.)*
15:40-16:00	Tailored Treatment of Cirrhotic Complications According to Hepatic Venous Pressure Gradient	*Jung Gil Park (Yeungnam Univ.)*
16:00-16:20	Non-Invasive Estimation of Hepatic Venous Pressure Gradient	*Young Seo Cho (Hanyang Univ.)*
16:20-16:30	Break	

16:30-17:50	**Special Interest Group Forum 5. Korea Alcohol-Related Problems Study Group: New Insight into Alcoholic Hepatitis**	*Dong Joon Kim (Hallym Univ.), Jae Young Jang (Soonchunhyang Univ.)*
16:30-16:50	Microbiome as a Potential Diagnostic Biomarker in Severe Alcoholic Hepatitis	*Soon Sun Kim (Ajou Univ.)*
16:50-17:10	Prognosis and Outcome of Patients with Alcohol-Associated Acute-On-Chronic Liver Failure	*Eileen L. Yoon (Hanyang Univ.)*
17:10-17:30	Clinical, Histological, and Molecular Profiling of Different Stages of Alcohol-Related	*Ramon Bataller (Univ. of Pittsburgh, USA)*
17:30-17:50	Non-Invasive Diagnostic Biomarkers in Alcohol-Related Liver Disease	*Young Kul Jung (Korea Univ.)*

08:40-09:40	**Free Paper Presentation 1 [Basic]**	*Soon Woo Nam (The Catholic Univ. of Korea), Baek-hui Kim Korea (Korea Univ.)*
08:40-08:50	Discovery of Novel Pyrimidine-Based Capsid Assembly Modulators as Potent Anti-HBV Agents	*Yuri Cho (National Cancer Center)*
08:50-09:00	A Fist-in-Class Small Molecule Targeting 17-Beta-Hydroxysteroid Dehydrogenase 13	*Ji Won Choi (Research Institute, HK inno.N)*
09:00-09:10	Intestinal Catecholamine/Hepatic Growth Differentiation Factor 15 Axis as a Homeostatic Keeper in Alcoholic Liver Disease	*Hee-Hoon Kim (KAIST)*
09:10-09:20	Association between Serum TNF-α and Sarcopenia in Liver Cirrhosis	*Ji Won Han (The Catholic Univ. of Korea)*
09:20-09:30	Diagnostic Performance of mRNA Panel as Potential Marker for Recurrence of Hepatocellular Carcinoma	*Ju A Son (Ajou Univ.)*
09:30-09:40	Prominent Portal T Cell Infiltration, rather than Ductulitis, Is an Indicator of Corticosteroid Response in Chronic Hepatic GVHD after Allogeneic Stem Cell Transplantation	*Pil Soo Sung (The Catholic Univ. of Korea)*
09:40-10:00	Opening Ceremony	
10:00-11:00	**Plenary Presentation 1**	*Byung Ki Kim (Sungkyunkwan Univ.), Han Chu Lee (Univ. of Ulsan), Chul Soo Ahn (Univ. of Ulsan)*
11:00-11:10	Break	
11:10-12:30	**Free Paper Presentation 2 [Viral Hepatitis]**	*Sang Hoon Ahn (Yonsei Univ.), Suk Bae Kim (Dankook Univ.)*
11:10-11:20	A Clinico-Epidemiological Study of Acute Hepatitis in Korea: A Prospective Multicenter Study	*Chan Young Jeong (Seoul National Univ.)*
11:20-11:30	The Outcomes of Entecavir, Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamide in Treatment-Naïve Patients with Chronic Hepatitis B Infection	*Hye Yeon Chon (Konyang Univ.)*
11:30-11:40	Association of Concurrent Fatty Liver with Hepatocellular Carcinoma and Mortality in Patients with Chronic Viral Hepatitis	*Mi Na Kim (CHA Univ.)*
11:40-11:50	Association between Daily Aspirin Therapy and Hepatocellular Carcinoma According to Metabolic Risk Factor Burden in Patients with Chronic Hepatitis B	*Cheol-Hyung Lee (The Armed Forces Medical Command)*
11:50-12:00	Cost-Effectiveness of Universal One-time Screening for Hepatitis C in the Korean Population: From a Societal Perspective	*Hye-Lin Kim (Sahmyook Univ.)*
12:00-12:10	Real-World Effectiveness and Safety of SOF/LDV for Patients with Chronic Hepatitis C in Taiwan	*Ming-Lung Yu (Kaohsiung Medical Univ., Taiwan)*
12:10-12:20	Effect of Direct-Acting Antivirals for Hepatitis C Virus-related Hepatocellular Carcinoma Recurrence and Death after Curative Treatment	*Soon Sun Kim (Ajou Univ.)*
12:20-12:30	Long-Term Oncologic Outcomes of Liver Resection for Hepatocellular Carcinoma in Adolescents and Young Adults: A Multicenter Study from a Hepatitis B Virus-Endemic Area	*Tian Yang (Eastern Hepatobiliary Surgery Hospital, China)*
12:30-13:30	Luncheon Symposium 8 [BMS]	

13:30-14:50	**Free Paper Presentation 3 [NAFLD, AIH, Others]**	*Sang Gyune Kim (Soonchunhyang Univ.), Won Kim (Seoul National Univ.)*
13:30-13:40	Efficacy of Sodium Glucose Co-Transporter 2 Inhibitor on a Progression of Nonalcoholic Steatohepatitis in a Murine Steatohepatitis Model	*Young Chang (Soonchunhyang Univ.)*
13:40-13:50	Exogenous 8-Hydroxydeoxyguanosine Prevents Liver Fibrosis through the Inhibition of Rac1-NADPH Oxidase Signaling in a Nonalcoholic Steatohepatitis Model	*Seung Kak Shin (Gachon Univ.)*
13:50-14:00	Diagnosis of Fatty Liver Using BIA: Comparison with Abdominal Ultrasound and CAP Score of Transient Elastography	*Jin Wook Choi (Soonchunhyaung Univ.)*
14:00-14:10	The Role of Genetic and Epigenetic Factors in Disease Development and Progression in Nonalcoholic Fatty Liver Disease	*Soo Min Bang (Korea Univ.)*
14:10-14:20	Effects of PNPLA3, TM6SF2, and SAMM50 on the Development and Severity of Nonalcoholic Fatty Liver Disease in Children	*Kyung Jae Lee (Hallym Univ.)*
14:20-14:30	The Association between Breastfeeding and Non-Alcoholic Fatty Liver Disease in Parous Women: A Nationwide Cohort Study	*Yewan Park (Sungkyunkwan Univ.)*
14:30-14:40	Metabolic Dysfunction Associated Fatty Liver Disease Identifies Patients with Cardiovascular Disease Risk Better Than Nonalcoholic Fatty Liver Disease	*Ho Soo Chun (Ewha Womans Univ.)*
14:40-14:50	Metabolic Dysfunction-Associated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study	*Hye Won Lee (Yonsei Univ.)*
14:50-15:00	Break	
15:00-16:20	**Free Paper Presentation 4 [Liver Cancer, Basic]**	*Won Young Tak (Kyungpook National Univ.), Yong-Han Paik (Sungkyunkwan Univ.)*
15:00-15:10	RalA Is Negatively Regulated by RalGAPA2 and Positively Regulated by Specific Transcription Factors to Exert Its Oncogenic Functions in HCC	*Lu Tian (The Univ. of Hong Kong, Hong Kong)*
15:10-15:20	SMAC-Survivin Apoptotic "Switch" Is Regulated through the PI3K- Src-p at the α1- Na/K-ATPase in NASH Related Hepatocellular Carcinoma: Studies In-Vitro/Vivo and in Humans	*Juan Sanabria (Marshall and Case Western Reserve Univ., USA)*
15:20-15:30	Circulating Exosomal LncRNA-ATB Promotes Myopenia in Human Hepatocellular Carcinoma	*Yu Rim Lee (Kyungpook National Univ.)*
15:30-15:40	Extracellular Vesicle-Derived Polymeric Immunoglobulin Receptor (pIgR) Activates PDK1/Akt/GSK3β/β-catenin Signaling to Drive Cancer Stemness and Tumorigenesis in Hepatocellular Carcinoma	*Samuel Wong Wan Ki (The Univ. of Hong Kong, Hong Kong)*
15:40-15:50	Significance of Telomerase Reverse Transcriptase Gene and Telomere Length with Clinical Phenotype of Hepatocellular Carcinoma	*Jin Seoub Kim (The Catholic Univ. of Korea)*
15:50-16:00	Clinical and Biological Implications of Cell Cycle-Related Gene Fusions and Mutations in Resectable Hepatocellular Carcinoma	*Jihyun An (Hanyang Univ.)*
16:00-16:10	Immunotherapy Biomarker-Based Classification and Its Potential Clinical Usefulness in Hepatocellular Carcinoma	*Jihyun An (Hanyang Univ.)*
16:10-16:20	Preferential Expression of Programmed Death-Ligand 1 Protein in Tumor-Associated Macrophages and Its Potential Role in Immunotherapy for Hepatocellular Carcinoma	*Dong Jun Park (The Catholic Univ. of Korea)*
16:20-16:30	Break	
16:30-18:00	**KLTS Coordinator Session** (*K)	*Kyung-Ock Jeon (Severance Hospital), Seung Heui Hong (Samsung Medical Center)*
16:30-17:05	Latest Treatment Drugs for Hepatitis B and C and Treatment of Hepatitis D and E	*Wonseok Kang (Sungkyunkwan Univ.)*
17:05-17:40	What Are the Optimal Time and Proper Indication for Simultaneous Liver-Kidney Transplantation?	*Man Ki Ju (Yonsei Univ.)*
17:40-18:00	Latest Issues in the Liver Transplant Site	*Hyung Sook Kim (Seoul ST. Mary's Hospital)*

PROGRAM AT A GLANCE

DAY 3 Saturday, May 15, 2021

K Session in Korean

	ROOM 1	ROOM 2	ROOM 3	ROOM4	ROOM 5
08:00	Listen to the Expert Viral Hepatitis K (08:00-08:30)	Listen to the Expert HCC K (08:00-08:30)	Breakfast Symposium 4 [GC] (07:50-08:30)		
09:00	KASL Symposium 4 (08:30-09:50)	KASL-KAHBPS-KLCA-KLTS Joint Symposium (08:30-09:50)		Publication Forum (08:30-09:50)	Free Paper Presentation 7 [Alcohol, Liver Cirrhosis] (08:30-09:50)
10:00	Break (09:50-10:00)				
	Plenary Presentation 2 (10:00-11:00)				
11:00	Break (11:00-11:10)				
12:00	State-of-the-Art Lectures (11:10-11:45) Break (11:45-11:50) KASL Clinical Practice Guideline K (11:50-12:30)	LCSGJ-KLCA Joint Symposium (11:10-12:30)	KAHBPS Symposium 1 (11:10-12:30)	US Education for Trainee K (11:10-12:30)	Free Paper Presentation 8 [Liver Cancer, Clinical] (11:10-12:30)
13:00	Luncheon Symposium 9 [Gilead] (12:30-13:30)	Luncheon Symposium 10 [Eisai] (12:30-13:30)	Luncheon Symposium 11 [Ildong] (12:30-13:30)	Luncheon Symposium 12 [Bukwang] (12:30-13:30)	
14:00	KASL Plenary Presentation (13:30-14:50)	KASL-KLCA Joint Symposium K (13:30-14:50)	KAHBPS Special Lecture (13:30-14:50)	Essential Hepatology for Clinicians K (13:30-14:50)	Free Paper Presentation 9 [Surgery, Technical Issues] (13:30-14:50)
15:00	Break (14:50-15:00)				
16:00	KASL Symposium 5 (15:00-16:20)	Free Paper Presentation 10 [Liver Cancer, Clinical] (15:00-16:20)	KAHBPS Symposium 2 (15:00-16:20)	Associate Course K (15:00-16:20)	Free Paper Presentation 11 [Biliary and Pancreatic Disease] (15:00-16:20)
	Break (16:20-16:30)				
17:00	The Liver Week 2021 Debrief K (16:30-17:30)				
18:00	Closing & Award Ceremony (17:30-18:00)				

08:00-08:30	**Listen to the Expert** [*K]	*Moderator: Dong Hyun Sinn (Sungkyunkwan Univ.)*
08:00-08:30	Viral Hepatitis: The Path I have Taken as a Clinician and Researcher of Viral Hepatitis	*Kwang-Hyub Han (NECA)*
08:30-09:50	**KASL Symposium 4. Recent Advances in the Management of Liver Diseases**	*Il Han Song (Dankook Univ.), Sang Hoon Park (Hallym Univ.)*
08:30-08:50	ABO-Incompatible Liver Transplantations: Achievements and Remaining Questions	*Jong Man Kim (Sungkyunkwan Univ.)*
08:50-09:10	Management of Immune-Related Adverse Events Caused by Immune Checkpoint Inhibitors	*Tae Yong Kim (Seoul National Univ.)*
09:10-09:30	Early TIPS for Improving Outcomes of Acute Variceal Bleeding: Who Are the Appropriate Candidates?	*Guohong Han (Fourth Military Medical Univ., China)*
09:30-09:50	Clinical Application of Liquid Biopsy as a Prognostic Biomarker in Hepatocellular Carcinoma	*Soo Young Park (Kyungpook National Univ.)*
09:50-10:00	Break	
10:00-11:00	**Plenary Presentation 2**	*Kwan Soo Byun (Korea Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.), Hyeon Kook Lee (Ewha Womans Univ.)*
10:00-10:15	Diagnostic Performance of Magnetic Resonance Imaging, Vibration-Controlled Transient Elastography and Controlled Attenuation Parameter in Predicting Steatohepatitis in NAFLD Patients	*Sun Young Yim (Korea Univ.)*
10:15-10:30	The Artificial Intelligence-Driven Model for Prediction of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients: Derivation and Validation Using 13,508 Patients from Asian and Caucasian Cohorts	*Hwi Young Kim (Ewha Womans Univ.)*
10:30-10:45	ADV Score Is a Quantifiable Prognostic Prediction Model for Surgical Resection of Hepatocellular Carcinoma: A Korea-Japan Collaboration Validation Study with 10,606 Patients	*Shin Hwang (Univ. of Ulsan)*
10:45-11:00	Activation of Metabotropic Glutamate Receptor 5 Ameliorates Liver Fibrosis through Cytotoxicity of NK Cells against Hepatic Stellate Cells	*Tom Ryu (KAIST)*
11:00-11:10	Break	
11:10-11:45	**State-of-the-Art Lecture**	*Sook-Hyang Jeong (Seoul National Univ.)*
11:10-11:45	Novel Insights of Translational Research in Nonalcoholic Steatohepatitis and Fibrosis	*Scott Friedman (Icahn School of Medicine, USA)*
11:45-11:50	Break	
11:50-12 :30	**KASL Clinical Practice Guideline** [*K]	*Dong Joon Kim (Hallym Univ.)*
11:50-12:30	KASL Clinical Practice Guidelines	*Yong Kyun Cho (Sungkyunkwan Univ.)*
12:30-13:30	Luncheon Symposium 9 [Gilead]	

13:30-14:50	**KASL Plenary Presentation**	*Oh Sang Kwon (Gachon Univ.), Tae Hun Kim (Ewha Womans Univ.)*
13:30-13:43	Gut Microbiome and Metabolomic Signatures in Alcoholic Liver Disease	*Raja Ganesan (Hallym Univ.)*
13:43-13:56	Impact of Expanding Antiviral Treatment Criteria at a Population Level in the Republic of Korea: A Modeling Analysis	*Young-Suk Lim (Univ. of Ulsan)*
13:56-14:09	An External Validation of FibroScan-AST Score (FAST) for Non-Invasive Identification of Patients at Risk of Progressive Non-Alcoholic Steatohepatitis	*Jae Seung Lee (Yonsei Univ.)*
14:09-14:22	Sarcopenia and Myosteatosis Are Independent Predictors for Long-Term Mortality in Korean Liver Cirrhosis Patients	*Han Ah Lee (Inje Univ.)*
14:22-14:35	Cancer Associated Fibroblast Derived SPP1 is the Potential Therapeutic Target of Sorafenib and Lenvatinib Resistance in Hepatocellular Carcinoma	*Hyo Jung Cho (Ajou Univ.)*
14:35-14:48	Clinical Aspect of Coronavirus Disease 2019 (COVID-19) on HBV Infected Patient	*Young Kul Jung (Korea Univ.)*
14:50-15:00	Break	
15:00-16:20	**KASL Symposium 5. Controversial Issues Pertaining to Fatty Liver Diseases**	*Joo Hyun Sohn (Hanyang Univ.), Yong Kyun Cho (Sungkyunkwan Univ.)*
15:00-15:15	MAFLD vs. NAFLD: What's in a Name? Pros: Not Just a Name	*Jacob George (The Univ. of Sydney, Australia)*
15:15-15:30	MAFLD vs. NAFLD: What's in the Name? Cons: Premature Proposition	*Ajay Duseja (PGIMER, India)*
15:30-15:40	Discussion	
15:40-15:55	Which Is the More Appropriate Surrogate and Target? Liver Fibrosis and/or Inflammation	*Vincent Wong (The Chinese Univ. of Hong Kong, Hong Kong)*
15:55-16:10	Which Is the More Appropriate Surrogate and Target? Metabolic Factors and/or Steatosis	*Dae Won Jun (Hanyang Univ.)*
16:10-16:20	Discussion	
16:20-16:30	Break	
16:30-17:30	**The Liver Week 2021 Debrief** [*K]	*Ji Hoon Kim (Korea Univ.), Kang Mo Kim (Univ. of Ulsan), Dong-Sik Kim (Korea Univ.)*
16:30-16:45	The Korean Association for the Study of the Liver (KASL)	
16:45-17:00	The Korean Association of Hepato-Biliary-Pancreatic Surgery (KAHBPS)	
17:00-17:15	The Korean Liver Cancer Association (KLCA)	
17:15-17:30	The Korean Liver Transplantation Society (KLTS)	
17:30-18:00	Closing & Award Ceremony	

(*K): Session in Korean

08:00-08:30	**Listen to the Expert** (*K)	*Moderator: Do Young Kim (Yonsei Univ.)*
08:00-08:30	The Path I have Taken as a Clinician and Researcher with Hepatocellular Carcinoma	*Joong-Won Park (National Cancer Center Korea)*
08:30-09:50	**KASL-KAHBPS-KLCA-KLTS Joint Symposium. New Perspective in Intrahepatic Cholangiocarcinoma**	*Ho Seong Han (Seoul National Univ.), Kwang Cheol Koh (Sungkyunkwan Univ.), Baek-Yeol Ryoo (Univ. of Ulsan)*
08:30-08:50	Intrahepatic Cholangiocarcinoma: Tumour Heterogeneity and Its Clinical Relevance	*Mina Komuta (Int'l Univ. of Health and Welfare, Japan)*
08:50-09:10	Differential Diagnosis between Hepatocellular Carcinoma and Cholangiocarcinoma through Radiology	*Ijin Joo (Seoul National Univ.)*
09:10-09:30	Update of Treatment in Intrahepatic Cholangiocarcinoma: Resection and Transplantation	*Gonzalo Sapisochin (Univ. of Toronto, Canada)*
09:30-09:50	Update of Treatment in Intrahepatic Cholangiocarcinoma: Systemic Therapy	*Hong Jae Chon (CHA Univ.)*
09:50-10:00	Break	
10:00-11:00	**Plenary Presentation 2**	*Kwan Soo Byun (Korea Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.), Hyeon Kook Lee (Ewha Womans Univ.)*
11:00-11:10	Break	
11:10-12:30	**LCSGJ-KLCA Joint Symposium. Updates on Molecular Signatures of Hepatocellular Carcinoma**	*Jin Wook Chung (Seoul National Univ.), Young Nyun Park (Yonsei Univ.)*
11:10-11:30	Hepatocellular Carcinoma Tumor Microenvironment	*Yutaka Kurebayashi (Keio Univ., Japan)*
11:30-11:50	Genetic and Molecular/Immune Profiling Analyses for Hepatocellular Carcinoma	*Naoshi Nishida (Kindai Univ., Japan)*
11:50-12:10	Hepatocellular Carcinoma Molecular Pathological Classification and Its Practical Applications	*Haeryoung Kim (Seoul National Univ.)*
12:10-12:30	Hepatocellular Carcinoma Progenitor Phenotype: K19 and Hepatocellular Carcinoma	*Hyungjin Rhee (Yonsei Univ.)*
12:30-13:30	Luncheon Symposium 10 [Eisai]	
13:30-14:50	**KASL-KLCA Joint Symposium. Technical Innovation: Approach to Liver Disease Utilizing Artificial Intelligence** (*K)	*Jin-Wook Kim (Seoul National Univ.), Young Seok Kim (Soonchunhyang Univ.)*
13:30-13:50	Technical Innovation of Artificial Intelligence in Liver Diseases from Idea to Idealization	*Namkug Kim (Univ. of Ulsan)*
13:50-14:10	Artificial Intelligence and Clinical Application Pertinent to Liver Disease	*Kwang Gi Kim (Gachon Univ.)*
14:10-14:30	Radiomics and Deep Learning: Focal Liver Disease and Tumor Detection	*Woo Kyoung Jeong (Sungkyunkwan Univ.)*
14:30-14:50	Risk Assessment and Decision Making of Hepatocellular Carcinoma Treatment through Artificial Intelligence	*Gwang Hyeon Choi (Seoul National Univ.)*
14:50-15:00	Break	

(*K): Session in Korean

15:00-16:20	**Free Paper Presentation 10 [Liver Cancer, Clinical]**	*Tae Hee Lee (Konyang Univ.), Do Young Kim (Yonsei Univ.)*
15:00-15:10	A comparative Study of Microwave and Radiofrequency Ablation Therapy for Hepatocellular Carcinoma	*Soon Kyu Lee (The Catholic Univ. of Korea)*
15:10-15:20	Comparison of Dexamethasone and Celecoxib for Prophylaxis for Transarterial Chemoembolization	*Min-Woo Chung (Chonnam National Univ.)*
15:20-15:30	Transarterial Chemoembolization plus Radiotherapy as a First-Line Treatment for Liver-Confined Hepatocellular Carcinoma with Macroscopic Vascular Invasion: Significance of Early Response	*Jinhong Jung (Univ. of Ulsan)*
15:30-15:40	Benefits of Local Treatment Including External Radiotherapy for Hepatocellular Carcinoma with Portal Invasion	*Chai Hong Rim (Korea Univ.)*
15:40-15:50	Comparison of Lenvatinib and Hepatic Arterial Infusion Chemotherapy on the Efficacy and Safety in Unresectable HCC: A Multi-Center, Propensity Score Analysis	*Jaejun Lee (The Catholic Univ. of Korea)*
15:50-16:00	Comparison of the Effects between Sorafenib and Lenvatinib as the First-Line Systemic Chemotherapy in HBV Associated Hepatocellular Carcinoma with Real-World Data	*Na Ryung Choi (Seoul National Univ.)*
16:00-16:10	Effectiveness of Lenvatinib versus Sorafenib for Unresectable Hepatocellular Carcinoma in Patients with Hepatic Decompensation	*Min Kyung Park (Seoul National Univ.)*
16:10-16:20	Real-World Experience of Atezolizumab/Bevacizumab in Hepatocellular Carcinoma	*Yeonjung Ha (CHA Univ.)*
16:20-16:30	Break	
16:30-17:30	**The Liver Week 2021 Debrief** (*K)	
17:30-18:00	Closing & Award Ceremony	

07:50-08:30	Breakfast Symposium 4 [GC]	
08:30-09:50	**KASL-KAHBPS-KLCA-KLTS Joint Symposium. New Perspective in Intrahepatic Cholangiocarcinoma**	
09:50-10:00	Break	
10:00-11:00	**Plenary Presentation 2**	*Kwan Soo Byun (Korea Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.), Hyeon Kook Lee (Ewha Womans Univ.)*
11:00-11:10	Break	
11:10-12:30	**KAHBPS Symposium 1. How to Achieve R0 Resection in Perihilar Cholangiocarcinoma Both Successfully and Safely**	*Chol Kyoon Cho (Chonnam National Univ.), Yang Won Nah (Univ. of Ulsan)*
11:10-11:30	Various Types of Vascular Resection and Reconstruction in Perihilar Cholangiocarcinoma	*Shin Hwang (Univ. of Ulsan)*
11:30-11:50	Surgical Resection for Longitudinally Infiltrative Perihilar Cholangiocarcinoma	*Yajin Chen (Sun Yat-Sen Univ., China)*
11:50-12:10	Transhepatic Hilar Approach for Perihilar Cholangiocarcinoma	*Naohisa Kuriyama (Mie Univ., Japan)*
12:10-12:30	Real Practice of Surgical Resection Following Neoadjuvant Chemoradiation Therapy in Perihilar Cholangiocarcinoma	*Gi Hong Choi (Yonsei Univ.)*
12:30-13:30	Luncheon Symposium 11 [Ildong]	
13:30-14:50	**KAHBPS Special Lecture**	*Hee Chul Yu (Jeonbuk National Univ.), Sang-Jae Park (National Cancer Center Korea)*
13:30-14:00	Solving the Equations of Portal Flow, Liver Regeneration, and Posthepatectomy Liver Failure	*Eric Vibert (Paris-Sud Univ., France)*
14:00-14:10	Discussion	
14:10-14:40	Clinicopathological Characteristics of Intraductal Papillary Neoplasm of the Bile Duct (IPNB): Surgeons' Point of View	*Keiichi Kubota (Dokkyo Medical Univ., Japan)*
14:40-14:50	Discussion	
14:50-15:00	Break	
15:00-16:20	**KAHBPS Symposium 2. Critical Thinking for Surgical Treatment of Metastatic Liver Tumor**	*Kyung Sik Kim (Yonsei Univ.), Ki-Hun Kim (Univ. of Ulsan)*
15:00-15:20	Oncologist's View of Determining Optimal Timing of Hepatectomy	*Myung Ah Lee (The Catholic Univ. of Korea)*
15:20-15:40	The Effects of Chemotherapy Associated Liver Injury (CALI) on Outcomes Following Hepatectomy	*Jai Young Cho (Seoul National Univ.)*
15:40-16:00	Surgical Treatment of Metastatic Neuroendocrine Tumors	*Jan Lerut (Université Catholique de Louvain, Belgium)*
16:00-16:20	To Do or Not To Do?: Non-Colorectal Liver Metastasis	*Sae Byeol Choi (Korea Univ.)*
16:20-16:30	Break	
16:30-17:30	**The Liver Week 2021 Debrief** (*K)	
17:30-18:00	Closing & Award Ceremony	

[*K]: Session in Korean

08:30-09:50	**Publication Forum**	*Yoon Jun Kim (Seoul National Univ.), Seung Up Kim (Yonsei Univ.)*
08:30-08:45	Tips to Write a Paper and Get It Published in High Impact Journals	*W. Ray Kim (Stanford Univ., USA)*
08:45-09:00	Sharing Experience in Handling High Impact Journal	*Yoshiyuki Ueno (Yamagata Univ., Japan)*
09:00-09:15	Long Journey of CMH to Be an International Journal	*Yoon Jun Kim (Seoul National Univ.)*
09:15-09:30	Further Step to Be a Valuable Journal	*Seung Up Kim (Yonsei Univ.)*
09:30-09:50	Discussion	
09:50-10:00	Break	
10:00-11:00	**Plenary Presentation 2**	*Kwan Soo Byun (Korea Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.), Hyeon Kook Lee (Ewha Womans Univ.)*
11:00-11:10	Break	
11:10-12:30	**Education for Ultrasonography Trainee** [*K]	*Hong Soo Kim (Soonchunhyang Univ.), Jaeyoun Cheong (Ajou Univ.)*
11:10-11:40	Normal Liver Anatomy and Basic Ultrasonography Scan Techniques	*Sang Gyune Kim (Soonchunhyang Univ.)*
11:40-12:05	Diffuse Liver Disease	*Baek Gyu Jun (Inje Univ.)*
12:05-12:30	Ultrasonography for Focal Liver Lesions: Focusing on Cases	*Sun Hong Yoo (The Catholic Univ. of Korea)*
12:30-13:30	Luncheon Symposium 12 [Bukwang]	
13:30-14:50	**Essential Hepatology for Clinicians** [*K]	*Se Hyun Cho (The Catholic Univ. of Korea), Chang Hyeong Lee (Daegu Catholic Univ.)*
13:30-13:50	Typical Histological Findings Pertaining to Parenchymal Liver Diseases	*Baek-hui Kim (Korea Univ.)*
13:50-14:10	Radiological Assessment of Hepatic Steatosis and Fibrosis	*So Yeon Kim (Univ. of Ulsan)*
14:10-14:30	The Practical Process of Enlisting, Allocation, and Operation of Liver Transplantation	*YoungRok Choi (Seoul National Univ.)*
14:30-14:50	Drug-Induced Liver Injury: Update and Clinical Application	*Eun Young Cho (Wonkwang Univ.)*
14:50-15:00	Break	
15:00-16:20	**Associate Course** [*K]	*Soo Hyung Ryu (Inje Univ.), Won Hyeok Choe (Konkuk Univ.)*
15:00-15:20	Interpreting More Than You Know: Liver Disease-Related Testing	*Yang Hyun Baek (Dong-A Univ.)*
15:20-15:40	Seems Complicated but Actually Quite Simple: Antiviral Therapy	*Young Youn Cho (Chung-Ang Univ.)*
15:40-16:00	Information of Welfare Service for the Patients with Liver Disease	*Kyoung Ae Lee (Hallym Univ. Sacred Heart Hospital)*
16:00-16:20	Realizing Your Dream of Becoming the Best Clinical Research Coordinator a Reality	*Sunyoun Youn (Asan Medical Center)*
16:20-16:30	Break	
16:30-17:30	**The Liver Week 2021 Debrief** [*K]	
17:30-18:00	Closing & Award Ceremony	

08:30-09:40	**Free Paper Presentation 7 [Alcohol, Liver Cirrhosis]**	*Jung Il Lee (Yonsei Univ.), Yeon Seok Seo (Korea Univ.)*
08:30-08:40	Diagnostic Efficacy of Serum Asialo α1-Acid Glycoprotein Levels for Liver Fibrosis and Cirrhosis in CHB Compared to Healthy Subjects: A Prospective Study	*Yoon Seok Lee (Korea Univ.)*
08:40-08:50	Lactobacillus and Pediococcus Attenuates the Progression of Alcoholic Liver Disease by Improving Inflammation	*Hyeong Seop Kim (Hallym Univ.)*
08:50-09:00	Impact of Previous Compensation on Tolerance to Acute-on-Chronic Liver Failure	*Eileen L. Yoon (Hanyang Univ.)*
09:00-09:10	Hepatopulmonary Syndrome is Related to the Development of Acute-on-Chronic Liver Failure and Poor Prognosis in Cirrhotic Patients	*Seul Ki Han (Yonsei Univ. Wonju)*
09:10-09:20	A Model to Predict Survival in Patients Undergoing Portosystemic Shunt Embolization	*Seo Yeon Yoo (Univ. of Ulsan)*
09:20-09:30	Elevated Transaminase Level at Admission as an Independent Predictor for Mortality in Coronavirus Disease 2019	*Hea-Eun Kim (Seoul National Univ.)*
09:30-09:40	A Nationwide Study of Pyogenic Liver Abscess in Korea: Incidence, Mortality, and Temporal Trends during 2007-2017	*Tae Kyu Lee (Soonchunhyang Univ.)*
09:50-10:00	Break	
10:00-11:00	**Plenary Presentation 2**	*Kwan Soo Byun (Korea Univ.), Joon Hyeok Lee (Sungkyunkwan Univ.), Hyeon Kook Lee (Ewha Womans Univ.)*
11:00-11:10	Break	
11:10-12:30	**Free Paper Presentation 8 [Liver Cancer, Clinical]**	*Dongho Choi (Hanyang Univ.), Woo Jin Chung (Keimyung Univ.)*
11:10-11:20	Prediction of Microvascular Invasion via Gadoxetic Acid-Enhanced MRI in Hepatocellular Carcinoma: The Implication of Planning Extent of the Hepatectomy	*Hyeo Seong Hwang (Yonsei Univ.)*
11:20-11:30	Comparison of Overall Survival between Surgical Resection and Radiofrequency Ablation for Early Hepatitis B-Related Hepatocellular Carcinoma after Adjusting Antiviral Treatment	*Moonhaeng Hur (Seoul National Univ.)*
11:30-11:40	The Effectiveness of Transarterial Radioembolization for Large Single Nodular Hepatocellular Carcinoma: A Comparison to Surgical Resection	*Jihye Kim (Seoul National Univ.)*
11:40-11:50	Models for Tumor Recurrence after Liver Transplantation can Predict Early Recurrence after Curative Liver Resection in Solitary Hepatocellular Carcinoma	*Sung Joon Kim (Sungkyunkwan Univ.)*
11:50-12:00	Liver Transplantation for Combined Hepatocellular Carcinoma and Cholangiocarcinoma in Korea	*Jong Man Kim (Sungkyunkwan Univ.)*
12:00-12:10	Impact of Anatomical Liver Resection for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis	*Seong Wook Shin (Keimyung Univ.)*
12:10-12:20	Long-Term Surgical Outcomes of Liver Resection for Hepatocellular Carcinoma in Patients with HBV and HCV Co-Infection: A Multicenter Observational Study	*Tian Yang (Eastern Hepatobiliary Surgery Hospital, China)*
12:20-12:30	Prognostic Significance of the Microscopic Serosal Invasion in Hepatocellular Carcinoma	*Incheon Kang (CHA Univ.)*
12:30-13:30	Lunch	

13:30-14:50	**Free Paper Presentation 9 [Surgery, Technical Issues]**	*Yang-Seok Koh (Chonnam National Univ.), Young Seok Han (Kyungpook National Univ.)*
13:30-13:40	Surgical Resection of Huge Hepatocellular Carcinoma: Prognostic Factors and Outcomes in a Mexican Cohort Study	*Carlos Florez-Zorrilla (Hospital Puerta de Hierro Andares Guadalajara, Mexico)*
13:40-13:50	Randomized Controlled Trial to Evaluate a New Sealant to Prevent Biliary Fistula in Liver Surgery: Should We Reconsider Bile Leak Classification?	*Matteo Maria Cimino (Humanitas Clinical and Research Center, Italy)*
13:50-14:00	Laparoscopic and Robotic Volume Preserving Major Hepatectomy	*Jin Hong Lim (Yonsei Univ.)*
14:00-14:10	A Novel Online Calculator for Estimating Survival Benefit of Adjuvant TACE in Patients Undergoing Surgery for HCC	*Tian Yang (Eastern Hepatobiliary Surgery Hospital, China)*
14:10-14:20	A Scoring System to Predict the Risk of Postoperative Complications after Laparoscopic Liver Resection in Elderly Hepatocellular Carcinoma Patients	*Boram Lee (Seoul National Univ.)*
14:20-14:30	Institutional Experience and Clinical Outcomes of Robotic Major Hepatectomy for Liver Tumors	*Iswanto Sucandy (Digestive Health Institute, USA)*
14:30-14:40	Simultaneous Ipsilateral Dual (DSM-TACE and PVE) Embolization (SIDE technique) for Preoperative Augmentation of Future Liver Remnant (FLR) in Patients with Solid Liver Malignancies	*Korshak Oleksandr (National Institute of Surgery and Transplantology, Ukraine)*
14:50-15:00	Break	
15:00-16:20	**Free Paper Presentation 11 [Biliary and Pancreatic Disease]**	*Wan Bae Kim (Korea Univ.), Chi-Young Jeong (Gyeongsang National Univ.)*
15:00-15:10	5-Year Study Results of Simultaneous Pancreas Resection during Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy	*Hanife Şeyda ÜLGÜR (Health Sciences Univ., Turkey)*
15:10-15:20	MCT4 as a Potential Therapeutic Target to Augment Gemcitabine Chemosensitivity in Resected Pancreatic Cancer	*Sung Hwan Lee (CHA Univ.)*
15:20-15:30	"Anatomic" Liver Resection Performed by Approaching the Umbilical Plate for Perihilar Cholangiocarcinoma	*Ji Su Kim (Yonsei Univ.)*
15:30-15:40	Precision Strategy Based on Cancer-Specific Molecular Subtypes of Bile Duct Cancer from Comprehensive Analysis Using Multi-Omics Dataset	*Sung Hwan Lee (CHA Univ.)*
15:40-15:50	The Comparison of Short-Term Postoperative Outcomes between Upfront Surgery and Surgery following Neoadjuvant Treatment in Pancreatic Ductal Adenocarcinoma	*Ji Hye Jung (Sungkyunkwan Univ.)*
15:50-16:00	Does Timing of Completion Radical Cholecystectomy Determine the Survival Outcome in Incidental Carcinoma Gallbladder -A Single Center Retrospective Analysis	*Rahul R (Sanjay Gandhi Post Graduate Institute of Medical Sciences, India)*
16:00-16:10	Organ Preserving Pancreatic Resections Offers Better Long-Term Conservation of Pancreatic Function at the Expense of Significantly High Perioperative Major Morbidity - A Fair Trade-Off for Benign or Low Malignant Potential Pancreatic Neoplasms	*Vikas Gupta (TATA Memorial Hospital, India)*
16:10-16:20	Impact of Neoadjuvant Chemoradiotherapy on Post-Operative Clinically Significant Pancreatic Fistula - A Systemic Review and Updated Meta-Analysis	*Bhavin Vasavada (Shalby Hospitals, India)*
16:20-16:30	Break	
16:30-17:30	**The Liver Week 2021 Debrief** [*K]	
17:30-18:00	Closing & Award Ceremony	

CONTENTS

DAY 1 Thursday, May 13, 2021

Research Workshop 1. Indispensable Novel Techniques for the Study of Liver Disease

Basic Research Symposium 1. Stress-Induced Fates of Hepatocyte in Nonalcoholic Steatohepatitis and Alcoholic Steatohepatitis

Research Workshop 2. Established Translational Techniques for the Study of Liver Disease

Basic Research Symposium 2. Intrinsic and Multifactorial Contribution to Cirrhosis and Hepatocellular Carcinoma

CONTENTS

Health Insurance Forum

Health Policy Forum. Hepatitis C Virus Elimination: Lesson from Worldwide Progress

DAY 2 Friday, May 14, 2021

KASL Symposium 1. Personalized Medicine in Liver Diseases: "Present and Future"

Young Investigators of the Year Session

KASL Symposium 2. Current Issues and Future Therapy for Chronic Hepatitis B

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

Associate Course

CONTENTS

Plenary Session 1

Plenary Session 2

KASL Plenary Sesssion

CONTENTS

Free Paper Session 1

1. Basic

2. Viral Hepatitis

3. NAFLD, AIH, others

4. Liver Cancer, Basic

5. Liver Cancer, Clinical

6. Liver Transplantation

Free Paper Session 2

7. Alcohol, Liver Cirrhosis

CONTENTS

8. Liver Cancer, Clinical

9. Surgery, Technical Issues

10. Liver Cancer, Clinical

11. Biliary and Pancreatic Disease

Free Paper VOD Presentation

1. Basic

2. Hepatitis B Virus

CONTENTS

CONTENTS

3. Hepatitis C Virus

4. Alcoholic Liver Disease

CONTENTS

5. Cirrhosis/Liver Fibrosis

6. Drug Induced Liver Injury

7. Nonalcoholic Fatty Liver Disease

CONTENTS

CONTENTS

8. Liver Cancer_Basic

9. Liver Cancer_Clinical

CONTENTS

10. Liver Transplantation

CONTENTS

11. Biliary and Pancreatic Disease

CONTENTS

12. Surgery, Technical Issues

13. Others

E-Poster Exhibition

1. Hepatitis B Virus

CONTENTS

2. Hepatitis C Virus

CONTENTS

7. Nonalcoholic Fatty Liver Disease

8. Liver Cancer

CONTENTS

9. Liver Transplantation

CONTENTS

10. Biliary and Pancreatic Disease

CONTENTS

11. Surgery, Technical Issues

12. Others

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (09:00-10:30)

ROOM 2

Research Workshop 1

Indispensable Novel Techniques for the Study of Liver Disease

Chairs:

So-Young Jin (Soonchunhyang Univ.)

Youngmi Jung (Pusan National Univ.)

Single-Cell Multi-Omics Approaches to Understand Human Development and Aging

Jong-Eun Park

Korea Advanced Institute of Science and Technology, Korea

Single-cell genomics approaches are opening a new way to understand complex biological phenomenon, such as human development and aging. Human blood and immune systems develop in parallel during early prenatal life, starting from the liver hematopoiesis and migrating to the bone marrow. T cell development starts from the thymus. We and others have profiled the onset of human hematopoiesis by profiling the developing organs at single-cell level. In this lecture, I will discuss about the current development in single-cell genomics techniques, and their application on human immune system development.

The thymus is the critical organ for T-cell development and T-cell receptor (TCR) repertoire formation, which shapes the landscape of adaptive immunity. While the thymus has been extensively studied using diverse animal models, the detailed atlas of human thymus is required to understand human immunity. To provide a comprehensive atlas of thymic cells across human life, we performed scRNAseq using dissociated cells from human thymus during development, childhood and adult life. We identified more than 50 different cell states in the human thymus, which dynamically change in abundance and gene expression profiles across development, paediatric and adult life. We computationally predicted the trajectory of human T-cell development from early progenitors in the hematopoietic fetal liver into diverse mature T cell types. Using this trajectory, we constructed a framework of putative transcription factors driving T-cell fate determination. Among thymic unconventional T cells, we noted a distinct subset of CD8αα+T cells, which is marked by GNG4 expression and uniquely located in the peri-medullary region of the thymus. This subset expressed high levels of XCL1 and co-localised with XCR1+ dendritic cells (DC1). Finally, we identified a strong bias in human VDJ usage shaped by recombination and multiple rounds of selection, including a TCRα V-J bias for CD8+ T cells. Our single-cell transcriptome profile of the thymus across human lifetime and across species provides a high-resolution census of T-cell development within the native tissue microenvironment. Systematic comparison between human and mouse thymus highlights human-specific cell states and gene expression signatures. Our detailed cellular network of the thymic niche for T-cell development will aid the establishment of in vitro organoid culture models that faithfully recapitulate human in vivo thymic tissue.

Transplantation of Bioengineered Livers into Immunosuppressed Pigs

Dong Jin Joo

Yonsei University, Korea

Organ shortage is a big hurdle for organ transplantation. Many end stage liver disease patients still died not having a chance of liver transplantation. There have been many efforts to overcome this hurdle to deal with various methods including bioartificial machine, tissue-engineered liver graft, or genetically engineered liver tissue.

Out of them, one of the promising tools could be the bioengineered liver graft. Many research teams are working on making the bioengineered liver graft from pigs. However, implanted bioengineered livers have not exceeded three days of continuous perfusion. Here we show that decellularized whole porcine livers revascularized with human umbilical vein endothelial cells and implanted heterotopically into immunosuppressed pigs whose spleens had been removed can sustain perfusion for up to 15 days. We identified peak glucose consumption rate as a main predictor of the patency of the revascularized bioengineered livers (rBELs). Heterotopic implantation of rBELs into pigs in the absence of anticoagulation therapy led to sustained perfusion for three days, followed by a pronounced immune responses directed against the human endothelial cells. A 10 day steroid-based immunosuppression protocol and a splenectomy at the time of rBEL implantation reduced the immune responses and resulted in continuous perfusion of the rBELs for over two weeks.

We also show that the human endothelial cells in the perfused rBELs colonize the liver sinusoids and express sinusoidal endothelial markers similar to those in normal liver tissue. Revascularized liver scaffolds that can maintain blood perfusion at physiological pressures might eventually help to overcome the chronic shortage of transplantable human livers.

References

1. Shaheen MF, Joo DJ, Ross JJ, Anderson BD, Chen HS, Huebert RC, et al. Sustained perfusion of revascularized bioengineered livers heterotopically transplanted into immunosuppressed pigs. Nat Biomed Eng.4:437-45. 2020.
2. Li Y, Chen HS, Shaheen M, Joo DJ, Amiot BP, Rinaldo P, et al. Cold storage of porcine hepatocyte spheroids for spheroid bioartificial liver. Xenotransplantation.26:e12512. 2019.
3. VanLith C, Guthman R, Nicolas CT, Allen K, Du Z, Joo DJ, et al. Curative Ex Vivo Hepatocyte-Directed Gene Editing in a Mouse Model of Hereditary Tyrosinemia Type 1. Hum Gene Ther.29:1315-26. 2018.
4. Nicolas CT, Hickey RD, Chen HS, Mao SA, Lopera Higuita M, Wang Y, et al. Concise Review: Liver Regenerative Medicine: From Hepatocyte Transplantation to Bioartificial Livers and Bioengineered Grafts. Stem Cells.35:42-50. 2017.
5. Meng F, Assiri A, Dhar D, Broering D. Whole liver engineering: A promising approach to develop functional liver surrogates. Liver Int. 2017.
6. Nicolas C, Wang Y, Luebke-Wheeler J, Nyberg SL. Stem Cell Therapies for Treatment of Liver Disease. Biomedicines.4. 2016.

Three Dimensional Human Liver-Chip

Yoon-Kyoung Cho

Ulsan National Institute of Science and Technology, Korea

Cancer is a leading cause of death worldwide. More than 90% of cancer deaths are caused by cancer metastasis. In metastasis, cancer cells are detached from the primary tumor, travel through the blood or lymphatic vessels, and form new tumor in a distant part of the body. Although cancer survival rate has been significant improved over the years, limited progress has been made in terms of the early diagnosis and treatment of cancer metastasis. Liquid biopsy utilizing circulating biomarkers such as circulating tumor cells (CTCs),[1-3] circulating tumor DNA (ct-DNA),[1,4] and extracellular vesicles (EVs)[5-9] have been highly recognized as a less invasive tools to provide better guidance for timely detection of tumor progression and personalized therapeutic options. Apart from conventional approaches in cancer studies targeting single type of cancer cells, we tackle the issue by studying intercellular communication.[9-10]

The liver is one of the most common site of cancer metastasis. Although the interaction between tumor cells and their microenvironment at the distant metastatic sites has been recognized as a key regulator of tumor progression, the underlying mechanism of the organotrophic cancer metastasis is not fully elucidated. Based on our preliminary results, we hypothesize that EVs play a critical role in organ-specific cancer metastasis. To test the hypothesis, we recapitulate the human liver microenvironment at the tissue level on a microfluidic chip that supports the growth of human liver sinusoidal endothelial cells (LSECs), primary liver fibroblasts (LFs), and liver hepatocytes.[11] This three-dimensional (3D) micro engineered organ-on-a-chip can be used as a normal liver microenvironment as well as a pre-metastatic niche primed by tumor-derived EVs. We applied this system to investigate how breast cancer-derived EVs trigger pre-metastatic niche formation, and breast cancer cell adhesion to this niche, as the first step in the metastasis to the liver.[11] In addition, we show that transforming growth factor β1 (TGFβ1) in breast cancer-derived EVs upregulates fibronectin, an adhesive extracellular matrix protein, on LSECs, which facilitates the adhesion of breast cancer cells to the liver microenvironment.[11] Furthermore, we observed that EVs isolated from triple-negative breast cancer (TNBC) patients with liver metastasis contain higher TGFβ1 levels and induce adhesion of more breast cancer cells to the 3D human liver-chip than do EVs isolated from healthy donors, or non-metastatic TNBC patients.[11] The EVs from breast tumor cell culture medium or plasma from patients were isolated using a commercial device based on the centrifugal microfluidic technology that we have previously developed.[5-9] These findings provide a better understanding of the mechanisms through which breast cancer-derived EVs guide secondary metastasis to the liver. Overall, this study provides a tool for improving our understanding of the mechanism involving primary tumor-derived EVs, pre-metastatic niche formation, and secondary metastasis to specific organs, which may potentially lead to the development of personalized diagnostic and therapeutic strategies to efficiently suppress secondary metastasis to specific

organs.

References

1. Minji Lim, Chi-Ju Kim, Vijaya Sunkara, Mi-Hyun Kim and Yoon-Kyoung Cho*, "Liquid biopsy in lung cancer: clinical applications of circulating biomarkers (CTCs and ctDNA)", Micromachines 9(3) 100, (2018) Invited review
2. Tae-Hyeong Kim, Juhee Park, Minji Lim, Jung Min Oh, Hyeongeun Kim, Hyunjin Jeong, Sun Ju Lee, Hee Chul Park, Sungmok Jung, Byung Chul Kim, Kyusang Lee, Mi-Hyun Kim, Do Youn Park, Gwang Ha Kim, and Yoon-Kyoung Cho*, "FAST: size-selective, clog-free isolation of rare cancer cells from whole blood at a liquid-liquid Interface ", Analytical Chemistry, 89 (2), 1155–1162, (2017) Journal cover
3. Minji Limi‡, Juhee Parki‡, Alarice C. Lowe, Hyoung-oh Jeong, Semin Lee, Hee Chul Park, Kyusang Lee, Gwang Ha Kim, Mi-Hyun Kim*, and Yoon-Kyoung Cho*, "A Lab-on-a-Disc platform enables serial monitoring of individual CTCs associated with tumor progression during EGFR-targeted therapy for patients with NSCLC", Theranostics, 10, 5181-5194, (2020) Journal cover
4. Chi-Ju Kim, Juhee Park, Vijaya Sunkara, Tae-Hyeong Kim, Yongjin Lee, Kyusang Lee, Mi-Hyun Kim and Yoon-Kyoung Cho*, "Fully automated, on-site isolation of cfDNA from whole blood for cancer therapy monitoring", Lab on a Chip, 18, 1320-1329, (2018)
5. Hyun-Kyung Woo, Vijaya Sunkara, Juhee Park, Tae-Hyeong Kim, Ja-Ryoung Han, Chi-Ju Kim, Hyun-Il Choi, Yoon-Keun Kim, and Yoon-Kyoung Cho*, "Exodisc for rapid, size-selective, and efficient isolation and analysis of nanoscale extracelluar vesicles from biological samples, ACS Nano, 11 (2), 1360–1370, (2017)
6. Sumit Kumar, Issac J. Michael, Juhee Park, Steve Granick, Yoon-Kyoung Cho*, "Cloaked exosomes: biocompatible, durable, and degradable encapsulation", Small 14 34 1870154, (2018) Journal cover
7. Hyun-Kyung Woo§, Juhee Park§, Ja Yoon Ku, Chan Ho Lee, Vijaya Sunkara, Hong Koo Ha, Yoon-Kyoung Cho*, "Urine-based liquid biopsy: non-invasive and sensitive AR-V7 detection in urinary EVs from patients with prostate cancer", Lab on a Chip, 19, 1, 87-97, (2019). Selected as a HOT paper
8. Vijaya Sunkara, Chi-Ju Kim, Juhee Park, Hyun-Kyung Woo, Dongyoung Kim, Hong Koo Ha, Mi-Hyun Kim, Youlim Son, Jae-Ryong Kim, Yoon-Kyoung Cho*, "Fully automated, label-free isolation of extracellular vesicles from whole blood for cancer diagnosis and monitoring", Theranostics, 9, 1851-1863, (2019)
9. Sumit Kumar, Jae-A Han, Issac J. Michael, Dongyeob Ki, Vijaya Sunkara, Juhee Park, Shreedhar Gautam, Hong Koo Ha, Liangfang Zhang, Yoon-Kyoung Cho*, Human platelet membrane functionalized microchips with plasmonic codes for cancer detection, Advanced Functional Materials, 1902669, (2019) Journal cover
10. Hacer Ezgi Karakas§, Junyoung Kim§, Juhee Park, Jung Min Oh, Yongjun Choi, Devrim Gozuacik*, Yoon-Kyoung Cho*, "A microfluidic chip for screening individual cancer cells via eavesdropping on autophagyinducing crosstalk in the stroma niche", Scientific Reports, 2050, (2017)
11. Junyoung Kim, Chaeeun Lee, Inun Kim, Jooyoung Ro, Jungmin Kim, Yoohong Min, Juhee Park, Vijaya Sunkara, Yang-Seok Park, Issac Michael, Young-Ae Kim, Hee Jin Lee, Yoon-Kyoung Cho*, "Threedimensional Human Liver-chip Emulating Pre-metastatic Niche Formation by Breast Cancer-derived Extracellular Vesicles", ACS Nano, 14, 11, 14971–14988, (2020) Journal cover, BRIC Top 5 research award

Fecal Microbiota Transplantation: Its Application to Nonalcoholic Steatohepatitis

Sowon Park

Yonsei University, Korea

As the prevalence of obesity and its associated disorders is increasing, nonalcoholic fatty liver disease (NAFLD) has become one of the most prevalent chronic liver disease worldwide. It represents a spectrum of conditions ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) with inflammation, fibrosis, and to cirrhosis. The onset of NAFLD and NASH is a complex process that involves genetic, environmental, and immunological factors, and recent studies show that alterations in gut microbial composition contribute to the pathogenesis of NAFLD. Although medical costs attributable to NAFLD keep increasing, the therapeutic approaches are still largely based on life-style modifications including diet and exercise.

The gut microbiota takes part in the digestion of food, absorption of the dietary molecules into the portal and systemic circulation, and interacts with the host immune system.[1] Physiologically, the metabolites derived from the ingested food, secondary bile acids, and microbiota in the intestine can reach the liver via portal vein through the absorption in the intestinal vein.[2] Since about 70% of the blood supply of the liver is from the portal vein, liver is vulnerable to the imbalance of intestinal microbiota and its subsequent impact on host immune system and inflammatory response.[3]

There are several studies demonstrating an association between gut microbiota and NASH. Germ-free mice were shown to exhibit lower levels of lipids in the liver compared to the conventional mice when fed high-fat diet, implying the importance of microbiota.[4] Also, when fecal microbiota of mice that developed fasting hyperglycemia and insulinemia were transferred to germ-free mice, but not that of healthy mice, the recipient mice developed NAFLD.[5] Human studies also show different microbial composition in NASH patients compared to the healthy control.[6,7]

Under the homeostatic condition, the gut microbiota has an interaction with the host to influence metabolism by affecting energy balance, inflammation, and gut barrier function. Alterations of gut microbiota disrupts the balance and immunity in animals and humans, leading to metabolic dysfunction and to inflammatory process of the liver.

Several studies demonstrated the linkage between gut barrier dysfunction to hepatic inflammation.[8,9] Disruption of gut mucosal barrier and increased intestinal permeability can lead to translocation of overgrowing bacteria and lipopolysaccharide (LPS) to the systemic circulation and consequently worsen hepatic inflammation and fibrosis.[10]

Other than the intestinal barrier disruption, alterations in short-chain fatty acids (SCFA) are related to the development of NASH since SCFA can act as signaling molecule and alter metabolism by binding to the G-protein-coupled receptors (GPR). SCFA can regulate insulin sensitivity, promote energy expenditure, and

inhibits fat accumulation in adipose tissue and liver.[11] Studies in murine model and human also show that SCFA may be related to NASH by reducing pro-inflammatory cytokines and inflammatory markers.[12,13]

Bile acids are important molecules that circulates within liver and intestinal tract. They are primarily synthesized in the liver, then released into the small intestine where they are metabolized to secondary bile acids by gut microbiota. Secondary bile acids are reabsorbed back to the liver by portal vein, where they continue on recirculation. In this process, some of the bile acids act as signaling molecules via FXR receptors.[14] Elevated bile acid levels were observed in liver, serum, and urine of NAFLD patients, and dysbiosis of gut microbiota may influence the bile acid pool, resulting in modulation of host metabolism.[15,16]

Interestingly, increasing evidences show that microbiota play crucial role in development and progression of NAFLD, and moreover, the phenotype can be transferred by transferring the gut microbiota. Germ-free mice fed with hypercaloric diet exhibited an impaired weight gain and lack of hepatic steatosis in contrast to the conventional mice.[17,18] Besides, when germ-free mice received gut microbiota from obese humans, hepatic steatosis was induced by modulation of lipid metabolism whereas when the mice received microbiota from the same donor after weight loss exhibit normal liver physiology.[19]

Several approaches for therapeutic modulation of gut microbiota are studied such as antibiotics, prebiotics, probiotics, fecal microbiota transplantation, and small molecule therapies to have effects on metabolism and hepatic inflammation. Although many animal studies presented some promising results, further understanding is needed to reveal more specific role of gut microbiota in NAFLD in order to establish microbiota-based precision medicine and mitigate the burden of this cureless disease.

References

1. Prakash S, Rodes L, Coussa-Charley M, et al. Gut microbiota: next frontier in understanding human health and development of biotherapeutics. Biologics 2011;5:71-86.
2. Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol 2018;15(7):397–411.
3. Poeta M, Pierri L, Vajro P. Gut-liver axis derangement in nonalcoholic fatty liver disease. Children (Basel) 2017;4(8):66.
4. Rabot S, Membrez M, Bruneau A, et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J. 2010;24:4948–4959.
5. Le Roy T, Llopis M, Lepage P, et al. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. Gut 2013;62:1787–1794.
6. Boursier J, Mueller O, Barret M, et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology 2016;63:764–775.
7. Michail S, Lin M, Frey MR, et al. Altered gut microbial energy and metabolism in children with non-alcoholic fatty liver disease. FEMS Microbiol Ecol 2015;91:1–9.
8. Miele L, Valenza V, La Torre G, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 2009;49:1877–1887.
9. Luther J, Garber JJ, Khalili H, et al. Hepatic injury in nonalcoholic steatohepatitis contributes to altered intestinal permeability. Cell Mol Gastroenterol Hepatol 2015;1:222–232.
10. Gäbele E, Dostert K, Hofmann C, et al. DSS induced colitis increases portal LPS levels and enhances hepatic inflammation and fibrogenesis in experimental NASH. J Hepatol 2011;55:1391–1399.
11. Kimura I, Ozawa K, Inoue D, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GR43. Nat Commun 2016;4:1829.

12. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature 2009;461:1282–1286.
13. Cortez-Pinto H, Jesus L, Barros H, et al. How different is the dietary pattern in non-alcoholic steatohepatitis patients? Clin Nutr 2006;25:816–823.
14. Pols TWH, Noriega LG, Nomura M, et al. The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J Hepatol 2011;54:1263–1272.
15. Aranha MM, Cortez-Pinto H, Costa A, et al. Bile acid levels are increased in the liver of patients with steatohepatitis. Eur J Gastroenterol Hepatol 2008;20:519–525.
16. Ferslew BC, Xie G, Johnston CK, et al. Altered bile acid metabolome in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60:3318–3328.
17. Kaden-Volynets V, Basic M, Neumann U, et al. Lack of liver steatosis in germ-free mice following hypercaloric diets. Eur J Nutr 2018;https://doi.org/10.1007/s00394-018-1748-4
18. Martinez-Guryn K, Hubert N, Frazier K, et al. Small intestine microbiota regulate host digestive and absorptive adaptive responses to dietary lipids. Cell Host Microbe 2018;23:458–469.e5.
19. Wang R, Li H, Yang X, et al. Genetically obese human gut microbiota induces liver steatosis in germ-free mice fed on normal diet. Front Microbiol 2018;9:1602.

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (10:40-12:10)

ROOM 2

Basic Research Symposium 1

Stress-Induced Fates of Hepatocyte in Nonalcoholic Steatohepatitis and Alcoholic Steatohepatitis

Chairs:

Jong Eun Yeon (Korea Univ.)

Wonhyo Seo (Ewha Womans Univ.)

Reprograming Hepatocytes in Severe Alcoholic Hepatitis

Jeongeun Hyun

Dankook University, Korea

Severe alcoholic hepatitis (SAH) is a deadly liver disease without an effective medical therapy. Although SAH mortality is known to correlate with hepatic accumulation of immature liver cells, why this occurs, and how it causes death is unclear. Here, we demonstrated that expression of epithelial splicing regulatory protein-2 (ESRP2), an RNA splicing factor that maintains the non-proliferative, mature phenotype of adult hepatocytes, was suppressed in both human SAH and various mouse models of SAH in parallel with the severity of alcohol consumption and liver damage. Inflammatory cytokines released by excessive alcohol ingestion reprogrammed adult hepatocytes into proliferative, fetal-like cells by suppressing ESRP2. Sustained loss of ESRP2 permitted re-emergence of a fetal RNA splicing program that attenuates the Hippo signaling pathway and thus, allows fetal transcriptional regulators to accumulate in adult liver. We further showed that depleting ESRP2 in mice exacerbated alcohol-induced steatohepatitis, enabling surviving hepatocytes to shed adult hepatocyte functions and become more regenerative but threatens overall survival by populating the liver with functionally-immature hepatocytes. Our findings revealed a novel mechanism that explains why liver failure develops in patients with the clinical syndrome of SAH, suggesting that recovery from SAH might be improved by limiting adult-to-fetal reprogramming in hepatocytes.

References

1. Louvet A, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. Nat Rev Gastroenterol Hepatol. 2015;12(4):231–242. doi: 10.1038/nrgastro.2015.35.
2. Jung Y, et al. Accumulation of hedgehog-responsive progenitors parallels alcoholic liver disease severity in mice and humans. Gastroenterology. 2008;134(5):1532–1543. doi: 10.1053/j.gastro.2008.02.022.
3. Sancho-Bru P, et al. Liver progenitor cell markers correlate with liver damage and predict short-term mortality in patients with alcoholic hepatitis. Hepatology. 2012;55(6):1931–1941. doi: 10.1002/hep.25614.
4. Yimlamai D, et al. Hippo pathway activity influences liver cell fate. Cell. 2014;157(6):1324–1338. doi: 10.1016/j.cell.2014.03.060.
5. Bangru S, et al. Alternative splicing rewires Hippo signaling pathway in hepatocytes to promote liver regeneration. Nat Struct Mol Biol. 2018;25(10):928–939. doi: 10.1038/s41594-018-0129-2.
6. Bhate A, et al. ESRP2 controls an adult splicing programme in hepatocytes to support postnatal liver maturation. Nat Commun. 2015;6:8768.
7. Hyun J, Oh SH, Premont RT, Guy CD, Berg CL, Diehl AM. Dysregulated activation of fetal liver programme in acute liver failure. Gut. 2019;68(6):1076–1087. doi: 10.1136/gutjnl-2018-317603.

Sphingomyelin Synthase 1 Mediates Hepatocyte Pyroptosis to Trigger Nonalcoholic Steatohepatitis

Eun Hee Koh

University of Ulsan, Korea

Lipotoxic hepatocyte injury is a primary event in non-alcoholic steatohepatitis (NASH), but the mechanisms of lipotoxicity are not fully defined. Sphingolipids and free cholesterol (FC) mediate hepatocyte injury, but their link in NASH has not been explored. We examined the role of free cholesterol and sphingomyelin synthases (SMSs) that generate sphingomyelin (SM) and diacylglycerol (DAG) in hepatocyte pyroptosis, a specific form of programmed cell death associated with inflammasome activation, and NASH.

Wild-type C57BL/6J mice were fed a high fat and high cholesterol diet (HFHCD) to induce NASH. Hepatic SMS1 and SMS2 expressions were examined in various mouse models including HFHCD-fed mice and patients with NASH. Pyroptosis was estimated by the generation of the gasdermin-D N-terminal fragment. NASH susceptibility and pyroptosis were examined following knockdown of SMS1, protein kinase Cδ (PKC δ), or the NLR family CARD domain-containing protein 4 (NLRC4).

HFHCD increased the hepatic levels of SM and DAG while decreasing the level of phosphatidylcholine. Hepatic expression of Sms1 but not Sms2 was higher in mouse models and patients with NASH. FC in hepatocytes induced Sms1 expression, and Sms1 knockdown prevented HFHCD-induced NASH. DAG produced by SMS1 activated PKCδ and NLRC4 inflammasome to induce hepatocyte pyroptosis. Depletion of Nlrc4 prevented hepatocyte pyroptosis and the development of NASH. Conditioned media from pyroptotic hepatocytes activated the NOD-like receptor family pyrin domain containing 3 inflammasome (NLRP3) in Kupffer cells, but Nlrp3 knockout mice were not protected against HFHCD-induced hepatocyte pyroptosis.

SMS1 mediates hepatocyte pyroptosis through a novel DAG-PKCδ-NLRC4 axis and holds promise as a therapeutic target for NASH.

Role of Intestine-Derived HDL on LPS Action in Gut-Liver Axis

Yong-Hyun Han

Kangwon National University, Korea

Generation of high density lipoprotein (HDL) requires ApoA1 and the cholesterol transporter ABCA1. Although the liver produces most HDL in circulation systems, HDL synthesis also occurs in the small intestine. However, distinct functions for intestinal HDL are unrevealed. Here, we showed that HDL in the portal vein, which connects intestine to liver, derived mainly from intestine via using photoconvertible GFP-tagged ApoA1 knockin mice. Intestine-derived HDL in portal vein was mainly composed of small-sized HDL3 and showed strong effects on neutralization of lipopolysaccharide (LPS). In a mouse model of short bowel syndrome which induces dramatic liver inflammation and fibrosis via TLR4, loss of intestine-derived HDL worsened liver injury, whereas liver pathology was improved by therapeutic challenge of low-dose oral LXR agonist that elevated and depended upon intestinal HDL production. Thus, we found that protection of the liver from injury in response to gut-derived signals like LPS is a major function of intestinally synthesized HDL.

Neutrophils in Alcohol-Associated Liver Disease

Bin Gao

National Institute on Alcohol Abuse and Alcoholism, USA

Alcohol-associated liver disease (ALD) encompasses a spectrum of diseases ranging from simple steatosis to alcohol-related steatohepatitis (ASH), cirrhosis, and liver cancer. At present, how simple steatosis progresses to ASH remains obscure. Multiple factors have been implicated in promoting inflammation in ASH including microbial dysbiosis, loss of barrier integrity in the intestine, hepatocellular stress and death, as well as inter-organ crosstalk.[1] Recent studies revealed that binge ethanol intake markedly elevated circulating and hepatic neutrophil infiltration in chronic ethanol-fed mice [2] and shifted macrophage to neutrophil infiltration in a hybrid model with high-fat and high cholesterol diet and alcohol infusion.[3] Mechanistically, binge ethanol challenge induced hepatic neutrophil infiltration by upregulating expression of chemokines (such as CXCL1) and adhesion molecules (such as E-selectin) in the liver and by elevating inflammatory mitochondrial DNA (mtDNA)-enriched extracellular vesicles (EV).[4] Binge ethanol-mediated elevation of circulating neutrophils and mtDNA-enriched EVs was also observed in alcoholics, which positively correlated with serum levels of ALT.[4,5]

Binge ethanol intake also markedly elevated circulating and hepatic neutrophils in high-fat diet (HFD)-fed mice, resulting in steatohepatitis and fibrosis.[6] Mechanistically, HFD and ethanol binge synergistically up-regulated hepatic expression of CXCL1, a key chemokine for neutrophil infiltration, in mice, resulting in high levels of CXCL1 protein (~1500 pg/ml) in the blood.[6] This synergistic induction of CXCL1 was due to binge ethanol blocking HFD-mediated hepatic PPAR-γ activation, a critical negative regulator for CXCL1 induction.[7] Genetic or pharmacologic inhibition of CXCL1 ameliorated binge ethanol-induction of hepatic neutrophil infiltration and injury in HFD-fed mice; whereas overexpression of CXCL1 alone in hepatocytes was sufficient to convert steatosis to steatohepatitis progression in HFD-fed mice. Furthermore, myeloid cell-specific deletion of neutrophil cytosolic factor 1 (Ncf1), a component of NADPH oxidase 2 complex that mediates neutrophil oxidative burst, markedly reduced oxidative stress and liver injury in ethanol- or HFD-fed mice, suggesting neutrophils play an important role in promoting liver injury in steatohepatitis by producing reactive oxygen species.

Although obesity and alcohol synergistically induce ALD,[8,9] the underlying mechanisms still remain obscure. It has been reported that alcohol feeding induces adipocyte death in mice;[10] however, how adipocyte death contributes to liver inflammation and injury in ALD is not fully understood. To answer this question, we employed two approaches. First, we developed adipocyte-specific Bcl-2 transgenic mice to prevent alcohol-induce adipocyte death and found alcohol-induced liver injury and inflammation were reduced in these mice. Second, we developed a Cre-inducible human CD59 transgenic mouse model of conditional and targeted cell death [11] including adipocyte death model.[12] By using this model, we demon-

strated that adipocyte death predominantly induces liver injury and inflammation, which is probably due to the superior sensitivity of hepatocytes to lipotoxicity and the activation of macrophages in the liver. Conclusions: Binge alcohol and obesity are deadly combination to induce steatohepatitis and injury by synergistically inducing adipocyte death, lipolysis, hepatic neutrophil infiltration and liver injury.

References

1. Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in alcoholic steatohepatitis. J Hepatol 2019; 70:249-259.
2. Bertola A, Mathews S, Ki SH, Wang H, Gao B. Mouse model of chronic and binge ethanol feeding (the NIAAA model). Nat Protoc 2013;8:627-37.
3. Lazaro R, Wu R, Lee S, Zhu NL, Chen CL, French SW, Xu J, Machida K, Tsukamoto H. Osteopontin deficiency does not prevent but promotes alcoholic neutrophilic hepatitis in mice. Hepatology 2015;61:129-40.
4. Cai Y, Xu MJ, Koritzinsky EH, Zhou Z, Wang W, Cao H, Yuen PS, Ross RA, Star RA, Liangpunsakul S, Gao B. Mitochondrial DNA-enriched microparticles promote acute-on-chronic alcoholic neutrophilia and hepatotoxicity. JCI Insight 2017;2.
5. Li M, He Y, Zhou Z, Ramirez T, Gao Y, Gao Y, Ross RA, Cao H, Cai Y, Xu M, Feng D, Zhang P, Liangpunsakul S, Gao B. MicroRNA-223 ameliorates alcoholic liver injury by inhibiting the IL-6-p47(phox)-oxidative stress pathway in neutrophils. Gut 2017;66:705-715.
6. Chang B, Xu MJ, Zhou Z, Cai Y, Li M, Wang W, Feng D, Bertola A, Wang H, Kunos G, Gao B. Short- or long-term high-fat diet feeding plus acute ethanol binge synergistically induce acute liver injury in mice: an important role for CXCL1. Hepatology 2015;62:1070-85.
7. Wang W, Xu MJ, Cai Y, Zhou Z, Cao H, Mukhopadhyay P, Pacher P, Zheng S, Gonzalez FJ, Gao B. Inflammation is independent of steatosis in a murine model of steatohepatitis. Hepatology 2017;66:108-123.
8. Parker R, Kim SJ, Gao B. Alcohol, adipose tissue and liver disease: mechanistic links and clinical considerations. Nat Rev Gastroenterol Hepatol 2018;15:50-59.
9. Hwang S, Gao B. How does your fat affect your liver when you drink? J Clin Invest 2019;129:2181-2183.
10. Sebastian BM, Roychowdhury S, Tang H, Hillian AD, Feldstein AE, Stahl GL, Takahashi K, Nagy LE. Identification of a cytochrome P4502E1/Bid/C1q-dependent axis mediating inflammation in adipose tissue after chronic ethanol feeding to mice. J Biol Chem 2011;286:35989-97.
11. Feng D, Dai S, Liu F, Ohtake Y, Zhou Z, Wang H, Zhang Y, Kearns A, Peng X, Zhu F, Hayat U, Li M, He Y, Xu M, Zhao C, Cheng M, Zhang L, Wang H, Yang X, Ju C, Bryda EC, Gordon J, Khalili K, Hu W, Li S, Qin X, Gao B. Cre-inducible human CD59 mediates rapid cell ablation after intermedilysin administration. J Clin Invest 2016;126:2321-33.
12. Kim SJ, Feng D, Guillot A, Dai S, Liu F, Hwang S, Parker R, Seo W, He Y, Godlewski G, Jeong WI, Lin Y, Qin X, Kunos G, Gao B. Adipocyte death preferentially induces liver injury and inflammation through the activation of chemokine (C-C Motif) receptor 2-positive macrophages and lipolysis. Hepatology 2019;69:1965-1982.

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (13:10-14:40)

ROOM 2

Research Workshop 2

Established Translational Techniques for the Study of Liver Disease

Chairs:

Neung Hwa Park (Univ. of Ulsan)

Eun Hee Koh (Univ. of Ulsan)

In Vivo and *In Vitro* Models for Alcoholic and Nonalcoholic Liver Disease

Hyo-Jung Kwon

Chungnam National University, Korea

Alcoholic liver disease (ALD) and non-alcoholic liver disease (NALD), leading causes of chronic liver injury worldwide, comprises a range of disorders including simple steatosis, steatohepatitis, cirrhosis, and hepatocellular carcinoma. Over the last five decades, many *in vivo* and *in vitro* models for the study of ALD and NALD pathogenesis have been developed and been used in recent years to unravel the molecular mechanisms involved in the onset but also the progression of this liver disease. However, the available models, be it *in vivo* or *in vitro* only mimic certain disease aspects found in humans and markedly differ in regards to the degree of hepatocellular damage and metabolic alterations associated with the development of the disease. Nevertheless, when chosen carefully, both *in vitro* and *in vivo* models can be used to verify hypotheses on mechanisms underlying the development of ALD and NALD and as tools to test new therapeutic and prevention strategies. This presentation provides a comprehensive summary of the most widely used experimental models of ALD and NALD. In addition, we focus on aspects such as reproducibility and practicality, discussing the advantages and weaknesses of available models based on previous our studies.

References

1. Animal models of alcoholic liver disease: pathogenesis and clinical relevance. Gao B, et al. Gene Expr. 2017;17(3):173-186.
2. Mouse model of chronic and binge ethanol feeding (the NIAAA model). Bertola A, et al. Nat Protoc. 2013;8(3):627-37.
3. Animal models for liver disease - A practical approach for translational research. Nevzorova YA, et al. J Hepatol. 2020;73(2):423-440.
4. Pathophysiology of NAFLD and NASH in experimental models: the role of food intake regulating peptides. L Kořínková, et al. Front Endocrinol (Lausanne). 2020;11:597583.
5. In vitro and in vivo models of non-alcoholic fatty liver disease: a critical appraisal. Soret PA, et al. J Clin Med. 2020;10(1):36.

Expandable and Functional Human Pluripotent Stem Cell-Derived Hepatic Organoids

Myung Jin Son

Korea Research Institute of Bioscience and Biotechnology, Korea

The development of hepatic models capable of long-term expansion with competent liver functionality in a personalized setting is technically challenging. Stem cell-based organoid technologies can provide an alternative source of patient-derived primary hepatocytes. However, self-renewing and functionally competent human pluripotent stem cell (PSC)-derived hepatic organoids are still lacking. We developed a novel method to efficiently and reproducibly generate functionally mature human hepatic organoids derived from PSCs, including human embryonic stem cells and induced PSCs. The maturity of the organoids was validated by a detailed transcriptome analysis and functional performance assays. The organoids were applied to screening platforms for predicting toxicity and evaluating drugs that target hepatic steatosis through real-time monitoring of cellular bioenergetics and high-content analyses. The organoids exhibited significant toxic responses to clinically relevant concentrations of drugs that had been withdrawn from the market due to hepatotoxicity and recapitulated human disease phenotypes such as hepatic steatosis. Our organoids may provide a versatile and valuable platform for physiologically and pathologically relevant hepatic models in the context of personalized medicine.

References

1. Mun SJ, Ryu J, Lee M, Son YS, Oh SJ, Cho H, Son M, Kim D, Kim SJ, Yoo HJ, Lee H, Kim J, Jung C, Chung K, Son MJ. Generation of expandable human pluripotent stem cell-derived hepatocyte-like liver organoids. J Hepatol, 71, 970, 2019.
2. Mun SJ, Hong Y, Ahn H, Ryu J, Chung K, Son MJ (2020) Long-term expansion of functional human pluripotent stem cell-derived hepatic organoids. Int J Stem Cells 13:279-286
3. Mun SJ, Lee J, Chung K, Son M, Son MJ. Effect of microbial short chain fatty acids on CYP3A4-mediated metabolic activation of human pluripotent stem cell-derived liver organoids. Cells, 10, E126, 2021

Hepatic Immune Cell Isolation and Analysis in Mice and Humans

Young-Sun Lee

Korea University, Korea

Introduction

Liver is a metabolic organ that absorbs, stores, and decomposes substances from the gastrointestinal tract. However, in recent years, research interest in liver as an immunologic organ has increased, and related studies are also actively conducted.[1] As 30% of the total blood in the body flows into the liver every minute through the hepatic artery and portal vein,[2] approximately 10^8 lymphocytes flow into the liver about every 24 hours.[3] In addition to the incoming immune cells, there are many different types of non-parenchymal cells in the liver, including Kupffer cells (liver resident macrophage), hepatic stellate cells (HSCs), and liver sinusoidal endothelial cells (LSEC). The interaction among these different cell types is important for the maintenance of liver homeostasis and occurrence of disease. Hepatic immune cell isolation and analysis are important to investigate the role of hepatic immune cells in various types of liver diseases. This manuscript briefly introduces a method for the isolation of hepatic immune cells and their characterization in mice and humans.

Hepatic immune cell isolation

Accurate and precise analysis of cell population and characterization of hepatic immune cells require fresh isolation of cells in viable state and high yield with adequate purity. There are two main procedures to isolate intrahepatic immune cells, such as mechanical disruption and enzymatic digestion. Since the techniques applied for the isolation of intrahepatic immune cells vary in literatures and laboratory,[4-6] these procedures should be applied individually based on the laboratory situation.

1. Mechanical disruption

Mechanical disruption can be easily implemented without the requirement of special equipment or skills. However, this method leads to low viability and yield of isolated cells due to insufficient dissociation of cells from the liver tissues.[7]

2. Enzymatic digestion

Enzymatic digestion using collagenase is considered for the isolation of hepatic immune cells with high yield and percentage of Kupffer cells and monocytes without causing mechanical damage. However, collagenase can impact the cell membrane through altering the cell surface markers,[4] and reduce NK cell activity.[8] Recently, the liver dissociation kit has been developed to isolate hepatic immune cells, LSECs, and

Kupffer cells from liver using Gentle MACS.[9] This seems to be a rapid and efficient method with high yield without preserving most cell surface epitopes.

Analysis of hepatic immune cells

1. Flow cytometric analysis

Multi-color flow cytometric analysis help identify the composition of immune cells, minor immune cell population, and production of intracellular cytokines. Cells stained with fluorescent antibody were analyzed using a flow cytometer. After running the samples through the flow cytometer, data was analyzed using the FlowJo software.[6]

2. Functional analysis

Since the isolated hepatic immune cells are heterogeneous, specific cell isolation technique is required to perform functional analysis using either a cell sorter or a magnetic-activated cell sorter (MACS).

3. Single-cell RNA sequencing

Recently, single-cell genomic-based studies have resulted in great advancements to better understand the heterogenous nature of hepatic immune cells.

Conclusion

Accurate isolation and characterization of hepatic immune cells are important for studying various types of liver diseases using a wide range of applications.

References

1. Racanelli V, Rehermann B. The liver as an immunological organ. Hepatology. 2006;43(2 Suppl 1):S54-62.
2. Sheth K, Bankey P. The liver as an immune organ. Curr Opin Crit Care. 2001;7(2):99-104.
3. Wick MJ, Leithauser F, Reimann J. The hepatic immune system. Crit Rev Immunol. 2002;22(1):47-103.
4. Dong ZJ, Wei HM, Sun R, Tian ZG, Gao B. Isolation of murine hepatic lymphocytes using mechanical dissection for phenotypic and functional analysis of NK1.1+ cells. World J Gastroenterol. 2004;10(13):1928-33.
5. Volarevic V, Mitrovic M, Milovanovic M, Zelen I, Nikolic I, Mitrovic S, et al. Protective role of IL-33/ST2 axis in Con A-induced hepatitis. J Hepatol. 2012;56(1):26-33.
6. Lee YS, Yi HS, Suh YG, Byun JS, Eun HS, Kim SY, et al. Blockade of Retinol Metabolism Protects T Cell-Induced Hepatitis by Increasing Migration of Regulatory T Cells. Molecules and cells. 2015;38(11):998-1006.
7. Blom KG, Qazi MR, Matos JB, Nelson BD, DePierre JW, Abedi-Valugerdi M. Isolation of murine intrahepatic immune cells employing a modified procedure for mechanical disruption and functional characterization of the B, T and natural killer T cells obtained. Clin Exp Immunol. 2009;155(2):320-9.
8. Gibson PR, Hermanowicz A, Verhaar HJ, Ferguson DJ, Bernal AL, Jewell DP. Isolation of intestinal mononuclear cells: factors released which affect lymphocyte viability and function. Gut. 1985;26(1):60-8.
9. McBeth C, Gutermuth A, Ochs J, Sharon A, Sauer-Budge AF. Automated tissue dissociation for rapid extraction of viable cells. Procedia CIRP. 2017:88-92.

Exosome Isolation Technique and Its Application to Liver Disease

Wonhyo Seo

Ewha Womans University, Korea

Extracellular vesicles (EVs) are nano-sized vesicles surrounded by a lipid bilayer that are released into extracellular space by diverse cells. EVs can be found in the most of bio-fluids (blood, urine, saliva and spinal fluids), and contain a variety of genetic information such as proteins, nucleic acids and lipids. Therefore, the understanding of EV biogenesis and the novel roles of EVs as a new mediator of intercellular communications have been emerged. According to mechanism of production, EVs can be further classified into "exosomes derived from endosomes" and "microvesicles derived from the plasma membrane", however, it is very difficult to separate them strictly from each other by differential centrifugation. Albeit exosomes and microvesicles are not distinguished well due to the similarity of their characteristics, there are several efforts to discriminate exosomes and microvesicles based on origin, size and density. In accordance with broad applications of EVs, different types of EV isolation techniques have been developed including ultracentrifugation, immunoaffinity, polymer precipitation and so on. The choice of a suitable isolation technique which maximizes effectiveness of EV isolation is very crucial to obtain high-yield and high-purity EVs for reliable data.

In addition, it has been reported that the involvement of hepatic cell-originated EVs in the progression of liver diseases. In detail, damaged hepatocytes produce a large amount of EVs, and those EVs play important roles in mediating the cellular communication of hepatic cells. Therefore, we believed that the interaction between damaged associated EVs and neighboring cells (hepatic stellate cells, Kupffer cells and sinusoidal endothelial cells) plays an important role in the progression of liver diseases. Furthermore, the understandings of EV-mediated signal pathways in liver diseases is expected to provide us with a new perspective on the diagnostic and therapeutic aspects. This presentation is going to discuss several types of EV isolation techniques and its application to the progression of liver diseases.

References

1. J Kowal et al. (2016) Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. Proceedings of the National Academy of Sciences of the United States of America
2. J Ma et al. (2020) Chronic-plus-binge alcohol intake induces production of proinflammatory mtDNA-enriched extracellular vesicles and steatohepatitis via ASK1/p38MAPKα-dependent mechanisms. JCI insight
3. H Kang et al. (2017) Methods to isolate extracellular vesicles for diagnosis. Micro and Nano Systems Letter
4. HC Yang et al. (2021) Single-step quipment-free extracellular vesicle concentration using super absorbent polymer beads. J Extracellular Vesicles
5. W Seo et al. (2016) Exosome-mediated activation of toll-like receptor 3 in stellate cells stimulates interleukin-17 production by $\gamma\delta$ T cells in liver fibrosis. Hepatology

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (14:50-16:20)

ROOM 2

Basic Research Symposium 2

Intrinsic and Multifactorial Contribution to Cirrhosis and Hepatocellular Carcinoma

Chairs:

Yong-Han Paik (Sungkyunkwan Univ.)

Hyo-Jung Kwon (Chungnam National Univ.)

Glutamine and Immune Checkpoint in Cancer Cells

Keun-Gyu Park

Kyungpook National University, Korea

Since the discovery that cancer cells can reprogram glucose metabolism towards aerobic glycolysis instead of oxidative phosphorylation by Warburg in the 1920s, there have been significant advancements in understating cancer metabolism (Vander Heiden et al., 2009). Metabolic reprogramming is a hallmark of cancer cells, whereby numerous changes in cellular bioenergetics occur, causing the cells to adapt to a variety of stress conditions (Yoshida, 2015). Cancer cells can orchestrate metabolic reprogramming by altering the uptake and catabolism of nutrients, enabling them to maintain proliferative capacity, conferring resistance to oxidative stress, and promoting the evasion of immune-mediated destruction (Hanahan and Weinberg, 2011). In early studies on cancer metabolism, dysregulated glucose metabolism, also called the "Warburg effect", received much attention as a hallmark of cancer, since the glycolytic pathway produces ATP and metabolic intermediates for cancer cell proliferation. However, glucose only supplies a carbon source for biosynthesis; it cannot supply the amino acids and glutathione that rapidly proliferating cancer cells require for the synthesis of nucleic acids.

Several studies have shown that glutamine is a major nutrient involved in multiple aspects of cancer metabolism (Hensley et al., 2013). Glutamine is the most abundant amino acid in the blood and muscle and is largely utilized for energy generation and as a precursor for the biomass required for rapid cancer cell proliferation (Windmueller and Spaeth, 1974). In addition to providing a carbon source, glutamine metabolism also acts as a source of nitrogen for the synthesis of nucleic acids and other amino acids and also participates in the regulation of cellular redox homeostasis through a variety of mechanisms (Altman et al., 2016). Therefore, most cancer cells are dependent on glutamine and cannot survive in the absence of exogenous glutamine, which has been termed "glutamine addiction" (Eagle, 1955). In light of the importance of glutamine in cancer cell biology, a comprehensive understanding of glutamine metabolism is important for developing effective therapeutic strategies.

In this seminar, I will summarize an overview of the role of glutamine metabolism in liver cancer cell survival and growth and highlight the mechanisms by which glutamine metabolism affects cancer cell signaling (Byun, 2015). In addition, I will briefly summarize the role of glutamine metabolism in sorafenib resistance in liver cancer cells (Kim, 2017). Furthermore, I will share with you the recent our findings showing the important role of glutamine metabolism in anti-tumor immunity (Byun, 2020).

Despite its outstanding clinical success, immune checkpoint blockade remains ineffective in many patients. Accordingly, combination therapy capable of achieving greater antitumor immunity is urgently required. Here, we report that limiting glutamine metabolism in cancer cells bolsters the effectiveness of anti-programmed death ligand-1 (PD-L1) antibody. Inhibition of glutamine utilization increased PD-L1 lev-

els in cancer cells, thereby inactivating co-cultured T-cells. Under glutamine-limited conditions, reduced cellular GSH levels caused upregulation of PD-L1 expression by impairing SERCA activity, which activates the calcium/NF-κB signaling cascade. Consequently, in tumors grown in immune-competent mice, inhibition of glutamine metabolism decreased the antitumor activity of T-cells. In combination with anti-PD-L1, however, glutamine depletion strongly promoted the antitumor efficacy of T-cells in vitro and in vivo due to simultaneous increases in Fas/CD95 levels. Our results demonstrate the relevance of cancer glutamine metabolism to antitumor immunity, and suggest that co-targeting of glutamine metabolism and PD-L1 represents a promising therapeutic approach.

References

1. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer (2016) 16, 619-634.
2. Byun JK, Choi YK, Kang YN, Jang BK, Kang KJ, Jeon YH, Lee HW, Jeon JH, Koo SH, Jeong WI, Harris RA, Lee IK, Park KG. Retinoic acid-related orphan receptor alpha reprograms glucose metabolism in glutamine-deficient hepatoma cells. Hepatology (2015) 61, 953-964
3. Byun JK, Park M, Lee S, Yun JW, Lee J, Kim JS, Cho SJ, Jeon HJ, Lee IK, Choi YK, Park KG. Inhibition of Glutamine Utilization Synergizes with Immune Checkpoint Inhibitor to Promote Antitumor Immunity. Mol Cell (2020) 80, 592-606
4. Choi YK, Park KG. Targeting glutamine metabolism for cancer treatment. Biomol Ther (2018) 26, 19-28
5. Eagle H. Nutrition needs of mammalian cells in tissue culture. Science (1955) 122, 501-514
6. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell (2011) 144, 646-674
7. Hensley CT, Wasti AT and DeBerardinis RJ. Glutamine and cancer: cell biology, physiology, and clinical opportunities. J Clin Invest (2013) 123, 3678-3684
8. Kim MJ, Choi YK, Park SY, Jang SY, Lee JY, Ham HJ, Kim BG, Jeon HJ, Kim JH, Kim JG, Lee IK, Park KG. PPARδ Reprograms Glutamine Metabolism in Sorafenib-Resistant HCC. Mol Cancer Res (2017) 15, 1230-1242
9. Vander Heiden MG, Cantley LC, and Thompson C B (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science (2009) 324, 1029-1033.
10. Windmueller HG and Spaeth AE. Uptake and metabolism of plasma glutamine by the small intestine. J Biol Chem (1974) 249, 5070-5079
11. Yoshida GJ. Metabolic reprogramming: the emerging concept and associated therapeutic strategies. J Exp Clin Cancer Res (2015) 34, 111

Hippo Signaling in HCC Development

Wantae Kim

Chungnam National Universitiy, Korea

Precise organ size control is required in both embryonic development and adult tissue regeneration and is ensured by tight regulation of duration and progression of cell division, disruption of which leads to devastating diseases including tumor formation. The recently discovered Hippo signaling pathway has gained interest as being critical regulators of cancer progression, besides its fundamental functions in tissue growth/organ size control and regeneration. We found that the Hippo, Wnt/β-catenin and Notch pathways form an interacting network in maintaining liver size and suppressing hepatocellular carcinoma (HCC). Ablation of Hippo kinase Mst1 and Mst2 in liver leads to rapid HCC formation and activates Yap, Wnt/β-catenin and Notch signaling, each one of these downstream events can lead to HCC. Rigorous genetic experiments revealed that in the Hippo deficient liver, Notch signaling forms a positive feedback loop with Hippo signaling effector Yap, which promotes severe hepatomegaly and rapid HCC initiation and progression. Surprisingly, Wnt/β-catenin signaling activation suppresses HCC formation by inhibiting the positive feedback loop between Yap and Notch signaling. In addition, we observed that Hippo pathway suppresses protumoral immune responses by inhibiting expression of chemokine Ccl2. Furthermore, we have observed strong correlation between Ccl2 expression and Yap transcription signature in HCC patients.

Mesenchymal Stem Cell-Derived Factors Regulate Liver Fibrosis

Youngmi Jung

Pusan National University, Korea

Liver fibrosis is a major characteristic of liver disease. When the liver is damaged, quiescent hepatic stellate cells (HSCs) transdifferentiate into proliferative myofibroblastic/activated HSCs, which are the main contributors to liver fibrosis.[1] Hence, a strategy for regulating HSC activation is important in the treatment of liver disease.

Mesenchymal stem cells (MSCs) are multipotent adult stem cells with the ability to self-renew and differentiate into multiple cell lineages.[2] Since MSCs possess considerable tissue regenerative effects and immunomodulatory properties, the therapeutic effects of MSC transplantation have been widely studied in clinical and experimental research, including in chronic liver disease. Many studies that have reported that the therapeutic effects of MSCs against liver fibrosis/cirrhosis are related to their capacity to undergo hepatocyte-like differentiation, immunomodulatory properties and secretory paracrine actions.[3-5]

Tumor necrosis factor-inducible gene 6 protein (TSG-6), a cytokine released from MSCs, influences MSC stemness.[6] We previously reported that TSG-6 promoted liver reconstitution by impacting hepatocyte survival. In chronically damaged liver, TSG-6 protected injured hepatocytes from apoptosis by increasing autophagy influx and decreasing fibrosis and inflammation, thus contributing to liver regeneration.[7] Because chronic injury includes extensive hepatocyte death, which accompanies HSC activation and replacement of parenchyma loss with ECM,[8] it is a reasonable explanation that the TSG-6-mediated reduction in hepatocyte loss leads to decreased HSC activation.[9] However, the direct effect of TSG-6 in HSCs remains unclear. Therefore, we investigated the biological effect of TSG-6 on HSCs. Human primary HSCs treated with TSG-6 showed significant downregulation of HSC activation markers and upregulation of senescence markers. TSG-6 promoted these cells to express stem cell markers and form spherical organoids, which exhibited elevated expression of stemness-related genes. These organoids differentiated into functional hepatocytic cells under specific culture conditions. Organoids derived from TSG-6-treated HSCs improved livers in organoid transplant mice subjected to CCl_4 treatment (which induces liver fibrosis). Furthermore, HSC transdifferentiation by TSG-6 was mediated by Yes-associated protein 1. These findings demonstrate that TSG-6 induces the conversion of HSCs into stem cell-like cells in vitro and that organoids derived from TSG-6-treated HSCs can restore fibrotic liver, suggesting that direct reprogramming of HSCs by TSG-6 can be a useful strategy to control liver disease.

Exosomes with a diameter around 30- 150 nm are secreted by all cell types and possess similar properties to their parental cells.[10] Since exosomes carry a variety of cargoes, including proteins, mRNAs, and small noncoding RNAs, they have emerged as crucial mediators of intercellular communication and modulators of cellular activities in recipient cells.[11] Because MSCs also produce and secrete exosomes, it has

been proposed that the regenerative ability of MSCs is mediated by exosomes and that their exosomes have a therapeutic potential similar to that of MSCs.[12] Human tonsil-derived MSCs (T-MSCs) is reported as a novel source of MSCs, but their effects on liver fibrosis remain unclear. Herein, we investigated the effects of T-MSCs-derived exosomes on liver fibrosis. Expression of profibrotic genes decreased in human primary HSCs co-cultured with T-MSCs. Treatment of T-MSC- exosomes inactivated human and mouse primary HSCs. Administration of T-MSC- exosomes ameliorated hepatic injuries and fibrosis in chronically damaged liver induced by CCl_4. MiR-486-5p highly enriched in T-MSC- exosome targeted the hedgehog receptor, Smo, was upregulated, whereas Smo and Gli2, hedgehog target gene, were downregulated in pHSCs and liver tissues treated with T-MSC- exosomes or miR-486-5p mimic, indicating that sEV-miR-486 inactivates HSC by suppressing hedgehog signaling. Our results showed that T-MSCs attenuate HSC activation and liver fibrosis by delivering exosomes, and miR-486 in the exosomes inactivates hedgehog signaling, indicating that T-MSCs and their exosomes are novel anti-fibrotic therapeutics for treating chronic liver disease.

References

1. B.E. Uygun, A. Soto-Gutierrez, H. Yagi, M.L. Izamis, M.A. Guzzardi, C. Shulman, et al: Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix, Nat Med 2010; 167; pp. 814-20.
2. Alhadlaq, A., and Mao, J.J. (2004). Mesenchymal stem cells: isolation and therapeutics. Stem Cells Dev. 13, 436-448.
3. Alfaifi, M., Eom, Y.W., Newsome, P.N., and Baik, S.K. (2018). Mesenchymal stromal cell therapy for liver diseases. J. Hepatol. 68, 1272-1285.
4. Rong, X., Liu, J., Yao, X., Jiang, T., Wang, Y., and Xie, F. (2019). Human bone marrow mesenchymal stem cells-derived exosomes alleviate liver fibrosis through the Wnt/β-catenin pathway. Stem Cell Res. Ther. 10, 98.
5. An, S.Y., Jang, Y.J., Lim, H.J., Han, J., Lee, J., Lee, G., et al. (2017). Milk Fat Globule-EGF Factor 8, Secreted by Mesenchymal Stem Cells, Protects Against Liver Fibrosis in Mice. Gastroenterology 152, 1174-1186.
6. B. Romano, S. Elangovan, M. Erreni, E. Sala, L. Petti, P. Kunderfranco, et al: TNF-Stimulated Gene-6 Is a Key Regulator in Switching Stemness and Biological Properties of Mesenchymal Stem Cells, Stem Cells 2019; pp. 1-15.
7. S. Wang, C. Lee, J. Kim, J. Hyun, M. Lim, H.J. Cha, et al: Tumor necrosis factor-inducible gene 6 protein ameliorates chronic liver damage by promoting autophagy formation in mice, Exp Mol Med 2017; 499; pp. e380.
8. Y. Jung, R.P. Witek, W.K. Syn, S.S. Choi, A. Omenetti, R. Premont, et al: Signals from dying hepatocytes trigger growth of liver progenitors, Gut 2010; 595; pp. 655-65.
9. S. Wang, J.S. Lee, J. Hyun, J. Kim, S.U. Kim, H.J. Cha, et al: Tumor necrosis factor-inducible gene 6 promotes liver regeneration in mice with acute liver injury, Stem Cell Res. Ther. 2015; 6; pp. 20.
10. Zhang, J., Li, S., Li, L., Li, M., Guo, C., Yao, J., et al. (2015). Exosome and exosomal microRNA: trafficking, sorting, and function. Genomics Proteomics Bioinformatics 13, 17-24.
11. Valadi, H., Ekstrom, K., Bossios, A., Sjostrand, M., Lee, J.J., and Lotvall, J.O. (2007). Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat. Cell Biol. 9, 654-659.
12. Keshtkar, S., Azarpira, N., and Ghahremani, M.H. (2018). Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. Stem Cell Res. Ther. 9, 63.

Non-Invasive Stool-Based Microbiome Profiling Predicts Liver Cirrhosis

Tae Gyu Oh, Susy Kim, Cyrielle Caussy, Jian Guo, Ting Fu, Shirin Bassirian, Seema Singh, Ricki Bettencourt, Emily Rizo, Lisa Richards, Ruth Yu, Annette Atkins, Tao Huan, David A. Brenner, Claude B. Sirlin, Michael R. Downes, Ronald M. Evans and Rohit Loomba

Salk Institute for Biological Studies, USA

Alcohol-associated liver disease (ALD) encompasses a spectrum of diseases ranging from simple steatosis to alcohol-related steatohepatitis (ASH), cirrhosis, and liver cancer. At present, how simple steatosis progresses to ASH remains obscure. Multiple factors have been implicated in promoting inflammation in ASH including microbial dysbiosis, loss of barrier integrity in the intestine, hepatocellular stress and death, as well as inter-organ crosstalk.[1] Recent studies revealed that binge ethanol intake markedly elevated circulating and hepatic neutrophil infiltration in chronic ethanol-fed mice[2] and shifted macrophage to neutrophil infiltration in a hybrid model with high-fat and high cholesterol diet and alcohol infusion.[3] Mechanistically, binge ethanol challenge induced hepatic neutrophil infiltration by upregulating expression of chemokines (such as CXCL1) and adhesion molecules (such as E-selectin) in the liver and by elevating inflammatory mitochondrial DNA (mtDNA)-enriched extracellular vesicles (EV).[4] Binge ethanol-mediated elevation of circulating neutrophils and mtDNA-enriched EVs was also observed in alcoholics, which positively correlated with serum levels of ALT.[4,5]

Binge ethanol intake also markedly elevated circulating and hepatic neutrophils in high-fat diet (HFD)-fed mice, resulting in steatohepatitis and fibrosis.[6] Mechanistically, HFD and ethanol binge synergistically up-regulated hepatic expression of CXCL1, a key chemokine for neutrophil infiltration, in mice, resulting in high levels of CXCL1 protein (~1500 pg/ml) in the blood.[6] This synergistic induction of CXCL1 was due to binge ethanol blocking HFD-mediated hepatic PPAR-γ activation, a critical negative regulator for CXCL1 induction.[7] Genetic or pharmacologic inhibition of CXCL1 ameliorated binge ethanol-induction of hepatic neutrophil infiltration and injury in HFD-fed mice; whereas overexpression of CXCL1 alone in hepatocytes was sufficient to convert steatosis to steatohepatitis progression in HFD-fed mice. Furthermore, myeloid cell-specific deletion of neutrophil cytosolic factor 1 (Ncf1), a component of NADPH oxidase 2 complex that mediates neutrophil oxidative burst, markedly reduced oxidative stress and liver injury in ethanol- or HFD-fed mice, suggesting neutrophils play an important role in promoting liver injury in steatohepatitis by producing reactive oxygen species.

Although obesity and alcohol synergistically induce ALD,[8,9] the underlying mechanisms still remain obscure. It has been reported that alcohol feeding induces adipocyte death in mice;[10] however, how adipocyte death contributes to liver inflammation and injury in ALD is not fully understood. To answer this question, we employed two approaches. First, we developed adipocyte-specific Bcl-2 transgenic mice to

prevent alcohol-induce adipocyte death and found alcohol-induced liver injury and inflammation were reduced in these mice. Second, we developed a Cre-inducible human CD59 transgenic mouse model of conditional and targeted cell death[11] including adipocyte death model.[12] By using this model, we demonstrated that adipocyte death predominantly induces liver injury and inflammation, which is probably due to the superior sensitivity of hepatocytes to lipotoxicity and the activation of macrophages in the liver. Conclusions: Binge alcohol and obesity are deadly combination to induce steatohepatitis and injury by synergistically inducing adipocyte death, lipolysis, hepatic neutrophil infiltration and liver injury.

References

1. Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in alcoholic steatohepatitis. J Hepatol 2019;70:249-259.
2. Bertola A, Mathews S, Ki SH, Wang H, Gao B. Mouse model of chronic and binge ethanol feeding (the NIAAA model). Nat Protoc 2013;8:627-37.
3. Lazaro R, Wu R, Lee S, Zhu NL, Chen CL, French SW, Xu J, Machida K, Tsukamoto H. Osteopontin deficiency does not prevent but promotes alcoholic neutrophilic hepatitis in mice. Hepatology 2015;61:129-40.
4. Cai Y, Xu MJ, Koritzinsky EH, Zhou Z, Wang W, Cao H, Yuen PS, Ross RA, Star RA, Liangpunsakul S, Gao B. Mitochondrial DNA-enriched microparticles promote acute-on-chronic alcoholic neutrophilia and hepatotoxicity. JCI Insight 2017;2.
5. Li M, He Y, Zhou Z, Ramirez T, Gao Y, Gao Y, Ross RA, Cao H, Cai Y, Xu M, Feng D, Zhang P, Liangpunsakul S, Gao B. MicroRNA-223 ameliorates alcoholic liver injury by inhibiting the IL-6-p47(phox)-oxidative stress pathway in neutrophils. Gut 2017;66:705-715.
6. Chang B, Xu MJ, Zhou Z, Cai Y, Li M, Wang W, Feng D, Bertola A, Wang H, Kunos G, Gao B. Short- or long-term high-fat diet feeding plus acute ethanol binge synergistically induce acute liver injury in mice: an important role for CXCL1. Hepatology 2015;62:1070-85.
7. Wang W, Xu MJ, Cai Y, Zhou Z, Cao H, Mukhopadhyay P, Pacher P, Zheng S, Gonzalez FJ, Gao B. Inflammation is independent of steatosis in a murine model of steatohepatitis. Hepatology 2017;66:108-123.
8. Parker R, Kim SJ, Gao B. Alcohol, adipose tissue and liver disease: mechanistic links and clinical considerations. Nat Rev Gastroenterol Hepatol 2018;15:50-59.
9. Hwang S, Gao B. How does your fat affect your liver when you drink? J Clin Invest 2019;129:2181-2183.
10. Sebastian BM, Roychowdhury S, Tang H, Hillian AD, Feldstein AE, Stahl GL, Takahashi K, Nagy LE. Identification of a cytochrome P4502E1/Bid/C1q-dependent axis mediating inflammation in adipose tissue after chronic ethanol feeding to mice. J Biol Chem 2011;286:35989-97.
11. Feng D, Dai S, Liu F, Ohtake Y, Zhou Z, Wang H, Zhang Y, Kearns A, Peng X, Zhu F, Hayat U, Li M, He Y, Xu M, Zhao C, Cheng M, Zhang L, Wang H, Yang X, Ju C, Bryda EC, Gordon J, Khalili K, Hu W, Li S, Qin X, Gao B. Cre-inducible human CD59 mediates rapid cell ablation after intermedilysin administration. J Clin Invest 2016;126:2321-33.
12. Kim SJ, Feng D, Guillot A, Dai S, Liu F, Hwang S, Parker R, Seo W, He Y, Godlewski G, Jeong WI, Lin Y, Qin X, Kunos G, Gao B. Adipocyte death preferentially induces liver injury and inflammation through the activation of chemokine (C-C Motif) receptor 2-positive macrophages and lipolysis. Hepatology 2019;69:1965-1982.

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (13:10-14:40)

ROOM 3

Health Insurance Forum

Chairs:

Hong Soo Kim (Soonchunhyang Univ.)

Hyung Joon Kim (Chung-Ang Univ.)

Role and Mission of Patient Classification System TFT in KASL

Hyun Woong Lee

Yonsei University, Korea

1. 환자분류체계란

환자분류체계란 입원환자를 자원소모나 임상적으로 유사한 그룹끼리 분류하는 방법으로, 이를 진단명 기준 환자군 (diagnosis related group, DRG)이라고 한다. 환자분류체계에 대한 논의는 진료의 대가로 의료공급자에게 지불되는 지불제도 보상방식의 변화와 함께 시작되었다. 우리나라는 1977년 처음 의료보험을 도입하면서 독일의 영향을 받은 일본의 점수제를 모방하였다. 이후 1981년부터 진료 행위마다 가격을 정하여 지급하였다. 2000년부터는 미국의 상대가치제를 도입하고, 행위별 수가계약제를 시행하였다. 행위별 수가계약제는 의료인이 제공한 진료행위(진찰, 검사, 수술, 처 치 등), 입원료, 약제 등의 가격을 각각 매긴 뒤 모두 합산하여 지불 받는 제도이다. 진료행위의 상대가치를 평가하기 위해 2010년 1차개정, 2017년 2차개정이 이루어 졌다. 2021년 최근 3차 개정에 대한 논의가 활발히 진행되고 있다.

그러나 행위별 수가제는 양질의 의료서비스를 제공할 수 있는 장점이 있음에도 불구하고 환자에게 많은 진료를 제공하면 할수록 의사 또는 의료기관의 수입이 늘어나게 되어 과잉진료 및 의료서비스 남용의 위험이 있으며 의료재정 증가의 위험이 발생할 수 있다. 이를 보완하기 위해 다른 지불제도로서 포괄수가제가 시도되었다. 2012년 7월부터 의원급에 선택적으로 실시하였던 7개 질병군 포괄수가제가 전면 도입되고 2013년 7월부터 종합병원 및 상급종합병원에서도 실시 되었으며 2020년에는 약 200여개의 병원에서 신포괄수가제가 시행되었다. 이에 따라 질병군별 포괄수가제 확대와 더불어 포괄수가제의 지불단위가 되는 환자분류체계(patient classification systems)에 대한 관심이 증가하게 되었다.

2. 환자분류체계 TFT 역할

현재의 환자분류체계는 외국과 달리 의사진료비를 고려하지 않았으며, 진료원가 조차도 반영되지 않은 상태로 심평원에서 주도적으로 진행되어 왔다. 그러나, 이미 현재의 환자분류체계가 상급종합병원 분류와 의료질 평가에 사용되고 있으며, 신포괄제도를 수용하는 병원이 앞으로 증가할 것으로 예상된다. 따라서, 간질환 분야에서 환자분류체계의 문제점을 파악하고 개선하고자 2020년 5월 보험위원회와 의료정책위원회가 연합하여 환자분류체계 TFT를 구성하였으며, 최근 대한간암학회 보험위원회가 함께 참여하였다.

주요활동범위는 한국표준질병 및 사인분류 (KCD)에 근거한 입원환자분류체계 (KDRG) 및 외래환자분류체계 (KOPG), 상급종합병원 지정기준 관련 환자분류체계, 신포괄수가제, 의료전달체계 등의 수정 및 개선안을 작성하여 의견을 개진하고 있다.

2020년 주요활동내용은 간질환 환자분류체계에서 KDRG 4.3의 문제점을 제시하여 KDRG 4.4 개정안에 반영하였으며, 이번에 수정되지 않은 부분에 대해 KDRG 4.5 개정에 포함되도록 노력하고 있다. 최근 심평원에서 문의한 상급종합

지정평가의 입원환자 구성상태에 대한 의견조회에서 심각한 오류를 지적하고 답변하였으며, 잘못된 정책이 실행되지 않도록 올바른 의견을 제시하는데 중추적인 역할을 하였다. 그 외에도 내과계 신포괄수가제의 문제점과 개선방안, 상급종합병원 지정평가를 위한 환자구성상태 개선 연구에 대한 외부 연자를 초청하여 심도 깊은 토론회를 진행하였으며, 2021년 4월 13일 보건의료 정책방향과 학회의 능동적 대처라는 주제로 대한간학회 제1회 의료정책포럼을 개최하였다.

3. 환자분류체계 TFT 미션

현재의 환자분류체계는 여러가지의 문제점을 가지고 있어서 향후 발생할 문제들이 여러 곳에 도사리고 있다. 첫째로, 의사진료비용에 대한 문제이다. 우리나라는 90% 이상이 민간병원이며, 의사와 병원에 대한 보상을 분리할 수 없는 형태로 의료기관을 운영하고 있다. 따라서 KDRG는 미국과 호주의 DRG 시스템을 참고하여 개발되었지만, 이를 지불제도로 활용한 7개 질병군 포괄수가제는 의사와 병원에 대한 보상을 모두 포함하고 있다. 이로 인해 포괄수가제를 시범 사업하면서 동반질환이 있거나 합병증이 발생하면 일반적으로 입원기간이 증가하고 약제 사용량이 증가하는 등 추가비용이 발생하지만 이는 고려되지 않았다. 특히 수술과 내과적 치료가 동시에 발생한 경우, 내과적 처치가 비용 소모가 클 때 이에 대한 보상을 충분히 받는 것은 어려운 실정이다. 따라서 외과계에 비해 내과계 질병군의 저평가를 재평가하여야 한다. 둘째로, 원가자료의 부재이다. 일반적으로 DRG 질병군은 ①임상적으로 유사하고(임상적 동질성), ②자원 소모량이 유사해야 하며(경제적 동질성), ③통계적으로 타당해야 한다. 따라서 임상 전문가에 의해 임상적으로 유사하다고 판단된 그룹들은 자원소모의 동질성을 판단하기 위해, 해당 질병군에서 발생한 모든 의료서비스에 대한 비용 자료가 수집되어야 한다. 그러나 우리나라는 민간의료가 주도하는 환경으로 원가자료를 수집하는데 어려움이 있다. 따라서 KDRG를 개발할 때 자원소모의 동질성을 판단하기 위해서, 원가자료가 아니라 행위별수가제 하에서 지불된 진료비를 사용하였다. 하지만 진료비는 급여기준 등으로 정부에서 규제한 자료이기 때문에 실제로 의사가 환자에게 사용한 의료서비스보다 종류나 양이 적을 수밖에 없다. 특히 평균값이 보상되는 포괄수가제는 현재 의료기관이 제공하는 의료 원가자료를 반영하지 못한다. 셋째로, 현재의 환자분류체계는 의료비 절감과 재원일수 감소가 주목적이다. 그러나, 고령화와 건강보험보장의 확대로 의료비는 지속적으로 상승할 것으로 예측된다. 특히, 고령 환자가 증가하면서 입원 중 복잡한 진료과정 및 동시 시술이 발생할 확률이 높아진다. 특히 간질환 환자들이 오래 생존하면서, 여러가지 합병증과 재입원률이 높아질 것으로 예측된다. 이러한 의료환경 속에서 가장 기본적인 의사진료 비용의 포함과, 원가자료에 대한 올바른 평가가 해결되지 않는 한 환자분류체계는 불완전할 수밖에 없다. 현재 환자분류체계는 상급종합병원 지정평가 및 의료질평가지원금 분배에 이르기까지 이미 다양한 방식으로 활용되고 있다. 의료계 전체가 반드시 관심을 가져야한다.

따라서, 환자분류체계 TFT의 미션은 간질환 질병군 분류에 대한 지속적인 관심과, 문제점 발견, 해결 방안에 대한 연구 및 도출을 통해 향후 개정될 환자분류체계에서 간질환 환자의 진료 현실을 반영하며, 간전문의들의 피해를 막고 환자들의 혜택을 늘리고자 한다. 궁극적으로, 환자분류체계 TFT는 간학회 회원들의 보건의료정책의 흐름과 방향을 이해하고, 간질환 환자들을 위한 올바른 보건의료정책이 준비되고, 결정되는데 있어서 간학회가 중추적인 역할을 하며, 보건의료정책에 대한 탄탄한 지식과 실력을 갖춘 간전문의들의 저변확대를 위해 노력할 것이다.

Expanding Reimbursement Policy on Non-Reimbursable Services in Hepatology

Soon Sun Kim

Ajou University, Korea

In August 2017, a 'Measures to Strengthen Health Insurance Coverage' was announced with the aim of becoming a 'Reliable country without worrying about hospital expenses.' The announced "Health Insurance Coverage Strengthening Measures" has three structural frameworks. The first is to increase the health insurance coverage rate, which is staying in the early 60%, by reimbursement of non-reimbursable services that is necessary for treatment but not covered by health insurance, and the second is to increase the health insurance burden of medical expenses for the medically disadvantaged class (elderly, children, etc.) and income level. It means that the maximum amount of medical expenses borne by patients will be appropriately managed by setting an upper limit on the amount of medical expenses borne by the individual patient in proportion to the medical expenses support system, and the role of health insurance as a social safety net will be reinforced through the medical expenses support system.

Of the three above, except for the "reimbursement of non-reimbursable services", it is expected that many parts can be solved by securing insurance finances to support and rational system design. There are also few conflicts of interest, so it is expected that there will be not many difficulties during the implementation process. However, in the sense that 'reimbursement of non-reimbursable services' requires understanding and cooperation of various stakeholders, and it is possible to succeed not only by resolving non-reimbursable but also by changing the fundamental paradigm of health insurance, there must be a strategy to overcome the difficulties in the implementation process.

According to the reimbursement of non-reimbursable services policy, medical services that were classified as standard non-reimbursement and registered non-reimbursement in liver disease have become reimbursed or pre-reimbursed, or are under discussion. Today, we will look into the status of payment for abdominal ultrasound, liver MRI, and various medical services in liver disease.

References

1. 비급여 보장성 강화정책의 이행전략, 장인숙, HIRA 정책동향 2018년 12권 1호
2. 비급여의 급여화: 성과 및 향후 정책 방향 제언, 여나금, 보건복지포럼 2020년 11월
3. 건강보험 보장성 강화정책 방향, 손영래, HIRA 정책동향 2018년 12권 1호
4. 비급여 관리 정책현황 및 발전 방안, 공인식, HIRA 정책동향 2020년 14권 6호

Unmet Need of National Reimbursement Policy for Hepatocellular Carcinoma

Eun Sun Jang

Seoul National University, Korea

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second cause of cancer-related death in South Korea. HCC is most prevalent in middle-aged people who are economically active, so its socioeconomic burden is high. According to the claims data of the National Health Insurance Service (NHIS) of Korea, the direct and non-direct cost for cancer in 2015 was $13,945,300,000, and the cost for liver cancer was the highest ($2,266,100,000), which accounted for 16.2% of the total cancer-related economic burden of the year in Korea.

NHIS has provided and revised many healthcare-related policies for HCC patients, and it helps many patients who are suffering from the disease and a financial problem. Nonetheless, there are still several unmet needs in the policies because the diagnostic process and treatments are not the same as the other solid tumors. For example, the diagnosis of HCC is mainly based on non-invasive methods, including blood tumor markers and imaging modalities. Moreover, the physicians treating HCC patients do not make a simple decision in a forward process. Instead, multidisciplinary local modalities are mandatory for HCC treatment, including radiofrequency ablation, transarterial therapy, surgery, and systemic therapy in various orders.

Besides, many systemic targeted agents and immunotherapeutic drugs for HCC have been rapidly developing and used in foreign countries. Because the advanced HCC patients who cannot be treated with local therapies have very few treatment options, adopting the newly developed systemic agents is an urgent problem. Nevertheless, the review process for the cost-effectiveness and financial impact assessment usually takes a long time. It is difficult to pass the evaluation process because of the high costs and limited clinical data of newly developed drugs.

Better policy measures that can strengthen health insurance coverage for HCC patients are still needed. All clinicians, patients, and policymakers have to keep discussing this issue and try to minimize the financial risk of both patients and NHIS without depriving HCC patients of the best treatment opportunities.

Future Policy Direction of Pharmaceutical Benefit in National Health Insurance

Yoon Suk Yang

Ministry of Health and Welfare, Korea

The Liver Week 2021

DAY 1: Thursday, May 13, 2021 (14:50-16:30)

ROOM 3

Health Policy Forum

Hepatitis C Virus Elimination: Lesson from Worldwide Progress

Chairs:

Dong Jin Suh (Daehang Hospital)

Han Chu Lee (Univ. of Ulsan)

The Political and Clinical Progress for Hepatitis C Virus Elimination in Taiwan: From Beginning to Present

Jia-Horng Kao

National Taiwan University, Taiwan

Chronic hepatitis C virus (HCV) infection is a global health threat because of the disease burden. WHO estimated that there are 71 million people with HCV infection worldwide. Of particular note, Taiwan is a country endemic for chronic HCV infection, with ~500,000 HCV patients. Annually, ~13,000 people die of chronic liver diseases and their complications. Among them, 8000 are attributable to hepatocellular carcinoma (HCC). Because of the heavy disease burden, Taiwan has been fighting hepatitis B virus (HBV) since late 1970s and HCV since early 1990s, with successful results. Taking the control of HCV infection as an example, the Taiwan National Health Insurance system reimbursed combination therapy of pegylated interferon plus ribavirin since 2003, and before the introduction of interferon-free DAA in 2017, nearly 80,000 HCV patients were treated. When the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis in 2016, Taiwanese government began to put efforts towards the elimination of HCV. The government leaders have culminated in a consensus of reaching the WHO goals in 2025, i.e. 5 years ahead of the 2030 deadline set by WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018–2025 was approved. The government will provide the financial support of USD 1.7 billion within 8 years for the control of HCV infection, with the following actions: lowering the barriers of access to direct-acting antivirals (DAA); screening strategies; continuum of care; preventive measures for high-risk populations; improving liver health literacy on the prevention of new infections and reinfections; liver disease management; outcome evaluation of policy and interventions. After the implementation of Hepatitis C Policy Guideline, the number of HCV patients treated has remarkably increased year by year, from 9,500 in 2017 to 46,000 in 2019. More than 58,000 patients are anticipated to be treated in 2020. Inclusion of HCV patients already cured by peginterferon and ribavirin therapy before the DAA era, the treatment coverage of HCV patients is projected to reach 50% by the end of 2020. Thus, the elimination of HCV in Taiwan by 2025 is optimistic and thus on track. A recent study using the age-period-cohort models to estimate the mortality trends of liver diseases from 1981 to 2016 and project these trends to 2035 showed that the age-adjusted mortality rates of chronic liver disease, cirrhosis and HCC for both sexes are projected to decrease by more than 30% from 2016 to 2025 and by more than 55% from 2016 to 2035. In summary, the Taiwanese experience of the successful control of HCV infection can be shared by other countries where infections are equally prevalent and the socioeconomic status is similar.

The Political and Clinical Progress for Hepatitis C Virus Elimination in Egypt: From Beginning to Present

Imam Waked

National Liver Institute, Egypt

Egypt was the country with the highest world prevalence of hepatitis C virus (HCV) infection, associated with substantial disease and economic burden; hence, HCV elimination became a national health priority.

In 2006, the Ministry of Health (MoH) established the National Committee for Control of Viral Hepatitis (NCCVH) to oversee the national program for HCV elimination. The NCCVH obtained quality epidemiological data by including HCV antibodies and RNA tests in the Demographic Health Survey, and initiated specialized HCV treatment centers in MoH and university health care facilities, interconnected through a central database. A national treatment protocol was introduced and then dynamically updated according to international guidelines, availability of treatment choices, and data from real-life response rates.

In 2014, the NCCVH negotiated prices of brand direct-acting antivirals (DAAs) to 1% of their international prices, which made them affordable to the limited resources of the country.

In anticipation of the huge flow of hundreds of thousands of patients living with the diagnosis who were waiting for DAA therapy, a web-based registration system was developed to assign patients to the nearest center geographically and schedule appointments according to each center's capacity. With the initial flow of patients registering for treatment (500,000 in the first month) and the limited supply of medication initially, patients had to wait for up to 6 months for evaluation and treatment in some centers. This wait time decreased with the increase in supply, with the increase in number of treatment centers, and with the introduction of locally produced generic drugs in 2016.

With the limited supply of DAAs initially, the guidelines prioritized treatment to patients with advanced fibrosis and compensated cirrhosis (F3-F4 on the metavir score). Fibrosis was initially assessed by evaluating liver stiffness by FibroScan, which proved a bottleneck for patient flow, with waiting times of more than 3 months. The guidelines were modified to allow fibrosis assessment using FIB-4, which improved patient flow.

The return rate for reporting sustained virologic response (SVR) was initially very low. Several interventions were devised to improve SVR report rates, including phone calls to identify the cause of "no show," issuing "certificates of cure," and initiating hepatitis B vaccination free of charge.

By 2018, about 2.5 million patients had been evaluated for and started treatment. However, most infected persons remained unidentified, and the number of new cases who presented for treatment decreased to less than 5000 a month.

With the decreasing cost of direct-acting antivirals in Egypt, treatment of more patients and accelerated disease elimination became possible. In early 2018, the Egyptian government decided to embark on a

massive effort to identify and treat all HCV-infected persons to achieve disease elimination over the shortest time period possible. A national population-based screening program was initiated in October 2018 to augment the treatment flow and meet the disease elimination targets. The program aimed at mass screening of adults older than 18 years (62.5 million) and schoolchildren aged 12 to 18 years (with parents' consent, a population of 15 million). The country was divided into three sections of 17 to 23 million adults, and the mass screening program was implemented in three phases, with screening for adults lasting between 2 and 3 months in each phase, followed by screening schoolchildren.

Screening was totally free of charge and included testing for anti-HCV antibody using a rapid diagnostic test, and screening for diabetes, hypertension, and obesity. Preparation for each phase included training teams of health care workers (physicians, nurses, data entry personnel), and preparing screening sites in MoH hospitals, clinics, rural health units, and in schools, sports facilities, and youth centers. Each phase included 4000 to 6000 screening sites, which worked 12-hour days, 7 days a week. Screening sites were augmented with specially outfitted vehicles targeting crowds in mosques on Fridays, churches on Sundays, sports clubs, factories, shopping malls, and subway stations. Results of antibody testing were immediate, and data were transmitted instantaneously to a central database through handheld devices and cellular networks. Appointments were set for HCV seropositive individuals through the web-based registration system at the nearest treatment center to their residence, where further evaluation and treatment were fully funded by the state.

Of a target population of 62.5 million, 49.6 million persons (79.4%) spontaneously participated in screening between October 2018 and April 2019. Overall HCV seroprevalence 4.6%. This varied across states, with the highest prevalence in states in the middle of the Nile Delta (8.4%) and the lowest in the desert states (2.2%). Seroprevalence was higher among men than among women, increased with age, and was higher in rural than in urban areas.

Of the seropositive patients, 76.5% had viremia, and 91.8% of those with viremia started treatment with the combination of sofosbuvir and daclatasvir, with reported SVR rate of 98.8%.

Several key factors drove the success of the screening campaign in Egypt and can guide other countries preparing similar HCV elimination programs.

- Political will and support were crucial for initiating and maintaining the program. The Egyptian president adopted the program, aligned the whole government behind it, and maintained continuous support throughout.
- Social pressure was essential to drive policymakers to start and scale up the national treatment program at the expense of the state.
- Mass procurement through a single negotiating body ensured low prices.
- Sufficient financial and human resources were allocated at the outset to ensure continuity and success.
- Efficient information-technology support, immediate results and immediate linkage to care resulted in smooth evaluation and treatment of patients.
- Simplified management guidelines allowed task shifting to non-specialist physicians,
- Providing tests and treatment at no cost to patients was a major factor driving adherence and program success.

Conclusion

The Egyptian program is the largest national HCV screening and treatment program in the world. With this screening program and the mass treatment effort, Egypt is on a fast track to HCV elimination and has achieved the WHO disease elimination targets a decade earlier than expected.

References

1. Elsharkawy A, El Raziky M, El Akel W, et al. Planning and prioritizing direct acting antivirals treatment for HCV patients in countries with limited resources: lessons from the Egyptian experience. J Hepatol 2018;68:691-698.
2. Esmat G, El-Sayed MH, Hassany M, et al. Further steps to elimination of hepatitis C in Egypt. Lancet Gastroenterol Hepatol 2018;3:665.
3. Abdel-Razek W, Hassany M, El-Sayed MH, et al. HCV in Egypt: Lessons Learned from the World's Largest National Program. Clinical Liver Disease. 2019, 14:203-206
4. Waked I, Esmat G, Elsharkawy A, et al. Screening and Treatment Program to Eliminate Hepatitis C in Egypt. N Engl J Med, 2020, 382: 1166-74

The Political and Clinical Progress for Hepatitis C Virus Elimination in Australia: From Beginning to Present

Gregory Dore

Kirby Institute, Australia

Major recent advances in hepatitis C virus (HCV) therapeutic development, with availability of highly curative well tolerated directing-acting antiviral (DAA) regimens, have raised the prospect that treatment will provide considerable individual and population-level impact, including potential treatment as prevention. Australia has established the foundation to achieve elimination of HCV as a major public health issue, including WHO goals of 80% treated, 90% reduction in HCV incidence, and 65% reduction in liver disease mortality, within the current decade. Key elements of this foundation include: a high HCV diagnosis rate (80%); Australian Government subsidisation of DAA therapy for all adults with chronic HCV infection, without liver disease stage or drug and alcohol use restrictions; approval for all medical practitioners to prescribe DAA therapy; several DAA regimens funded; a well-established harm reduction framework for people who inject drugs (PWID); and a sophisticated surveillance system to enable ongoing monitoring and evaluation of HCV elimination strategies.

In the initial five years (2016-2020) of the DAA program an estimated 92,000 people were treated, equivalent to 45-50% of the chronic HCV population. Prescriber patterns over this period demonstrate and increasing proportion of DAA prescriptions by primary care and other non-specialist physicians. Preliminary data also suggests a high proportion (>80%) of people with HCV-related cirrhosis have initiated DAA therapy, and that treatment uptake among PWID is higher than the broader population, key populations to reduce liver-related mortality and incidence of new infections, respectively. Around 6% of people treated have been re-treated for either virological failure or reinfection.

Key strategies to enable HCV elimination to be achieved include: continued use of diverse models of care; enhanced HCV screening (HCV RNA) and linkage to care (role for point-of-care HCV RNA); integration of HCV screening within drug treatment, homelessness, and mental health services; further simplification of HCV treatment assessment and delivery; increased DAA treatment in prison and community PWID populations (e.g. needle syringe programs, acute hospital); and monitoring and evaluation.

The Critical Appraisal for Policy Progress to Date: What Is Needed and How Should It Proceed?

Young-Suk Lim

University of Ulsan, Korea

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (08:20-09:40)

ROOM 1

KASL Symposium 1

Personalized Medicine in Liver Diseases: "Present and Future"

Chair:

Seung Kew Yoon (The Catholic Univ. of Korea)

Young Oh Kweon (Kyungpook National Univ.)

Clinical Implication of Personalized Medicine in Hepatic and Biliary Cancer

Yeul Hong Kim

Korea University, Korea

Precision medicine is an approach to patient care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease. Cancer is a disease of the genome and as more is learned about cancer tumors, the more we are finding that each tumor has its own set of genetic changes. Understanding the genetic changes that are in cancer cells is leading to more effective treatment strategies that are tailored to the genetic profile of each patient's cancer. Precision oncology or precision medicine of cancer focuses on matching the most accurate and effective treatment to each individual cancer patient based on the genetic profile of the cancer and the individual. Because every single cancer patient exhibits a different genetic profile and the profile can change over time, more patients will benefit if therapeutic options can be tailored to that individual, thus avoiding the idea that "one-size-fits-all" in terms of cancer treatment.

The pathogenesis of hepatocellular carcinoma (HCC) is a complex process. During the last decade, advances in genomic technologies enabled delineation of the genomic landscape of HCC, resulting in the identification of the common underlying molecular alterations. The genomic landscape using the whole exome-sequencing of 363 HCC cases from the TCGA revealed that the significantly mutated tumor suppressor gene, tumor protein *TP53* (12-48%), is frequently present in advanced tumors. Other highly mutated suppressor genes were *AXIN1* (5-15%) and *CTNNB1* (11-37%).[1] Whole-exome sequencing led to the discovery of telomerase reverse transcriptase (*TERT*) promoter mutations as the most common somatic mutation (40-65%) detected in HCC. In the study of the large-scale analysis of blood-derived ctDNA in HCC in United States, the most frequently altered genes (≥20 events/gene) were as follows: within actionable genes—*EGFR, MET, ARID1A, MYC, NF1, BRAF,* and *ERBB2*.[2] The tumor microenvironment, regulated by inflammatory cells, including cancer cells, stromal tissues, and the surrounding extracellular matrix, has been extensively studied using molecular data. The integration of molecular, immunological, histopathological, and clinical findings has provided clues to uncover predictive biomarkers to enhance responses to novel therapies.[3]

IHCCs, EHCCs, and GBCs have different molecular profiles, reflecting differences in underlying tumor etiology. IHCCs had higher rates of *IDH1*, *BAP1*, and *PBRM1* mutations and *FGFR2* fusions; *EHCCs* had higher rates of *KRAS*, *CDKN2A*, and *BRCA1* mutations; and GBCs had higher rates of homologous recombination repair deficiency and Her2/neu overexpression and amplification.[4] IHCCs and GBCs had higher rates of potential positive predictive biomarkers for immune checkpoint inhibition (PD-L1 expression, high microsatellite instability, and high tumor mutational burden) than EHCCs.

For the success of cancer precision medicine, new clinical trial design is mandatory. Since the therapeutic paradigm is shifting from cytotoxic agents to targeted agents, new approach is needed. Also, therapeutic strategy is tailored based on biomarker. However, the selection of specific biomarker positive patients using traditional clinical trial design is very expensive and inefficient. Thus, new clinical trial design is necessary, such as master protocol trial, basket trials, umbrella trials, and platform trials. Especially, the master protocol trial has many advantages in precision medicine era. Inter-patient, intra-patient heterogeneity can be evaluated efficiently from multiple sub-studies, which is parallelly conducted. Specific signal pathway can be obtained, which is related with target. The clinical trials with Combining two or more targeted therapies can be conducted. Thus, it can be easily expanding the studied genetic mutations. Additional advantage is that we can Increase the chance of participation in a clinical trial. Also, we can obtain the natural history from waiting list patients. Since These master protocol trials cannot be initiated and operated by pharmaceutical company, usually master protocol trials are supported by government or large comprehensive cancer hospital, which has a specific infra and research fund. The typical examples are K-MASTER program or SCRUM Japan project. The genomic profiling data from K-MASTER program will be reviewed in hepatic and biliary cancers.

References

1. The Cancer Genome Atlas Research Network, David A. Wheeler, and Lewis R. Roberts. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell. 2017; 169(7): 1327–1341.
2. Ahmed O. Kaseb, Nora S. Sánchez, Shiraj Sen, et al. Molecular Profiling of Hepatocellular Carcinoma Using Circulating Cell-Free DNA. Clin Cancer Res. 2019; 25(20): 6107-6118.
3. Sun Young Yim & Ju-Seog Lee. The Genomic Landscape and Its Clinical Implications in Hepatocellular Carcinoma. J Liver Cancer 2019; 19(2): 97-107.
4. Benjamin A. Weinberg, Joanne Xiu, Michael R. Lindberg, et al. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. J Gastrointest Oncol. 2019: 10(4):652-662.

Personalized Medicine in Nonalcoholic Fatty Liver Disease: From Genetics and Systems Biology

Silvia Sookoian

University of Buenos Aires, Argentina

Nonalcoholic fatty liver disease (NAFLD) is a complex disorder that affects a large proportion of the world population of all ages.[1] The disease pathogenesis involves a myriad of factors, including genetic susceptibility and predisposing metabolic comorbidities, such as obesity and type 2 diabetes, as well as environmental exposure and lifestyle, which jointly shape the NAFLD epigenome.[2-9] NAFLD is a heritable and complex trait.[6,7,9] According to the available data, the heritability estimates is about 20-30%, depending on the study design, ethnicity and the methodology used to characterize the phenotype, which is similar to the heritability of many other complex traits.[10]

Keystones of genetic assessment in complex diseases are to predict the onset of the disease and the disease progression [7]. Thus, patients may be classified into high or low risk for disease onset or severity, and therapeutic interventions can be personalized.

Discoveries of variants of genes that regulate metabolic traits represent a large proportion of the genetic component of NAFLD and NASH.[8] Variants in metabolic-related loci represent up to ~20-30% of the variance NAFLD-related phenotypes.[6,7,9,11] Hence, it is clear that knowledge of the phenotypic variance of NAFLD and NASH is still lacking, resulting in what is known as missing heritability.[7] It is plausible to presume that the NAFLD-NASH-heritability gap might be explained by the intricate relationship among genetic variance of the nuclear and mitochondrial genome,[12-13] the phenotype, and interactions with epigenetic and environmental factors, including the liver tissue microbiome.[14]

The ultimate goal of precision medicine is to develop precision treatment strategies that rely upon a holistic understanding of differences in genetic and underlying molecular pathogenic factors, as well as responses to environmental stressors, among patients. Milestones in the path towards precision medicine include the integration of big data and machine learning strategies, such as artificial intelligence.[9] In addition, collections of biological samples in large biobanks linked to patient data increase the likelihood of finding robust disease pathogenesis signatures derived from OMICs state-of-the-art approaches. Knowledge integration and data modeling and analysis are vital processes at the interface with drug discovery. Precision medicine has emerged as a result of comprehensive knowledge of the druggable genome/proteome.[9] Thus, advancing the chemical genetics research, which is based on the screening of low-molecular weight compounds that act by binding to specific receptors/proteins, is crucial to move this promising research domain forward in the right direction. It is worth mentioning that the incomplete knowledge on the druggable genome of NAFLD/NASH severely undermines the drug discovery progress and reduces the chances of having robust and safe drug candidates. Therefore, the substantial gap between the knowl-

edge of NAFLD-predisposing genes and that related to putative protein ligands needs to be urgently addressed.

Polygenic risk scores (PRSs) are theoretically designed to explain the relative risk of a disease, as these scores provide information on how a person compares with others with different genetic susceptibility background.[9] PRSs could be conceptually very advantageous not only for allowing early disease detection, but also for implementing timely actionable measures. In the case or NAFLD and NASH, PRSs could be conceptually very advantageous not only for allowing early disease detection, but also for implementing timely actionable measures. Some emerging disciplines, such as chemical genetics, that may accelerate accurate identification of the druggable NAFLD genome/proteome.[9]

References

1. Brunt EM, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, Bugianesi E, Sirlin CB, Neuschwander-Tetri BA, Rinella ME. Nonalcoholic fatty liver disease. Nat Rev Dis Primers 2015;1:15080.
2. Pirola CJ, Gianotti TF, Burgueno AL, Rey-Funes M, Loidl CF, Mallardi P, Martino JS, Castano GO, Sookoian S. Epigenetic modification of liver mitochondrial DNA is associated with histological severity of nonalcoholic fatty liver disease. Gut 2013;62:1356-1363.
3. Pirola CJ, Fernandez GT, Castano GO, Mallardi P, San MJ, Mora Gonzalez Lopez LM, Flichman D, Mirshahi F, Sanyal AJ, Sookoian S. Circulating microRNA signature in non-alcoholic fatty liver disease: from serum non-coding RNAs to liver histology and disease pathogenesis. Gut 2015;64:800-812.
4. Pirola CJ, Sookoian S. Epigenetics factors in nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol 2020;1-16.
5. Sookoian S, Rosselli MS, Gemma C, Burgueno AL, Fernandez GT, Castano GO, Pirola CJ. Epigenetic regulation of insulin resistance in nonalcoholic fatty liver disease: impact of liver methylation of the peroxisome proliferator-activated receptor gamma coactivator 1alpha promoter. Hepatology 2010;52:1992-2000.
6. Sookoian S, Pirola CJ. Genetic predisposition in nonalcoholic fatty liver disease. Clin Mol Hepatol 2017;23:1-12.
7. Sookoian S, Pirola CJ. Genetics of Nonalcoholic Fatty Liver Disease: From Pathogenesis to Therapeutics. Semin Liver Dis 2019;39:124-140.
8. Sookoian S, Pirola CJ, Valenti L, Davidson NO. Genetic pathways in nonalcoholic fatty liver disease: Insights from systems biology. Hepatology 2020; 72(1):330-346
9. Sookoian S, Pirola CJ. Precision medicine in nonalcoholic fatty liver disease: New therapeutic insights from genetics and systems biology. Clin Mol Hepatol 2020;26:461-475.
10. Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. Classification of common human diseases derived from shared genetic and environmental determinants. Nat Genet 2017;49:1319-1325.
11. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology 2011;53:1883-1894.
12. Sookoian S, Flichman D, Scian R, Rohr C, Dopazo H, Gianotti TF, et al. Mitochondrial genome architecture in non-alcoholic fatty liver disease. J Pathol 2016;240:437-449.
13. Liver mitochondrial DNA damage and genetic variability of Cytochrome b - a key component of the respirasome - drive the severity of fatty liver disease. Pirola CJ, Garaycoechea M, Flichman D, Castaño GO, Sookoian S. J Intern Med. 2021;289:84-96.
14. Sookoian S, Salatino A, Castano GO, Landa MS, Fijalkowky C, Garaycoechea M, Pirola CJ. Intrahepatic bacterial metataxonomic signature in non-alcoholic fatty liver disease. Gut 2020; 69:1483-1491.

Personalized Medicine in Liver Disease via Modulating the Gut Microbiota

Ki Tae Suk

Hallym University, Korea

Nonalcoholic fatty liver disease (NAFLD) is one of the most common types of liver disease worldwide. NAFLD includes a broad spectrum of disorders, including steatosis, nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis.[1] Recent advances in our understanding of gut microbiota have dramatically transformed our view on human disease and treatment. Human gut microbiota is an ecological community comprised of commensal, symbiotic, and pathogenic microorganisms totaling 1-2 kg in weight. Gut microbiota are integral for immunological, hormonal, and metabolic homeostasis of the host. However, an overall understanding of gut microbiota, including variations due to geographical region, gender, and age, has yet to be established. The close relationship between the gut and liver appears to be a crucial factor in liver injury.[2] The liver receives most of its blood and nutritional supply from the gut through the portal vein and is the first organ to be exposed to gut-derived toxic factors, including bacteria, damage-associated metabolites (i.e., damage-associated molecular patterns), and bacterial products (i.e., pathogen-associated molecular patterns [PAMPs]). Furthermore, some gut microbes produce ammonia, ethanol, and acetaldehyde, which are largely metabolized in the liver and associated with activation of Kupffer cells and inflammatory cytokine pathways. Additionally, dysbiosis, which is defined as quantitative and qualitative changes in intestinal bacteria, and small intestine bacterial overgrowth can both lead to an increase in intestinal permeability and translocation of endotoxins to the portal tract, which activates the signal pathways of a wide array of inflammatory cytokines in the liver.[3]

Worldwide, alcohol consumption ranks third among the various risk factors for disease and disability. The large absolute increase in alcohol consumption has led to a rapid increase in alcohol-related diseases and accidents.[3] Alcoholic liver disease (ALD) is responsible for approximately 25% of deaths resulting from alcohol consumption. Activation of Kupffer cells has been identified as an essential element in the pathogenesis of ALD. Alcohol induces bacterial overgrowth (especially that of gram-negative bacteria) and the translocation of the endotoxin lipopolysaccharide (LPS) from the gut to the liver. Alcohol has been known to disrupt the gut barrier function, which consequently promotes the translocation of microbial LPS from the lumen of the intestines to the portal vein, where it travels to the liver. Kupffer cells and macrophages recruited to the liver can be activated by bacterial endotoxin such as LPS through toll-like receptor (TLR) 4.[4] The levels of LPS in the portal vein and in the systemic circulation are increased with excessive alcohol intake. These observations suggest that gut-derived LPS is the central mediator of inflammation in alcoholic steatohepatitis. Moderate alcohol consumption has also been identified as a strong risk factor for small intestinal bacterial overgrowth. This process of alcohol consumption bringing about changes in the intestinal

milieu and inducing consequent downstream immune responses in the liver.

Metabolites produced by bacteria, such as short chain fatty acids, volatile organic compounds, and bile acids, are involved in ALD pathology. Alcohol fed mice exhibited decreased expression of bacterial genes involved in the biosynthesis of saturated fatty acids and decreased levels of saturated long-chain fatty acids. In the comparison of the fecal metabolites, 13 biomarkers are related to ALD and the most discriminating molecules were bile acid derivatives and fatty acids.[5]

References

1. Friedman SL, Neuschwander-Tetri BA, Rinella M, et al. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908-922.
2. Panasevich MR, Peppler WT, Oerther DB, et al. Microbiome and NAFLD: potential influence of aerobic fitness and lifestyle modification. Physiol Genomics 2017;49:385-399.
3. Kirpich IA, Parajuli D, McClain CJ. Microbiome in NAFLD and ALD. Clin Liver Dis (Hoboken) 2015;6:55-58.
4. Saltzman ET, Palacios T, Thomsen M, et al. Intestinal Microbiome Shifts, Dysbiosis, Inflammation, and Non-alcoholic Fatty Liver Disease. Front Microbiol 2018;9:61.
5. Chen P, Schnabl B. Host-microbiome interactions in alcoholic liver disease. Gut Liver 2014;8:237-41.

Personalized Medicine in Autoimmune Hepatitis

Atsumasa Komori

Nagasaki University, Japan

Introduction

Autoimmune hepatitis (AIH) is an immunoinflammatory liver disease of non-self-limiting clinical course for which immunosuppressive agents are required in the majority of affected patients. Recently, treatment strategies for AIH have been updated and almost standardized by practice guidance and guidelines, including the one published by the American Association of the Study of Liver Disease in 2019.[1] Nevertheless, due to its dynamic and rather heterogenous disease manifestation, the latter of which are exemplified by atypical cases without elevation of immunoglobulin G (IgG)[2] or anti-nuclear antibodies (ANA), personalized medicine in AIH to ensure precision medicine is much anticipated beyond standardization.[2] In this presentation, we summarize and discuss personalized aspects of clinical practice in AIH to highlight unmet needs which serve as the driving force behind establishment of next-generation molecular personalized medicine in AIH.

Personalized diagnosis

As AIH is a disease without signature diagnostic features, composite diagnostic criteria have been established, consisting of 1) histological abnormalities (interface hepatitis with plasma cell infiltrates), 2) characteristic laboratory findings (elevated serum hepatic enzymes and increased serum IgG), and 3) positive results of disease-defining autoantibodies, coupled with 4) the exclusion of other liver diseases that may resemble AIH. The lack of diagnostic accuracy is evident for atypical cases of autoantibody-negative hepatitis and acute-onset AIH with normal IgG values, as well as for AIH that is overlapped with a primary biliary cholangitis, primary sclerosing cholangitis, or non-alcoholic steatohepatitis (NASH). Moreover, even pure NASH which is often characterized by prominent periportal hepatitis coupling with positive ANA, is difficult to be discriminated from chronic active AIH. Not only lack of disease specific autoantibodies and pathological features, but also evolving nature of disease phenotype during the progression and transition of clinical course are the likely reasons for the diagnostic inaccuracy. Characterization and tracking of rare, but disease-specific autoreactive T cell populations in peripheral blood, such as soluble-liver antigens (SLA)-specific $CD4^+$ T cells,[3] is a relevant and highly-anticipated next-generation diagnostics.

Personalized induction and maintenance treatment

The aims of the treatment of AIH are to relieve symptoms first, and then to achieve a biochemical remis-

sion (BR; a surrogate endpoint, defined as normalization of serum AST, ALT, and IgG within upper limit of normal), alleviating hepatic inflammation toward histological remission, to ultimately prevent the disease progression from liver-related outcomes, and to promote the regression of fibrosis, if possible.[4] The first-line treatment recommended by the 2019 AASLD practice guidance and guidelines is either prednisolone (PSL) monotherapy, or a combination of PSL or budesonide and azathioprine (AZA).[1] Treatment protocol and response-guided management is a matter of personalization, according to disease phenotypes and comorbidities; PSL monotherapy is likely to be appropriate for patients including those with drug-induced AIH like injury in whom the treatment duration is expected to be <6 months.[1] The proper selection and dosing of first-line therapy (budesonide or PSL) to decrease unnecessary side effects to intolerant patients is of importance. Even after treatment introduction, the time point for the evaluation of treatment response must be determined with regard to prevention of liver-related adverse events, e.g., at 7-14 days is preferable for acute-severe AIH to re-evaluate diagnosis and to consider second-line drugs, which make it possible to initiate timely assessment of liver transplantation in case of deterioration to acute liver failure. As for second-line treatments for AIH to manage refractoriness, incomplete biochemical response, and drug intolerance to first-line treatments, mycophenolate mofetil, calcineurin inhibitors (cyclosporin A, tacrolimus), mercaptopurine, and biologics (e.g., infliximab) have been introduced anecdotally. Recently, aberrant B cell activation is regarded as an alternative promising target for second or third-line add-on therapy for AIH; B cell depletion is exerted with either anti-CD20 antibody (rituximab),[5] B cell-activating factor (BAFF) inhibitor (e.g., belimumab) or anti-BAFF receptor antibody, the latter of which is in under way of phase II/III clinical trial. Companion biomarkers to those agents for the evaluation of pathological B cell activation in peripheral blood to determine applicability is also necessary for personalized second or third-line add-on therapy.

Personalized duration and termination of treatment

AIH is generally considered as a chronic disease demanding life-long maintenance therapy. Is it feasible to withdraw immunosuppressive agents in specific subpopulation of AIH, simultaneously pursuing the lowest risk of drug-induced complications? Could such cure for AIH be diagnosed by surrogate non-invasive biomarkers, to precisely predict histological remission? As patients with only normalized ALT for 2 years resulted in almost universal relapse,[6] the AASLD proposed sustained BR of ≥2 years as the eligibility criterion for attempting a treatment withdrawal.[1] Alternatively, the negative-predictive capacity of serum cytokeratin-18 cell death marker M65 was recently demonstrated to noninvasively detect incomplete histological remission.[7] A retrospective single-center analysis demonstrated that only 5% of AIH patients achieved sustained remission for >1 year after drug withdrawal and they were all characterized by ALT values ≤0.5× ULN and IgG values ≤1,200 mg/dL.[8] Non-cirrhotic patients with sustained low values of vibration-controlled transient elastography (VCTE), along with stringent BR for >2 years, may predict the patients who are at low risk of decompensation even when relapse occurs after treatment withdrawal.[9] A novel serum fibrosis marker, i.e., Mac-2 binding protein glycosylation isomer (M2BPGi), is likely to become an alternative to the use of VCTE, because the M2BPGi value is influenced by both inflammation and fibrosis in AIH patients, in a similar way to VCTE.[10] A 'one-serum parameter fits all' approach to predict when and for whom the treatment termination is feasible could be achievable with serum M2BPGi. In the

era of molecular personalized medicine, immune homeostasis restoration by regulatory T cells functions/ numbers, as well as the absence of pathogenic CD4 infiltrate in the AIH liver, could be monitored by blood-based liquid biopsy for the precision in the cure of AIH.

Conclusion

Improvement of the health-related quality of life of AIH patients must be accomplished in the future by the realization of personalized medicine.

Reference

1. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020; 72:671-722.
2. Hartl J, Miquel R, Zachou K, Wong GW, Asghar A, Pape S, et.al. Features and outcome of AIH patients without elevation of IgG. JHEP Reports 2020; 2:100094.
3. Renand A, Cervera-Marzal I, Gil L, Dong C, Garcia A, Kervagoret E, et al. Integrative molecular profiling of autoreactive CD4 T cells in autoimmune hepatitis. J Hepatol 2020; 73:1379-1390.
4. Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol 2021; 27:58-69.
5. Than NN, Hodson J, Schmidt-Martin D, Taubert R, Wawman RE, Botter M, et al. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: Results from the International Autoimmune Hepatitis Group. JHEP Reports 2019;1: 437-444
6. van Gerven NM, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol 2013; 58:141-147.
7. Derben FC, Engel B, Zachou K, Hartl J, Hartleben B, Bantel H et al. CK-18 cell death markers improve the prediction of histological remission in autoimmune hepatitis during biochemical remission. Liver Int 2021; 41:123-127.
8. Hartl J, Ehlken H, Weiler-Normann C, Sebode M, Kreuels B, Pannicke N, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. J Hepatol 2015; 62:642-646.
9. Hartl J, Ehlken H, Sebode M, Peiseler M, Krech T, Zenouzi R, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2018;68: 754–763.
10. Migita K, Horai Y, Kozuru H, Koga T, Abiru S, Yamasaki K, et al. Serum cytokine profiles and Mac-2 binding protein glycosylation isomer (M2BPGi) level in patients with autoimmune hepatitis. Medicine (Baltimore) 2018; 97: e13450.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (11:10-12:30)

ROOM 1

Young Investigators of the Year Session

Chairs:

Jeong Ill Suh (Dongguk Univ.)

So Young Kwon (Konkuk Univ.)

My Research Interests in the Field of Hepatology and Gastroenterology

Jeong-Hoon Lee

Seoul National University, Korea

Optimizing the Secondary Prevention of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B: A Lesson from Real-World Evidence

Jonggi Choi

University of Ulsan, Korea

The goal of antiviral treatment for chronic hepatitis B (CHB) is to reduce the risk of liver-related complications, including liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).

For the past decades, real-world evidence (RWE) has enlarged the field of CHB research. Presently, there is mounting evidence that randomized clinical trials are not technically and ethically possible to conduct. Recently, dramatic advancements have been made in HBV treatment; the development of an HBV vaccine and antiviral agents against HBV have tremendously improved clinical outcomes, including viral hepatitis and its fatal complications. Unfortunately, no current drug can eliminate HBV nor can it completely eliminate the risk of HCC. Therefore, CHB should be properly managed with appropriate and timely use of antiviral treatments for secondary prevention, given the enormous clinical and socio-economical burdens of HCC caused by HBV. Many recent RWEs have provided important insights into secondary prevention of HCC, making clinicians reconsider the indications for antiviral treatment beyond the current treatment guidelines set forth for patients with CHB. Clinicians should be aware of the limitations of RWE before applying it in research, but the method may be used across a wide spectrum of CHB research through judicious selection of data sources, refinement of study designs, and appropriate analytic approaches. This will bring researchers a step closer to optimizing the secondary prevention of HCC in patients with CHB.

Recent Epidemiology of Hepatocellular Carcinoma in the USA

Ju Dong Yang

University of California, Los Angeles, USA

Hepatocellular carcinoma (HCC) incidence rates in the United States (US) have increased over several decades and it is one of the leading causes of cancer-related death in the US and the world.[1,2] However, recent data from the Surveillance, Epidemiology, and End Results (SEER) program show HCC incidence rates have started to plateau in 2013 with an annual percent change (APC) of -1.44%/year.[3,4] There has historically been significant geographic variation in HCC incidence, with an incidence rate ratio (IRR) as high as 4 between high- and low-incidence states.[5] It remains unknown whether or not there is state-level variation in the recent decreasing trend of HCC incidence and mortality.

The burden of metabolic syndrome continues to increase and has emerged as a major etiology of HCC,[6,7] with its population attracted fraction in the US increasing from 26% to 36% between 2000 and 2011.[8] Independent of obesity, physical inactivity is also associated with higher HCC incidence and mortality.[9,10] Considering the regional variation in the burden of metabolic syndrome and physical inactivity in the US,[11] there could be an ecological correlation between state-level obesity and physical inactivity and incidence trends of HCC.

Our first study investigated state-level temporal trend of HCC incidence and ecological correlation between HCC incidence and obesity/physical activity levels in the US.[12] We used US Cancer Statistics Database (2001–2017), which includes cancer incidence and population data for all 50 states and the District of Columbia (DC), providing information on more than 25 million cancer cases using Center for Disease Control and Prevention (CDC)'s National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI)'s SEER. Annual percent change (APC) in rates were calculated. State-level percent of obesity and level of physical activity were obtained from the CDC, and the correlation between obesity, physical activity, and state-specific average APC (AAPC) was tested by Pearson correlation coefficient. Despite overall decreasing HCC incidence rates after 2015, HCC incidence continued increasing in 26 states over recent years. HCC incidence trends had a moderate correlation with state-level obesity (r=0.45, P<0.001) and a moderate inverse correlation with state-level physical activity (r=-0.40, P=0.004).

In our second study, we investigated the recent trends of primary liver cancer (excluding intrahepatic cholangiocarcinoma) mortality and HCC stage, treatment, and overall survival (OS) in the US.[13] US Cancer Mortality database was analyzed to investigate the trend of HCC mortality. We analyzed the SEER 18 database to assess the temporal trend of tumor size, stage, treatment, and OS of HCC. During 2000-2018, liver cancer mortality rates increased until 2013, plateaued during 2013-2016 (annual percent change [APC] = 0.1%/ yr, 95% confidence interval [CI] = -2.1% to 2.4%; P=0.92), and started to decline during

2016-2018 (APC = -1.5%/yr, 95% CI= -3.2% to 0.2%; *P*=0.08). However, mortality continues to increase in American Indians/Alaska Natives, individuals aged 65 or older, and in 33 states. There was a 0.61% (95% CI = 0.53% to 0.69%; *P*<0.001) increase in localized stage HCC and 0.86 mm (95% CI= -1.10 to -0.62; *P*<0.001) decrease in median tumor size per year. One-year OS rate increased from 36.3% (95% confidence interval [CI]= 34.3% to -38.3%) to 58.1% (95% CI = 56.9% to -59.4%) during 2000-2015, and five-year OS rate almost doubled from 11.7% (95% CI = 10.4% to -13.1%) to 21.3% (95% CI = 20.2% to -22.4%) during 2000-2011. Diagnosis year (per year) (adjusted hazard ratio = 0.96; 95% CI= 0.96 to -0.97) was independently associated with OS in multivariable analysis.

In conclusion, the incidence and mortality of HCC started downtrending in the US. In addition to decreasing incidence, increased early HCC detection and advances in treatment allocation and efficacy likely contributed to decreases in mortality. Prognosis of HCC patients will continue to improve with the advent of novel curative, locoregional, and systemic treatments. Future studies should further investigate the underlying causes of demographic and state-level variation in liver cancer incidence and mortality and outcome. Finally, targeted interventions and resource allocation are needed to minimize HCC disparities in the US.

References

1. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16:589-604.
2. Yang JD, Mohamed EA, Aziz AO, Shousha HI, Hashem MB, Nabeel MM, Abdelmaksoud AH, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. Lancet Gastroenterol Hepatol 2017;2:103-111.
3. Shiels MS, O'Brien TR. Recent Decline in Hepatocellular Carcinoma Rates in the United States. Gastroenterology 2020.
4. Rich NE, Yopp AC, Singal AG, Murphy CC. Hepatocellular Carcinoma Incidence Is Decreasing Among Younger Adults in the United States. Clin Gastroenterol Hepatol 2020;18:242-248.e245.
5. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology 2017;152:812-820.e815.
6. Kanwal F, Kramer JR, Li L, Dai J, Natarajan Y, Yu X, Asch SM, et al. Effect of Metabolic Traits on the Risk of Cirrhosis and Hepatocellular Cancer in Nonalcoholic Fatty Liver Disease. Hepatology 2020;71:808-819.
7. Hirode G, Wong RJ. Trends in the Prevalence of Metabolic Syndrome in the United States, 2011-2016. JAMA 2020;323:2526-2528.
8. Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, Greten TF, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer 2016;122:1757-1765.
9. Baumeister SE, Schlesinger S, Aleksandrova K, Jochem C, Jenab M, Gunter MJ, Overvad K, et al. Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study. J Hepatol 2019;70:885-892.
10. Simon TG, Kim MN, Luo X, Yang W, Ma Y, Chong DQ, Fuchs CS, et al. Physical activity compared to adiposity and risk of liver-related mortality: Results from two prospective, nationwide cohorts. J Hepatol 2020;72:1062-1069.
11. Gurka MJ, Filipp SL, DeBoer MD. Geographical variation in the prevalence of obesity, metabolic syndrome, and diabetes among US adults. Nutr Diabetes 2018;8:14.

12. Lee YT, Wang JJ, Luu M, Tseng HR, Rich NE, Lu SC, Nissen NN, et al. State-Level Hepatocellular Carcinoma Incidence and Association with Obesity and Physical Activity in the United States. Hepatology 2021;In press.
13. Yi-Te Lee JJW, Michael Luu, Mazen Noureddin, Kambiz Kosari, Vatche G. Agopian, Nicole E. Rich, Shelly C. Lu, Hsian-Rong Tseng, Nicholas N. Nissen, Amit G. Singal, Ju Dong Yang. The Mortality and Overall Survival Trends of Primary Liver Cancer in the United States. JNCI 2021.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (13:30-14:50)

ROOM 1

KASL Symposium 2

Current Issues and Future Therapy for Chronic Hepatitis B

Chairs:

Jung-Hwan Yoon (Seoul National Univ.)

Kyun-Hwan Kim (Sungkyunkwan Univ.)

Advancing Age and Comorbidity in Patients with Chronic Hepatitis B

Yun Bin Lee

Seoul National University, Korea

Chronic hepatitis B (CHB) is one of the most common chronic viral infections worldwide, and especially in Asian countries.[1] Although clinical outcomes of patients with CHB has been improved by antiviral therapy with effective and well-tolerated oral nucleos(t)ide analogues with little or no risk of antiviral resistance, the risk for developing liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) has not been eliminated in those patients, leading to a huge burden on public health.[2-5] Moreover, aging of the CHB population over time owing to prolonged survival with improved health care for CHB patients must not be overlooked.[6]

In a recent Korean population-based cohort study using the Health Insurance Review & Assessment Service 2007–2016 database, the age of CHB patients significantly increased from a mean 46.9 years in 2007 to 52.3 years in 2016.[7] Moreover, prevalence of liver as well as non-liver comorbidities in patients with CHB increased over time, approximately 50% of CHB patients had more than one comorbidity among chronic kidney disease, diabetes, dyslipidemia, and osteoporosis/fracture. We recently demonstrated an association of the burden of metabolic risk factors with risks of HCC using a large nationwide population-based cohort of CHB patients.[8] In this nationwide population-based study of 317,856 adults with CHB, we found that an increasing burden of metabolic risk factors (i.e., obesity, high blood pressure, hypercholesterolemia, and diabetes) was associated with higher risks of developing HCC, non-HCC cancer, and all-cause mortality in a dose-responsive manner (all $P<.0001$ for trend). Compared to patients without any metabolic risk factors, those with 3 or more metabolic risk factors showed adjusted hazard ratios (HRs) of 1.23 (95% confidence interval [CI], 1.16–1.31; $P<.0001$) for HCC, 1.34 (95% CI, 1.27–1.41; $P<.0001$) for non-HCC cancer, and 1.31 (95% CI, 1.23–1.39; $P<.0001$) for overall death. In addition, even among patients in whom HBV replication was assumed to have been suppressed through long-term antiviral treatment for over 5 years, the risk-increasing association of the burden of metabolic risk factors with the risks of the development of HCC and all-cause mortality remained evident (all $P<.0001$ for trend).

These recent studies suggest that CHB patients are getting older with increasing prevalence of many common comorbidities. These comorbidities should be taken into account when choosing antiviral treatment; those with a good long-term safety profile and antiviral potency should be preferred. In addition, thorough assessment and management of metabolic risk factors may be necessary to lower the risk of developing cancer and increase survival in patients with CHB. Moreover, the burden of metabolic risk factors should be considered to establish an individually tailored surveillance strategy for HCC, also in patients undergoing long-term antiviral treatment.

References

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-1555.
2. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988;61:1942-1956.
3. McMahon BJ. The natural history of chronic hepatitis B virus infection. Semin Liver Dis 2004;24 Suppl 1:17-21.
4. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin Liver Dis 2006;26:130-141.
5. Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014;384:2053-2063.
6. Nguyen MH, Lim JK, Ozbay AB, Fraysse J, Liou I, Meyer N, et al. Advancing age and comorbidity in a United States insured population-based cohort of patients with chronic hepatitis B. Hepatology 2019;69:959-973.
7. Oh H, Jun DW, Lee IH, Ahn HJ, Kim BO, Jung S, et al. Increasing comorbidities in a South Korea insured population-based cohort of patients with chronic hepatitis B. Aliment Pharmacol Ther. 2020;52:371-381.
8. Lee YB, Moon H, Lee JH, Cho EJ, Yu SJ, Kim YJ, et al. Association of metabolic risk factors with risks of cancer and all-cause mortality in patients with chronic hepatitis B. Hepatology 2020.

Hepatocellular Carcinoma Prediction Model for Antiviral-Treated Chronic Hepatitis B Patients

Hwi Young Kim

Ewha Womans University, Korea

Hepatocellular carcinoma (HCC) is an important global health problem and the second-most common cause of cancer-related death worldwide.[1] Chronic hepatitis B (CHB) is still one of the leading causes of HCC despite vaccination and effective treatment, especially in East Asia.[2] The overall risk of HCC in patients with CHB is estimated to be between 10 and 25% during their lifetime.[3] A growing body of evidences suggests that the risk of HCC occurrence can be decreased, albeit incompletely, by antiviral treatment, primarily with nucleos(t)ide analogues (NAs).[4-7]

Recommendations of current practice guidelines emphasize surveillance for early HCC detection and early and potentially curative treatment in patients with CHB, with specifying higher-risk subgroups in some guidelines.[8-10] Ideal surveillance program should take into account individual level of HCC risk in potential candidates. However, CHB patient population consists of heterogeneous subgroups with different levels of risk at any given time point, in terms of several relevant pathophysiological characteristics such as age, serum HBV DNA level, HBeAg status, and hepatic fibrosis.[11] NA therapy should also be considered for risk stratification, which may modify some of the abovementioned HCC risk factors. In this regard, various risk scores have been developed to predict HCC occurrence in patients with CHB treated with or without NAs during the last couple of decades.[12-20] These risk scores are mostly based on various combinations of risk variables, such as disease-related factors (e.g., serum HBV DNA level, HBeAg status, presence of fibrosis) and host factors (e.g., age, sex, comorbidities), which exhibit acceptable performances with the reported areas under the receiver operating characteristic curve between 0.6 and 0.8.[21-26]

In the current era of potent NA treatment, more accurate prediction of HCC risk would be accomplished with individualized risk stratification. In addition, more comprehensive approaches to develop novel prediction models including artificial intelligence-assisted methods and independent validation of such models are under investigation.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology. 2015;62(4):1190-200.
3. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis. 2015;19(2):223-38.

4. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010;53(2):348-56.
5. Hsu YC, Wu CY, Lane HY, Chang CY, Tai CM, Tseng CH, et al. Determinants of hepatocellular carcinoma in cirrhotic patients treated with nucleos(t)ide analogues for chronic hepatitis B. J Antimicrob Chemother. 2014;69(7):1920-7.
6. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013;58(1):98-107.
7. Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology. 2014;147(1):143-51 e5.
8. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
9. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-50.
10. Korean Liver Cancer A, National Cancer C. 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. Gut Liver. 2019;13(3):227-99.
11. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. Hepatology. 2021;73 Suppl 1:4-13.
12. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol. 2009;50(1):80-8.
13. Wong VW, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol. 2010;28(10):1660-5.
14. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol. 2011;12(6):568-74.
15. Lee MH, Yang HI, Liu J, Batrla-Utermann R, Jen CL, Iloeje UH, et al. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatology. 2013;58(2):546-54.
16. Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol. 2016;64(4):800-6.
17. Lee HW, Yoo EJ, Kim BK, Kim SU, Park JY, Kim DY, et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. Am J Gastroenterol. 2014;109(8):1241-9.
18. Sohn W, Cho JY, Kim JH, Lee JI, Kim HJ, Woo MA, et al. Risk score model for the development of hepatocellular carcinoma in treatment-naive patients receiving oral antiviral treatment for chronic hepatitis B. Clin Mol Hepatol. 2017;23(2):170-8.
19. Hsu YC, Yip TC, Ho HJ, Wong VW, Huang YT, El-Serag HB, et al. Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. J Hepatol. 2018;69(2):278-85.
20. Sharma SA, Kowgier M, Hansen BE, Brouwer WP, Maan R, Wong D, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol. 2017.
21. Kim JH, Kim YD, Lee M, Jun BG, Kim TS, Suk KT, et al. Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy. J Hepatol. 2018;69(5):1066-73.
22. Jung KS, Kim SU, Song K, Park JY, Kim DY, Ahn SH, et al. Validation of hepatitis B virus-related hepatocellular carcinoma prediction models in the era of antiviral therapy. Hepatology. 2015;62(6):1757-66.
23. Arends P, Sonneveld MJ, Zoutendijk R, Carey I, Brown A, Fasano M, et al. Entecavir treatment does not eliminate the risk of hepatocellular carcinoma in chronic hepatitis B: limited role for risk scores in Caucasians. Gut. 2015;64(8):1289-95.

24. Abu-Amara M, Cerocchi O, Malhi G, Sharma S, Yim C, Shah H, et al. The applicability of hepatocellular carcinoma risk prediction scores in a North American patient population with chronic hepatitis B infection. Gut. 2016;65(8):1347-58.
25. Lee HW, Kim SU, Park JY, Kim DY, Ahn SH, Han KH, et al. External validation of the modified PAGE-B score in Asian chronic hepatitis B patients receiving antiviral therapy. Liver Int. 2019;39(9):1624-30.
26. Kim SU, Seo YS, Lee HA, Kim MN, Kim EH, Kim HY, et al. Validation of the CAMD Score in Patients With Chronic Hepatitis B Virus Infection Receiving Antiviral Therapy. Clin Gastroenterol Hepatol. 2020;18(3):693-9 e1.

Clinical Implications of Novel Biomarkers of Hepatitis B Virus

Man-Fung Yuen

The University of Hong Kong, Hong Kong

Conventional biomarkers for hepatitis B virus (HBV) infection include HBsAg, HBeAg and HBV DNA. All these markers have been standardized and utilized for many decades. Their importance in defining and managing HBV infection are well characterized. They are particularly useful in the disease prognostication and assessment treatment efficacy. In spite of the profound viral suppressive effects from nucleos(t)ide analogues (NA), their roles in particular, the serum HBV DNA levels become relatively limited in reflecting the intrahepatic total HBV DNA and cccDNA content. Furthermore, reliable markers predicting viral rebound after cessation of long-term NA therapy are lacking. In recent years, measurements of two novel HBV markers have been actively explored, with the aim of providing better correlations with regard to the disease activity and treatment outcome. They are hepatitis B core-related antigen (HBcrAg) and HBV RNA.

HBcrAg is a composite measurement of three viral proteins from pre-core/core gene transcription. They are HBcAg, HBeAg and p22cr. It has been found that HBcrAg has a strong correlation with intrahepatic cccDNA level even in patients with undetectable serum HBV DNA. In addition, HBcrAg has clinical significance in different scenarios of HBV disease including its reduction in levels during NA treatment, detectability in patients with HBsAg seroclearance, development of cirrhosis and HCC, and HBV reactivations from cessation of treatment and from occult HBV infected patients undergoing immunosuppressive therapy.

HBV RNA is another new HBV marker being actively explored in different aspects of HBV infection. Pregenomic HBV RNA acts as the template for reverse transcription to relaxed circular DNA after encapsidation. HBV RNA levels are therefore detectable in the majority of HBV patients and possess distinct profiles in different disease phases. Serum HBV RNA levels are usually lower than that of serum HBV DNA. It has been shown to have good correlations with serum HBV DNA and intrahepatic cccDNA especially in HBeAg positive patients. NA treatment was shown to have suppressive effect on HBV RNA levels. Novel treatments targeting HBV RNA knockdown had also shown decrease in HBV RNA levels. In addition, detectable HBV RNA was associated with a higher chance of HCC development and also HBV relapse after cessation of the NA treatment.

It is expected that measurements of these two new markers would provide more insightful information for clinicians to have better disease prognostication and management for HBV disease.

HBV-Host Genome Integration: How Can We Detect It and What Is Its Impact?

Thomas Tu

The University of Sydney, Australia

Chronic infection with the Hepatitis B virus (HBV, a small DNA virus) is the single greatest cause of liver disease and is currently incurable. More than 360 million people are chronically infected worldwide, resulting in ~1 million annual deaths due to liver cancer or liver failure. Current treatments (reverse transcriptase inhibitors) are taken for indefinite periods as they simply suppress virus replication, but do not cure the infection.[1] The risks of life-threatening disease (such as liver cancer) and the lifelong persistence of HBV infection lead to considerable stigma of people living with chronic hepatitis B[2] causing life-changing impacts and suffering.

One of the main goals of our group is to understand the role of integrated HBV DNA in liver disease and viral persistence.[3] Integrated HBV DNA (replication-defective viral sequences that are inserted into the host cell genome upon the infection) can occur in ~1 in 10^4 cells and we have shown that they occur directly after HBV infection.[4-6] HBV DNA integration occurs at random double stranded DNA breaks in the host genome by non-homologous end-joining, and so are distributed across the genome.

Integrations and their role in HBV-associated liver cancer

Despite this relatively low frequency, HBV DNA integrations are found in >60% of liver cancers in HBV patients, suggesting that they are associated with the tumorigenic process. Using the highly sensitive inverse nested PCR (invPCR) assay to quantify HBV DNA integrations,[7,8] we used patient tissues and *in vitro* models to answer fundamental questions regarding the relationship between HCC and HBV DNA integrations.

First, we showed that cells with integrations undergo selective clonal expansion during chronic HBV infection in non-tumour tissue[9] and confirmed that they occurred in histologically-normal hepatocytes by laser-capture microscopy. Clonal expansion is a known risk factor for cancer, so we investigated potential mechanisms by which integrations could be driving clonal expansion.

Cis-mediated mechanisms

One potential mechanism was that integrations were occurring in particular cellular genes that induced a change in cell growth. We compared HBV DNA integration sites: i) generated *in silico* by random integration; ii) detected *in vitro* directly after infection; iii) found in patients early in chronic HBV infection (HBeAg-positive); and iv) found in patients late in chronic HBV infection (HBeAg-negative). Bioinformatic

analysis compared the 1024, 161, 367, and 194 integrations detected in each group and found no significant differences in enrichment in functional genomic sites nor in cancer-related genes.[10,11] This strongly suggests that cis-mediated mechanisms were not involved in clonal expansion of hepatocytes.

Trans-mediated mechanisms

Another potential mechanism was that some integrations encode a mutant viral protein (e.g. mutations in HBV surface antigen) that induces ER stress or activates other pro-oncogenic pathways. We investigated this by first discovering HBV integrations with invPCR in tumour and non-tumour tissues from HBV patients. We then used this sequence information to develop primers to amplify the entire integrated DNA sequence. Our preliminary results (6 from tumour and 7 from non-tumour tissues) show that integrations associated with tumour tissues were indistinguishable from those in non-tumour tissue, suggesting that mutations in integrated sequences did not drive HCC initiation.

Integration as a marker of pro-oncogenic cells

We then explored the possibility of integrations occurring preferentially in pre-cancerous cells, rather than being specific drivers. After *in vitro* infection with a novel "reporter" HBV encoding an antibiotic resistance gene, we selected for HepG2-NTCP and Huh7-NTCP cells that contained HBV DNA integrations. We found that integration-containing cells had significantly altered DNA repair enzymes compared to parental cells. Thus, we believe that integrations may be a marker of pre-cancerous cells rather than a specific driver of HCC.

Integrations and their role in HBV functional cure

The loss of serum HBV surface antigen (HBsAg) has been selected as one of the primary endpoints for novel therapies (defining a "functional cure"). Recent studies have suggested that the replication-incompetent integrated HBV DNA plays a key role in producing HBsAg, reportedly being the major source in later phases of infection.[12] Thus, a reduction in integrated forms would be expected to accompany HBs loss, which would suggest that integrated forms need to be eliminated (or at least targeted) by therapeutic strategies intended to induce a functional cure.

We directly tested this hypothesis by determining the frequency of integrated HBV DNA in those who have undergone HBs loss compared to those with active HBV infection. Using a novel quantitative invPCR assay, we showed that no changes in integration rate were observed between HBsAg-negative and -positive patients, suggesting that it may not be necessary to eliminate integrated HBV DNA to induce functional cure.

Summary

In recent years, integrated HBV DNA has transformed from a poorly-studied "dead-end" pathway of the virus into an important phenomenon to be considered in HBV-associated disease and persistence studies. The field still does not completely understand the contribution of integrated HBV DNA to HCC initiation and progression. We have shown that the effects of integration may be more subtle than direct induction

of HCC, and instead may simply be associative. More powerful molecular tools and new models will allow us to investigate these concepts in greater detail in future and hopefully contribute to a reduction in the global HBV disease burden.

References

1. European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
2. Tu T, Block JM, Wang S, Cohen C, Douglas MW. The Lived Experience of Chronic Hepatitis B: A Broader View of Its Impacts and Why We Need a Cure. Viruses. 2020;12(5).
3. Tu T, Budzinska MA, Shackel NA, Urban S. HBV DNA Integration: Molecular Mechanisms and Clinical Implications. Viruses. 2017;9(4).
4. Tu T, Budzinska MA, Vondran FWR, Shackel NA, Urban S. Hepatitis B virus DNA integration occurs early in the viral life cycle in an in vitro infection model via NTCP-dependent uptake of enveloped virus particles. J Virol. 2018.
5. Tu T, Zehnder B, Qu B, Urban S. De novo synthesis of Hepatitis B virus nucleocapsids is dispensable for the maintenance and transcriptional regulation of cccDNA JHEP Reports. 2020.
6. Tu T, Zhang H, Urban S. Hepatitis B Virus DNA Integration: In Vitro Models for Investigating Viral Pathogenesis and Persistence. Viruses. 2021;13(2):180.
7. Tu T, Jilbert AR. Detection of Hepatocyte Clones Containing Integrated Hepatitis B Virus DNA Using Inverse Nested PCR. Methods Mol Biol. 2017;1540:97-118.
8. Tu T, Urban S. Detection of Low Copy Number Integrated Viral DNA Formed by In Vitro Hepatitis B Infection. J Vis Exp. 2018(141).
9. Tu T, Mason WS, Clouston AD, Shackel NA, McCaughan GW, Yeh MM, et al. Clonal expansion of hepatocytes with a selective advantage occurs during all stages of chronic hepatitis B virus infection. J Viral Hepat. 2015.
10. Budzinska MA, Shackel NA, Urban S, Tu T. Sequence analysis of integrated hepatitis B virus DNA during HBeAg-seroconversion. Emerg Microbes Infect. 2018;7(1):142.
11. Budzinska MA, Shackel NA, Urban S, Tu T. Cellular Genomic Sites of Hepatitis B Virus DNA Integration. Genes (Basel). 2018;9(7).
12. Wooddell CI, Yuen MF, Chan HL, Gish RG, Locarnini SA, Chavez D, et al. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg. Sci Transl Med. 2017;9(409).

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (15:00-16:20)

ROOM 1

Distinguished Lectures

Chairs:

Masao Omata (Yamanashi Central and Kita Hospitals, Japan)

Jin Mo Yang (The Catholic Univ. of Korea)

Progress and Challenges in Achieving Hepatitis B Virus Cure

Fabien Zoulim

Lyon University, France

Hepatitis B virus (HBV) affects more than 250 million people worldwide, being one of the major etiological factors for the development of liver cirrhosis and hepatocellular carcinoma. In spite of universal vaccination programs, HBV infection cases are still a public health problem, with the limited number of therapeutic approaches available complicating the clinical management of these patients. Therefore, HBV infection emerges as an unmet medical need that requires a continuous effort in the development of new individual molecules, combinations and even completely novel therapeutic strategies in order to achieve the goal of HBV elimination. Functional cure defined by the sustained clearance of HBsAg in serum after treatment cessation is considered as the main attainable goal within the next few years. Major progress has been made in our understanding of the molecular biology and the immunology of HBV persistence, and thus has paved the way for the development of novel cure strategies. Several approaches are being explored either with direct acting antivirals to deplete directly or indirectly the intrahepatic pool of HBV cccDNA, the viral minichromosome, or to restore adaptive immune responses to eliminate infected cells and control the infection. Many compounds or strategies are now evaluated in phase II clinical trials. Direct acting antivirals include, beside nucleos(t)ide analogues, entry inhibitors, viral RNA targeting agents (SiRNA, antisense oligonucleotides, and other small molecules), capsid assembly modulators, and HBsAg release inhibitors. Drugs targeting cccDNA to induce degradation or permanent silencing are still explored in pre-clinical models. Thus, since cccDNA eradication remains challenging, the antivirals in current development will likely be combined with immunotherapy to control the infection and maintain the antiviral effect on the long term. Immunotherapeutics in development include strategies to invigorate immune responses through the stimulation of innate immunity with TLR7 or TLR8 agonists, or the inhibition of immune check points with PD1 or PDL1 blocking agents. They also include strategies to stimulate the HBV specific adaptive responses. Since HBV specific B and T cells are profoundly exhausted, it is most likely that the latter strategy will require combination with agents decreasing viral antigen expression and with agents that invigorate the exhausted immune cells. The development of novel biomarkers, such as circulating viral RNAs and HBcrAg (among others), to assess target engagement and predict treatment endpoints is also needed to assist drug development especially in the early phase. We are thus entering a very exciting time for HBV research and several clinical trial programs are ongoing to assess the efficacy and safety of the emerging combination therapies. There is hope that these research programs will increase the rate of functional cure with finite duration of treatment in a near future.

References

1. Revill PA, Penicaud C, Brechot C, Zoulim F. Meeting the Challenge of Eliminating Chronic Hepatitis B Infection. Genes (Basel). 2019;10(4).
2. Fanning GC, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov. 2019;18(11):827-44.
3. Maini MK, Burton AR. Restoring, releasing or replacing adaptive immunity in chronic hepatitis B. Nat Rev Gastroenterol Hepatol. 2019;16(11):662-75.
4. Cornberg M, Lok AS, Terrault NA, Zoulim F, Faculty E-AHTEC. Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. J Hepatol. 2020;72(3):539-57.
5. Testoni B, Levrero M, Zoulim F. Challenges to a Cure for HBV Infection. Semin Liver Dis. 2017;37(3):231-42.
6. Le Bert N, Gill US, Hong M, Kunasegaran K, Tan DZM, Ahmad R, et al. Effects of Hepatitis B Surface Antigen on Virus-Specific and Global T Cells in Patients With Chronic Hepatitis B Virus infection. Gastroenterology. 2020;159(2):652-64.

Acute-on-Chronic Liver Failure: Achievements and Future Perspectives

Shiv Kumar Sarin

Institute of Liver & Biliary Science, India

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (16:30-17:50)

ROOM 1

KASL Symposium 3

Updates on Management of Cirrhosis and Related Complications

Chairs:

June Sung Lee (Inje Univ.)

Si Hyun Bae (The Catholic Univ. of Korea)

Individualized Risk Stratification of Compensated Advanced Chronic Liver Disease (cACLD)

Annalisa Berzigotti

University of Bern, Switzerland

Patients with compensated cirrhosis/advanced chronic liver disease (cACLD) have a variable prognosis. Liver-related mortality is low in this stage (ranging 1-10% at 1 year), and is almost exclusively related to the onset of hepatocellular carcinoma.[1] On the other hands, patients who progress to a decompensated stage (ascites, variceal bleeding, hepatic encephalopathy) have a much higher chance of developing further decompensation, acute on chronic liver failure and death (20-80% at 1 year, according to the type and number of clinical decompensation episodes).[1] Therefore, identifying prognostic indicators of progression to decompensation in patients with cACLD is a major clinical need to personalize care and avoid progression.

Previous work showed that the major driver of the progression from the compensated to the decompensated stage is the presence of clinically significant portal hypertension (CSPH, indicated by a hepatic venous pressure gradient, HVPG, ≥ 10 mmHg), which is independent of liver function (albumin; MELD score).[2] Presence of gastroesophageal varices indicates that patients have CSPH and patients with varices are at higher risk of clinical decompensation. However, the absence of gastroesophageal varices does not rule-out CSPH, and the measurement of HVPG through hepatic vein catheterization remains the reference standard to identify CSPH and evaluate the severity of portal hypertension in cACLD.[3] Despite largely validated in several settings, the measurement of HVPG is not widely available and requires specific expertise. In the last 20 years, non-invasive surrogates of CSPH became available and have been validated, providing simple and readily available tools to improve prognostic stratification in cACLD.

Non-invasive surrogates of CSPH

Spleen size/splenomegaly and platelet count have been used in many studies to predict the presence of CSPH and gastroesophageal varices in cirrhosis, but their accuracy is limited. Liver stiffness measurement (most studies performed using transient elastography) represented a major advance allowing improving the accuracy of non-invasive tests to detect CSPH in cACLD.[4] LSM over 20 kPa is strongly associated with HVPG≥10 mmHg, and its accuracy to detect this hemodynamic threshold in cACLD is over 85%.[5] Specificity using this cut-off is above 90%, and LSM, alone or in combination with platelet count and spleen size, is recommended to non-invasively identify patients with likely CSPH. LSM <20 kPa together with a normal platelet count (>150 G/L) is considered sufficient to safely avoid endoscopic screening for varices, since the risk of varices needing treatment is below 5% in patients meeting these non-invasive criteria ("Baveno VI

criteria"),[6] which have been validated in all the major etiologies of cACLD. Spleen stiffness has been more recently proposed as additional tool to further refining the risk of CSPH and events in the follow-up.[4]

In addition, LSM has a strong prognostic value for clinical decompensation and mortality in cACLD, and rather than using a single cut-off, the probability of events in the follow-up should be estimated on a continuous scale: the higher the LSM, the higher the risk.[4,7] Furthermore, the use of LSM and other non-invasive tools (imaging, for instance), in a dynamic way, looking at changes over the follow-up, would likely improve prognostication. This concept has been used in studies addressing the risk of HCC in patients with chronic hepatitis B with positive results.

Other factors impacting prognosis in cACLD

The main etiology of liver disease, the presence of co-factors or additional causes of liver damage, and whether the liver injury is ongoing or has been removed play a major role in the risk of clinical decompensation and liver-related death.[6] Lifestyle factors impact the individual risk of liver-related events.[8] Alcohol consumption is associated with increased risk of HCC and liver-related death, in particular when associated with overweight. Obesity has proven to increase the risk of decompensation by three times independent of portal hypertension and liver function.[9] Since weight loss of at least 10% of initial body weight, obtained by diet and exercise, decreases portal pressure,[10] lifestyle measures aimed at reducing overweight should be taken into consideration. Diabetes, often due to obesity, has been consistently associated with worse outcomes in patients with cACLD.

Cigarette smoke increases the risk of hepatocellular carcinoma[8]

Genetic polymorphisms associated with worsening the progression of liver fibrosis have been identified, and play a role in the individual risk of liver-related events. The genotype MZ of alpha-1-antitrypsin gene is associated with higher risk of decompensation.[11] In patients with cACLD and portal hypertension due to non-alcoholic or alcoholic fatty liver disease the PNPLA3-G/G-genotype is associated with a two-fold risk of clinical decompensation and liver-related mortality.[12] However, the relative impact of these mutations has not been characterized in large, international cohorts yet. As for the HSD17B13 variant, which has been associated with reduced progression to cirrhosis in non-alcoholic fatty liver disease, in the only study reported so far in patients with alcoholic and viral cirrhosis and portal hypertension it was not associated with a reduced rate of clinical decompensation and liver-related death.[13]

Conclusions

Prognostic models going beyond simple clinical rules, integrating clinical variables, LSM, laboratory tests and potentially with genetic information might allow in the future an individualization of risk stratification for clinical decompensation and liver-related death. This to predict the risk of clinical decompensation would be useful tools that require specific studies.

References

1. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563-576.
2. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.
3. Berzigotti A, Seijo S, Reverter E, Bosch J. Assessing portal hypertension in liver diseases. Expert Rev Gastroenterol Hepatol 2013;7:141-155.
4. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol 2017.
5. You MW, Kim KW, Pyo J, Huh J, Kim HJ, Lee SJ, Park SH. A Meta-analysis for the Diagnostic Performance of Transient Elastography for Clinically Significant Portal Hypertension. Ultrasound Med Biol 2017;43:59-68.
6. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-752.
7. Abraldes JG BC, Stefanescu H, Augustin S, Ney M, Blasco H, Procopet B, Bosch J, Genesca J, Berzigotti A. Non-Invasive Tools and Risk of Clinically Significant Portal Hypertension and Varices in Compensated Cirrhosis: the "Anticipate" Study. Hepatology 2016.
8. Tandon P, Berzigotti A. Management of Lifestyle Factors in Individuals with Cirrhosis: A Pragmatic Review. Semin Liver Dis 2020;40:20-28.
9. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, Escorsell A, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011;54:555-561.
10. Berzigotti A, Albillos A, Villanueva C, Genesca J, Ardevol A, Augustin S, Calleja JL, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology 2017;65:1293-1305.
11. Schaefer B, Mandorfer M, Viveiros A, Finkenstedt A, Ferenci P, Schneeberger S, Tilg H, et al. Heterozygosity for the alpha-1-antitrypsin Z allele in cirrhosis is associated with more advanced disease. Liver Transpl 2018;24:744-751.
12. Mandorfer M, Scheiner B, Stattermayer AF, Schwabl P, Paternostro R, Bauer D, Schaefer B, et al. Impact of patatin-like phospholipase domain containing 3 rs738409 G/G genotype on hepatic decompensation and mortality in patients with portal hypertension. Aliment Pharmacol Ther 2018;48:451-459.
13. Scheiner B, Stattermayer AF, Schwabl P, Bucsics T, Paternostro R, Bauer D, Simbrunner B, et al. Impact of HSD17B13 rs72613567 genotype on hepatic decompensation and mortality in patients with portal hypertension. Liver Int 2020;40:393-404.

How to Prevent Decompensation in Compensated Cirrhosis?

Moon Young Kim

Younsei Universtiy Wonju, Korea

Cirrhosis is the final stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and formation of regenerative nodules. In general, cirrhosis can be divided into two stages; compensated and decompensated cirrhosis. The compensated cirrhosis is a relatively early stage with preserved liver function. The decompensated cirrhosis is the advanced stage with decreased liver function and complications; variceal hemorrhages, ascites formation, and its related complications, hepatic encephalopathy, jaundice, etc. These two stages show different prognoses in natural course. If a patient could stay persistently at compensated cirrhosis, his prognosis would be very good as a 5-year mortality rate is less than 5%. However, he once has been progressed to decompensated cirrhosis, his prognosis is very poor, and expected 5-year survival could be less than 50%. Therefore, to prevent the progression of compensated to decompensated cirrhosis should be the first management goal in early-stage cirrhosis.

Treatment of the underlying cause of cirrhosis may be the first step to prevent the development of disease progression and decompensation. Early diagnosis of chronic hepatitis B and C and early antiviral treatment is essential. To control alcohol use disorder and maintain abstinence is also important.

Together with etiological treatment, control of portal hypertension (PHT) should be considered. In the progression of cirrhosis, the most important underlying pathogenesis is the development of portal hypertension and its aggravation. Patients with a hepatic venous pressure gradient (HVPG) <10 mmHg have a 90% probability of not developing clinical decompensation in a median follow-up of 4 years. So, clinically significant PHT (CSPH, HVPG ≥ 10mmHg) is a very important clinical turning point in cirrhosis. However, early detection of CSPH is not easy in clinical practice, because HVPG measurement is relatively invasive and has clinical limitations. Recently applying vibration-controlled transient elastography (Fibroscan®) combined with platelet count has been suggested to diagnose CSPH and it has been widely validated.

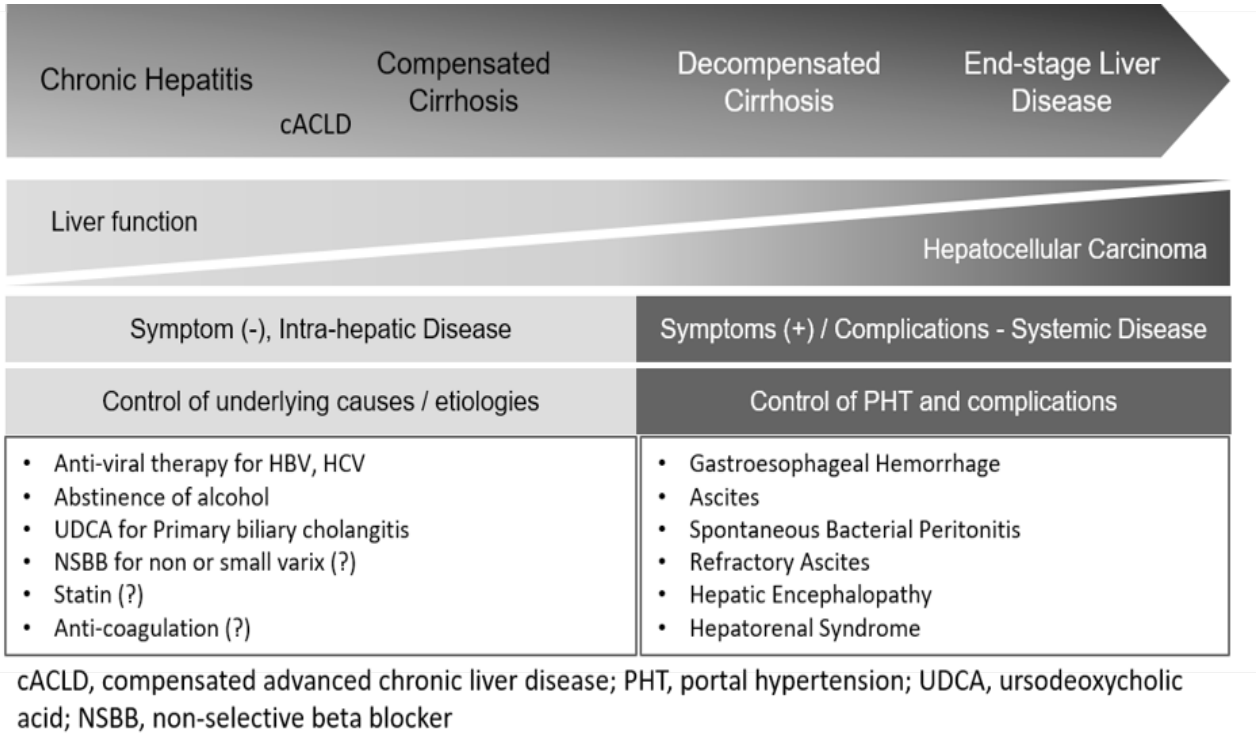
Even if CSPH is detected early, there are no established treatments to prevent the progression of PHT and the development of decompensation except the control of underlying etiology.

Non-selective beta-blockers (NSBB) are the only drug class endorsed for the long-term treatment of portal hypertension, especially the prevention of variceal hemorrhage. According to recent guidelines, NSBB is recommended not to be used in compensated cirrhosis with no evidence of varices; be used in cirrhotic patients with varices at risk of bleeding or re-bleeding independent of the absence/presence of ascites. Because of the risk to compromise renal function and hemodynamic stability in advanced decompensation, it is recommended to be used with caution in cirrhotic patients with refractory ascites and discontinued if hemodynamic or renal compromise arises.

However, recently one randomized clinical trial reported the usefulness of NSBB to prevent decompensation (PREDESCI study). In this study, long-term treatment with NSBB showed increased decompensation-free survival in patients with compensated cirrhosis and CSPH without high-risk varices, mainly by reducing the incidence of ascites. This study also reported bacterial infection as one of the risk factors for the development of decompensation.

Despite initial hepatotoxicity concerns, the safety of statin administration has been demonstrated in compensated cirrhosis. Furthermore, recent several meta-analyses showed that statins have protective effects upon fibrosis progression, decompensation, and mortality through their pleiotropic properties which comprise antioxidant, anti-fibrotic, anti-infective, and anti-inflammatory effects. However, the majority of evidence regarding the effects of statins in chronic liver disease is derived from observational studies and small-scale trials, adequately powered randomized controlled trials are required.

In conclusion, the first step to prevent progression from compensated cirrhosis to decompensation is the optimal treatment of underlying etiologies. Simultaneously, early diagnosis of CSPH and its management is also important. Until now, there is no established anti-portal hypertensive pharmacological treatment for compensated cirrhosis. Recent studies showed the possibility of NSBB as one option however, more validations are needed. Statin is also attracting attention, and many further studies are expected.



cACLD, compensated advanced chronic liver disease; PHT, portal hypertension; UDCA, ursodeoxycholic acid; NSBB, non-selective beta blocker

Figure 1. The natural courses of cirrhosis and management.

References

1. Gennaro D'Amico 1, Guadalupe Garcia-Tsao, Luigi Pagliaro. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006 Jan;44(1):217-31.
2. Clinical states of cirrhosis and competing risks. Gennaro D'Amico, Alberto Morabito, Mario D'Amico et al. J Hepatol 2018 Mar;68(3):563-576.
3. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445-1449.
4. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. Korean J Hepatol 2010;16:347-352.
5. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.
6. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254-2261.
7. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. World J Gastroenterol 2014;20:4300-4315.
8. Kim MY, Cho MY, Baik SK, Park HJ, Jeon HK, Im CK, et al. Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension. J Hepatol 2011;55:1004-1009.
9. Kim SU, Oh HJ, Wanless IR, Lee S, Han KH, Park YN. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012;57:556-563.
10. Annalisa Berzigotti. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol 2017 Aug;67(2):399-411.
11. Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology 2016;64:2173-2184
12. Villanueva C, Albillos A, Genescà J, et al. Beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019 Apr 20;393(10181):1597-1608
13. Villanueva C, Albillos A, Genescà J, et al. Bacterial infections adversely influence the risk of decompensation and survival in compensated cirrhosis. J Hepatol 2021 Apr. Online ahead of print.
14. Kamal S, Khan MA, Seth A, et al. Beneficial Effects of Statins on the Rates of Hepatic Fibrosis, Hepatic Decompensation, and Mortality in Chronic Liver Disease: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2017; 112: 1495-1505.
15. Kim RG, Loomba R, Prokop LJ, et al. Statin Use and Risk of Cirrhosis and Related Complications in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2017; 15: 1521-1530.

Current and Novel Treatment Strategies of Hepatic Encephalopathy

Rajiv Jalan

University College London, UK

Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute decompensation of cirrhosis, organ failure(s) and high short-term mortality. One-third of patients who are hospitalized for acute decompensation present with ACLF at admission or develop the syndrome during hospitalization. Common precipitants include bacterial and viral infections, alcoholic hepatitis, and surgery, but in more than 40% of patients no precipitating event is identified. The pathophysiology of ACLF is still unclear. Systemic inflammation and susceptibility to infection are characteristic features. ACLF is a dynamic syndrome characterised by probabilities of resolution or improvement of 50%, stabilisation of 30%, and worsening of 20%. Treatment of ACLF is mainly supportive but the understanding of the pathophysiological basis of ACLF has led to the development of several novel therapeutic strategies. Trials of the toll-like 4 receptor inhibitor, TAK-242; liver dialysis device, DIALIVE and, plasma exchange are underway whilst new approaches targeting the mechanisms underlying inflammation are being investigated intensely. Liver transplantation has emerged as a treatment that saves the lives of the sickest patients with ACLF.

Understanding Coagulation and Hemostasis in Cirrhosis

Jung Il Lee

Yonsei Universtiy, Korea

Hemostasis in cirrhosis

Patients with liver cirrhosis have altered hemodynamics and hemostatic pathways which may favor bleeding and at the same time may favor thrombosis. In stable cirrhosis, the system is rebalanced by off-setting factors.[1] Thrombocytopenia which is attributed to splenic sequestration and decreased thrombopoientin (TPO) is one of the most well-known anticoagulant change in liver cirrhosis. This anticoagulant change may be balanced by increased endothelial-derived von Willebrand factor (vWF).[2] Similarly, diminished liver derived procoagulant factors, such as factors V, VII, and X are offset by decreased liver-derived anti-coagulant factors, especially protein C.[3] However, this "rebalanced hemostasis" is precarious and may significantly be influenced by factors such as volume status, systemic infection and renal function. The hemostatic balance is much harder to maintain when the levels of the pro and anticoagulant factors are reduced by further deteriorated hepatic function, and the balance may be easily disrupted by the occurrence of stressful conditions such as infections and complications of liver cirrhosis.

Test of the coagulation system in cirrhosis

Currently available laboratory tests of the coagulation system are of limited value in estimating hemostatic competency in cirrhosis. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and bleeding time (BT) are generally prolonged in patients with cirrhosis in accordance with the degree of hepatic decompensation. While these indices are useful for predicting prognosis in chronic liver disease, these tests perform poorly in assessing coagulation capacity in patients with liver disease.[4] International normalized ratio (INR) and PT reflect level of procoagulant factors I, II, V, VII and X, whereas do not measure the deficit of liver-derived anticoagulant factors such as protein C, and have a limitation in measuring in vivo activity of the coagulation system in cirrhosis.[5] Thrombocytopenia, while indirectly correlates with the degree of portal hypertension, may not necessarily indicates defect in thrombin generation since elevated vWF and increased circulating activated platelets may compensate the situation.[6]

Alternative means of assessing hemostatic pathway in cirrhosis have been suggested, but they are still for research use, and further development is required. The thrombin generation assay (TGA) measures the rate of production and decay of thrombin after introduction of a triggering agent such as tissue factor and phospholipid.[7] With addition of thrombomodulin, the integrity of the protein C anticoagulant system can also be assessed. However, TGA is not clinically available yet. Viscoelastic tests (VETs) measure clot strength and integrity in whole blood under low shear conditions to recreate the environment in vivo dur-

ing clot formation.[8] Although this may provide a more physiologic assessment of coagulation, VETs are not standardized in patients with cirrhosis and do not appear to predict bleeding of thrombosis objectively.

Coagulation assessment for invasive procedures

Despite the limitations of measuring platelet count and fibrinogen level in assessing hemostasis in cirrhosis, they are still the only tools for standard of care assessment of coagulation for all patients with cirrhosis when determination of values is indicated before a procedure.

Pre-procedure correction is recommended for high risk procedures. While there is no evidence that prophylactic platelet transfusion improves hemostatic potential,[9] current guidelines and expert opinion recommend considering platelet transfusion prior to high-risk procedures in patients with platelet counts below 50,000/uL.[10] Routing prophylaxis for low or moderate risk procedures is generally not recommended.[1] However, the prophylactic measures need to be individualized.

Table 1. Examples of procedure risk[11]

High risk procedures	Intermediate risk procedures	Low risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
Major surgery such as cardiac, intra-abdominal and orthopaedic surgery	Percutaneous or transjugular liver biopsy	Thoracentesis
Intra-cranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt	Dental extraction
Invasive endoscopy such as large polypectomy with endoscopic mucosal resection, natural orifice transluminal endoscopy	Endoscopy with moderate invasiveness such as percutaneous gastrostomy placement, cystgastrostomy, biliary sphincteerotomy	Endoscopy with lower invasiveness such as diagnostic variceal band ligation, uncomplicated polypectomy
	Percutaneous biopsy of extra-hepatic organ of lesions	Cardiac catheterization
	Trans-arterial or percutaneous HCC therapies	Central line plascement

Conclusions

The coagulation cascade is rebalanced in patients with cirrhosis, involving changes in both pro and anticoagulant factors. Although bleeding issues in cirrhotic patients have been recognized as the dominant clinical problems, inappropriate clotting has become more important as evidenced by the increased risk for both portal vein thrombosis (PVT) and venous thromboembolism (VTE).

References

1. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology 2019;157:34.
2. Lisman T, Bongers TN, Adelmeijer J, Janssen HLA, de Maat MPM, de Groot PG, et al. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology 2006;44:53-61.
3. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to

the procoagulant imbalance in cirrhosis. Journal of Hepatology 2013;59:265-270.
4. Ewe K. Bleeding after Liver-Biopsy Does Not Correlate with Indexes of Peripheral Coagulation. Digestive Diseases and Sciences 1981;26:388-393.
5. Lisman T, Bakhtiari K, Pereboom ITA, Hendriks HGD, Meijers JCM, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. Journal of Hepatology 2010;52:355-361.
6. Giannini EG, Savarino V. Thrombocytopenia in liver disease. Current Opinion in Hematology 2008;15:473-480.
7. Hemker HC, Willems GM, Beguin S. A Computer-Assisted Method to Obtain the Prothrombin Activation Velocity in Whole Plasma Independent of Thrombin Decay Processes. Thrombosis and Haemostasis 1986;56:9-17.
8. Mallett SV. Clinical Utility of Viscoelastic Tests of Coagulation (TEG/ROTEM) in Patients with Liver Disease and during Liver Transplantation. Seminars in Thrombosis and Hemostasis 2015;41:527-537.
9. Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver International 2013;33:362-367.
10. Northup PG, Caldwell SH. Coagulation in Liver Disease: A Guide for the Clinician. Clinical Gastroenterology and Hepatology 2013;11:1064-1074.
11. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F, et al. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference: October 6th and 7th, 2017 Rome, Italy. Thrombosis and Haemostasis 2018;118:1491-1506.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (08:20-09:40)

ROOM 2

KLCA Symposium 1

Diagnosis and Surveillance in Hepatocellular Carcinoma

Chairs:

Seung Woon Paik (Sungkyunkwan Univ.)

Yong Moon Shin (Univ. of Ulsan)

LI-RADS Classification and Its Impact on the Prognosis of Primary Liver Cancer

Sang Hyun Choi

Seoul National University, Seoul, Korea

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the third most frequent cause of cancer-related deaths.[1,2] Currently, HCC in patients with liver cirrhosis can be diagnosed noninvasively by means of imaging analysis. Many advances have been made in contrast-enhanced magnetic resonance imaging (MRI) including the use of hepatocyte-specific contrast agents, and it resulted in the improved sensitivity in detecting small HCCs.[3] However, the imaging diagnosis of HCC have been confused and inconsistent in its application in both clinical care and research because no established consensus regarding the exact definition of imaging diagnostic criteria.[4]

To standardize performance of liver imaging in patients at risk for HCC as well as interpretation and reporting of the results, the Liver Imaging Reporting and Data System (LI-RADS) was introduced in 2011,[4] recently updated in 2018.[5] In 2018, the American Association for the Study of Liver Disease (AASLD) integrated LI-RADS into its clinical practice guidance for HCC.[6] With LI-RADS, each hepatic observation is categorized according to its likelihood of benignity and HCC (ie, LR-1 to LR-5), as well as non-HCC malignancies (LR-M). The performance of LI-RADS for diagnosing HCC in at-risk patients has been validated in several previous studies,[7-9] demonstrating that the LR-5 category allows for a highly specific diagnosis of HCC and that the LR-M category includes non-HCC malignancies and HCCs with atypical imaging features.[9]

In addition to the noninvasive diagnosis of HCC, previous studies have suggested that imaging examinations have a role in predicting the prognosis of primary liver cancers.[10-12] In this lecture, I will briefly show the clinical value of LI-RADS for predicting the prognosis in patients at risk for HCC as well as for making an accurate imaging diagnosis.

Reference

1. El-Serag HB. Hepatocellular carcinoma. The New England journal of medicine 2011;365:1118-1127. doi: 10.1056/NEJMra1001683
2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-2576. doi: 10.1053/j.gastro.2007.04.061
3. Lee YJ, Lee JM, Lee JS, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology 2015;275:97-109. doi: 10.1148/radiol.14140690
4. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015;61:1056-1065. doi: 10.1002/hep.27304

5. Amefican College of Radiology. CT/MRI LI-RADS v2018 core. https://wwwacrorg/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Corepdf?la=en
6. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750. doi: 10.1002/hep.29913
7. Joo I, Lee JM, Lee DH, Ahn SJ, Lee ES, Han JK. Liver imaging reporting and data system v2014 categorization of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: Comparison with multiphasic multidetector computed tomography. J Magn Reson Imaging 2017;45:731-740. doi: 10.1002/jmri.25406
8. Kim YY, An C, Kim S, Kim MJ. Diagnostic accuracy of prospective application of the Liver Imaging Reporting and Data System (LI-RADS) in gadoxetate-enhanced MRI. Eur Radiol 2018;28:2038-2046. doi: 10.1007/s00330-017-5188-y
9. Fraum TJ, Tsai R, Rohe E, et al. Differentiation of Hepatocellular Carcinoma from Other Hepatic Malignancies in Patients at Risk: Diagnostic Performance of the Liver Imaging Reporting and Data System Version 2014. Radiology 2018;286:158-172. doi: 10.1148/radiol.2017170114
10. Lee S, Kim SH, Lee JE, Sinn DH, Park CK. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. J Hepatol 2017;67:526-534. doi: 10.1016/j.jhep.2017.04.024
11. An C, Kim DW, Park YN, Chung YE, Rhee H, Kim MJ. Single Hepatocellular Carcinoma: Preoperative MR Imaging to Predict Early Recurrence after Curative Resection. Radiology 2015;276:433-443. doi: 10.1148/radiol.15142394
12. Lee J, Kim SH, Kang TW, Song KD, Choi D, Jang KT. Mass-forming Intrahepatic Cholangiocarcinoma: Diffusion-weighted Imaging as a Preoperative Prognostic Marker. Radiology 2016;281:119-128. doi: 10.1148/radiol.2016151781

Imaging Phenotype of Hepatocellular Carcinoma Subtypes

Jin-Young Choi

Younsei Universtiy, Korea

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor and the third leading cause of cancer-related deaths worldwide. Advancements in imaging techniques have allowed imaging diagnosis to become a critical part of managing HCC in the clinical setting. HCC is a heterogeneous group of tumors in terms of histology, genetic aberration, and protein expression, leading to the recognition of various subtypes of HCCs. Specific genetic alterations and activation of biologic pathways have been associated with these different HCC subtypes. The understanding of histologic and molecular subtype of HCC is important, as it provides information on the mechanism of tumor progression, on predicting prognosis, as well as on facilitating personalized treatment strategy. In the era of precision medicine, the importance of histologic and molecular diagnosis of a specific subtype of HCC is increasing, emphasizing the need for actual tissue samples for histologic diagnosis. However, considering the risk of bleeding and seeding metastasis, the application of liver biopsy should be minimized to select cases. With the advancement of imaging technology, there is increasing evidence for a close correlation between imaging phenotype and histologic/molecular subtypes of HCCs. Those imaging features may help specify the cases in which invasive liver biopsy is compelled.

Recent studies show a high degree of phenotypic heterogeneity for HCC and close associations between distinct morphological phenotypes of HCC and different genetic defects and biological pathways of tumorigenesis. Comprehensive morphological and molecular profiling has given rise to the identification of HCC variants which can be divided into two major subgroups, the low proliferation class and high proliferation class, according to transcriptome profiles (Table).

The low proliferation class retains the expression markers of normal hepatocellular differentiation and chromosomal stability. This class is associated with well-differentiated phenotypes, including steatohepatitic HCC and CTNNB1-mutated HCC. Low proliferation HCC shows either the microtrabecular and pseudoglandular pattern with the activated Wnt/β-catenin pathway or the preserved gene expression profile of normal hepatocytes, with the latter usually showing up as small lesions without satellite nodules or vascular invasion.

The high proliferation class exhibits the overexpression of signaling pathways associated with cell cycle progression and survival. Clinically, these variants of proliferative HCC show higher serum alpha-fetoprotein (AFP) levels, poor differentiation, frequent vascular invasion and worse prognosis. HCC subtypes included in this class are macrotrabecular-massive HCC (MTM-HCC), scirrhous HCC, and K19-positive HCC.

In recent years, correlations between radiologic findings and histologic, molecular and clinical characteristics of HCC subtypes have come to light. Although now well established, radiologic diagnosis alone

or in combination with clinical and histologic findings still require improvement before being utilized as non-invasive biomarkers in actual clinical settings. Further research on the radiological characteristics of HCC subtypes will enable non-invasive diagnosis and serve as biomarkers for predicting prognosis, molecular characteristics and therapeutic effects. A multidisciplinary effort to develop an integrated radiologic and clinical diagnostic system for various HCC subtypes is necessary for appropriate clinical management, prognosis prediction and individualized therapeutic decision-making.

Table. Clinical features and imaging phenotypes of various HCCs

	Clinical implications and prognosis	Imaging phenotypes
Steatohepatitic HCC	• Associations with risk factors for metabolic syndrome • Better or similar prognosis than conventional HCC	• Low attenuation on CT • T1 hyperintensity and signal loss on opposed phase MRI
CTNNB1-mutated HCC	• Lower serum AFP • Less aggressive nature • Rare portal vein invasion • Good prognosis	• HBP hyperintensity on GA-enhanced MRI • Lower CNR on DWI • Higher ADC
Macrotrabecular massive (MTM)-HCC	• Frequent HBV infection • High serum AFP • Well-differentiation • Worse prognosis	• Substantial necrosis (T2 hyperintensity) (high specificity of >50% central necrosis with more than two ancillary features*) • Hypovascular component on AP • Peritumoral enhancement on AP • Peritumoral hypointensity on HBP
Scirrhous HCC	• Less frequent HBV infection • Similar or lower serum AFP • Similar or better prognosis than conventional HCC	• Peripheral rim-like enhancement on AP and PP • Gradual central enhancement without washout on equilibrium phase • No encapsulation • Confluent multinodularity
K19-positive HCC	• More frequent vascular invasion, poor differentiation and extrahepatic metastasis • Resistance to chemoradiation therapy, higher rate of metastasis and recurrence • Decreased OS and DFS	• Progressive or persistent enhancement similar to cholangiocarcinoma • Irregular tumor margin with no encapsulation • Lower tumor-to-liver ADC ratio Lower tumor-to-liver SI ratio on HBP
Fibrolamellar HCC	• Adolescent and young adults • No underlying liver disease • No known risk factors • Vascular invasion, lymph node and distant metastases • Similar prognosis as conventional HCC	• T1 hypointensity and T2 hyperintensity • T1 and T2 hypointense fibrous central scar • Inhomogeneous AP enhancement and HBP hypointensity on GA-enhanced MRI
Sarcomatoid HCC	• Low serum AFP • History of viral hepatitis • Resistance to TACE • Early recurrence • Poor prognosis	• Large mass with peripheral delayed enhancement with central necrosis • Variable enhancement of intratumoral solid portion • Infiltrative margins with or without tumor capsules • Intrahepatic and extrahepatic metastasis

Different Hepatocellular Carcinoma Risk and Surveillance Strategies According to Situations: Young Age

Nae-Yun Heo

Inje University, Korea

Introduction

Primary liver cancer, especially, hepatocellular carcinoma (HCC) is one of the cancers which pose a heavy disease burden in the world. Therefore, major academic societies have recommended the surveillance for HCC at a high-risk population,[1-3] and several countries have established the surveillance program nationwide. Ideally, the surveillance of HCC would give a chance to detect the tumor at early stage, and get a curative treatment, and then improve survival ultimately. A randomized controlled trial in China showed that the patients with chronic viral hepatitis B who had surveillance by ultrasonography (US) and □-fetoprotein (AFP) showed better survival compared with controls.[4] And, a meta-analysis showed that surveillance by US detected the majority of tumors before they presented clinically.[5] Meanwhile, there was a cut-off incidence of HCC in chronic liver disease in which HCC surveillance is considered cost-effective. According to this threshold incidence for efficacy of surveillance, the American Association for the Study of Liver Diseases clinical practical guideline defined the subject of HCC surveillance such as cirrhosis regardless of etiology, Asian male with chronic viral hepatitis B (CHB) over 40 years old, Asian female with CHB over 50 years old, and African and/or North American blacks with hepatitis B.[2] In Korea, the working group for the guideline for HCC surveillance mentioned that the target population was identified as hepatitis B virus or hepatitis C virus carriers and cirrhotic patients, and the starting age of surveillance was determined as 40 years.[6] Although it is well known that HCC risk is associated with older age, there has been reported the early onset of HCC in young people below 40 years old especially among CHB patients.

How frequently does HCC occur at young age?

Hepatitis B carriers younger than 40 years old in males or 50 years old in females are considered as a group in which HCC surveillance benefit is uncertain because the estimated incidence of HCC is <0.2%/year that is below the threshold for efficacy of surveillance.[2] According to the study based on random cohort among the Korean Central Cancer Registry database between 2003 and 2005, in HBV-related HCC, mean age at diagnosis was 54 years, 193 of 2,785 patients (7%) were less than 40 years.[7] A retrospective population-based cohort study of Alaska Natives of children and young adults showed that the highest HCC incidence was observed among persons with HBV genotype F1 (0.44%/year), which was above the threshold for efficacy of surveillance.[8] A previous study showed that African blacks with HBV might develop HCC at an age younger than 40 years.[9] In contrast, a recent study from Veterans with HBV in United

States published that African Americans had a lower risk of HCC than whites or Asian-Pacific Islanders and most patients had HCC over 40 years. In this study, the proportion of age <40 years was 8% in whites, 12% in African Americans, and 35% in Asian-Pacific Islanders among the patients with HBV-related HCC.[10] In Qidong, a hot spot of HCC occurrence in China which is HBV-endemic area, the age-specific incidence rates increased with age from <10/100,000 in childhood, about 100/100,000 in the group of 35 years, and reached the highest rate of 202/100,000 in the age group of over 60 years.[11] Interestingly, in this epidemic region, not only vertical HBV infection, but also exposure to aflatoxin in the diet, and microcystin in the drinking water were considered as risk factors for HCC. These studies suggest that the patient with CHB in HBV-endemic area or immigrants with CHB from this area might have a risk of HCC occurrence below 40 years compared to the patients with CHB in the area in which the prevalence of HBV is low.

HCC risk of the patients with HBV in immune tolerant phase

In HBV-endemic area, most patients of CHB are infected via vertical transmission at birth. And, many among them remain in the immune tolerance phase in which no evidence of hepatic necro-inflammation and significant fibrosis despite high viral load before 40 years. Recently, a study in Korea reported that untreated immune tolerant phase patients were associated with significantly higher risk of HCC than the immune active phase patients with nucleos(t)ide analogues, and suggested that high risk of HCC in patients with CHB in immune tolerant phase.[12] However, this study was criticized in that it was possible to include some immune active phase patients into immune tolerant phase group because HBV DNA level at enrollment was relatively low. When another study adopted the more stringent definition of immune tolerant phase such as age <40 years and serum HBV DNA >6 $\log_{10}$IU/mL, no actual HCC was identified during follow-up.[13] Therefore, the patients with CHB in pure immune tolerant phase in young adult period have a negligible risk of HCC occurrence. In contrast, there would be possibility of HCC risk in immune active phase patients although the patients are less than 40 years.

Different characteristics of early onset HCC

A retrospective analysis for HCC based on Korean cancer registry data showed that among 4,234 patients, there were 38 patients younger than 30 years (0.9%). This group with early onset HCC showed low frequency of smoking history, high positive HBsAg, no association with anti-HCV, high frequency of AFP ≥400 ng/mL, well-preserved liver function, larger tumor size, and more advanced stage compared with late onset HCC groups.[14] Another study from Taiwan presented that the patients with HCC below 40 years were likely to be a male HBV carriers and to have larger tumor and associated with worse 1-year survival compared with the older patients. However, if the young HCC patient can survive more than 1 year, he would probably better survival in the following years than the older patients.[15] These results suggest that early onset HCC is rare, but associated with male patients with CHB and presented as more advanced tumors compared with older patients, it is necessary to diagnose as soon as possible.

Risk factors for HCC among young people

In a retrospective study including Asian immigrants with HBV at a hospital at New York, the proportion

of cirrhosis was lower in early onset HCC group (male <40 years, female <50 years) than in late onset HCC group (29.5% vs 54.8%). And, risk factors for HCC across all ages included cirrhosis and male gender, while family history of HCC and smoking were associated with early onset of HCC.[16] HBV infection is the most common cause of pediatric HCC in endemic area, and liver cirrhosis, as a predisposing factor, is more frequently present in HBV endemic areas than in the West.[17] This results suggest that cirrhosis is still an important risk factor for HCC in young people with CHB despite reduced weight, and further studies should find other specific risk factors for HCC in this population in detail. At present, several HCC risk scoring models could be applied to young people with CHB for prediction of HCC. REACH-B model was developed to predict HCC with 5 variables such as sex, age, ALT, HBeAg, and HBV DNA level.[18] Risk calculator of HCC for patients with CHB based on REVEAL-HBV study included the variables gender, age, family history of HCC, alcohol consumption, ALT, HBeAg, HBV DNA, and genotype.[19] PAGE-B model including age, gender, and platelet count was developed for prediction of HCC in Caucasian CHB under nucleos(t)ide analogue.[20] However, these prediction models were developed across all age, therefore their efficacy of prediction in young population was not fully validated now.

Conclusion

Although the incidence of HCC is relatively lower in young population, there is a concern about the early onset of HCC in the residents with CHB in HBV-endemic area or immigrants from that area. Not only cirrhotic patients, but also the patients into immune active phase, the patients with family history of HCC, or the patients exposed to carcinogen such as aflatoxin should be monitored for HCC occurrence carefully. In the future, it is necessary to develop more sophisticated prediction model of HCC in young population for individual approach for HCC surveillance.

Refrences

1. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
2. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.
3. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370.
4. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-422.
5. Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.
6. Kim DY, Kim HJ, Jeong SE, et al. The Korean guideline for hepatocellular carcinoma surveillance. J Korean Med Assoc 2015;58:385-397.
7. Sinn DH, Gwak GY, Cho J, Paik SW, Yoo BC. Comparison of clinical manifestations and outcomes between hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma: analysis of a nationwide cohort. PLoS One 2014;9:e112184.
8. Gounder PP, Bulkow LR, Snowball M, Negus S, Spradling PR, McMahon BJ. Hepatocellular Carcinoma Risk in Alaska Native Children and Young Adults with Hepatitis B Virus: Retrospective Cohort Analysis. J Pediatr 2016;178:206-213.

9. Kew MC, Macerollo P. Effect of age on the etiologic role of the hepatitis B virus in hepatocellular carcinoma in blacks. Gastroenterology 1988;94:439-442.
10. Mittal S, Kramer JR, Omino R, et al. Role of Age and Race in the Risk of Hepatocellular Carcinoma in Veterans With Hepatitis B Virus Infection. Clin Gastroenterol Hepatol 2018;16:252-259.
11. Chen J, Zhu J, Wang G, Groopman JD, Kensler TW. Qidong: a crucible for studies on liver cancer etiology and prevention. Cancer Biol Med 2019;16:24-37.
12. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018;67:945-952.
13. Lee HW, Chon YE, Kim BK, et al. Negligible HCC risk during stringently defined untreated immune-tolerant phase of chronic hepatitis B. Eur J Intern Med 2021;84:68-73.
14. Kim JH, Choi MS, Lee H, et al. Clinical features and prognosis of hepatocellular carcinoma in young patients from a hepatitis B-endemic area. J Gastroenterol Hepatol 2006;21:588-594.
15. Chen CH, Chang TT, Cheng KS, et al. Do young hepatocellular carcinoma patients have worse prognosis? The paradox of age as a prognostic factor in the survival of hepatocellular carcinoma patients. Liver Int 2006;26:766-773.
16. Wan DW, Tzimas D, Smith JA, et al. Risk factors for early-onset and late-onset hepatocellular carcinoma in Asian immigrants with hepatitis B in the United States. Am J Gastroenterol 2011;106:1994-2000.
17. Yu SB, Kim HY, Eo H, et al. Clinical characteristics and prognosis of pediatric hepatocellular carcinoma. World J Surg 2006;30:43-50.
18. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011;12:568-574.
19. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. J Gastroenterol Hepatol 2011;26:628-638.
20. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800-806.

Different Hepatocellular Carcinoma Risk and Surveillance Strategies According to Situations: After Virologic Cure

Jung Hyun Kwon

The Catholic University of Korea, Korea

Introduction

The majority of persons currently treated for chronic hepatitis B require long-term or lifelong therapy. The goal of developing new therapies is to achieve HBV cure, i.e. elimination of HBV, thereby allowing treatment to be stopped with no risk of virological relapse and no risk of liver disease progression.[1-3] The observation that HBsAg may become undetectable in serum after clinical recovery from acute hepatitis B, spontaneously during the course of chronic HBV infection, and during or after nucleosid(t)e analogue (NA) or interferon (IFN) therapy. However, a true cure may not be feasible because HBV DNA is integrated into the host genome; even among persons who recovered from acute HBV, viral covalently closed circular DNA (cccDNA) can be detected in the liver explaining the reactivation of HBV replication when these "recovered" persons are profoundly immunosuppressed.[4-6]A functional cure characterized by sustained loss of HBsAg which is associated with improved clinical outcomes although a complete sterilizing cure i.e. viral eradication from the host is unlikely to be feasible.[7]

Definition of HBV cure

Three definitions of HBV cure were proposed[8]: (1) Complete sterilizing cure with undetectable HBsAg in serum and eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA. (2) Functional cure with sustained, undetectable HBsAg and HBV DNA in serum with or without seroconversion to anti-HBs after completion of a finite course of treatment, resolution of residual liver injury and a decrease in risk of HCC over time. Several levels of functional cure including complete shutdown of cccDNA transcription, elimination of cccDNA, complete resolution of liver damage, and elimination of risk of HCC were discussed. (3) Partial cure with detectable HBsAg but persistently undetectable HBV DNA in serum after completion of a finite course of treatment.

Cumulative rate and prognosis of spontaneously or antiviral induced HBsAg seroclearance

Spontaneous HBsAg seroclearance in chronic HBV infection has long been suggested as a rare event; a rate of 0.5 to 1% per year.[1,3] Korean patients reportedly experience a relatively low rate of HBsAg loss (0.4% annually).[2] The prognosis following spontaneous HBsAg seroclearance is known to be good, except in patients with cirrhosis or those with concurrent hepatitis C virus or hepatitis delta virus infection. Anyway, HCC developed even in a minority of cases.

In Taiwan study,[9] cumulative rate of HBsAg seroclearance in asymptomatic adult carriers from high endemic areas was approximately 40% after 25 years of follow-up. In another Taiwan study,[10] a total of 218 patients who had undergone spontaneous HBsAg seroclearance were followed up for 12–179 months. Of the 189 patients who were noncirrhotic at the time of HBsAg clearance, 3 (1.6%) developed cirrhosis, 2 (1.1%) developed hepatocellular carcinoma (HCC), and 1 died of HCC. These complications all developed in patients with concurrent hepatitis C virus or hepatitis delta virus infection ($P < 0.001$). In Korean study,[4] 49 (9.5%) out of 432 inactive HBsAg carriers had no detectable level of circulating HBsAg during 20 years. During a mean follow-up period of 19.6 months after HBsAg seroclearance, 5 of 49 (10.2%) patients were noted to have HCC. In the study of HBsAg negative patients with newly diagnosed HCC, HBV reactivation (defined as the reappearance of HBV DNA or sero-reversion of HBsAg) occurred in the anticancer therapy such as TACE.[11] It also shows that HCC could develop in the patients with HBsAg seroclearance.

During NA treatment, a Korean study reported that annual HBsAg seroclearance rate was 0.33%.[12] NA-induced HBsAg seroclearance showed similar durability to spontaneous HBsAg seroclearance and was associated with favourable clinical outcome, if achieved.[12,13]

During a median follow-up period of 6 years of 5409 CHB patients who were initially treated with NA, a total of 110 achieved HBsAg seroclearance (0.33% annual seroclearance rate).[12] During follow-up for 287 patient-years after HBsAg seroclearance, only two patients with baseline cirrhosis developed hepatocellular carcinoma (HCC) or died (0.7% annual risk), which was of a significantly lower rate compared with propensity score-matched patients without HBsAg seroclearance (HR 0.09, $P<0.01$).[12] A retrospective analysis of 829 patients (mean age: 52.3 years; 575 males; 98 with cirrhosis) achieving HBsAg seroclearance showed that the cumulative incidence of HCC at 5, 10, and 12 years was 1.6%, 5.9%, and 15.2%, respectively.[14] In all, 724 (87.3%) achieved spontaneous HBsAg seroclearance and 105 (12.7%) achieved therapy-induced HBsAg seroclearance. In another Korean multicenter study of 276 patients who achieved NA-induced HBsAg seroclearance, 10 patients (3.6%) experienced HBsAg reversion, 6 (2.2%) showed HBV DNA redetection and 8 (2.9%) developed HCC.[15]

HCC risk after HBsAg seroclearance and surveillance scoring systems

Current guidelines suggested that patients with CHB should be tested for HCC regardless of hepatitis B treatment; abdominal ultrasonography and serum alfa-fetoprotein are the surveillance tools that should be performed every 6 months.[1-3] HBsAg-positive adults at high risk for HCC (including Asian or black men over 40 years and Asian women over 50 years of age), persons with a first-degree family member with a history of HCC, or persons with HDV should be screened with US examination with or without AFP every 6 months.[1]

Little is known about surveillance for HCC for in patients who have achieved HBsAg seroclearance. Moreover, the reported rates of HCC after HBsAg seroclearance are markedly low (between 2.9% and 30.7% in cirrhotic patients and between 0% and 3.1% in non-cirrhotic patients) compared to rates of HCC in still HBsAg positive patients.[12,16-18] This is because there is the low number of patients who achieve HBsAg seroclearance but still develop HCC.

Several studies reported the risk of HCC development in patients with HBsAg seroclearance. In previous Korean study, liver cirrhosis, a history of perinatal infection and long-standing duration (at least 30

years) of HBsAg positivity were associated with a significantly higher risk of developing HCC.[4] Also, in the large scaled Korean study (829 patients with HBsAg seroclearance), liver cirrhosis (HR: 10.80; 95% CI: 4.25–27.43), male gender (HR: 8.96; 95% CI: 1.17–68.80), and age > 50 years at the time of HBsAg seroclearance (HR: 12.14; 95% CI: 1.61– 91.68) were independently associated with HCC.[14] Among the non-cirrhotic patients, the annual rate of HCC was higher in the male patients than in the females (0.40% vs. 0%, respectively), and all the HCCs developed after age 50.[14] In a large scaled Hongkong study (4,568 patients with HBsAg seroclearance), female patients aged 50 years or below have zero risk of hepatocellular carcinoma (HCC) after HBsAg seroclearance, whereas female patients aged above 50 years and all male patients are still at risk of HCC.[19]

In both studies, CU-HCC score is still predictive of HCC development for patients who cleared HBsAg with an AUROC of 0.73~0.85.[14,19] In a recent report, NA discontinuation after NA-induced HBsAg seroclearance was as safe as NA continuation.[15] NA discontinuation was not associated with a higher risk of either HBsAg reversion, serum HBV DNA redetection or HCC development compared with NA continuation among patients who achieved HBsAg seroclearance with NA. Whether HCC risk after HBsAg seroclearance differs between AVT-induced or spontaneous seroclearance cases was investigated.[20] The HCC incidence rate was higher in the AVT-induced cases than that in the spontaneous cases (3.9%vs 0.9% at 5 years). AVT and cirrhosis were independent factors associated with HCC. Among the 6 predictive HCC models tested (CU-HCC, REACH-B, GAG-HCC, PAGE-B, modified PAGE-B, and aMAP scores), Chinese University-HCC score (0.82) showed the highest C-statistics.[20]

Conclusion

Patients with AVT induced or spontaneously HBsAg seroclearance have a lower risk of HCC. However, persistence of intrahepatic HBV DNA integration in patients developing HCC after HBsAg seroclearance was observed and HCC still developed.[5] Thus, ongoing HCC surveillance and clinical management should continue even after HBsAg seroclearance. In addition, further studies to establish a model of risk prediction are warranted in the grey zone patients after HBsAg seroclearance without high risk factor such as cirrhosis, male sex and age more than 50.

References

1. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
2. KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2019;25:93-159.
3. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.
4. Ahn SH, Park YN, Park JY, Chang HY, Lee JM, Shin JE, et al. Long-term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. J Hepatol 2005;42:188-194.
5. Jang JW, Kim JS, Kim HS, Tak KY, Nam H, Sung PS, et al. Persistence of intrahepatic hepatitis B virus DNA integration in patients developing hepatocellular carcinoma after hepatitis B surface antigen seroclearance. Clin Mol Hepatol 2021;27:207-218.
6. Lee HL, Jang JW, Han JW, Lee SW, Bae SH, Choi JY, et al. Early Hepatitis B Surface Antigen Seroclearance Following Antiviral Treatment in Patients with Reactivation of Resolved Hepatitis B. Dig Dis Sci 2019;64:2992-3000.

7. Liaw YF, Sheen IS, Chen TJ, Chu CM, Pao CC. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. Hepatology 1991;13:627-631.
8. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: From discovery to regulatory approval. Hepatology 2017;66:1296-1313.
9. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. Hepatology 2007;45:1187-1192.
10. Chen YC, Sheen IS, Chu CM, Liaw YF. Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. Gastroenterology 2002;123:1084-1089.
11. Jang JW, Kim YW, Lee SW, Kwon JH, Nam SW, Bae SH, et al. Reactivation of hepatitis B virus in HBsAg-negative patients with hepatocellular carcinoma. PLoS One 2015;10:e0122041.
12. Kim GA, Lim YS, An J, Lee D, Shim JH, Kim KM, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014;63:1325-1332.
13. Yip TC, Wong GL, Wong VW, Tse YK, Lui GC, Lam KL, et al. Durability of hepatitis B surface antigen seroclearance in untreated and nucleos(t)ide analogue-treated patients. J Hepatol 2017.
14. Kim GA, Lee HC, Kim MJ, Ha Y, Park EJ, An J, et al. Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. J Hepatol 2015;62:1092-1099.
15. Kim MA, Kim SU, Sinn DH, Jang JW, Lim YS, Ahn SH, et al. Discontinuation of nucleos(t)ide analogues is not associated with a higher risk of HBsAg seroreversion after antiviral-induced HBsAg seroclearance: a nationwide multicentre study. Gut 2020;69:2214-2222.
16. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, et al. Long-term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. Am J Med 2006;119:71.e79-16.
17. Yuen MF, Wong DK, Fung J, Ip P, But D, Hung I, et al. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008;135:1192-1199.
18. Tong MJ, Nguyen MO, Tong LT, Blatt LM. Development of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. Clin Gastroenterol Hepatol 2009;7:889-893.
19. Yip TC, Chan HL, Wong VW, Tse YK, Lam KL, Wong GL. Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Hepatol 2017;67:902-908.
20. Park Y, Lee JH, Sinn DH, Park JY, Kim MA, Kim YJ, et al. Risk and Risk Score Performance of Hepatocellular Carcinoma Development in Patients With Hepatitis B Surface Antigen Seroclearance. Clin Transl Gastroenterol 2021;12:e00290.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (11:10-12:30)

ROOM 2

KLCA Symposium 2

Evolving Trends in Management of Hepatocellular Carcinoma

Chairs:

Jinsil Seong (Yonsei Univ.)

Seung Kew Yoon (The Catholic Univ. of Korea)

Role of Systemic Therapy in Intermediate-Stage Hepatocellular Carcinoma

Masatoshi Kudo

Kindai University, Japan

The largest therapeutic effect of cTACE is observed in encapsulated simple nodular type HCCs. In contrast, a high frequency of vascular invasion and a poor therapeutic effect of cTACE are observed in confluent multinodular type, massive type, infiltrative type and simple nodular type HCCs with extranodular growth, all of which lack capsule formation.[1,2] Similar to these types, the efficacy of TACE is also low in poorly differentiated and undifferentiated HCCs, due to resistance to TACE.[3]

TACE induces hypoxic and chemotherapeutic stress in HCC, and the surviving hypoxic tumors frequently change to sarcomatous or mixed hepatocholangiocellular phenotypes (20% and 35%, respectively), which are more aggressive and often TACE-resistant.[4,5] Generally, small intrahepatic tumors that develop frequently are likely to be intrahepatic disseminated nodules. In these cases, even superselective TACE is often followed by the appearance of new recurrent lesions outside the embolized area; therefore, repeated TACE is required. This repeated TACE causes damage to the hepatic artery and deterioration of hepatic function, which worsen the prognosis of patients. Moreover, disseminated lesions (satellite nodules) usually have no capsule and show marked resistance to TACE.[6]

A number of reports, such as the global observational study OPTIMIS and two other studies, indicate that repeated TACE procedures lead to deterioration in liver function in up-to seven criteria out patients.[7-11] In terms of liver function, ALBI grade 2 especially mALBI grade 2b is a poor prognostic factor for OS after TACE.[9,11]

Lenvatinib is the only first-line agent to demonstrate an OS benefit over TACE in TACE-naïve patients with up-to-seven criteria out tumor burden although this is a retrospective propensity score matched study.[12] Lenvatinib is associated with significantly better PFS (16.0 months) and ORR (73.3%) than TACE alone (PFS:3.0 months, ORR: 33.3%), In addition, the ALBI score in the TACE group is worsen over time compared with that in the lenvatinib group. At the end of treatment, worsen ALBI score was not recovered in TACE treated group whereas it was recovered to the baseline level in lenvatinib treated group. Lenvatinib extends the overall survival significantly than TACE (37.9 M vs 21.3 M).[12,13] Lenvatinib treatment also shows favorable results in TACE-unresponsive tumors such as poorly differentiated, confluent multinodular type or infiltrated type HCCs.[14-16]

In the OPTIMIS study, only 9% of patients received sorafenib after developing TACE refractoriness; indeed, in clinical practice, sorafenib is rarely used in TACE-unsuitable patients who easily develop TACE-refractoriness. In TACE-unsuitable patients, there is no solid evidence that sorafenib has a benefit over TACE.[17] Similarly, hepatic arterial infusion chemotherapy (HAIC) plus sorafenib does not show a greater

benefit than sorafenib alone in patients with bilobar multiple tumors; therefore, HAIC is not indicated for this population.[18,19] Transarterial radioembolization using Y90 (TARE) does not offer a greater benefit than sorafenib alone in those with intrahepatic multiple tumors; therefore, TARE may not be indicated routinely for patients with bilobar multiple intrahepatic tumors.[20,21]

The TACTICS trial showed the benefit of sorafenib followed by TACE as a treatment option to improve the clinical outcome of patients with intermediate-stage HCC.[22] Pretreatment with systemic therapy (both sorafenib and lenvatinib) improves the clinical outcome of TACE[23] presumably by promoting vascular normalization and improving the distribution of lipiodol mixed with anticancer drugs.[24-27] Since OS benefit has not yet been proved with TACTICS trial, panelists decided that lenvatinib is the preferred agent for TACE-unsuitable patients based on the high response rate, survival benefit over TACE, and possibility of conversion to resection or ablation therapy as of 2020.

Second-line treatment options include sorafenib, regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab, or superselective TACE, depending on the patient's tumor condition. It should be kept in mind that TACE unsuitable HCC is not always contraindicated for TACE monotherapy and some "up-to-seven criteria out" tumors may also be indicated for superselective cTACE when tumors are localized in limited segments.

Immunotherapy (nivolumab or pembrolizumab) failed to achieve the primary endpoint of OS in Phase III trials;[28,29] however, because a clinical benefit was observed, panelists indicated that immunotherapy should be considered as an alternative treatment in TACE-unsuitable patients who are not candidates for molecular targeted therapy. Atezolizumab plus bevacizumab resulted in better OS, PFS, and ORR than sorafenib alone in patients with advanced HCC.[30] Thus, panelists suggested that this combination is worth considering in patients with intermediate-stage HCC.

Although TACE represents the standard of care for intermediate-stage HCC, intermediate-stage HCC constitutes a very heterogeneous patient population that is characterized by marked differences in tumor burden and liver function. Real-world experience indicates that loco-regional therapy is overused in most patients outside clinical practice guidelines, which frequently leads to deterioration of liver function and thereby to exclusion of patients from systemic therapy and/or clinical trials.

Because of its high anti-tumor effect of lenvatinib on massive, confluent multinodular, infiltrative, poorly differentiated and simple nodular with extranodular growth tumor types, LEN-TACE sequential therapy is a rational and effective treatment strategy for patients who do not benefit from TACE alone and are susceptible to deterioration of hepatic functional reserve. Other systemic therapy such as combination immunotherapy of atezolizumab plus bevacizumab may play a role in intermediate stage HCC in the near future since ORR by atezolizumab plus bevacizumab is as high as 70 % in intermediate stage HCC in phase 1b study.[31] Sorafenib in combination with TACE is a choice of treatment in intermediate-stage HCC[22] as shown in TACTICS trial. This trial is still ongoing, therefore, this combination will be more important and persuasive when survival benefit is shown in the near future.

Current advances in development of new anticancer agents will lead to a paradigm shift or even paradigm change in the treatment of HCC, and systemic therapy may become the first choice of treatment, followed by curative/selective TACE for treatment of intermediate-stage HCC with a high tumor burden.[32]

References

1. Kanai T, Hirohashi S, Upton MP, Noguchi M, Kishi K, Makuuchi M, et al. Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer 1987;60:810-819.
2. Hashimoto T, Nakamura H, Hori S, Tomoda K, Nakanishi K, Murakami T, et al. Hepatocellular carcinoma: efficacy of transcatheter oily chemoembolization in relation to macroscopic and microscopic patterns of tumor growth among 100 patients with partial hepatectomy. Cardiovascular and interventional radiology 1995;18:82-86.
3. Yamashita Y, Matsukawa T, Arakawa A, Hatanaka Y, Urata J, Takahashi M. US-guided liver biopsy: predicting the effect of interventional treatment of hepatocellular carcinoma. Radiology 1995;196:799-804.
4. Kojiro M, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer chemotherapy and pharmacology 1989;23 Suppl:S4-8.
5. Zen C, Zen Y, Mitry RR, Corbeil D, Karbanova J, O'Grady J, et al. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2011;17:943-954.
6. Kuroda C, Sakurai M, Monden M, Marukawa T, Hosoki T, Tokunaga K, et al. Limitation of transcatheter arterial chemoembolization using iodized oil for small hepatocellular carcinoma. A study in resected cases. Cancer 1991;67:81-86.
7. Arizumi T, Minami T, Chishina H, Kono M, Takita M, Yada N, et al. Time to Transcatheter Arterial Chemoembolization Refractoriness in Patients with Hepatocellular Carcinoma in Kinki Criteria Stages B1 and B2. Digestive diseases (Basel, Switzerland) 2017;35:589-597.
8. Cheng AL, Raoul JL, Lee HC, et al. Acute and chronic deterioration in liver function after transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC): the final analysis of OPTIMIS. ILCA, 12th Annual Conference, Abstr # P-34.
9. Kimura H, Ohkawa K, Miyazaki M, Sakakibara M, Imanaka K, Tamura T, et al. Subclassification of patients with intermediate-stage (Barcelona Clinic Liver Cancer stage-B) hepatocellular carcinoma using the up-to-seven criteria and serum tumor markers. Hepatology international 2017;11:105-114.
10. Eso Y, Takai A, Takahashi K, Ueda Y, Taura K, Marusawa H, et al. Combination of Mac-2 Binding Protein Glycosylation Isomer and Up-To-Seven Criteria as a Useful Predictor for Child-Pugh Grade Deterioration after Transarterial Chemoembolization for Hepatocellular Carcinoma. Cancers 2019;11.
11. zumoto H, Hiraoka A, Ishimaru Y, Murakami T, Kitahata S, Ueki H, et al. Validation of Newly Proposed Time to Transarterial Chemoembolization Progression in Intermediate-Stage Hepatocellular Carcinoma Cases. Oncology 2017;93 Suppl 1:120-126.
12. Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. Cancers 2019;11.
13. Kudo M. A New Treatment Option for Intermediate-Stage Hepatocellular Carcinoma with High Tumor Burden: Initial Lenvatinib Therapy with Subsequent Selective TACE. Liver cancer 2019;8:299-311.
14. Kudo M, Ueshima K, Aikata H, Tamai T, Saito K, Ikeda K. Association Between Tumor Response by mRECIST and Overall Survival in Patients With Poorly Differentiated HCC in REFLECT Study. Liver Cancer 8:90, 2019 (abstr O-007).
15. Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Kasuya K, Sano T, et al. (18)F-Fluorodeoxyglucose Uptake in Hepatocellular Carcinoma as a Useful Predictor of an Extremely Rapid Response to Lenvatinib. Liver cancer 2020;9:84-92.
16. Kawamura Y, Kobayashi M, Shindoh J, Kobayashi Y, Kasuya K, Sano T, et al. Pretreatment Heterogeneous Enhancement Pattern of Hepatocellular Carcinoma May Be a Useful New Predictor of Early Response to Lenvatinib and Overall Prognosis. Liver cancer 2020;9:275-292.

17. Peck-Radosavljevic M, Kudo M, Raoul J, et al. Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): Global OPTIMIS final analysis. J Clin Oncol 36, 2018 (suppl; abstr 4018).
18. Kudo M, Ueshima K, Yokosuka O, Ogasawara S, Obi S, Izumi N, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. The lancet Gastroenterology & hepatology 2018;3:424-432.
19. Ueshima K, Ogasawara S, Ikeda M, Yasui Y, Terashima T, Yamashita T, et al. Hepatic Arterial Infusion Chemotherapy versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma. Liver cancer 2020;9:583-595.
20. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. The Lancet Oncology 2017;18:1624-1636.
21. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36:1913-1921.
22. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2019.
23. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet (London, England) 2018;391:1163-1173.
24. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science (New York, NY) 2005;307:58-62.
25. Kano MR, Komuta Y, Iwata C, Oka M, Shirai YT, Morishita Y, et al. Comparison of the effects of the kinase inhibitors imatinib, sorafenib, and transforming growth factor-beta receptor inhibitor on extravasation of nanoparticles from neovasculature. Cancer science 2009;100:173-180.
26. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249-257.
27. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res 2014;2014:638747.
28. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. Ann Oncol 30 (suppl 5):v874-v875, 2019.
29. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2020;38:193-202.
30. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. The New England journal of medicine 2020;382:1894-1905.
31. Lee MS, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. The Lancet Oncology 2020;21:808-820.
32. Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements. Liver cancer 2020;9:245-260.

Role of Loco-Regional Treatment in Advanced-Stage Hepatocellular Carcinoma

Ju Hyun Shim

University of Ulsan, Korea

Hepatocellular carcinoma (HCC) at an advanced stage referred to as BCLC-C stage includes liver cancers that have lymphatic or distant organ metastasis, or portal vein tumor thrombosis, regardless of metastatic foci. In principle, the hard-to-treat disease is not primarily eligible for surgical resection or local therapies alone, although sometimes treated with such modalities in clinical practice. Since the approval of sorafenib based on the improved survival benefit to patients with HCC in 2007, it has been globally accepted as the standard first-line treatment for advanced HCC. Thereafter a decade of clinical trials investigating other molecularly targeted drugs as monotherapy or in combination compared with sorafenib have failed to meet their primary endpoints, prior to the success of lenvatinib. On the other hand, intrahepatic tumor status is a robust parameter predicting prognosis and treatment response in advanced-stage HCC patients, even with extrahepatic metastasis. Reversely, it has been found that the effective intrahepatic control of tumors is of vital importance in prolonging survival of patients with the disease. In this context, several liver-directed therapies, including transarterial chemoembolization, radioembolization, and hepatic arterial infusion chemotherapy, alone or in combination with sorafenib or radiotherapy, have been tested in advanced HCC patients, and some positive results were reported mainly for a particular set of tumors invading portal vein. Most recently, atezolizumab plus bevacizumab has emerged as the first chemotherapeutic regimen significantly increasing the survival rate seen with sorafenib in patients with unresectable HCC. Moreover, a network meta-analysis confirmed the best efficacy of the combination in direct or indirect comparisons with other agents targeting VEGF or PD-1/PD-L1. Until now, there are no studies comparing this new first-line regimen versus transarterial therapies with or without sorafenib in patients with HCC. In the current turbulent times of the treatment for advanced HCC, we should address questions about the proper indication and therapeutic role of transarterial approaches, and keep watching future results from on-going or novel combinations of transarterial and immune therapies. The development of biomarker-driven therapeutic strategies is urgently required to implement precision medicine in the future care for advanced HCC patients.

References

1. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.

3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
4. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
5. Park JW, Kim YJ, Kim DY, Bae SH, Paik SW, Lee YJ, et al. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial. J Hepatol 2019;70:684-691.
6. Ricke J, Bulla K, Kolligs F, Peck-Radosavljevic M, Reimer P, Sangro B, et al. Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. Liver Int 2015;35:620-626.
7. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-1905.
8. Kudo M, Ueshima K, Yokosuka O, Ogasawara S, Obi S, Izumi N, et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol 2018;3:424-432.
9. Sonbol MB, Riaz IB, Naqvi SAA, Almquist DR, Mina S, Almasri J, et al. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. JAMA Oncol 2020;6:e204930.

Optimizing Radiotherapy with Immune Checkpoint Blockade in Hepatocellular Carcinoma

Jeong Il Yu

The Catholic University of Korea, Korea

Introduction

Immunotherapy targeting evading immune destruction which is one of the hallmarks of cancer, especially immune checkpoint blockade (ICB), is complementing or replacing previous standard managements in many tumor types.[1] With the promising and/or superior oncologic outcomes of ICBs in many oncologic fields, researches have been attempted to apply those agents to hepatocellular carcinoma (HCC).[2,3]

Radiotherapy (RT) which is one of the main modalities in the management of many tumor types, including HCC is well-known as a powerful method to induce immunogenic cell death (ICD), unique type of programmed cell death.[4] The ICD generated by RT can activate systemic immune responses and result in regression of non-irradiated distant metastatic lesions outside of radiotherapy target lesion which is a phenomenon known as the abscopal (from the Latin, meaning "away from the target") effect of RT.[5] It has been known for a long time, but it was extremely rare in actual clinical practice. However, along with the active application of ICB in oncologic fields, outcomes of preclinical and clinical researches about immune modulation effect of RT combined with ICBs has been reported constantly.[6] In this review, we will discuss optimal RT strategies with ICB in HCC patients.

Toxicity in combination treatment of RT and ICB

In the several tumor types, mainly non-small cell lung cancer (NSCLC) or melanoma, the combination treatment of RT and ICB with or without previous standard chemotherapy have been reported to be relatively safe in many prospective or retrospective studies. A systematic meta-analysis also reported comparable grade 3 or 4 toxicity in using combination treatment of RT and ICB compared to ICB alone in melanoma brain metastases, NSCLC, and prostate cancer.[7] In HCC, unfortunately, prospective studies evaluating safety of radiotherapy and ICB combination has been reported very rarely so far, although it appears to be promising.[8]

Optimal strategies in combination treatment of RT and ICB

ICB showed many improvement of clinical outcomes, especially in terms of progress-free in patients showed objective response. The main limitation of ICB, however, only 20 to 30% of immune inflamed patients actually responded. Combination of RT could be considered, if it is difficult to expect response with ICB, for example microsatellite stable or low tumor mutational burden. For this point, there will be a need

for a more active pathologic confirmation in HCC management. In particular, in the case of locally advanced HCC with infiltrating vessels and/or bile duct, oligo-metastasis or oligo-progression, effective local control as well as immune modulation can be expected.

In terms of optimal timing of RT addition with ICB, further clinical studies should be needed evaluating efficiency and safety. It actually depends on the mechanism of action of ICB according to the results of preclinical and/or clinical studies to date. Anti-CTLA4 showed higher benefit using before or with RT concurrently to deplete preexisting Treg and/or inhibition of TGF-β.[9] On the other hand, Anti-PD1/PD-L1 and other checkpoints targeting CD8+ T-cell seems to be immediately after or with RT concurrently to correspond to PD-L1 upregulation with radiating inducing interferon.

Optimizing of fraction size and number of RT is highly affected to balance between immune enhancement and immune suppression. Vanpouille-Box et al. reported that abscopal responses are only seen in radiotherapy of three fractions of eight gray (Gy) with anti-CTLA4 and not in 30 Gy with anti-CTLA4.[10] Desalem et al. reported that single fraction of 2 Gy sensitizes tumor cells to immune rejection.[11] On the contrary, lymphopenia related with long treatment periods and/or large radiation doses is clearly associated with poor prognosis.[12,13] As mentioned, there is not yet a fixed value for a clearly superior dose regimen of RT with ICB combination, it is thought that hypofraction with single fraction of less than 10 Gy would be appropriate. It should be tailored, however, to suit the patient and disease's condition and treatment purpose.

Further research on the optimal target volume of radiotherapy should be needed. Abscopal effect is difficult to expect without effective T cell can be represented as lymphopenia.[14] On the contrary, low dose radiotherapy causes normalization of aberrant tumor vessels and recruitment of tumor specific T cells.[15] Appropriate radiotherapy targets should be set according to the treatment purpose of local control or immune modulation.

Conclusion

Radiotherapy could enhance the effect of ICB ether in irradiated target or distant non-irradiated targets by inducing immunogenic cell death. There are many preclinical or clinical studies in progress to identify the optimal combination of radiotherapy and ICB.

References

1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 2020;11(1):3801.
2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382(20):1894-905.
3. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in keynote-240: A randomized, double-blind, phase iii trial. J Clin Oncol 2020;38(3):193-202.
4. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer 2020;8(1).
5. Yilmaz MT, Elmali A, Yazici G. Abscopal effect, from myth to reality: From radiation oncologists' perspective. Cureus 2019;11(1):e3860.
6. Procureur A, Simonaggio A, Bibault JE, Oudard S, Vano YA. Enhance the immune checkpoint inhibitors efficacy

with radiotherapy induced immunogenic cell death: A comprehensive review and latest developments. Cancers (Basel) 2021;13(4).
7. Sha CM, Lehrer EJ, Hwang C, Trifiletti DM, Mackley HB, Drabick JJ, et al. Toxicity in combination immune checkpoint inhibitor and radiation therapy: A systematic review and meta-analysis. Radiother Oncol 2020;151:141-8.
8. Lee YH, Tai D, Yip C, Choo SP, Chew V. Combinational immunotherapy for hepatocellular carcinoma: Radiotherapy, immune checkpoint blockade and beyond. Front Immunol 2020;11:568759.
9. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, Babb JS, Formenti SC, et al. Tgfβ is a master regulator of radiation therapy-induced antitumor immunity. Cancer Res 2015;75(11):2232-42.
10. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, et al. DNA exonuclease trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.
11. DeSelm C, Palomba ML, Yahalom J, Hamieh M, Eyquem J, Rajasekhar VK, et al. Low-dose radiation conditioning enables car t cells to mitigate antigen escape. Mol Ther 2018;26(11):2542-52.
12. Chen D, Verma V, Patel RR, Barsoumian HB, Cortez MA, Welsh JW. Absolute lymphocyte count predicts abscopal responses and outcomes in patients receiving combined immunotherapy and radiation therapy: Analysis of 3 phase 1/2 trials. Int J Radiat Oncol Biol Phys 2020;108(1):196-203.
13. Crocenzi T, Cottam B, Newell P, Wolf RF, Hansen PD, Hammill C, et al. A hypofractionated radiation regimen avoids the lymphopenia associated with neoadjuvant chemoradiation therapy of borderline resectable and locally advanced pancreatic adenocarcinoma. J Immunother Cancer 2016;4:45.
14. Kim N, Yu JI, Park HC, Yoo GS, Choi C, Hong JY, et al. Incorporating sarcopenia and inflammation with radiation therapy in patients with hepatocellular carcinoma treated with nivolumab. Cancer Immunol Immunother 2020.
15. Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, et al. Low-dose irradiation programs macrophage differentiation to an inos^{+}/m1 phenotype that orchestrates effective t cell immunotherapy. Cancer Cell 2013;24(5):589-602.

Treatment of Advanced Hepatocellular Carcinoma with Child-Pugh B Cirrhosis

Chang Wook Kim

The Catholic University of Korea, Korea

Advanced hepatocellular carcinoma generally refers to Barcelona Clinic Liver Cancer (BCLC) stage C as hepatocellular carcinoma with intrahepatic vascular invasion or extrahepatic metastasis such as lymph node, lung or bone metastases and in this case, it is not possible to try curative therapy, which aims to treat life prolongation through palliative therapy.[1-7] BCLC stage B can also be seen as advanced or progressive in terms of not being able to be completely cured, but in this case, it is expressed as intermediate stage, and if TACE treatment is not possible or its effect is expected to be limited, it can also be seen as advanced hepatocellular carcinoma.

BCLC stage C HCC's best treatment is systemic therapy, and 1st line and 2nd line systemic therapy have been steadily evolving in recent years. However, the subjects included in these licensed Phase III clinical studies include only study design to Child A patients, and most of the data performed included >95% Child A patients, so no well-designed clinical study shows that Child B advanced HCC patients would actually have survival gain through systemic therapy.

Almost all attempts to see the safety and efficacy of various systematic therapy in Child B advanced HCC were observational cohort studies, mostly retrospective studies.[8-20] According to these studies, Child B advanced HCC tended to reduce the duration of use of study drug due to worsening of liver function or the frequency of decompensation by study drug, but the safety profile was not significantly different from that of Child A patients, and progression-free survival (PFS) and overall survival (OS) evaluating survival gain were significantly lower than in Child A patients. Therefore, among Child B, there are several efforts to identify patients who can reliably obtain survival gain through systemic therapy, and when analyzing patients according to Child-Pugh score among Child B, Child score 7 patients showed better efficacy than Child score 8 or 9 patients, so systemic therapy can be expanded to child score 7, but there is no strong evidence.[21]

The ECOG performance scale and Child-Pugh class are used as factors to determine the patient's prognosis. Recently, due to the limitation of the Child-Pugh class, MELD score or ALBI score is used to more accurately evaluate the underlying liver function status.[22] Also, the concept of “preserved liver function” is applied. In order to obtain the optimal treatment results, patients with preserved liver function should be selected. In general, this is evaluated as a preserved liver function for a child A who has not experienced decompensation events such as ascites.[1]

In conclusion, the optimal treatment results in advanced HCC patients are in a good basal liver function like Child A, but well-selected patients among Child B, though not well-preserved liver function, can get

good treatment results. Efforts are needed to select patients who can obtain good or acceptable treatment results among Child B patients.

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-1314.
2. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370.
3. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.
4. Korean Liver Cancer A, National Cancer C. 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. Gut Liver 2019;13:227-299.
5. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
6. Blanc JF, Debaillon-Vesque A, Roth G, et al. Hepatocellular carcinoma: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, AFEF, SIAD, SFR/FRI). Clin Res Hepatol Gastroenterol 2021;45:101590.
7. Vogel A, Martinelli E, clinicalguidelines@esmo.org EGCEa. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. Ann Oncol 2021.
8. Worns MA, Weinmann A, Pfingst K, et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009;43:489-95.
9. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol 2016;65:1140-1147.
10. Kudo M, Ikeda M, Takayama T, et al. Safety and efficacy of sorafenib in Japanese patients with hepatocellular carcinoma in clinical practice: a subgroup analysis of GIDEON. J Gastroenterol 2016;51:1150-1160.
11. Kim DY, Kim HJ, Han KH, et al. Real-Life Experience of Sorafenib Treatment for Hepatocellular Carcinoma in Korea: From GIDEON Data. Cancer Res Treat 2016;48:1243-1252.
12. Ye SL, Chen X, Yang J, et al. Safety and efficacy of sorafenib therapy in patients with hepatocellular carcinoma: final outcome from the Chinese patient subset of the GIDEON study. Oncotarget 2016;7:6639-48.
13. Scheiner B, Kirstein MM, Hucke F, et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. Aliment Pharmacol Ther 2019;49:1323-1333.
14. Kambhampati S, Bauer KE, Bracci PM, et al. Nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis: Safety and clinical outcomes in a retrospective case series. Cancer 2019;125:3234-3241.
15. Cheon J, Chon HJ, Bang Y, et al. Real-World Efficacy and Safety of Lenvatinib in Korean Patients with Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Analysis. Liver Cancer 2020;9:613-624.
16. Ogushi K, Chuma M, Uojima H, et al. Safety and Ef fi cacy of Lenvatinib Treatment in Child-Pugh A and B Patients with Unresectable Hepatocellular Carcinoma in Clinical Practice: A Multicenter Analysis. Clin Exp Gastroenterol 2020;13:385-396.
17. Komiyama S, Numata K, Ogushi K, et al. Therapeutic effects of regorafenib after sorafenib monotherapy with advanced hepatocellular carcinoma including Child-Pugh classification B: A retrospective observational study. Medicine (Baltimore) 2020;99:e21191.
18. Kim HD, Bang Y, Lee MA, et al. Regorafenib in patients with advanced Child-Pugh B hepatocellular carcinoma: A multicentre retrospective study. Liver Int 2020;40:2544-2552.
19. Sung PS, Jang JW, Lee J, et al. Real-World Outcomes of Nivolumab in Patients With Unresectable Hepatocellular Carcinoma in an Endemic Area of Hepatitis B Virus Infection. Front Oncol 2020;10:1043.

20. Fessas P, Kaseb A, Wang Y, et al. Post-registration experience of nivolumab in advanced hepatocellular carcinoma: an international study. J Immunother Cancer 2020;8.
21. Chiu J, Tang YF, Yao TJ, et al. The use of single-agent sorafenib in the treatment of advanced hepatocellular carcinoma patients with underlying Child-Pugh B liver cirrhosis: a retrospective analysis of efficacy, safety, and survival benefits. Cancer 2012;118:5293-301.
22. Ogasawara S, Chiba T, Ooka Y, et al. Liver function assessment according to the Albumin-Bilirubin (ALBI) grade in sorafenib-treated patients with advanced hepatocellular carcinoma. Invest New Drugs 2015;33:1257-62.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (13:30-14:50)

ROOM 2

KLCA Symposium 3

Changing Landscape of Systemic Therapy in Advanced Hepatocellular Carcinoma

Chairs:

Soon Ho Um (Korea Univ.)

Joong-Won Park (National Cancer Center Korea)

Selecting First-Line Therapy for Advanced Hepatocellular Carcinoma: TKI vs. ICI

Kyung-Hun Lee

Seoul National University, Korea

Sorafenib, which is a multiple inhibitor of the vascular endothelial growth factor receptor (VEGFR) and other kinases, had been the first and the only approved systemic agent for hepatocellular carcinoma (HCC) for almost 10 years since 2007. Two multicenter randomized placebo-controlled phase III trials were conducted for patients with advanced HCC who had not received any prior systemic therapy in Europe and America (SHARP trial) and in the Asia-Pacific region.[1,2] The SHARP trial demonstrated a significantly longer median overall survival (OS) duration of 10.7 months in patients receiving sorafenib, compared to an OS of 7.9 months for patients who received placebos (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55–0.87; $P < 0.001$). Similarly, the Asia-Pacific trial also showed a significantly superior median OS of 6.5 months in patients receiving sorafenib, compared with 4.2 months in patients receiving placebos (HR, 0.57; 95% CI, 0.42–0.79; $P = 0.014$).

Lenvatinib is another multiple kinase inhibitor and was found to be noninferior to sorafenib in overall survival in patients with advanced HCC who had not received any prior systemic therapy.[3] OS for lenvatinib was non-inferior to sorafenib (13.6 months vs 12·3 months, respectively; HR 0·92, 95% CI 0·79–1·06), meeting criteria for non-inferiority. Lenvatinib also showed a greater objective response rate than did sorafenib (24.1% vs 9.2%, respectively). Side effects are different between the two drugs: hypertension, diarrhea, decreased appetite, and decreased weight for lenvatinib, and palmar-plantar erythrodysesthesia, diarrhea, hypertension, and decreased appetite for sorafenib.

Immunotherapy has demonstrated some single-agent efficacy in patients with hepatocellular cancer as the first-line treatment. In a phase I/II trial in patients with advanced HCC (CheckMate 040 trial), the response rate for nivolumab was 20% (including 3 complete responses [CRs]).[4] However, in the phase III CheckMate 459 trial, nivolumab did not improve OS compared to sorafenib.[5] Median OS was 16.4 months with nivolumab compared to 14.7 months with sorafenib ($P = 0.0752$). The response rate for nivolumab was 15% in the patient population. In patients with low (<1%) PD-L1 expression and high (≥1%), the response rate was 12% and 28%, respectively.

Beyond tumor angiogenesis, VEGF has multiple roles in modulating the tumoral immune environment. VEGF promotes the tumoral infiltration of inhibitory immune cells such as regulatory T cells and myeloid-derived suppressor cells. Additionally, VEGF suppresses dendritic cell maturation, decreases the T-cell immune response, and alters lymphocyte development and trafficking.[6] The combination of VEGF inhibition with immunotherapy is a rational approach in hepatocellular carcinoma and it was demonstrated in recent trials.

GO30140 was a phase 1b study of atezolizumab and bevacizumab and it included 2 cohorts for hepatocellular carcinoma (group A and F).[7] In group A, all patients received atezolizumab and bevacizumab and the response rate for the combination treatment was 36% (37/104 patients). In group F, patients were 1:1 randomized to receive the combination or atezolizumab alone and median progression-free survival (PFS) was longer for the patients who received the combination (5.6 months vs 3.4 months; HR 0.55; 80% CI 0.40-0.74; $P = 0.011$).

Finally, IMbrave150 trial was an open-label phase 3 trial of atezolizumab plus bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma who had received no prior systemic therapy.[8] OS was significantly improved in the atezolizumab plus bevacizumab group (stratified HR 0.58, 95% CI 0.42–0.79, $P<.001$). OS at 12 months was 67.2% vs 54.6%. Median PFS was 6.8 months vs 4.3 months (stratified HR 0.59, 95% CI 0.47–0.76, $P < .001$), with 6-month rates of 54.5% vs 37.2%. Objective response rates were 27.3% vs and 11.9% ($P < .001$), with a complete response in 18 vs 0 patients. The duration of response was at least 6 months in 87.6% vs 59.1%.

Atezolizumab plus bevacizumab is considered the current standard treatment in patients with advanced unresectable hepatocellular carcinoma meeting the study inclusion criteria. Future studies are warranted to determine predictive biomarkers and to get more data in patients with less well-preserved liver function. Also, the results of another combination of VEGFR and immunotherapy in LEAP-002 trial (phase 3 trial of pembrolizumab and lenvatinib combination in comparison with lenvatinib alone as first-line treatment) are awaited (NCT03713593).

References

1. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008.
2. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
3. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma. Lancet 391:1163-1173, 2018.
4. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040). Lancet 389:2492-2502, 2017.
5. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: a randomized, multi-center phase III study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. Ann Oncol. 2019;30(Suppl 5):v874–5.
6. Ohm JE, Carbone DP. VEGF as a mediator of tumor-associated immunodeficiency. Immunol Res 23:263-272, 2001.
7. Lee MS, Ryoo B, Hsu C, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. Lancet Oncol. 2020 Jun;21(6):808-820.
8. Finn RS, Qin S, Ikeda M, et al: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382:1894-1905, 2020.

How to Optimize Sequence of Systemic Treatment in Advanced Hepatocellular Carcinoma

Ann-Lii Cheng

National Taiwan University, Taiwan

Contemporary guidelines of systemic therapy for hepatocellular carcinoma largely belong to two schools. The first school, including of ASCO and ESMO, indicates a preference for the use of atezolizumab and bevacizumab (Atezo-Bev) as 1L therapy, and leaves sorafenib and lenvatinib for those who are unsuitable for Atezo-Bev. The second school, which consists of most of the other guidelines, depicts no preference of either sorafenib, lenvatinib, or Atezo-Bev for 1L therapy, and thus leave room for physicians to make decision based on their individual real-world medical environments.

Second-line treatment after Atezo-Bev or lenvatinib is becoming a clinically urgent issue. Robust evidence will unlikely to emerge as clinical trials are facing practical difficulties. For example, a placebo control arm may not be ethically acceptable, and a comparison among contemporary drugs apparently lack motivation. At this point, a rational approach based on individualized treatment goals, as well as real world evidence is advised.

Other than sequencing to other drugs, it is important to point out that patients with isolated or oligo escapes from a prolonged remission may benefit from resection or other locoregional therapy. This approach may lead to a cure in some selective patients.

Hepatocellular Carcinoma Patients on Systemic Therapy: Prediction of Prognosis

Beom Kyung Kim

Yonsei University, Korea

Sorafenib is an oral kinase inhibitor that enhances survival in patients affected by advanced hepatocellular carcinoma (HCC). According to the results of two randomized controlled trials (RCTs), this anti-cancer agent had been accepted as a gold standard in the first line treatment of advanced HCC. Recently, lenvatinib showed similar results in terms of survival in a non-inferiority RCT considering the same subset of patients, but without macroscopic vascular invasion. The most recent RCT assessing the efficacy of atelovizumab plus bevacizumab showed the significantly better overall survival compared to sorafenib arm. As 2nd-line regimen of advanced HCC, currently, regorafenib, cabozantinib, and ramucirumab have been accepted on the basis upon the data from RCTs. However, the enrolled subset of patients was primarily limited to those who experienced treatment failure to sorafenib. So far, except well-known prognostic factors universally applicable to any kinds of cancer patients, that is, those associated with tumor burden in terms of quantitative and biological viewpoint, predictive and prognostic markers in HCC patients treated with systemic chemotherapy have been scarce. Expectedly, since sorafenib had been only one approved systemic anti-cancer agent against advanced HCC for approximately 10 years until lenvatinib was available in 2017, such kinds of studies primarily had focused on those treated with sorafenib and there have been only a few literatures where other prognostic factors including biomarkers among those treated with other 1st-line or 2nd-line treatment were analyzed. Identification of such factors could help clinicians in the daily management of these patients, mostly in light of the new therapeutic options available.

Assessment of Tumor Response in Patients Receiving Systemic Therapy: RECIST 1.1, Modified RECIST, or Other Options

Min-Hee Ryu

University of Ulsan, Korea

In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) were developed for response evaluation of solid tumors.[1] RECIST criteria define a limited number of measurable target lesions and other non-target lesions to be evaluated qualitatively. These criteria are based on the measurement of the longest diameter of a patient's tumor lesions using CT and MRI. It is crucial to use the same imaging methods throughout the whole patient follow-up. The overall response is defined with a combination of the responses of target lesions and non-target lesions and presence of new lesions. The objective response is defined in comparison with the pretreatment examination at baseline, while progression is defined in comparison with the nadir.

RECIST criteria were revised in 2009, based on an analysis of the literature and simulations from a large database.[2] The new version of RECIST is called version 1.1. The main changes were to reduce the number of target lesions and to measure lymph nodes by their short axis. RECIST 1.1 has become the most widely used response criteria in most solid tumors with exception of malignant lymphoma.

Although RECIST 1.1 has provided a standardized framework for assessing the efficacy of treatments in solid tumors, RECIST 1.1 is not adequate for the evaluation of some organs including bone and liver. Moreover, the thresholds for response (-30%) and progression (20%) were chosen arbitrarily. There was no validation demonstrating that they reflect patient ultimate outcomes such as overall survival.

Therefore, other diverse response criteria have been developed which are based on a different threshold of response or tumor viability.

Modified RECIST (mRECIST) criteria were developed for response evaluation of hepatocellular carcinoma in 2010.[3] mRECIST only takes into account the viable portion showing enhancement in arterial phase of contrast enhanced CT/MRI, whereas RECIST 1.1 focuses mainly on quantifying the tumor size irrespective of viability of the tumor. mRECIST may address antitumor activity more properly, compared with RECIST 1.1 which measures only tumor size irrespective of tumor viability.

Recently, a consensus guideline, iRECIST (a modified RECIST 1.1 for immune-based therapeutics), was developed by the RECIST working group in cancer immunotherapy trials.[4] This guideline provides a standard approach for response evaluation in trials in which an immunotherapy is used.

References

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United

States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205-216
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1·1). Eur J Cancer. 2009;45:228-247
3. Lencioni R and Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30: 52-60
4. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143-52

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (15:00-16:20)

ROOM 2

KLTS-KLCA Joint Symposium

Updates on Liver Transplantation for Hepatocellular Carcinoma

Chairs:

Kyung-Suk Suh (Seoul National Univ.)

Jong Young Choi (The Catholic Univ. of Korea)

Expanding Criteria for Liver Transplantation: Sero-Positive Donors

Hae Won Lee

Seoul National University, Korea

Liver transplantation (LT) might be the only therapeutic option in various clinical conditions including end-stage liver disease, metabolic disease, and unresectable hepatocellular carcinoma (HCC). However, the need for liver grafts has been consistently increasing and thus the gap between organ demand and supply has been widening despite active efforts to expand donor pool.[1] According to the UNOS data, the number of recipients on the waiting list is more than twice the number of performed transplants in 2014.[1] Korean situation is worse. A total of 1,579 LTs including 391 living donor LTs have been performed in 2019, while the number of patients still awaiting deceased donor allocation were 5,804 in the same year. This organ scarcity of available organs is eventually forcing the use of grafts from the expanded criteria donors, which might include sero-positive donors as well as old-aged donors or donors with severe fatty liver.

After the introduction of effective combined prophylaxis with antiviral agents and hepatitis B Immunoglobulin, an Italian group first transplanted HBsAg-positive liver grafts into HBV-infected patients. The outcome was not good. Two recipients with HDV coinfection developed progressive liver disease after LT. Only one HBV mono-infected recipient experienced an uneventful post-LT course.[2] However, subsequent studies showed successful outcomes in situation without HDV infection.[3-5] In almost all of HBV recipients who received HBsAg-positive grafts, post-transplant clinical condition were stable although serum HBsAg remained positive persistently in most cases. Therefore, the use of HBsAg-positive liver grafts in HBV-infected patients would be safe and feasible under the effective HBV prophylaxis. To date, HBsAg-positive liver grafts have been preferentially given to HBsAg-positive recipients. Korean allocation system also operates in the same way. Data regarding the use of HBsAg-positive grafts for HBsAg-negative recipients is lacking. However, there are several reports showing the results of this specific setting. According to one study analyzing UNOS database, the post-LT outcomes of 78 recipients receiving HBsAg-positive grafts were not inferior to those of the matched control group receiving HBsAg-negative grafts. Interestingly, in this study, in term of etiology leading to LT, HBV infection represented only 19% of the group transplanted with an HBsAg-positive graft.[6] Some suggest that patients with a previously HBV immune control (HBcAb-positive or both HBcAb- and HBsAb-positive) are likely the best candidates to receive an HBsAg-positive liver graft because a past HBV infection can re-evoke their effective specific immune response, leading to spontaneous HBsAb production and HBsAg loss.[1] However, more experiences are required to confirm such a possibility.

In fact, the major concern of Western countries is the use of HCV-positive liver grafts. Among all deceased donors in US, 2017, HCV-seropositivity was 7.3% while HCV RNA-positivity was 4.9%.[7] Before the advent of direct-acting antivirals (DAAs), grafts from HCV-positive donors were reserved for patients with

active HCV infection. It was reasonable because post-transplant HCV reinfection developed universally in such patients regardless of the donor's HCV status. Early data suggested that this strategy was not associated with impaired outcomes. In term of graft and patient survivals, there were no significant differences observed between the HCV-positive graft group and the HCV-negative graft group.[8-10] Hence, it has been standard of care to offer HCV-positive grafts to HCV-positive recipients for the last 15-20 years.[11] The introduction of DAAs changed many things including physician's attitude. Because post-transplant HCV treatment got easier, the discard rate of HCV-positive grafts has markedly declined from 28% in the pre-DAA era and around to 11% in the DAA era. Mirroring this, the proportion of HCV-positive recipients who were transplanted with HCV-positive grafts has also increased from 6.2% in the pre-DAA era to 16.9% in the DAA era.[12] Furthermore, DAA also enabled the transplantation of HCV-positive grafts to HCV-negative patients. A recent study based on US database showed that the number of non-HCV patients receiving an HCV-positive graft increased from 7 in 2008 to 107 in 2017, or from 55 in the pre-DAA era to 202 in the DAA era. The graft survival rate of those was equivalent to that of non-HCV patients receiving an HCV-negative graft in the DAA ear. In addition, the result was similar also in cases receiving HCV-viremic grafts.[13] Thus, even non-HCV patients might have survival benefit from an HCV-positive graft in the DAA era, especially in the situation when LT is urgent or when a risk of waitlist dropout is high.

In conclusion, the high efficacy and safety of anti-HBV or HCV antiviral therapy has recently expanded the opportunity to utilize organ grafts from HBV/HCV infected donors. The use of HBsAg-positive and HCV-positive grafts in HBsAg-positive and HCV-positive recipients is evidently feasible if graft quality is good. In the case of HCV, the almost 100% cure rates of DAA therapy means that HCV-positive grafts can be considered for patients without active HCV infection. On the other hand, the use of HBsAg-positive grafts in HBV-negative patients might not be recommended because current anti-HBV antiviral therapy can only suppress and not cure the infection. The safety of the use of HBsAg-positive grafts for non-HBV patients should be evaluated by further studies.

References

1. Loggi E, Conti F, Cucchetti A, Ercolani G, Pinna AD, Andreone P. Liver grafts from hepatitis B surface antigen-positive donors: A review of the literature. World J Gastroenterol. 2016;22(35):8010-6.
2. Franchello A, Ghisetti V, Marzano A, Romagnoli R, Salizzoni M. Transplantation of hepatitis B surface antigen-positive livers into hepatitis B virus-positive recipients and the role of hepatitis delta coinfection. Liver Transpl. 2005;11(8):922-8.
3. Hwang S, Lee SG, Park KM, Kim KH, Ahn CS, Oh HB, et al. Five-year follow-up of a hepatitis B virus-positive recipient of hepatitis B surface antigen-positive living donor liver graft. Liver Transpl. 2006;12(6):993-7.
4. Jiang L, Yan L, Li B, Wen T, Zhao J, Jiang L, et al. Successful use of hepatitis B surface antigen-positive liver grafts in recipients with hepatitis B virus-related liver diseases. Liver Transpl. 2011;17(10):1236-8.
5. Choi Y, Choi JY, Yi NJ, Lee K, Mori S, Hong G, et al. Liver transplantation for HBsAg-positive recipients using grafts from HBsAg-positive deceased donors. Transpl Int. 2013;26(12):1173-83.
6. Li Z, Hu Z, Xiang J, Zhou J, Yan S, Wu J, et al. Use of hepatitis B surface antigen-positive grafts in liver transplantation: a matched analysis of the US National database. Liver Transpl. 2014;20(1):35-45.
7. Levitsky J, Formica RN, Bloom RD, Charlton M, Curry M, Friedewald J, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. Am J Transplant. 2017;17(11):2790-802.

8. Vargas HE, Laskus T, Wang LF, Lee R, Radkowski M, Dodson F, et al. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. Gastroenterology. 1999;117(1):149-53.
9. Marroquin CE, Marino G, Kuo PC, Plotkin JS, Rustgi VK, Lu AD, et al. Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. Liver Transpl. 2001;7(9):762-8.
10. Ballarin R, Cucchetti A, Spaggiari M, Montalti R, Di Benedetto F, Nadalin S, et al. Long-term follow-up and outcome of liver transplantation from anti-hepatitis C virus-positive donors: a European multicentric case-control study. Transplantation. 2011;91(11):1265-72.
11. Crismale JF, Ahmad J. Expanding the donor pool: Hepatitis C, hepatitis B and human immunodeficiency virus-positive donors in liver transplantation. World J Gastroenterol. 2019;25(47):6799-812.
12. Bowring MG, Kucirka LM, Massie AB, Luo X, Cameron A, Sulkowski M, et al. Changes in Utilization and Discard of Hepatitis C-Infected Donor Livers in the Recent Era. Am J Transplant. 2017;17(2):519-27.
13. Cotter TG, Paul S, Sandikci B, Couri T, Bodzin AS, Little EC, et al. Increasing Utilization and Excellent Initial Outcomes Following Liver Transplant of Hepatitis C Virus (HCV)-Viremic Donors Into HCV-Negative Recipients: Outcomes Following Liver Transplant of HCV-Viremic Donors. Hepatology. 2019;69(6):2381-95.

Hepatocellular Carcinoma Recurrence after Liver Transplantation: Risk Factors

Wonseok Kang

Sungkyunkwan University, Korea

Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancer and is the third leading cause of cancer-related deaths worldwide. Liver transplantation (LT) is considered the best treatment option for patients with HCC and end-stage liver diseases based on Milan criteria. The introduction of Milan criteria – where LT is limited to HCC patients with a single tumor of 5 cm diameter or less or up to 3 tumors, none larger than 3 cm – resulted in excellent post-transplant recurrence-free survival for patients meeting the specified size criteria. In attempts to meet the growing demand for LT and to extend the life-saving benefit of LT, expanded criteria for the eligibility of LT among patients with HCC have been proposed, allowing for transplantation of a larger size and number of tumors. Despite careful selection of patients for LT, HCC recurrence after LT remains a significant cause of graft loss and mortality. HCC recurrence after liver transplantation is considered multifactorial. The predictors for HCC recurrence have been extensively studied, including pathological tumor stage, vascular invasion, serum alpha-fetoprotein levels, and histological differentiation, as well as the type and duration of immunosuppressive therapy. Several molecular markers have been proposed as predictors of HCC recurrence, yet they are still considered experimental. This talk will discuss the available data on the risk factors of HCC recurrence after LT.

Management of Hepatocellular Carcinoma Recurrence after Liver Transplantation: Surgery and Locoregional Therapy

Dong-Hwan Jung

Universtity of Ulsan, Korea

Introduction

Improvements in the medical, surgical, and pharmacological management of liver transplantation (LT) recipients have led to a better long-term outcome and expansion of the indications for this procedure. When the Milan criteria are fulfilled, the long-term survival after LT for HCC is similar to that following transplantation in patients without HCC. Despite the effect of HCC recurrence in LT recipients, there is no established guideline addressing its management. An understanding of the clinical experience with HCC recurrence in the available published literature is critical to developing a rational strategy for care of these patients.

Prevention of HCC recurrence after LT for HCC

Calcineurin inhibitors (CNI) including cyclosporine and tacrolimus, the most-common immunosuppressants used, have been reported to increase posttransplant risk of recurrence of HCC in a dose-dependent manner. A novel group of immunosuppressants, mammalian target of rapamycin (mTOR) inhibitors including sirolimus and everolimus, have antineoplastic effects, and can maintain antiproliferative effects at drug levels achieved with current immunosuppression dosages. In a recent meta-analysis, authors found a clear benefit on 1-, 3-, and 5-year patient survival for sirolimus-based immunosuppression versus sirolimus-free regimens. Additionally, sirolimus-based regimens were associated with a significant decrease in HCC recurrence rates with no significant decrease in the frequency of posttransplant complications.

Treatment of recurrent HCC after LT

1. Resection

Most patients present with disseminated disease and are not candidates for surgical treatment. A few groups have reported good results in a small number of patients suggesting increased survival for patients undergoing resection. Survival in patients treated with surgical resection was significantly better than those who were not. Multivariate analyses identified late after LT tumor relapse and surgical therapy as independent predictors of long-term survival after tumor recurrence. While aggressive resection of recurrent disease is not possible in many patients, survival advantage may be achieved in only patients with localized disease.

2. Locoregional Therapies

Selected patients with unresectable HCC recurrence may undergo locoregional therapy with potential improvement in survival. Among the loco-regional therapies for HCC recurrence, TACE was the most frequently reported. Overall, TACE was well tolerated and not associated with major adverse events. Anecdotal reports described radioembolization, RFA, and CT guided brachytherapy as effective, well tolerated and safe loco-regional treatment approaches. It is likely that any survival benefit locoregional therapy may confer to patients with HCC recurrence after transplant is due to control of the recognized tumor rather than preventing new recurrences.

Conclusions

Many challenges persist in treating HCC recurrence after LT. Much of the research performed in this field is composed of small retrospective studies, sometimes with no control group as the patient sample size is relatively small. Resection is associated with improved survival and should therefore be considered when feasible. Among the loco-regional therapies for HCC recurrence, TACE was the most frequently reported. Anecdotal reports described SIRT, RFA, and CT guided brachytherapy as effective, well tolerated and safe loco-regional treatment approaches. Improving study quality with multicenter prospective trials, while difficult, will lead to a better understanding of appropriate treatment in patients with HCC recurrence after LT.

Management of Hepatocellular Carcinoma Recurrence after Liver Transplantation: Systemic Therapy

Bo Hyun Kim

National Cancer Center, Korea

Liver transplantation (LT) is a highly effective cure for early-stage hepatocellular carcinoma (HCC). Even for HCC beyond the Milan criteria or the University of California San Francisco criteria, LT can provide an excellent treatment option in selected patients. A higher pre-transplantation tumor burden confers a higher risk of HCC recurrence and thus an increased probability of receiving systemic chemotherapy after LT.

Nowadays, several systemic agents, molecular targeted agents or immune checkpoint inhibitors, are used for advanced HCC. First-line systemic agents include atezolizumab plus bevacizumab, sorafenib, and lenvatinib while second-line agents are regorafenib, cabozantinib, ramucirumab, and nivolumab with or without ipilimumab. Sorafenib has been the only first-line systemic agents for a long time; however, the use of sorafenib in post-LT HCC recurrence is limited to small studies.[1-3] The median overall survival after sorafenib treatment ranges from 14.2 to 21.3 months.[1-3] There is scarce evidence of increased toxicity from sorafenib in patients after LT.

Treatment with immune checkpoint inhibitors in liver transplant recipients is rarely reported because of the increased risk of allograft rejection and graft lost. A recent systematic review of 83 published cases (melanoma 46 cases; hepatocellular carcinoma 12 cases) receiving immune checkpoint inhibitors after solid organ transplantation showed that allograft rejection occurred in 40% of patients (kidney, 43%; liver, 38%; heart, 17%) after a mean time of 5.6 weeks. Rejection resulted in end-stage organ failure in 75% of 8 cases with HCC.[4] Of 48 patients with a reported cause of death, 79% and 19% died from cancer and organ rejection, respectively.

In conclusion, molecular targeted agents can be used in patients with recurrent HCC after liver transplantation; however, available data do not warrant the use of ICIs in this setting.

References

1. Gomez-Martin C, Bustamante J, Castroagudin JF, Salcedo M, Garralda E, Testillano M, et al. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. Liver Transpl 2012;18:45-52.
2. Sposito C, Mariani L, Germini A, Flores Reyes M, Bongini M, Grossi G, et al. Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: a case-control study. J Hepatol 2013;59:59-66.
3. Kang SH, Cho H, Cho EJ, Lee JH, Yu SJ, Kim YJ, et al. Efficacy of Sorafenib for the Treatment of Post-Transplant Hepatocellular Carcinoma Recurrence. J Korean Med Sci 2018;33:e283.
4. d'Izarny-Gargas T, Durrbach A, Zaidan M. Efficacy and tolerance of immune checkpoint inhibitors in transplant patients with cancer: A systematic review. Am J Transplant 2020;20:2457-2465.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (08:20-09:40)

ROOM 3

KLTS Symposium 1

How to Overcome Hurdles of ABO-Incompatible Living Donor Liver Transplantation

Chairs:

Jae-Won Joh (Sungkyunkwan Univ.)

Young Kyoung You (The Catholic Univ. of Korea)

ABO-Incompatible Living Donor Liver Transplantation and Biliary Complications

Gi-Won Song

Universtiy of Ulsan, Korea

ABO-Incompatible Living Donor Liver Transplantation in High-Risk Patients: Hepatocellular Carcinoma and Infection

Dong-Jin Joo

Yonsei University, Korea

ABO incompatible living donor liver transplantation has become more popularized in many Asian centers. Recently, comparable outcomes of ABOi LDLT to ABO compatible LDLT were reported from many centers. To do ABOi LDLT, we should deplete B cells and do over immunosuppression before transplantation. This desensitization protocol led us to successful ABOi LDLT these days, which has been more simplified without splenectomy and/or local infusion therapy. However, we do not have enough evidences to allow extension of indication to hepatocellular carcinoma for ABOi LDLT. A couple of reports about oncologic outcomes of those patients who underwent ABOi LDLT showed good results comparable to ABOc LDLT. In this session, we are looking at the recent outcomes and further issues to do ABOi LDLT for HCC patients.

Another issue of ABOi LDLT should be the infectious outcomes. There are several reports to show some infectious complication after ABOi LDLT. And long-term effect of Rituximab could be a potential risk of infectious disease. We are summarizing the infectious outcomes of ABOi LDLT as well in this session.

References

1. Honda M, Sugawara Y, Kadohisa M, Shimata K, Sakisaka M, Yoshii D, Uto K, Hayashida S, Ohya Y, Yamamoto H, Yamamoto H, Inomata Y, Hibi T. Long-term Outcomes of ABO-incompatible Pediatric Living Donor Liver Transplantation. Transplantation 2018; 102: 1702-9.
2. Yamada Y, Hoshino K, Fuchimoto Y, Matsubara K, Hibi T, Yagi H, Abe Y, Shinoda M, Kitago M, Obara H, Yagi T, Okajima H, Kaido T, Uemoto S, Suzuki T, Kubota K, Yoshizumi T, Maehara Y, Inomata Y, Kitagawa Y, Egawa H, Kuroda T. Rituximab Induction to Prevent the Recurrence of PSC After Liver Transplantation-The Lessons Learned From ABO-Incompatible Living Donor Liver Transplantation. Transplant Direct 2018; 4: e342.
3. Yoon YI, Song GW, Lee SG, Hwang S, Kim KH, Kim SH, Kang WH, Cho HD, Jwa EK, Kwon JH, Tak EY, Kirchner VA. Outcome of ABO-incompatible adult living-donor liver transplantation for patients with hepatocellular carcinoma. J Hepatol 2018; 68: 1153-62.
4. Kim SH, Lee EC, Na BG, Park SJ. Impact of ABO-incompatibility on hepatocellular carcinoma recurrence after living donor liver transplantation. Eur J Surg Oncol 2019; 45: 180-6.
5. Hsu SC, Thorat A, Jeng LB, Li PC, Chen TH, Yang HR, Poon KS. ABO-Incompatible Living Donor Liver Transplantation with Reduced Rituximab Dose: A Retrospective Analysis of 65 Patients - Can We Fast-Track Liver Transplant Surgery and Improve Long-Term Survival? Ann Transplant 2020; 25: e923502.
6. Oh J, Kim JM. Immunologic strategies and outcomes in ABO-incompatible living donor liver transplantation. Clin Mol Hepatol 2020; 26: 1-6.
7. Kim JM, Kim DG, Kim J, Lee K, Lee KW, Ryu JH, Kim BW, Choi DL, You YK, Kim DS, Nah YW, Kang KJ, Cho JY, Hong G, Yu HC, Moon JI, Choi D, Hwang S, Kim MS. Outcomes after Liver Transplantation in Korea: Incidence and Risk Factors from Korean Transplantation Registry. Clin Mol Hepatol 2021.

An Optimal Protocol to Overcome Weak Points of ABO-Incompatible Living Donor Liver Transplantation

Nam-Joon Yi

Seoul National University, Korea

What are weak points in ABO incompatible living donor liver transplantation (ABOi LDLT) compared to ABO compatible or identical LDLT?

Apparently, to prepare ABOi LDLT, a recipient should measure isoagglutinin titer and take rituximab. To reduce isoagglutinin titer, the recipient sometimes undergoes plasmapheresis, splenectomy, and immunoglobulin therapy before and/or after transplantation. Those things are more burden to the recipient of ABOi LDLT and its family in terms of medical and economical aspects.

As consequences of those procedures to reduce graft failure rates in ABOi LDLT, these recipients have higher rates of infection and a long-term risk of metabolic syndrome related to over immunosuppression.

For this reason, we should measure the risk-related factors of graft failure or biliary complications. According to weighing measured risk/benefit, tailored desensitization and immunosuppression should be introduced to the recipient of ABOi LDLT.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (11:10-12:30)

ROOM 3

KLTS Special Lecture

Chairs:

Myoung Soo Kim (Yonsei Univ.)

Shin Hwang (Univ. of Ulsan)

KLTS Special Lecture

Post-Transplant Lymphoproliferative Disorder after Liver Transplantation

Olivia M. Martinez

Stanford University, USA

Post-transplant lymphoproliferative disorder (PTLD) encompasses a spectrum of abnormal lymphoproliferations that is often associated with Epstein Barr virus infection (EBV). EBV+ PTLD is responsible for significant morbidity and mortality in the transplant population and can affect recipients of bone marrow and solid organ grafts including liver recipients. In its most serious form PTLD can manifest as potentially fatal EBV+ B cell lymphomas. Early onset EBV+ PTLD can occur in the first one-two years post-transplant with later onset occurring in year 5-10 post-transplant and may reflect differences in the EBV status of the lesion, with EBV+ PTLD seen more commonly, but not exclusively, in the early period post-transplant. EBV+ PTLD in children tends to occur earlier post-transplant than in adults.

EBV is a DNA double stranded gammaherpes virus that can infect B cells, epithelial cells, T cells and NK cells. The viral life cycle is complex and includes a lytic and latent phase. Despite substantial efforts over the years there is currently no effective EBV vaccine. In immunocompetent individuals the expansion of EBV-infected B cells is controlled by viral-specific T cell and natural killer (NK) cells that can target EBV-infected B cells. The NKG2A+ NK cell population appears to be particularly important in controlling EBV infection. Ultimately the virus persists in a subset of recirculating infected memory B cells for the lifetime of the host. Periodic reactivation of the virus may occur but this is typically controlled by the immune response. Inhibition of viral-specific T cells by immunosuppression required to prevent allograft rejection is thought to be a major contributor to development of EBV+ PTLD and typically involve virally-driven transformation of recipient B cells. EBV also employs a variety of immune evasion strategies to avoid recognition and elimination by the host immune response. In liver recipients the incidence of EBV+ PTLD is typically 1-4% but can be higher in children who have not been exposed to the virus previously and for which primary viral infection occurs in the setting of immunosuppression. The PTLD lesion site can be extranodal and often involves the gastrointestinal tract. The prognosis for monomorphic EBV+ PTLD is poorer than for early lesions or polymorphic PTLD.

Currently there are no validated approaches to assess the risk or predict the development of EBV+ PTLD. Most commonly EBV PCR is utilized to measure the level of viral DNA in the circulation in order to monitor viral load levels. Chronic EBV DNAemia is often observed in pediatric liver transplant recipients, however, elevations or even chronic viral DNAemia does not necessarily portend development of EBV+ PTLD. Assessment of EBV-specific T cells, either by the use of peptide-multimers or by functional assays, so far has not been established to be useful in monitoring for the risk of EBV+ PTLD. EBV genomic diversity within the EBV oncogene, latent membrane protein 1, has also been analyzed as an indicator for risk of development

of EBV+ PTLD.

Reduction of immunosuppression early on may allow the host immune system to recover and mediate regression of PTLD. Other treatments include the use of Rituximab in CD20+ lymphomas, chemotherapy or surgery with five-year survival generally over 50% in reports from various centers. Antivirals are not typically effective once PTLD is established since the virus is in a latent phase in EBV+ B cell lymphomas and the anti-virals are only effective again the lytic phase of infection. More recently, cellular immunotherapy using autologous or allogeneic cytotoxic T cell infusions have shown some promise in treatment of EBV+ PTLD and limited case reports are beginning to emerge describing the use of CAR T cells as a therapeutic approach for EBV+ PTLD.

This lecture will discuss our current understanding of EBV+ PTLD pathogenesis, characteristics, monitoring strategies, treatments and outcomes in liver transplantation.

Outcome of Liver Retransplantation Using Living Donor Grafts

Kaori Kuramitsu

Kobe University, Japan

Background: Liver transplantation is the most suitable treatment option available for end-stage liver disease. However, some patients require re-transplantation, despite medical advances that have led to improved survival. We aimed to compile a definitive, nationwide resource of liver re-transplantation data in Japan, seeking to identify the predictors of patient survival post-transplantation.

Methods: Questionnaires were sent to 32 institutions that had conducted 281 retransplantation before 2015.

Results: Among the 265 patients included in this study (142 pediatric cases), the average age at primary transplantation was 23 years, and re-transplantation was performed after an average of 1,468 days. The main indication for re-transplantation was graft rejection (95 patients). Living donor liver transplantation accounted for 94.7% of primary transplantations and 73.2% of re-transplantation. Patient survival at 1, 3, or 5 years did not differ by type of transplantation, but was better for pediatric (70.8%, 68.3%, 60.1%, respectively) than for adult (57.2%, 50.4%, 45.2%, respectively) recipients (P=0.0003). Small-for-size syndrome, re-transplantation within 365 days, and inpatient status at re-transplantation were significant predictors of poor survival in pediatric cases. Re-transplantation within 365 days and conditions warranting re-transplantation were significant predictors of poor survival in adult patients.

Conclusions: In Japan, where more than 70% of re-transplantations are performed using living donors, the indications and timing are different from those in previous reports from other countries, while maintaining comparable survival rates. Considering technical challenges, graft failure within 365 days should be thoroughly restricted to justify the use of living donor.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (13:30-14:50)

ROOM 3

KAHBPS-KLTS Joint Symposium

Strategies for Posthepatectomy Liver Failure: From Prevention to Treatment

Chairs:

In Seok Choi (Konyang Univ.)

Kwang-Woong Lee (Seoul National Univ.)

Preoperative Assessment of Liver Function in Patients Requiring Hepatectomy

Young Seok Han

Kyungpook National University, Koewa

Liver resection is the mainstay of treatment of both primary and many secondary liver tumors. However, post- hepatectomy liver failure (PHLF) is a dreaded complication following liver resection, resulting in significant morbidity, mortality and resource utilization.

Factors associated with PHLF are old age, patients receiving pre-operative chemotherapy, steatosis, major hepatectomy (more than 3 segments resected), and future liver remnant volume and future liver remnant function. Scoring systems such as the Child-Turcott-Pugh (CTP) score and the model for end-stage liver disease (MELD) have also been investigated to aid in patient selection.

Thrombocytopeina was identified as a significant independent predictor for PHLF. And, a preoperative serum bilirubin level >1.9 mg/dl was also a significant independent risk factor for PHLF. Portal hypertension (PHT) can be also suspected in cases of splenomegaly, esophageal varies or hypersplenism, but the reliable quantification of the portal gradient requires a central venous catheterization. Alternatively, hepatic venous pressure gradient (HVPG) measurement showed a strong correlation with postoperative liver dysfunction and 90-day mortality but is not routinely performed due to its invasiveness. More advanced techniques - like the use of novel biomarkers such as Mac-2 binding protein glycosylation isomer (M2BPGi) - were evalu- ated to predict PHLF in the preoperative setting but still require further validation. Within the last years, the combined information of future liver remnant volume and actual liver function yielded additional diagnostic and prognostic benefit in the prediction of hepatectomy-related morbidity and mortality even in patients with compromised liver parenchyma. In this context, liver function analysis by means of indocyanine green plasma disappearance rate (ICG-PDR), maximum liver function capacity (LiMAx) test and ^{99m}Tc-mebrofinin hepatobiliary have been applied widely in the preoperative setting. However, not all liver function tests have the prognostic potential to predict postoperative morbidity following liver resection.

With the development of new technologies, imaging methods including elastography, diffusion-weighted magnetic resonance imaging (MRI), and Gd-EOB-DTPA—enhanced MRI play a more significant role in the pre-operative prediction and assessment of PHLF.

Liver failure after hepatectomy remains the most feared postoperative complication. Many risk factors are already known, related to patient's comorbidities, underlying liver disease, received treatments and type of resection. Preoperative assessment of functional liver reserve must be a priority for the surgeon.

Prevention of Post Hepatectomy Liver Failure (PHLF): Where Are We? (PVE, ALPPS, HVE, Ischemic Preconditioning)

Albert Chan

The University of Hong Kong, Hong Kong

Early Detection of PHLF and Non-Surgical Management for PHLF

Dong-Sik Kim

Korea University, Korea

According to the definition of PHLF by International Study Group of Liver Surgery (ISGLS) as well as '50-50' criteria, the diagnosis of PHLF can only be made on or after postoperative day 5. Considering the pathophysiology underlying PHLF relating shear stress on hepatic sinusoidal endothelium caused by rapidly increased portal pressure and flow, it looks obvious that the disease process and insults to the remnant liver is initiated during or immediately after the liver resection and early detection of PHLF can be a critical factor enabling early treatment for possibly better outcomes. At the same time, traditional treatment for PHLF was mainly supportive treatment without specific treatment target. Development of effective non-surgical treatment for PHLF is a critical unmet need in the field of hepatobiliary surgery.

In this session, although it is not conclusive yet, potential candidates of biomarkers for early diagnosis of PHLF will be discussed. In addition, current status and outcomes of candidates of non-surgical treatment modalities for PHLF will be discussed as well as traditional conservative treatments available.

Timing and Results of Liver Transplantation for PHLF

Pål-Dag Line

University of Oslo, Norway

Post hepatectomy liver is associated with high morbidity rates and the mortality risk in severe post hepatectomy liver failure is may be as high as 60-80%.[1,2] The risk profile associated with severe PHLF is similar to that seen in transplant candidates with high MELD scores (>30), and that raises the question whether liver transplantation can be utilized as a "bail-out" strategy for selected patients with PHLF.

Unfortunately, there is no evidence-based criteria to select candidates nor guide the optimal timing of transplantation, and the current knowledge is essentially based on small retrospective cohort studies and case reports. Nevertheless, there are clear similarities between acute liver failure from other causes and PHLF.

A fundamental problem is that liver resections are mainly performed for primary or secondary malignant tumors, and many of these patients will usually not be candidates for liver transplantation. It is therefore important to have exact knowledge on tumor stage, the histologic examination of the resected specimen and any significant preoperative comorbidity to make sound assessments whether transplantation is justifiable. During the later years, there has been an increased focus on transplant oncology, and more patients with primary and secondary liver tumors are considered as possible transplant candidates, although this is still an area of controversy.[3-5]

The cause of PHLF is most often related to insufficient functional liver remnant volume, but intraoperative events such as massive bleeding, prolonged ischemia, sepsis and iatrogenic injuries to vasculature or main bile ducts may be determining factors, even in more limited resections, particularly in patients with underlying liver disease. The post-transplant prognosis is determined both by the the severity of PHLF and the disease that indicated liver resection. Thus, there may be a clear difference between PHLF after extensive resection surgery for high hepatic tumor load and smaller resections for limited disease when the liver failure is attributable to iatrogenic injuries or pre-existing liver cirrhosis.

The current literature mainly consists of case reports and small retrospective observational studies. In a series from UCLA, severe PHLF was observed in 9 patients during a 14-year period (2% of total cases). Seven of the nine patients underwent transplantation, whereas the remainder two patients were deemed unfit and had a mean survival of 1.4 months. The 1 and 5-year survival in transplanted patients was 88% and 40% respectively.[6]

In our own series of 1510 transplantation at Oslo University Hospital, 13 were rescue transplants.[7] Seven patients were transplanted for PHLF, the remainder six developed liver failure due to trauma, iatrogenic injuries or surgical complications. The PHLF patients had a median survival of 45 months, three patients died at 9, 45 and 78 months respectively due to recurrence of colorectal cancer metastases. The interval from

primary procedure to transplant was median 17 days. Timing of liver transplantation in this setting is crucial. Most patients with reversible PHLF will display signs of improved condition after about one week, and with prolonged time the incidence of multi-organ failure and infection is high.[8] It is therefore advisable to list the patients before severe complications ensue that can lead to adverse outcomes. The results following rescue transplantation for PHLF is highly dependent on patient selection. Patients with HCC that are within accepted transplant criteria should as a rule be offered transplant if age or comorbidity does not contraindicate transplant. For patients with primary or secondary liver tumors where there is published evidence for the efficacy of liver transplantation (like colorectal liver metastases or liver metastases from NET tumors) transplantation may be considered as long as the patients satisfy main recommended selection criteria published in the literature. For pediatric patients, there are few data, but a more liberal approach is probably justifiable.[9]

References

1. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F ois. The "50-50 Criteria" on Postoperative Day 5. Ann Surg [Internet]. 2005 Dec;242(6):824–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1409891/
2. Shoup M, Gonen M, D'Angelica M, Farnagin WR, DeMatteo RP, Schwartz LH, Tuorto S, Blumgart LH, Fong Y. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg. 2003;7(3):325–30.
3. Hibi T, Itano O, Shinoda M, Kitagawa Y. Liver transplantation for hepatobiliary malignancies: a new era of "Transplant Oncology" has begun. Surg Today. 2016 Apr 29;47(4):1–13.
4. Hibi T, Rela M, Eason J, Line PD, Fung J, Sakamoto S, Selzner N, Man NK, Ghobrial RM, Sapisochin G. Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020;1.
5. Sapisochin G, Hibi T, Toso C, Man K, Berenguer M, Heimbach J, Greten TF, Pugh TJ, Dawson LA, Mazzaferro V. Transplant Oncology in Primary and Metastatic Liver Tumor: Principles, Evidence and Opportunities. Ann Surg. 2020;Publish Ahead of Print.
6. Otsuka Y, Duffy JP, Saab S, Farmer DG, Ghobrial RM, Hiatt JR, Busuttil RW. Postresection hepatic failure: Successful treatment with liver transplantation. Liver Transplant. 2007;13(5):672–9.
7. Thorsen T, Solheim JM, Labori KJ, Line P-D, Aandahl EM. Liver transplantation as a lifesaving procedure for posthepatectomy liver failure and iatrogenic liver injuries. Langenbeck's Archives Surg. 2019 Apr 26;404(3):1–8.
8. Broek MAJVD, Damink SWMO, Dejong CHC, Lang H, Malagó M, Jalan R, Saner FH. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int. 2008;28(6):767–80.
9. Hirata Y, Sanada Y, Omameuda T, Katano T, Miyahara G, Yamada N, Okada N, Onishi Y, Sakuma Y, Sata N. Liver Transplant for Posthepatectomy Liver Failure in Hepatoblastoma. Exp Clin Transplant. 2020;18(5):612–7.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (08:20-09:40)

ROOM 4

Special Interest Group Forum 1

Viral Hepatitis: Unresolved Issue for Chronic Hepatitis B Virus Infection

Chairs:

Seong Gyu Hwang (CHA Univ.)

Jin-Wook Kim (Seoul National Univ.)

Targeting cccDNA for Cure of Hepatitis B Virus Infection

Kyun-Hwan Kim

Sungkyunkwan University, Korea

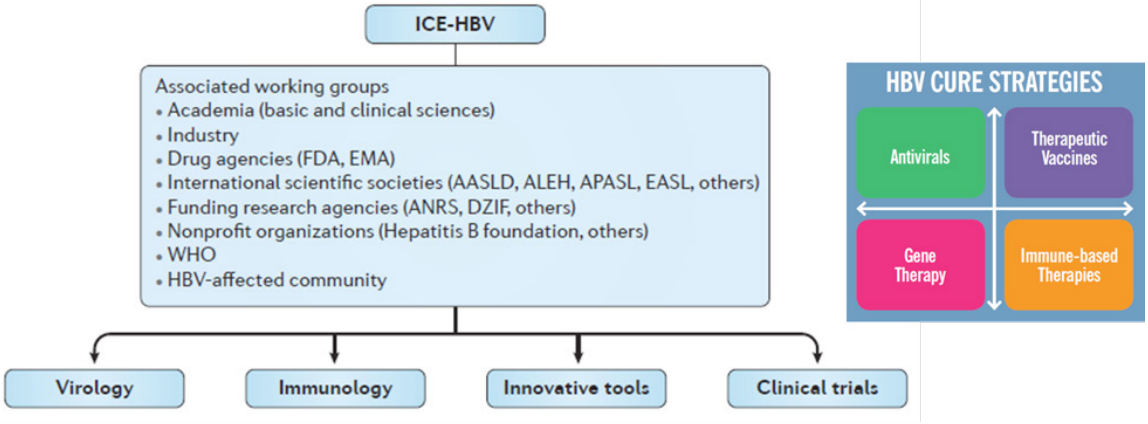
Chronic hepatitis B virus (HBV) infection is associated with significant morbidity and mortality, fibrosis, cirrhosis, end-stage liver diseases and primary hepatocellular carcinoma (HCC). More than 240 million people are chronically infected with HBV, with some 600,000 deaths per year attributed to the 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.

HBV cccDNA can be targeted by several approaches. 1) The cellular factors or enzymes involved in cccDNA formation are recently identified. These essential factors can be targeted to inhibit cccDNA synthesis. 2) cccDNA can be degraded by treatment with antiviral cytokine. The cellular factors in this process can be targeted to accelerate the degradation of cccDNA. 3) cccDNA can be inactivated by transcriptional silencing or epigenetic modifications.

Since it is currently almost impossible to remove cccDNA from infected hepatocytes, inhibition of cccDNA function through its transcriptional silencing is a realistic goal to achieve functional cure of HBV infection. Combining induction of immune control to safely eliminate infected cells will accelerate the functional cure of HBV infection. These approaches will be introduced in this presentation.

In this talk, I review the recent scientific advances in HBV cccDNA study. Especially, I will focus on the action mechanisms of cccDNA targeting strategies in detail.

International Coalition to Eliminate the Hepatitis B Virus (ICE-HBV)



1. Curing of HBV infection without killing infected cells
2. Inducing immune control to safely eliminate infected cells

Overview of Current HBV Drug Development

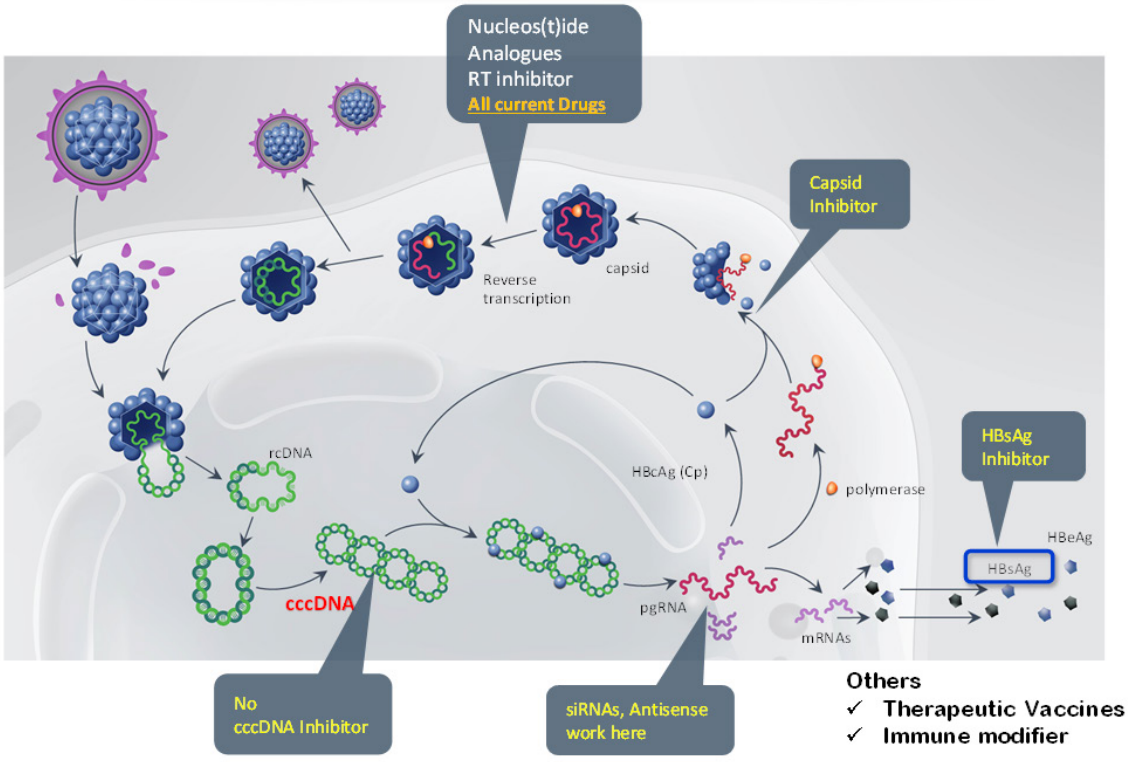


Table. Capsid Inhibitors in Development (updated May 2019)

Capsid Inhibitors: Interferes with the viral DNA protein shield				
Morphothiadin (GLS4)	Capsid inhibitor	HEC Pharma, PR China	pharm.hec.cn/en	Phase II
JNJ 56136379	Capsid inhibitor	Janssen, Scotland	janssen.com	Phase II
ABI-H0731	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase II
AB-423	Capsid inhibitor	Arbutus Biopharma, USA	arbutusbio.com	Phase I
AB-506	Capsid inhibitor	Arbutus Biopharma, USA	arbutusbio.com/	Phase I
ABI-H2158	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase I
RG7907	Capsid inhibitor	Roche, Switzerland	roche.com	Phase I
QL-007	Capsid inhibitor	Qilu, China	qilu-pharma.com	Phase I
GLP-26	Capsid inhibitor	Emory University	emory.edu	Preclinical
EP-027367	Capsid inhibitor	Enanta Pharmaceuticals, USA	enanta.com	Preclinical
QL-0A6a	Capsid inhibitor	Qilu, China	qilu-pharma.com	Preclinical
CB-HBV-001	Capsid inhibitor	ZhiMeng Biopharma, China	core-biopharma.com	Preclinical

Unresolved Issues of Immune Tolerance in Chronic Hepatitis B: Earlier Treatment the Better?

Hye Won Lee

Yonsei University, Korea

It is difficult to define true immune-tolerant phase. Indeed, it is debatable whether such a phase exists.[1] No international consensus definition has appeared, and few studies have addressed the prognosis and treatment responsiveness of patients in true immune-tolerant phase. The need to treat patients in this phase has been questioned.

The rationale for opposing early antiviral treatment (in the immune-tolerant phase) follows. First, early natural history studies of that phase revealed a benign disease course. A study using paired liver biopsy data revealed minimal liver injury progression over 5 years among patients who remained in the immune-tolerant phase.[2] Second, the risk of hepatocellular carcinoma (HCC) is low in immune-tolerant phase.[3] The cumulative HCC risks were similar for patients in immune-tolerant phase and those exhibiting virologic responses groups to antivirals (1.1 and 2.7% vs. 1.0 and 2.9% at 5 and 10 years respectively; p = 0.704).[4] Third, patients in the immune-tolerant phase respond poorly to antiviral therapies and exhibit a high rate of relapse after antiviral cessation.[5,6]

However, the support for early antiviral treatment (in the immune-tolerant phase) follows. First, the immune-tolerant phase is not benign. Clonal hepatocyte expansion and hepatitis B virus (HBV) DNA integration are in play, associated with hepatocarcinogenesis.[7] Second, HCC risk increases in untreated immune-tolerant patients. A Korean study showed that the 10-year cumulative HCC incidence was 12.7% among patients in the immune-tolerant phase compared to 6.0% of those in the immune-active phase, although some immune-tolerant patients may have been misclassified.[8] Third, suppression of HBV DNA levels (to prevent HCC and cirrhosis) is cost-effective in immune-tolerant chronic hepatitis B patients.[9] The low cost of antiviral drugs today has reduced the financial barriers that previously prevented universal HBV treatment coverage in most countries.

Most clinicians agree that it is important to identify and appropriately treat advanced fibrosis in older hepatitis B e antigen-positive patients with high viral loads and normal alanine aminotransferase levels, but the age and viral load cutoffs remain unclear. If our question "Is earlier treatment better?" is to be answered, a clear consensus what constitutes the immune-tolerant phase must emerge. Also, further studies are needed to optimize the long-term assessment and treatment of immune-tolerant patients.

References

1. Lee HW, Chan HL. Unresolved issues of immune tolerance in chronic hepatitis B. J Gastroenterol 2020;55:383-389.

2. Hui CK, Leung N, Yuen ST, Zhang HY, Leung KW, Lu L, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology 2007;46:395-401.
3. Lee HW, Chon YE, Kim BK, Yip TC-F, Tse Y-K, Wong GL-H, et al. Negligible HCC risk during stringently defined untreated immune-tolerant phase of chronic hepatitis B. European Journal of Internal Medicine 2021;84:68-73.
4. Lee HW, Kim SU, Oidov B, Park JY, Kim DY, Ahn SH, et al. Comparison between chronic hepatitis B patients with untreated immune-tolerant phase vs. those with virological response by antivirals. Sci Rep 2019;9:2508.
5. Chan HL, Chan CK, Hui AJ, Chan S, Poordad F, Chang TT, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014;146:1240-1248.
6. Wong VW, Hui AJ, Wong GL, Chan RS, Chim AM, Lo AO, et al. Four-year Outcomes After Cessation of Tenofovir in Immune-tolerant Chronic Hepatitis B Patients. J Clin Gastroenterol 2018;52:347-352.
7. Koffas A, Petersen J, Kennedy PT. Reasons to consider early treatment in chronic hepatitis B patients. Antiviral Res 2020;177:104783.
8. Kim GA, Lim YS, Han S, Choi J, Shim JH, Kim KM, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018;67:945-952.
9. Kim HL, Kim GA, Park JA, Kang HR, Lee EK, Lim YS. Cost-effectiveness of antiviral treatment in adult patients with immune-tolerant phase chronic hepatitis B. Gut 2020. doi:10.1136/gutjnl-2020-321309.

Prognostic Impact of Concurrent Hepatic Steatosis in Chronic Hepatitis B: Can Lifestyle Modification Reduce Hepatocellular Carcinoma Risk?

Yun Bin Lee

Seoul National University, Korea

Despite the widespread use of vaccines, chronic hepatitis B (CHB) is one of the most common chronic viral infections worldwide, and especially in Asian countries.[1] Although the long-term prognosis for CHB patients has been improved by antiviral therapy with potent nucleos(t)ide analogues (i.e., entecavir, tenofovir disoproxil or tenofovir alafenamide), the risk for developing liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) has not been eliminated in those patients, leading to a huge burden on public health.[2-5]

Nonalcoholic fatty liver disease (NAFLD) is another serious global health problem because of the increasing prevalence even in Asian countries. Although its pathogenesis is not fully understood, NAFLD is primarily associated with obesity and insulin resistance, and is regarded as a hepatic manifestation of metabolic syndrome.[6] A diverse spectrum of liver diseases including nonalcoholic steatohepatitis (NASH) and liver cirrhosis results from NAFLD, and NAFLD is a well-known risk factor for HCC.[7] Patients with NASH-related cirrhosis are at a greatly increased risk for HCC, with a yearly cumulative incidence of 2.6%.[8] Theoretically, NAFLD and chronic HBV infection may synergistically potentiate HCC development.

We recently reported a study evaluating the effect of histologically proven fatty liver on the development of HCC in CHB patients.[9] In this study, we included 321 consecutive CHB patients without significant alcohol consumption undergoing liver biopsy and subsequent histologic diagnosis and analyzed the association between hepatic steatosis (≥ 5%) and the risk for HCC. Our study demonstrated that the prevalence of histologically proven fatty liver was 21.8% in patients with CHB, and coexisting fatty liver was associated with a 3–fold increased risk for developing HCC (adjusted hazard ratio [HR] 3.005, 95% confidence interval [CI] 1.122–8.051; *P*=.03). However, after inverse probability weighting based on each patient's propensity score to rigorously adjust for patient characteristics, including metabolic factors, no significant association between coexistence of fatty liver and HCC development was observed (adjusted HR 1.709, 95% CI 0.404–7.228; *P*=.47). In contrast, diabetes was significantly associated with the risk for developing HCC (adjusted HR 3.562, 95% CI 1.117–11.359; *P*=.03). These results suggest that superimposed NAFLD as a hepatic manifestation of metabolic syndrome, not hepatic steatosis per se, increases the risk for HCC in CHB patients. Moreover, Chan and colleagues recently reported that histologically proven fatty liver was associated with a 7.3–fold increased risk for HCC development in CHB patients.[10]

In a previous Taiwanese study, when the influence of metabolic risk factors, such as obesity, diabetes, hypertension, and hypertriglyceridemia, on HCC risk and liver-related mortality in male CHB patients was

analyzed, patients with ≥ 3 metabolic risk factors were at a 2.3–fold higher risk for HCC, suggesting a synergistic hepatocarcinogenic effect of metabolic factors and chronic viral hepatitis.[11] Recently, we validated an association of the burden of metabolic risk factors with risks of HCC using a large nationwide population-based cohort of CHB patients.[12] In this nationwide population-based study of 317,856 adults with CHB, we demonstrated that an increasing burden of metabolic risk factors (i.e., obesity, high blood pressure, hypercholesterolemia, and diabetes) was associated with higher risks of developing HCC, non-HCC cancer, and all-cause mortality in a dose-responsive manner (all $P<.0001$ for trend).

On the basis of these study findings, concurrent hepatic steatosis is associated with an increased risk for HCC development in CHB patients. However, fatty liver as a hepatic manifestation of metabolic syndrome, may possess important predictive value for HCC rather than hepatic steatosis per se. Thorough assessment and management of metabolic risk factors may be necessary to lower the risk of developing HCC and increase survival in patients with CHB. Moreover, the burden of metabolic risk factors should be considered to establish an individually tailored surveillance strategy for HCC, also in patients undergoing long-term antiviral treatment.

References

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-1555.
2. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988;61:1942-1956.
3. McMahon BJ. The natural history of chronic hepatitis B virus infection. Semin Liver Dis 2004;24 Suppl 1:17-21.
4. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin Liver Dis 2006;26:130-141.
5. Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014;384:2053-2063.
6. Sanyal AJ, American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-1725.
7. Contos MJ, Sanyal AJ. The clinicopathologic spectrum and management of nonalcoholic fatty liver disease. Adv Anat Pathol 2002;9:37-51.
8. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-1978.
9. Lee YB, Ha Y, Chon YE, Kim MN, Lee JH, Park H, Kim KI, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019;25:52-64.
10. Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017;32:667-676.
11. Yu MW, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with chronic hepatitis B: A large cohort study. Gastroenterology 2017;153:1006-1017.
12. Lee YB, Moon H, Lee JH, Cho EJ, Yu SJ, Kim YJ, Zoulim F, et al. Association of metabolic risk factors with risks of cancer and all-cause mortality in patients with chronic hepatitis B. Hepatology 2020.

Chemo-Preventive Strategies of HBV-Related Hepatocellular Carcinoma: The Emerging Role of Non-Viral Risk Factors

Jonggi Choi

University of Ulsan, Korea

Over the past decades, marked advancement has been made in the prevention and treatment of hepatitis B virus (HBV) infection. Despite of highly effective antiviral therapies for chronic hepatitis B (CHB), disease burden of hepatocellular carcinoma (HCC) in patients with CHB has yet been improved. Therefore, non-viral risk factors and chemo-preventive strategies have been highlighted recently to further reduce the risk of HCC. Chemo-prevention indicates that the use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of certain cancer. Statin, metformin, aspirin, NSAID and dietary agents such as coffee, vitamin E and fish oil might be candidate of chemo-prevention for HCC given the possible association by multiple studies. However, randomized controlled trials for these agents are hardly to be conducted. Therefore, well-designed, prospective, population-based cohort studies might provide better evidence for chemo-preventive efficacy of this chemo-preventive strategies.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (11:10-12:30)

ROOM 4

Special Interest Group Forum 2

Korea Nonalcoholic Fatty Liver Study Group: Advanced Knowledge in Nonalcoholic Fatty Liver Disease

Chairs:

Jin-Woo Lee (Inha Univ.)

Yoon Jun Kim (Seoul National Univ.)

Introduction of the Useful Big Database for Researchers in Nonalcoholic Fatty Liver Disease

Donghee Kim

Stanford University, USA

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic fat accumulation either by histology or imaging after excluding other causes of hepatic steatosis such as viral hepatitis, significant alcohol consumption, a medication known to produce hepatic steatosis, or the different causes of liver disease.[1] NAFLD encompasses a broad spectrum ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and eventually end-stage liver disease, including cirrhosis and hepatocellular carcinoma.[1] The increasing incidence of type II diabetes and obesity leads to an increased prevalence of NAFLD, with an estimated prevalence of 20-30% in the world.[1,2] The increasing prevalence of NAFLD is particularly worrying because individuals with NAFLD appear to have higher mortality from non-liver-related, as well as liver-related death, compared to the general population.[3] Therefore, concerted efforts to better understand NAFLD are warranted to influence the future disease burden and healthcare utilization favorably.[4,5] There are several useful publicly available big database for NAFLD research. My talks aim to introduce useful big database for researchers in NAFLD as below:

1. National Health and Nutrition Examination Survey (NHANES)

This survey (https://www.cdc.gov/nchs/nhanes/index.htm) examines the US nationally representative sample of approximately 5,000 individuals annually. The NHANES includes 1) Interview: socioeconomic, demographic, dietary, health-related variables, 2) Examination: medical, dental, physiologic measurements; 3) Laboratory test, 4) Mortality data. This database is a helpful tool for the NAFLD study because it includes many metabolic variables, anthropometric measures, diet, health-related questionnaires, hepatic ultrasonography, and all-cause/cause-specific mortality. This database could be used to determine the prevalence of NAFLD, the association between NAFLD and mortality, and risk factors for NAFLD. There are some study examples for information using this database.[6-8]

2. National Vital Statistic System (NVSS)

The Centers for Disease Control and Prevention (CDC)'s NVSS maintains an annual mortality database (https://www.cdc.gov/nchs/nvss/index.htm), with data provided by various jurisdictions legally responsible for the information extracted from death certificates. This database encompasses over 99% of US residents' deaths in all 50 states and the District of Columbia. This database could produce an annual national US data set on multiple-cause mortality, making available representative mortality for chronic liver disease,

including NAFLD. Some study examples are provided using this database.[3,9,10]

3. National Inpatient Sample (NIS) Database

The NIS (https://www.hcup-us.ahrq.gov/nisoverview.jsp) is a database developed for the Healthcare Cost and Utilization Project (HCUP).[11] This database is the largest publicly available all-payer inpatient healthcare database, yielding national estimates of inpatient utilization, quality, healthcare access, medical charges, length of stay, and in-hospital mortality. This database consist of a 20% stratified sample of discharges from US community hospitals, which comprises more than 97% of the hospitalization in the US. It contains nationally representative data from more than 7 million hospital stays each year with estimates of more than 35 million hospitalizations, which are weight-adjusted. Currently, the NIS database includes hospitalization data between the years 1988 and 2018. Some study examples are shown for references.[12,13]

4. Surveillance, Epidemiology, and End Results (SEER)

The National Cancer Institute's (NCI) SEER Program (https://seer.cancer.gov) provide information on cancer statistics to reduce the cancer burden among the US population. SEER-Medicare database provides a unique population-based source of information that can be used for an array of epidemiological and health services research including NAFLD-related hepatocellular carcinoma. There is a study example using the SEER database.[14]

References

1. Murag S, Ahmed A, Kim D. Recent Epidemiology of Nonalcoholic Fatty Liver Disease. Gut Liver 2021;15:206-216.
2. Li AA, Ahmed A, Kim D. Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease. Gut Liver 2020;14:168-178.
3. Kim D, Adejumo AC, Yoo ER, Iqbal U, Li AA, Pham EA, et al. Trends in Mortality From Extrahepatic Complications in Patients With Chronic Liver Disease, From 2007 Through 2017. Gastroenterology 2019;157:1055-1066 e1011.
4. Yoo ER, Kim D, Vazquez-Montesino LM, Escober JA, Li AA, Tighe SP, et al. Diet quality and its association with nonalcoholic fatty liver disease and all-cause and cause-specific mortality. Liver Int 2020;40:815-824.
5. Yoo ER, Ahmed A, Kim D. Economic burden and healthcare utilization in nonalcoholic fatty liver disease. Hepatobiliary Surg Nutr 2019;8:181-183.
6. Kim D, Murag S, Cholankeril G, Cheung A, Harrison SA, Younossi ZM, et al. Physical Activity, Measured Objectively, Is Associated With Lower Mortality in Patients With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol Epub Jul 16 2020.
7. Kim D, Vazquez-Montesino LM, Escober JA, Fernandes CT, Cholankeril G, Loomba R, et al. Low Thyroid Function in Nonalcoholic Fatty Liver Disease Is an Independent Predictor of All-Cause and Cardiovascular Mortality. Am J Gastroenterol 2020;115:1496-1504.
8. Kim D, Vazquez-Montesino LM, Li AA, Cholankeril G, Ahmed A. Inadequate Physical Activity and Sedentary Behavior Are Independent Predictors of Nonalcoholic Fatty Liver Disease. Hepatology 2020;72:1556-1568.
9. Kim D, Li AA, Gadiparthi C, Khan MA, Cholankeril G, Glenn JS, et al. Changing Trends in Etiology-Based Annual Mortality From Chronic Liver Disease, From 2007 Through 2016. Gastroenterology 2018;155:1154-1163 e1153.
10. Kim D, Konyn P, Cholankeril G, Wong RJ, Younossi ZM, Ahmed A, et al. Decline in Annual Mortality of Hepatitis C Virus-Related Hepatocellular Carcinoma in the United States, From 2009 to 2018. Gastroenterology 2020;159:1558-1560 e1552.

11. Healthcare Cost and Utilization Project. National Inpatients Sample. Available: https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed on Apr 2021.
12. Kim D, Cholankeril G, Li AA, Kim W, Tighe SP, Hameed B, et al. Trends in hospitalizations for chronic liver disease-related liver failure in the United States, 2005-2014. Liver Int 2019;39:1661-1671.
13. Kim D, Yoo ER, Li AA, Tighe SP, Cholankeril G, Ahmed A. Trends in Hospitalizations for Clostridioides difficile Infection in End-Stage Liver Disease, 2005-2014. Dig Dis Sci 2021;66:296-307.
14. Kim D, Konyn P, Cholankeril G, Bonham CA, Ahmed A. Trends in the Mortality of Biliary Tract Cancers Based on Their Anatomical Site in the United States From 2009 to 2018. Am J Gastroenterol Feb 2 2021.

Metabolic Associated Fatty Liver Disease and Cardiovascular Disease

Jian-Gao Fan

Shanghai Jiao Tong University, China

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver diseases in the world. It's interaction relationship with metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) is established, but an independent impact of NAFLD on vascular risk and progression of cardiovascular disease (CVD) still needs to be confirmed.

According to the nationwide population-based study in South Korea, NAFLD itself was independently associated with increased risk of incident CVD, heart failure, and atrial fibrillation in healthy adults after comprehensive control of metabolic risk factors. Dyslipidemia and T2DM may be common links between NAFLD and CVD, and there is a potential synergistic increase of CVD risk in NAFLD patients with dyslipidemia, T2DM. Regardless of overweight and obesity, NAFLD patients may progress to cirrhosis, develop metabolic comorbidities, CVD, and hepatic and extrahepatic cancer. Of them, CVD is the most important complication and leading cause of death. Patients with NAFLD should be evaluated for metabolic cardiovascular risk and be treated accordingly.

Regarding to patients with NAFLD, dyslipidaemia, hypertension and T2DM should be identified and treated accordingly to reduce the risk of CVD and mortality. NAFLD patients, especially with MetS, T2DM, and high serum LDL-C level should be considered at high risk of CVD and could benefit from more intensive CV prevention. Several anti-diabetic therapies such as glucagon-like peptide-1 analogue (GLP-1a) andsodium glucose cotransporter 2 inhibitors (SGLT2i) have shown beneficial effect on MetS and CVD and may be useful for treatment of steatohepatitis. Recently, increased studies provide data for biochemical and histological improvement of experimental NAFLD with statins and in the clinical studies large reductions in CVD events in comparison with those also on statins and normal liver. However, the use of statins, though considered safe by the guidelines, have very limited use; only 10% in high CVD risk patients are on statins by tertiary centers in the US. People with NAFLD are less likely to achieve optimal management of LDL-C than those without NAFLD in Korea. The Asian CAP study also highlights the suboptimal treatment of dyslipidemia using statin and calls for action to improve the treatment of dyslipidemia in NAFLD patients. Therefore, physicians should bear in mind that CVD is the main cause of death in NAFLD patients, and should consider using statin in those with NAFLD at high CVD risk, alone and/or preferably in combination with some antidiabetic agents, for the primary or secondary prevention of CVD.

From Nonalcoholic Steatohepatitis to Diabetes vs. from Diabetes to Nonalcoholic Steatohepatitis: Different or Similar in Treatment?

Yongho Lee

Yonsei University, Korea

Nonalcoholic fatty liver disease (NAFLD) and diabetes are common metabolic disorders whose prevalence rates are expected to rise worldwide, corresponding to aging and increasingly obese populations. Compared to the general population (around 25%), 50% to 70% of people with diabetes have NAFLD, and NAFLD severity (including fibrosis) tends to be worsened by the presence of diabetes. NAFLD is considered an emerging risk factor for type 2 diabetes mellitus and a contributor to the development of chronic diabetes-related complications. This reciprocal relationship demonstrates the importance of confirming suspected NAFLD in patients with diabetes.

The spectrum of NAFLD ranges from simple steatosis, a non-progressive disease entity with absence of hepatic inflammation and fibrosis, to non-alcoholic steatohepatitis (NASH), the most progressive and severe condition which can develop into cirrhosis, hepatocellular carcinoma and liver-related mortality. Over the next decade, NASH is projected to be the most common indication for liver transplantation. The absence of an effective pharmacological therapy for NASH is a major interest for research into novel therapeutic approaches for this condition. Here, I will summarize how anti-diabetic drugs such as thiazolidinediones, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter-2 inhibitors can affect NASH conditions. In addition, I will review whether carnitine-orotate, ezetimibe and new investigating agents targeting NASH such as FXR agonists and PPARα/δ agonist (Elafibranor) have impact on both hepatic and glycemic profiles.

How Nonalcoholic Fatty Liver Disease Patients Die: Heart, Liver, or Other Cancers?

Jeong-Ju Yoo

Soonchunhyang University, Korea

Nonalcoholic fatty liver disease (NAFLD) is a liver disease associated with components of metabolic syndrome, including insulin resistance, diabetes mellitus, and obesity.[1] Recent studies showed that 13% of the world's adult population is currently obese and 39% are overweight, and the prevalence of NAFLD is approaching nearly 50%.[2,3] Therefore, NAFLD and obesity are considered significant global health threats. Despite the significant burden posed by NAFLD, cause of death or population-level nonalcoholic fatty liver disease (NAFLD) death rate data are sparse. In this topic, we will review existing reports on mortality and causes of death in patients with NAFLD.[1,4-11]

References

1. Paik JM, Henry L, De Avila L, Younossi E, Racila A, Younossi ZM: Mortality Related to Nonalcoholic Fatty Liver Disease Is Increasing in the United States. Hepatology communications, 3: 1459-1471, 2019 10.1002/hep4.1419
2. World Health Assembly: Obesity and Overweight. http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. 2018
3. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al.: Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology, 69: 2672-2682, 2019 10.1002/hep.30251
4. Lin Y, Gong X, Li X, Shao C, Wu T, Li M, et al.: Distinct Cause of Death Profiles of Hospitalized Non-alcoholic Fatty Liver Disease: A 10 Years' Cross-Sectional Multicenter Study in China. Frontiers in medicine, 7: 584396, 2020 10.3389/fmed.2020.584396
5. Calzadilla Bertot L, Adams LA: The Natural Course of Non-Alcoholic Fatty Liver Disease. International journal of molecular sciences, 17, 2016 10.3390/ijms17050774
6. Younossi ZM: Non-alcoholic fatty liver disease - A global public health perspective. Journal of hepatology, 70: 531-544, 2019 10.1016/j.jhep.2018.10.033
7. Milroy CM: Fatty Liver and the Forensic Pathologist. Academic forensic pathology, 8: 296-310, 2018 10.1177/1925362118782061
8. Liu Y, Zhong GC, Tan HY, Hao FB, Hu JJ: Nonalcoholic fatty liver disease and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis. Scientific reports, 9: 11124, 2019 10.1038/s41598-019-47687-3
9. Dam-Larsen S, Franzmann M, Andersen IB, Christoffersen P, Jensen LB, Sorensen TI, et al.: Long term prognosis of fatty liver: risk of chronic liver disease and death. Gut, 53: 750-755, 2004 10.1136/gut.2003.019984
10. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al.: Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology, 65: 1557-1565, 2017 10.1002/hep.29085
11. Younossi Z, Henry L: Contribution of Alcoholic and Nonalcoholic Fatty Liver Disease to the Burden of Liver-Related Morbidity and Mortality. Gastroenterology, 150: 1778-1785, 2016 10.1053/j.gastro.2016.03.005

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (13:30-14:50)

ROOM 4

Special Interest Group Forum 3

Korean Autoimmune Liver Disease Study Group: Recent Update on Autoimmune Liver Disease

Chairs:

Sook-Hyang Jeong (Seoul National Univ.)

Joon Hyeok Lee (Sungkyunkwan Univ.)

Updates on the Histopathology of Autoimmune Hepatitis

Haeryoung Kim

Seoul National University, Korea

Autoimmune hepatitis (AIH) is diagnosed on the basis of the clinical presentation, laboratory findings and histopathology. Scoring systems for research purposes and clinical practice have been devised and developed by the International Autoimmune Hepatitis Group (IAHG), and these include the revised IAHG scoring system of 1999[1] and the 2008 simplified scoring system.[2] For pathologists, important features of AIH that are emphasized in the 1999 revised scoring system consist of interface hepatitis, lymphoplasmacytic infiltration, hepatocyte rosette formation and the absence of biliary changes or other features suggesting alternative etiologies. Interestingly, according to the simplified criteria of 2008, the histology is graded into three categories: (1) "typical histology for AIH", which requires the presence of interface hepatitis, emperipolesis and hepatocyte rosette formation; (2) "histology compatible with AIH", described as a chronic hepatitis pattern of injury with lymphocytic infiltration, but lacking some of the features considered "typical"; and (3) "atypical histology for AIH", in which features suggestive of other etiologies are present. From the pathologist's perspective, emphasizing the presence of emperipolesis and hepatocyte rosette formation in this system may be problematic, as there may be inter/intraobserver variability in interpretation and the sensitivity is modest at best. Moreover, hepatocyte rosettes and emperipolesis are not specific for AIH. With this background, a histological scoring system for AIH has been proposed by a group of pathologists in 2017,[3] which puts more emphasis on the necroinflammatory activity, embraces the different patterns of necroinflammatory activity (including the acute hepatitis variant), and adds copper and/or CK7 stains to help identify biliary patterns of injury. The application of this method has helped increase the sensitivity of AIH diagnosis, although further validation is necessary.

Liver biopsy plays an important role in the diagnosis and management of AIH, by 1) confirming or suggesting the diagnosis of AIH on the basis of histopathological features, 2) assessing the severity of necroinflammatory activity and extent of fibrosis, 3) excluding other potential causes of liver disease, and 4) identifying variant syndromes or uncommon forms of AIH. It may also be used to evaluate response to therapy; however, the histological improvements have been demonstrated to lag behind the biochemical improvements by several months, and mild necroinflammatory activity is often seen in liver biopsies several months after the normalization of transaminase levels, and histological resolution does not guarantee complete and sustained remission.

In this presentation, the histopathological features of typical AIH and less common forms of AIH will be discussed, with a comparison of the different scoring systems. In addition, more challenging situations for pathologists will be briefly introduced, including drug/toxin-induced liver injury with AIH pattern, AIH-like injury after immunotherapy, post-treatment AIH, and AIH in liver allografts.

References

1. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-38.
2. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-76.
3. Balitzer D, Shafizadeh N, Peters MG, Ferrell LD, Alshak N, Kakar S. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. Mod Pathol 2017;30:773-83.

Interpretation of Autoantibody Tests for Autoimmune Liver Diseases

Yun-Jong Lee

Seoul National Universtiy, Korea

Autoimmune response is defined by the presence of autoantibodies or autoreactive T cells and is not always pathological. Additionally, because the formation of autoantibodies precedes the development of autoimmune diseases, autoantibodies could be positive in the preclinical period of an autoimmune disease. Therefore, we should not automatically translate the presence of an autoantibody into the presence of an autoimmune disease.

In the diagnostic approach to autoimmune diseases, various immunoassay methods have been developed. Common methods to detect autoantibodies include immunofluorescence (IF), ELISA, and immunoblots. The results of these immunoassays are dependent on various factors including methods itself and substrates (antigens or epitopes). Generally, IF is less sensitive than immunoblot, ELISA, or radio-immunoassays (RIA). Moreover, IF can capture antibodies reacting to native antigens or conformational epitopes, while immunoblot, ELISA, or RIA cannot detect these antibodies. Therefore, it bears in mind that different methods can lead to different results.

Because of lack of the gold standard diagnostic criteria, it has been recommended that the diagnosis of autoimmune hepatitis (AIH) should be made based on biochemical, immunological, and pathological findings. Immunological investigations include hyper-gammaglobulinemia and autoimmune liver disease (AILD)-associated autoantibodies. The autoantibody domain in the 1999 and 2008 International Autoimmune Hepatitis Group (IAIHG) scoring systems includes ANA, anti-smooth muscle (SMA), anti-liver-kidney microsome (LKM-1), and anti-soluble liver antigen (SLA) antibodies. Additionally, the 2019 American Association for the Study of Liver Diseases (AASLD) diagnostic algorithm for AIH are based on ANA, SMA, LKM1, SLA, anti-mitochondrial (AMA) and perinuclear anti-neutrophil cytoplasmic antibody (ANCA).

These antibodies are related to a clinical subtype of AILD. In Korean studies, ANA and SMA were positive in about 80-90% and 30% of patients with AIH, respectively. LKM-1 was positive in less than 5% of AIH cases and AMA was positive in more than 98% of PBC cases. Therefore, getting familiar with autoantibodies profiles is helpful in the diagnostic approach to AILD. This lecture will briefly review diagnostic implications of major AILD-associated autoantibodies, focusing on ANA, SMA, SLA, LKM-1, and AMA.

References

1. Tan EM, et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum. 1997;40(9):1601-11.
2. Hoffman GS, et al. Antineutrophil cytoplasmic antibodies. Arthritis Rheum. 1998;41(9):1521-37
3. Alvarez F, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune

hepatitis. J Hepatol. 1999;31(5):929-38.
4. Arbuckle MR, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003;349(16):1526-33.
5. Shmerling RH. Autoantibodies in systemic lupus erythematosus--there before you know it. N Engl J Med. 2003;349(16):1499-500.
6. Hennes EM, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48(1):169-76.
7. Villa-Blanco I, et al. Predictive Value of High Levels of Antinuclear Antibodies in People without Other Feature of Autoinmunity. A Prospective Study. Arthritis Rheum. 2010;62(10 Supple):S782 (Abstract No. 1871).
8. Craig WY, et al. The relationship between antinuclear antibody data and antibodies against extractable nuclear antigens in a large laboratory cohort. Clin Chem Lab Med. 2011;50(3):497-502.
9. Mariz HA, et al. Pattern on the antinuclear antibody-HEp-2 test is a critical parameter for discriminating antinuclear antibody-positive healthy individuals and patients with autoimmune rheumatic diseases. Arthritis Rheum. 2011;63(1):191-200.
10. Dimitrov JD, et al. Antibody polyreactivity in health and disease: statu variabilis. J Immunol 2013;191(3):993-9.
11. Chan EK, et al. Report of the First International Consensus on Standardized Nomenclature of Antinuclear Antibody HEp-2 Cell Patterns 2014-2015. Front Immunol. 2015;6:412.
12. Dahlqvist G, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-163.
13. Pisetsky DS. Antinuclear antibody testing - misunderstood or misbegotten? Nat Rev Rheumatol. 2017;13(8):495-502.
14. Jeong SH. Current epidemiology and clinical characteristics of autoimmune liver diseases in South Korea. Clin Mol Hepatol. 2018;24(1):10-19.
15. Terziroli Beretta-Piccoli B, et al. The clinical usage and definition of autoantibodies in immune-mediated liver disease: A comprehensive overview. J Autoimmun. 2018;95:144-158.
16. Terziroli Beretta-Piccoli B, et al. Serology in autoimmune hepatitis: A clinical-practice approach. Eur J Intern Med. 2018;48:35-43.
17. Becker Y, et al. Autoantibodies in Systemic Lupus Erythematosus Target Mitochondrial RNA. Front Immunol. 2019;10:1026.
18. Damoiseaux J, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. 2019;78(7):879-889.
19. Mack CL, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. Hepatology. 2020;72(2):671-722.
20. Zandanell S, et al. Low rate of new-onset primary biliary cholangitis in a cohort of anti-mitochondrial antibody-positive subjects over six years of follow-up. J Intern Med. 2020;287(4):395-404.
21. Ramponi G, et al. The biology, pathogenetic role, clinical implications, and open issues of serum anti-neutrophil cytoplasmic antibodies. Autoimmun Rev. 2021;20(3):102759.

Management of Difficult Cases of Autoimmune Hepatitis and New Therapeutics

Atsumasa Komori

Nagasaki University, Japan

Introduction

The aim of the treatment of autoimmune hepatitis (AIH), an immunoinflammatory liver disease of non-self-limiting clinical course, is to prevent disease progression from liver-related outcomes, ensuring healthy quality-of life.[1] To achieve the goal, surrogate endpoints are necessary to monitor treatment response to immunosuppressive agents: Biochemical remission (BR, defined as normalization of serum AST, ALT, and IgG within upper limit of normal), ideally within 6 months after the initiation of treatment, is now regarded as a milestone toward histological remission, which is diagnosed with hepatitis activity index (HAI-score) of up to 3 out of 18.[2] In this regard, AIH patients, who are not able to achieve BR, due to either incomplete biochemical response, refractoriness, or intolerance to treatment, are considered as difficult to treat cases. In this presentation, we summarize and discuss about the management of these patients, with special attention to second/third-line therapy and potential new therapeutics.

Second and third-line therapy for difficult to treat cases

The mainstay of the first-line treatment of AIH is a combination of prednisolone (PSL) or budesonide and azathioprine (AZA),[2] that is, standard of care (SOC). AZA is a key drug in SOC, not only to spare PSL on the way to BR, but also to maintain BR. A recent position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group (IAIHG) recommended measuring drug-levels of AZA metabolites in patient with insufficient response,[3] because widely-varying metabolizing activity for AZA to 6-thioguanine nucleotides (6-TGN) that contain the main active drug 6-thioguanine triphosphate or non-adherence to AZA are two main reasons for insufficient response. With the cut-off levels of 6-TGN as 220 pmol/8x10^8 red blood cells, the lower value is an indicator for optimization of 6-TGN either by dose-escalation, or by the combination of low-dose AZA and allopurinole, whereas the higher implicate the need for alternative or concomitant diagnosis of AIH before intensification of steroid and AZA.[3] For patients in AZA intolerance, switching from AZA to *6-mercaptopurine* (*6-MP), which is the first metabolite of AZA, is a recommended option.*[3] Third-line therapy for patients with genuine insufficient response to SOC and second-line therapy for those in AZA/6-MP intolerance are then introduced anecdotally, either with mycophenolate mofetil (MMF), calcineurin inhibitors (cyclosporin A, tacrolimus [TAC]), or biologics (e.g., infliximab). A DNA synthesis inhibitor MMF is indicated for immunosuppression after organ transplant or lupus nephritis. In a meta-analysis, the combination of MMF + PSL was shown to

be the most widely prescribed second-line treatment, achieving histological remission in 89% of the patients.[4] A systemic review to compare the efficacies of MMF and TAC for treatment failure or incomplete biochemical response by the AASLD results in a conditional recommendation favoring MMF over TAC as initial second line therapy even with a very low level of certainty.[5]

Potential new therapeutics

Although new therapeutics are primarily in development for difficult to treat cases, novel agents whose mechanisms of action are based on growing knowledge on the immune-pathophysiology of AIH should also be potential candidates to restore immune tolerance in the liver, leading to cure of AIH.[7] Aberrant B cell activation is regarded as one promising target for second or third-line add-on therapy for AIH. B cell depletion exerted with anti-CD20 antibody (rituximab) was reported to be effective in improvement of liver enzymes and reduction of PSL dosage.[8] A case-series with B cell-activating factor (BAFF) inhibitor belimumab, which minimizes the survival of autoreactive B cells, demonstrated complete response and remission in two refractory AIH patients.[9] Lastly, a phase II/III clinical trial entitled "ADCC mediated B-cell depletion through BAFF-R blockade (AMBER) "with anti-BAFF receptor antibody, is in under way, using ALT normalization as primary outcome.

Another potential target therapy is for putatively deficient intrahepatic regulatory T cells (Treg) functions and numbers. Supplementation of low dose interleukin-2, which selectively potentiate and expand Treg, but not T effector cell (Teff) in vivo,[10] in 14 autoimmune/autoinflammatory diseases including AIH is under way[7].

Conclusion

Improvement of the health-related quality of life in difficult to treat AIH patients must be accomplished in the future by personalized medicine with new therapeutics.

Reference

1. Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol 2021; 27:58-69.
2. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020; 72:671-722.
3. Lohse AW, Sebode M, Jørgensen MH, Ytting H, Karlsen TH, Kelly D, et al. Second-line and third-line therapy for autoimmune hepatitis: A position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. J Hepatol 2020; 73:1496-1506.
4. De Lemos-Bonotto M, Valle-Tovo C, Costabeber AM, Mattos AA, Azeredo-da-Silva ALF. A systematic review and meta-analysis of second-line immunosuppressants for autoimmune hepatitis treatment. Eur J Gastroenterol Hepatol 2018; 30:212-216.
5. Vierling JM, Kerkar N, Czaja AJ, Mack CL, Adams D, Assis DN, et al. Immunosuppressive Treatment Regimens in Autoimmune Hepatitis: Systematic Reviews and Meta-Analyses Supporting American Association for the Study of Liver Diseases Guidelines. Hepatology 2020; 72: 753-769.
6. Dyson JK, De Martin E, Dalekos GN, Drenth JPH, Herkel, J, Hubscher SG et al. Review article: unanswered clinical and research questions in autoimmune hepatitis-conclusions of the International Autoimmune Hepatitis Group

Research Workshop. Aliment Pharmacol Ther 2019;49:528-536.
7. Taubert R, Hupa-Breier-KL, Jaeckel E, Manns MP. Novel therapeutic targets in autoimmune hepatitis. J Autoimmun 2018; 95:34-46.
8. Than NN, Hodson J, Schmidt-Martin D, Taubert R, Wawman RE, Botter M, et al. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: Results from the International Autoimmune Hepatitis Group. JHEP Reports 2019;1: 437-444
9. Arvaniti P, Giannoulis G, Gabeta S, Zachou K, Koukoulis GK, Dalekos.GN. Belimumab is a promising third-line treatment option for refractory autoimmune hepatitis. JHEP Reports 2020;2: 100123
10. Lim T, Martinez-Llordella M, Kodela E, Gray E, Heneghan, MA, Sanchez-Fueyo A. Low-dose interleukin-2 for refractory autoimmune hepatitis. Hepatology 2018; 68:1649-1652.

Update on Management of Primary Biliary Cholangitis

Kyung-Ah Kim

Inje University, Korea

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by an immune-mediated destruction of intrahepatic bile ducts. It can progress to end-stage liver diseases and hepatocellular carcinoma without adequate treatment.

Ursodeoxycholic acid (UDCA) at a dose of 13~15 mg/kg/day is the first-line therapy. UDCA is a naturally occurring tertiary bile acid. UDCA treatment improves liver biochemistry, histology, and liver transplantation-free survival. The response to UDCA determines the prognosis of PBC. Pretreatment parameters associated with inadequate UDCA response include higher alkaline phosphatase (ALP), higher bilirubin, lower transaminase, younger age, longer interval from diagnosis to the start of UDCA, and worsening of ALP from diagnosis. Up to 40% of PBC patients can have inadequate responses to treatment. Multiple studies show a high risk of adverse events for patients with insufficient response to UDCA treatment- usually judged 1 year after initiation by scoring systems such as GLOBE score or UK-PBC risk score. Therefore, biochemical response to UDCA should be evaluated at 6-12 months after treatment initiation to determine whether patients should be considered for second-line therapy. There are several criteria to define a biochemical response which are consisted of changes in ALP, bilirubin, and/or aminotransferase.

Obeticholic acid (OCA), a derivative of chenodeoxycholic acid, is a potent agonist of the nuclear hormone receptor farnesoid X receptor (FXR), which regulates bile acids synthesis and transport. In phase 3 trial, nearly half of patients at high risk of disease progression had biochemical response to 12-month OCA therapy. Administration of OCA is associated with worsening of pruritus which is manageable in most cases. OCA treatment (starting at 5mg/day with dose titration to 10mg according to tolerability) should be considered for patients with inadequate response or intolerant to UDCA. OCA dose needs to be adjusted for patients with advanced liver disease.

Fibrates, widely used lipid-lowering medications, activate peroxisome proliferator activator receptor (PPAR)-alpha which regulates bile acid synthesis and detoxification, phospholipid secretion, and inflammatory pathways. For PBC patients with inadequate response to UDCA, addition of fibrates significantly improved serum ALP activity and pruritus. Therefore, fibrates can be considered as off-label alternatives for patients with inadequate response to UDCA.

A recent study showed triple therapy including UDA, OCA and fibrates had a significant reduction of ALP in patients who failed second-line therapy and could be an alternative in difficult-to-treat patients. The budesonide treatment in non-cirrhotic PBC patients with inadequate response to UDCA was not associated with histology improvement. Newer agents including the selective PPAR agonist and FXR agonists are also under investigation for patients with inadequate response to UDCA.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145-172.
2. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018 ;69(1):394-419.
3. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016;375(7):631-43.
4. Corpechot C, Chazouillères O, Rousseau A, et al. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. N Engl J Med. 2018;378:2171-2181.
5. Carbone M, Nardi A, Flack S, et al. Pretreatment prediction of response to ursodeoxycholic acid in primary biliary cholangitis: development and validation of the UDCA Response Score. Lancet Gastroenterol Hepatol. 2018;3(9):626-634.
6. Soret PA, Lam L, Carrat F, et al. Combination of fibrates with obeticholic acid is able to normalise biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis. Aliment Pharmacol Ther. 2021 Mar 25. doi: 10.1111/apt.16336. Epub ahead of print. PMID: 33764590.
7. Hirschfield GM, Beuers U, Kupcinskas L, Ott P, Bergquist A, Färkkilä M, Manns MP, Parés A, Spengler U, Stiess M, Greinwald R, Pröls M, Wendum D, Drebber U, Poupon R. A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA. J Hepatol. 2021;74(2):321-329.
8. Lleo A, Wang GQ, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet. 2020;396(10266):1915-1926.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (15:00-16:20)

ROOM 4

Special Interest Group Forum 4

Korean Study Group of Portal Hypertension: Application of Hepatic Venous Pressure Gradient to Clinical Practice

Chairs:

Soon Ho Um (Korea Univ.)

Young Seok Kim (Soonchunhyang Univ.)

Measurement of Hepatic Venous Pressure Gradient and Its Clinical Significance during TIPS or BRTO/PARTO: Tips and Pitfalls

Hitoshi Maruyama

Juntendo University, Japan

Cirrhosis is the most advanced stage of chronic liver disease. It is accompanied with a risk of developing serious complications, including variceal bleeding, ascites, icterus, and hepatic encephalopathy.[1] These events limit quality of life and long-term outcomes, therefore, patients with these conditions need to be properly monitored.[2,3] Portal hypertension is the principal pathophysiology of cirrhosis, and the hepatic venous pressure gradient (HVPG) is a representative marker for the severity of the condition. A HVPG of 10 to 12 mmHg is the threshold level for the development of esophageal varices, ascites, and the occurrence of variceal bleeding,[4,5] and a HVPG higher than 16 mmHg suggests an increased risk of death.[6,7] Moreover, a HVPG higher than 20 mmHg is the best independent prognostic marker for acute variceal bleeding,[8-11] and thus indicates the presence of much more severe status.

Hepatic venous catheterization is a safe and an established technique which enables measurement of HVPG by either jugular approach or femoral approach. It is necessary to select appropriate size of balloon for the main right hepatic vein. Hepatic venogram is useful to demonstrate the typical appearance of cirrhosis and non-cirrhotic portal hypertension, which could be obtained by using either iodinated contrast material or carbon dioxide. However, we should be careful when we interpret the data because there are some pitfalls; firstly, there is a difference of HVPG between different branches of hepatic veins. The difference between 1st vein measurement and 2nd vein measurement was larger in cirrhosis than in control.[12] In addition, more than 60% of the patients showed the wide-range difference from 4 to 34 mmHg. Some part may be physiological variations, but there is a definite variation.

Next pitfall is a presence of intrahepatic venous-venous communications. Hepatic venography sometimes detects intrahepatic venous-venous communications, which have an incidence of 13–35% in cirrhosis patients.[12-14] The study by Osada et al has shown that wedged hepatic venous pressure underestimates the portal pressure in cases with venous-venous communications.[13] In addition, the presence of venous-venous communications may influence the findings of hepatic venography, as the escape of the contrast material through another hepatic vein might lead to a false negative appearance of the intrahepatic portal vein on the retrograde venogram.[15] Considering the possible errors in clinical interpretation following hepatic venous catheterization, prediction of the findings of hepatic venography may be useful for avoiding unnecessary radiation exposure. Against the background, it is reported that saline-enhanced ultrasound is effective in predicting the findings of hepatic venogram, and type II (showing negative parenchymal enhancement with detection of hepatic vein) strongly suggests the shunt-modified venogram.[16] Sonograms taking in these cases would be superfluous with the added advantage of avoiding unnecessary radiation

exposure. Third pitfall is the deep sedation; that with propofol and remifentanil adds substantial variability and uncertainty to HVPG measurements.[17]

There are two different therapeutic methods for patients with portal hypertension showing opposite effect, BRTO/PARTO which increases portal pressure and TIPS which decreases portal pressure. HVPG is an effective marker to predict the clinical outcomes of patients with guiding treatment direction including TIPS for variceal rebleeding in cirrhosis, for the prognosis after TIPS placement for refractory ascites, and to predict the outcomes (aggravation of esophageal varices, and changes of liver function) after BRTO/PARTO.[18-23]

In conclusion, hepatic venous catheterization is a safe technique which enables measurement of HVPG and characterization of chronic liver diseases. Care should be taken when performing this technique and interpreting the data by assessing the tips and pitfall.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749-1761.
2. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS; Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.
3. Ge PS, Runyon BA. Treatment of Patients with Cirrhosis. N Engl J Med 2016;375:767-777.
4. Turon F, Casu S, Hernandez-Gea V, et al. Variceal and other portal hypertension related Bleeding. Best Pract Res Clin Gastroenterol 2013;27:649-664.
5. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310-335.
6. Bosch J, Garcia-Pagan JC, Berzigotti A, et al. Measurement of portal pressure and its role in the management of chronic liver disease. Semin Liver Dis 2006;26:348-362.
7. Bosch J, Abraldes JG, Berzigotti A, et al. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573-582.
8. Abraldes JG, Tarantino I, Turnes J, et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis Hepatology 2003;37:902-908.
9. Abraldes JG, Villanueva C, Bañares R, Aracil C, Catalina MV, Garci A-Pagán JC, Bosch J; Spanish Cooperative Group for Portal Hypertension and Variceal Bleeding. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48:229-236.
10. Moitinho E, Escorsell A, Bandi JC, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology 1999;117:626-631.
11. Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40:793-801.
12. Keiding S, Vilstrup H. Intrahepatic heterogeneity of hepatic venous pressure gradient in human cirrhosis. Scand J Gastroenterol 2002;37:960-964.
13. Osada Y, Kanazawa H, Narahara Y, et al. Wedged hepatic venous pressure does not reflect portal pressure in patients with cirrhosis and hepatic veno-venous communications. Dig Dis Sci 2008;53:7-13.
14. Sakaguchi T, Suzuki S, Inaba K, et al. Analysis of intrahepatic venovenous shunt by hepatic venography. Surgey 2010;147:805-810.
15. Debernardi-Venon W, Bandi JC, García-Pagán JC, et al. CO2 wedged hepatic venography in the evaluation of portal hypertension. Gut 2000;46:856–860.

16. Maruyama H, Kiyono S, Kamesaki H, et al. Saline-enhanced ultrasonography: Prediction of X-ray appearance of hepatic venography in patients with cirrhosis. Scan J Gastroenterol 2014;49:625-631.
17. Reverter E, Blasi A, Abraldes JG, et al. Impact of deep sedation on the accuracy of hepatic and portal venous pressure measurements in patients with cirrhosis. Liver Int. 2014:34:16–25.
18. Gonz´alez, A, Augustin S, Perez M, et al. Hemodynamic response–guided therapy for prevention of variceal rebleeding: An uncontrolled pilot study. Hepatology 2006;44:806-812.
19. Li GQ, Yang B, Liu J, et al. Hepatic venous pressure gradient is a useful predictor in guiding treatment on prevention of variceal rebleeding in cirrhosis. Int J Clin Exp Med 2015;8:19709-16.
20. Lodato F, Berzigotti A, Lisotti A, et al. Transjugular intrahepatic portosystemic shunt placement for refractory ascites: a single-centre experience. Scan J Gastroenterol 2012;47:1494-1500.
21. Park JW, Yoo JJ, Kim SG, et al. Change in portal pressure and clinical outcome in cirrhotic patients with gastric varices after plug-assisted retrograde transvenous obliteration. Gut Liver 2020;14:783-791.
22. Jogo A, Nishida N, Yamamoto A, et al. Factors associated with aggravation of esophageal varices after B-RTO for gastric varices. Cardiovasc Intervent Radiol 2014;37:1243–1250.
23. Uehara H, Akahoshi T, Tomikawa M, et al. Prediction of improved liver function after balloon-occluded retrograde transvenous obliteration: Relation to hepatic vein pressure gradient. J Gastroenterol Hepatol 2012;27:137–141.

Application of Hepatic Venous Pressure Gradient for Predicting Prognosis in Liver Cirrhosis

Young Chang

Soonchunhyang University, Korea

Portal hypertension (PHT) is a common clinical syndrome induced by cirrhosis and is responsible for the major complications of cirrhosis such as ascites, hepatic encephalopathy, and variceal bleeding [1]. PHT is defined as a pathological increase of the portal venous pressure gradient between the portal vein and inferior vena cava.[1,2] Since Myers and Taylor initially used the wedged hepatic venous pressure by occlusive hepatic vein catheterization to estimate portal venous pressure,[3] safe, reproducible, and less invasive methods to estimate the portal venous pressure have been developed.[4] Several indicators of portal hypertensive syndrome have been developed; of these, the measurement of hepatic venous pressure gradient (HVPG) is considered the most direct and accessible approach.[5] HVPG has been regarded as a surrogate indicator of PHT and widely used for risk stratification, prognostic assessment, and monitoring of treatment responses in patients with chronic liver disease.[4,5]

Since mounting evidence has demonstrated that cirrhosis is neither static nor relentlessly progressive, but rather dynamic and sometimes bidirectional, the stratification of cirrhotic patients based on their hemodynamic status in relation with PHT is required.[6] The impact of PHT on the prognosis of cirrhotic patients is well established.[5,7] Currently, reevaluation of the role of PHT indexes combined with conventional scoring systems has been suggested considering that PHT had been regarded as the third parameter most frequently found to be a significant predictor of survival in cirrhosis.[5,7] Several efforts combining PHT to the model for end stage liver disease (MELD) score has been made, considering that the MELD does not directly reflect PHT.[5,8-10] Although adding to the MELD common complications of PHT such as ascites, variceal bleeding, spontaneous bacterial peritonitis, and hepatic encephalopathy had improved the predictive power of the model to a minimum in the initial validation,[8,11] other studies have shown that the inclusion of hepatic encephalopathy or moderate ascites improves the prognostic value of the MELD.[9,10] However, each individual PHT-related complication reflects only a single aspect but not the unique hemodynamics of the portal hypertensive syndrome as a whole.[5] In this context, HVPG can be potentially used as a variable that reflects PHT properly because it is a directly measured portal pressure expressed by numeric scale. Several studies have confirmed HVPG as a prognostic indicator of death in cirrhosis.[5,12]

Recently, large-scale Asian population cohort studies have been reported that HVPG plays a beneficial role as a prognostic marker in patients with cirrhosis. Kim and Suk et al.[13] demonstrated that there were significant differences in mortality rates between groups stratified according to HVPG, and proposed a new cut-off value for HVPG that differentiate the prognosis of cirrhotic patients. Especially in patients with hypoalbuminemia or intermediate MELD score, the mortality rate were significantly higher for HVPG of

13–20 mmHg (hazard ratio [HR], 2.54 and 3.85, respectively) and HVPG >20 mmHg (HR, 5.45 and 8.77, respectively) than for HVPG of 6–12 mmHg. Chang and Suk et al.[14] derived a new prognostic model, the H6C score, using the HVPG and Child-Pugh score to predict prognosis in cirrhotic patients with low MELD score. Patients with an H6C score below 45 demonstrated an excellent overall survival with a 5-year survival rate of 91.5%, whereas patients with an H6C score above 64 showed a dismal prognosis with a 5-year survival rate of 51.1%. The H6C score showed great predictive power for overall survival with a time-dependent area under the curve (AUC) of 0.733, which was much improved to 0.850 in patients with viral etiology. The authors suggested to consider early liver transplantation in patients with H6C above 64, even when the MELD score is low.

In conclusion, HVPG represents the actual dynamic status of cirrhosis and can be utilized as a useful indicator in predicting the prognosis of cirrhotic patients.

References

1. Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. Gastroenterology 2008;134:1715-1728.
2. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: rational basis, available treatments and future options. J Hepatol 2008;48 Suppl 1:S68-92.
3. Myers JD, Taylor WJ. Occlusive hepatic venous catheterization in the study of the normal liver, cirrhosis of the liver and noncirrhotic portal hypertension. Circulation 1956;13:368-380.
4. Suk KT. Hepatic venous pressure gradient: clinical use in chronic liver disease. Clin Mol Hepatol 2014;20:6-14.
5. Ripoll C, Banares R, Rincon D, Catalina MV, Lo Iacono O, Salcedo M, et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. Hepatology 2005;42:793-801.
6. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445-1449.
7. Pagliaro L. MELD: the end of Child-Pugh classification? J Hepatol 2002;36:141-142.
8. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
9. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. J Hepatol 2004;40:897-903.
10. Somsouk M, Kornfield R, Vittinghoff E, Inadomi JM, Biggins SW. Moderate ascites identifies patients with low model for end-stage liver disease scores awaiting liver transplantation who have a high mortality risk. Liver Transpl 2011;17:129-136.
11. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567-580.
12. Ripoll C. Hepatic venous pressure gradient and outcomes in cirrhosis. J Clin Gastroenterol 2007;41 Suppl 3:S330-335.
13. Kim TY, Suk KT, Jeong SW, Ryu T, Kim DJ, Baik SK, et al. The New Cutoff Value of the Hepatic Venous Pressure Gradient on Predicting Long-Term Survival in Cirrhotic Patients. J Korean Med Sci 2019;34:e223.
14. Chang Y, Suk KT, Jeong SW, Yoo JJ, Kim SG, Kim YS, et al. Application of Hepatic Venous Pressure Gradient to Predict Prognosis in Cirrhotic Patients with a Low Model for End-Stage Liver Disease Score. Diagnostics (Basel) 2020;10.

Tailored Treatment of Cirrhotic Complications According to Hepatic Venous Pressure Gradient

Jung Gil Park

Yeungnam Universtiy, Korea

The clinical states of cirrhosis is usually divided into compensated and decompensated cirrhosis, and can be staged using multi-stage model according to recent guideline.[1] However, there was no decision making guidance using these multi-stage model in clinical practice at present. The risk of patients for clinical decision making can be stratified with various score-based models including Child-Pugh (CP) score, and Model for End stage Liver Disease (MELD) score. Child-Pugh score is widely used in decision for treatment of hepatocellular carcinoma and antiviral treatment.[2-4] MELD score is initially used for stratification of transjugular intrahepatic portosystemic shunt and now widely used for setting priority of liver transplantation recipients.[5] Factors in CP score includes clinical condition, such as encephalopathy and ascites, but factors in MELD score includes only laboratory data, sush as bilirubin, creatinine, and INR. While clinical factors in score system reflect clinical condition of the patients well, its predictive performance can be varied by clinician in practice.

Hepatic venous pressure gradient (HVPG) is considered as gold standard for assessment of portal hypertension (PH), which correlated with stage of fibrosis, variceal bleeding, ascites, and mortality.[6] Though measurement of HVPG is invasive, it reflects PH accurately and has a very low variability. In addition, it can be measured as continuous trait like MELD score as well as reflect pathophysiological condition of patients like CP score. A recent study has demonstrated that HVPG could predict prognosis of cirrhotic patients with a low MELD score.[7]

Repeated measurement of HVPG as has considered as a treatment target in the prevention of variceal rebleeding.[8] A recent study has suggested immediate HVPG decease $\geq$ 10% as a surrogate endpoint for decreasing intrahepatic resistance, which prevented hepatic decompensation, in patients who achieved sustained virologic response to interferon-free therapy.[9]

In this session, we discuss HVPG as a surrogate marker to treat cirrhotic complication.

References

1. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563-576.
2. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-380.
3. Korean Association for the Study of the L. 2017 KASL clinical practice guidelines management of hepatitis C: Treatment of chronic hepatitis C. Clin Mol Hepatol 2018;24:169-229.

4. Korean Association for the Study of the L. KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2019;25:93-159.
5. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
6. Suk KT. Hepatic venous pressure gradient: clinical use in chronic liver disease. Clin Mol Hepatol 2014;20:6-14.
7. Chang Y, Suk KT, Jeong SW, Yoo JJ, Kim SG, Kim YS, et al. Application of Hepatic Venous Pressure Gradient to Predict Prognosis in Cirrhotic Patients with a Low Model for End-Stage Liver Disease Score. Diagnostics (Basel) 2020;10.
8. Villanueva C, Graupera I, Aracil C, Alvarado E, Minana J, Puente A, et al. A randomized trial to assess whether portal pressure guided therapy to prevent variceal rebleeding improves survival in cirrhosis. Hepatology 2017;65:1693-1707.
9. Mandorfer M, Kozbial K, Schwabl P, Chromy D, Semmler G, Stattermayer AF, et al. Changes in Hepatic Venous Pressure Gradient Predict Hepatic Decompensation in Patients Who Achieved Sustained Virologic Response to Interferon-Free Therapy. Hepatology 2020;71:1023-1036.

Non-Invasive Estimation of Hepatic Venous Pressure Gradient

Young Seo Cho

Hanyang University, Korea

Portal hypertension (PH) is defined as an increased hepatic venous pressure gradient (HVPG) and represents a common complication of liver cirrhosis. The current gold standard of portal hypertension evaluation is HVPG measurement and obviously an invasive technique requiring venous catheterization. A major challenge for patients with chronic liver disease (CLD) and PH remains the ability to assess disease severity, risk of decompensation events, and predict outcome. Non-invasive methods that can be reliably used to estimate the presence and the degree of portal hypertension are urgently needed in clinical practice.

Serum marker

Many attempts have been made to detect and quantify PH using serum biomarkers, and a series of models for PH detection have been proposed. Despite substantial efforts to generate such a method, up until a few years ago only disappointing and unsatisfactory results were obtained. Since the primary cause of PH is the mechanical increase in intrahepatic resistance due to fibrosis and distortion of liver architecture, it is reasonable to assume that non-invasive parameters of liver fibrosis may indicate the presence of portal hypertension.

Grayscale and Doppler US

Ultrasonography (US) is a mainstay in the assessment of patients with chronic liver disease; a noninvasive, widely available, and inexpensive technique that allows the evaluation of liver morphology as well as of functional parameters with Doppler US Gray scale ultrasonography allows the evaluation of various elements including the liver size and its surface, the coarseness of the parenchyma, portal vein dilatation (diameter > 13 mm) and thrombosis, and the presence of signs of PH. The main signs (pathognomonic) of PH are the presence of portosystemic collaterals (flow in paraumbilical vein and development of splenorenal collaterals) and the reversal of portal vein flow. Doppler US can evaluate several parameters related with blood hemodynamics, such as portal vein velocity, congestion index, pulsatility index, and hepatic vein Doppler US pattern. However, none of these parameters allowed the grading of portal hypertension. It is clear that the findings of collaterals or of ascites associate with severe PH and a worse prognosis, however, the above mentioned US parameters show a poor correlation with HVPG and cannot, at the present time, substitute HVPG measurement

Liver stiffness

More attractive is the measurement of tissue elastography which may be accomplished by transient

elastography (TE, FibroScan®, Echosens, Paris, France) or different shear-wave-based techniques, such as point-shear wave elastography (p-SWE) and two-dimensional shear wave elastography (2D-SWE) that have been developed and incorporated in ultrasound equipment. Both p-SWE and 2D-SWE are based on acoustic radiation force impulse imaging (ARFI).

Elastography techniques are commonly used for the evaluation of liver fibrosis and in the evaluation of PH. A meta-analysis, performed on 18 studies, showed that liver stiffness (LS) has high accuracy (90% sensitivity, 79% specificity, and an AUC of 0.93) for the detection of clinically significant PH. Recently, the Baveno VI Consensus Conference recommended LS values of 20–25 kPa as an accurate cutoff to identify patients with clinically significant PH. Despite the good results described in different studies, the main drawbacks of liver TE are the low accuracy in obese patients and the overestimation of LS in patients with elevated ALT serum values. Several studies have shown that the accuracy of p-SWE for the evaluation of liver fibrosis is comparable to that of TE. Similar to TE, p-SWE has been studied as a noninvasive tool to evaluate PH. However, studies published until now have reported conflicting results about the correlation of p-SWE and HVPG. Real-time 2D-SWE, which was developed subsequent to TE, can measure tissue elasticity with the real-time guidance of B-mode image. Recently there have been many studies of 2D-SWE, related especially to examination technique and clinical applications. In this article, we review the focusing 2D SWE technique using the Aixplorer ultrasound (US) system. As expected, 2D-SWE performed as well as TE in assessing liver fibrosis with a higher accuracy in the diagnosis of mild and severe fibrosis and with a greater applicability. More recently, studies from different groups have reported a moderate or good correlation of 2D-SWE with HVPG suggesting that it might be a useful tool in the assessment of PH. Another modality of elastography of the liver is MR elastography (MRE). Recent meta-analyses have reported good results for MRE in the evaluation of fibrosis. Differently from US-based methods, MRE allows the evaluation of the entire liver and is not limited by body habitus or meteorism. Recent meta-analyses have reported good results for MRE in the evaluation of fibrosis. Differently from US-based methods, MRE allows the evaluation of the entire liver and is not limited by body habitus or meteorism. However, long-term studies are not available yet and, as abovementioned, its use is limited by costs.

Spleen stiffness

According to a recent meta-analysis, Spleen Stiffness (SS) values measured by 2D-SWE are useful for predicting clinically significant PH in CLD. They are significantly correlated with the presence of esophageal varix, and are superior to LS values. In addition, 2D-SWE can check real-time grayscale images at the time of measurement, so that SS can be measured in the most appropriate region. SS is measured by left intercostal or subcostal scans, and is not fundamentally different from LS measurements. The spleen is smaller than the liver and varies in size, and the measurement success rate is lower than that of LS (over 90%). The success rate of SS in all patient groups according to the meta-analysis was 75.5%, and most of the studies included (many) portal hypertension patients with advanced liver cirrhosis. However in a study by Grgurevic et al, which included many non-cirrhotic chronic liver disease patients, the success rate of SS measurements was only 53.7%. As spleen size increases, the measurement success rate of SS by 2D-SWE also increases, so that the LS and SS success rates are not significantly different in patients with advanced liver cirrhosis versus severe portal hypertension.

CT and MR Morphological and Quantitative parameters

About CT, scan irradiation represents another factor weighing on its use. This radiologic technique can give an accurate representation of the morphology of the portal venous system and on the presence and extent of thrombosis as well as on the presence of collaterals. This accurate imaging may be particularly useful before TIPS placement in patients with posthepatic PH such as in the Budd-Chiari syndrome. With regard to varix detection, the performance of CT and MRI are good for large varices, but lower for small varices. Recent advances in imaging-based three-dimensional modeling combined with computational fluid dynamics analysis have permitted noninvasive calculation of blood flow pressure. Relevant techniques have been successfully applied in the coronary artery for the diagnosis of ischemia. In this study, A computational model based on CT angiographic images, which termed virtual HVPG enabled the accurate estimation of HVPG in patients with cirrhosis.

References

1. de Franchis R, Baveno VIF (2015) Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 63 (3):743-752.
2. Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, Schiumerini R, Turco L, Di Biase AR, Mazzella G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology. 2012;143:646–654.
3. Procopet B, Berzigotti A, Abraldes JG, Turon F, Hernandez-Gea V, García-Pagán JC, Bosch J. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol. 2015;62:1068–1075.
4. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, Pinzani M, Bosch J. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology. 2013;144:102–111.e1
5. Massimo B, Marco DP, David S Clinical role of non-invasive assessment of portal hypertension World J Gastroenterol. 2017 Jan 7; 23(1): 1–10
6. Paul K, Octavia B, Stefanie JH et al. Noninvasive imaging assessment of portal hypertension Abdom. Radiol. 2020 45(11): 3473-3495
7. Federico Ravaioli, Marco Montagnani, Andrea Lisotti Noninvasive Assessment of Portal Hypertension in Advanced Chronic Liver Disease: An Update Gastroenterol Res Pract. 2018: 1-11
8. Kim G, Cho YZ, Baik SK, Kim MY, Hong WK, Kwon SO (2015) The accuracy of ultrasonography for the evaluation of portal hypertension in patients with cirrhosis: a systemic review. Korean J Radiol 16:314–324. 10.3348
9. Grgurevic I, Bokun T, Salkic NN et al. Liver elastography malignancy prediction score for noninvasive characterization of focal liver lesions. Liver Int. 2018;38:1055–1063.
10. Jeong JY, Cho YS, Sohn JH. Role of two-dimensional shear wave elastography in chronic liver diseases: a narrative review. World J Gastroenterol 2018;24:3849–3860.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (16:30-17:50)

ROOM 4

Special Interest Group Forum 5

Korea Alcohol-Related Problems Study Group: New Insight into Alcoholic Hepatitis

Chairs:

Dong Joon Kim (Hallym Univ.)

Jae Young Jang (Soonchunhyang Univ.)

Microbiome as a Potential Diagnostic Biomarker in Severe Alcoholic Hepatitis

Soon Sun Kim

Ajou University, Korea

Severe alcoholic hepatitis (SAH) is a serious form of acute decompensation of alcoholic liver disease, which is characterized by the rapid onset of jaundice, malaise, anorexia, tender hepatomegaly and features of systemic inflammatory response syndrome.[1] The Maddrey discriminant function (MDF) formula was developed in 1977, and patients with MDF >32 showed high 28-day mortality (>50%) and benefited from treatment with glucocorticoids.[2,3]

The gut-liver axis is a major pathway for alcoholic liver disease development and progression. The liver plays an essential role in the modulation of gut microbiota and its effects through multiple routes, including bile acid production and enterohepatic circulation, as well as by modulating the responsiveness to gut bacterial end products and nutrients received via the portal vein.[4] Patients with SAH show dysbiosis of the gut microbiome, characterized by an increase in streptococci, enterobacteria, bifidobacteria and Actinobacteria, and a decrease in *Atopobium, Akkermansia muciniphila* and Bacteroidetes.[5-7] In a previous study, transfer of dysbiotic human faecal microbiota into germ-free or conventionally raised mice conferred increased susceptibility to alcoholic liver disease.[5]

We conducted the case-control study that enrolled the 24 patients with SAH and 24 healthy controls.[8] Through comparing the gut microbiome composition in 24 patients with SAH and 24 healthy controls, we selected 144 common taxa that showed increased or decreased abundances in patients for both bacteria and bacteria-derived EVs. Furthermore, we revealed 15 common taxa in bacteria and EVs that showed a significant pattern of recovery after rifaximin treatment, 6 of which decreased in abundance and 9 of which increased in abundance after rifaximin administration. Among them, *Veillonella* and *Veillonella parvula* group showed the most significant increases in patients with SAH, and they significantly decreased after rifaximin treatment. Moreover, *Prevotella* and Prevotellaceae were significantly less abundant in patients with SAH and were restored after rifaximin treatment.

References

1. Mitchell MC, Friedman LS, McClain CJ. Medical management of severe alcoholic hepatitis: expert review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol. 2017; 15: 5- 12.
2. Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology. 1978; 75: 193- 199.
3. Carithers RL Jr, Herlong HF, Diehl AM, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med. 1989; 110: 685- 690.

4. Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol. 2019; 16: 235- 246.
5. Llopis M, Cassard AM, Wrzosek L, et al. Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease. Gut. 2016; 65: 830- 839.
6. Grander C, Adolph TE, Wieser V, et al. Recovery of ethanol-induced Akkermansia muciniphila depletion ameliorates alcoholic liver disease. Gut. 2018; 67: 891- 901.
7. Ciocan D, Voican CS, Wrzosek L, et al. Bile acid homeostasis and intestinal dysbiosis in alcoholic hepatitis. Aliment Pharmacol Ther. 2018; 48: 961- 974.
8. Kim SS, Eun JW, Cho HJ, et al. Microbiome as a potential diagnostic and predictive biomarker in severe alcoholic hepatitis. Aliment Pharmacol Ther. 2021; 53: 540– 551.

Prognosis and Outcome of Patients with Alcohol-Associated Acute-On-Chronic Liver Failure

Eileen L. Yoon

Hanyang University, Korea

Definition of acute-on-chronic liver failure (ACLF)

The concept of ACLF is widely accepted.[1,2] and the prevalence of ACLF is predicted to be 40% in admitted decompensated cirrhosis patients.[3] Although the definitions are not unified, they share common prerequisites in the definition that ACLF is distinguished from the mere acute decompensation. Additionally, ACLF is characterized by the presence of either hepatic or extrahepatic organ failures which develops in the setting of chronic liver disease (including liver cirrhosis), with high short-term mortality.

Alcohol as the important precipitating factor of ACLF

Alcohol is the most common etiology for the liver disease and the second most common types of hepatic insult or precipitating factors for ACLF regardless of the regions.[3] Serste et al. reported that ACLF was prevalent in 47.9% of the biopsy-proven alcoholic hepatitis (AH) with modified DF scores over 32.[4] The cumulative incidence of ACLF among biopsy-proven severe AH was 23% (95% C.I 15-33) at day 28 and 33% (95% C.I 24-44) at day 168. Prior incidental infection was the only independent variable predicting the ACLF incidence in 28-day. However, about the half the patients who had ACLF were without any overt infection.

PIRO (Predisposition, Injury, Response, Organ failure) concept in Alcohol-related ACLF

- Predisposition
  - Age, Alcohol as etiology of liver disease, Presence of previous decompensation
- Injury (Precipitating factors)
  - Active alcohol consumption, bacterial infection (cf. not categorized as a hepatic insult in AARC definition)
- Response
  - Associated infection, systemic inflammation, and/or immune failure
- Organ failure
  - Type and number of organ failure

Prognosis of alcohol - associated ACLF

Prognosis can be affected by each component of PIRO and their effect may be accentuated when they

are combined. Among those with prevalent ACLF with severe AH, 28-day and 168-day cumulative incidence of death were 54% (95% C.I 43-59) and 71% (95% C.I 65-79), getting worse with the severity of ACLF grades. The relative risk of death in patients with incident ACLF was 41.87 (95% C.I 5.231-335.1, *P*<0.001) at day 28.[4]

Factors affecting the prognosis of alcohol-associated ACLF are listed as below.

- Grades of ACLF at baseline and 3rd to 7th day[1,5]
  - CLIF-C ACLF
    - CLIF-C ACLF grade, CLIF-C Organ failure score
    - Number or types of organ failure (kidney and/or neurological)
  - APASL ACLF Research Consortium score
    - Active alcohol consumption in 50%
    - Bilirubin, hepatic encephalopathy, INR, lactate, serum Creatinine[2]
- Grade of systemic inflammation
  - CLIF-C ACLF score[6]
    - Combining organ failure with age and WBC count

Summary

ACLF is frequently developed in alcoholic liver disease and reveals high short-term mortality. Understanding the PIRO concept may be the basis for the prediction of prognosis in alcohol-associated ACLF. The interaction between infection/inflammation/immune dysfunction and alcohol-associated ACLF may be important to understand the characteristics of alcohol-associated ACLF.

References

1. Moreau, R., et al., Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology, 2013. 144(7): p. 1426-37, 1437.e1-9.
2. Sarin, S.K., et al., Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int, 2019. 13(4): p. 353-390.
3. Mezzano, G., et al., Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. Gut, 2021.
4. Sersté, T., et al., The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol, 2018. 69(2): p. 318-324.
5. Gustot, T., et al., Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology, 2015. 62(1): p. 243-52.
6. Jalan, R., et al., Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol, 2014. 61(5): p. 1038-47.

Clinical, Histological, and Molecular Profiling of Different Stages of Alcohol-Related Steatohepatitis

Ramon Bataller

University of Pittsburgh, USA

Non-Invasive Diagnosis and Biomarkers in Alcohol-Related Liver Disease

Young Kul Jung

Korea University, Korea

Alcohol is a key risk factor for liver-related and overall mortality, contributing to 3.3 million annual deaths worldwide. Liver biopsy is considered the gold standard for establishing a definite diagnosis and assessing the fibrosis of alcoholic liver disease (ALD), however, it is an invasive procedure, associated with significant morbidity and mortality. During the last decade, non-invasive technique have been developed to measure the severity of liver fibrosis and steatosis. Although ultrasound is still accepted as an initial screen for fatty liver diagnosis, new methods have recently been developed to detect steatosis. Controlled attenuation parameter (CAP) is a novel method for the non-invasive assessment of steatosis, which measures the increased attenuation of ultrasound waves when penetrating fatty hepatic tissue. And also, magnetic resonance imaging techniques are highly accurate and reproducible, with superior sensitivities and specificities for detecting histological steatosis than ultrasound. But, low availability and high cost is huddle to use magnetic resonance techniques in routine clinical practice. Biochemical tests have also been evaluated to assess liver fibrosis in ALD. The commercially available Enhanced Liver Fibrosis test and FibroTest have comparable performance for the diagnosis of advanced fibrosis in ALD, with studies suggesting that they are comparable to FIB-4 and APRI. Measurement of liver stiffness by transient elastography has become the most commonly used non-invasive parameter to evaluate fibrosis. In ALD, transient elastography shows an excellent performance to detect advanced fibrosis and cirrhosis. In ALD pathologic progression is largely driven by inflammatory responses. In general, infection and cell death are the 2 most common reasons for inflammation, and Emerging data from both preclinical and clinical studies suggest some of the inflammatory mediators identified may serve as potential diagnostic markers. miRNAs and EVs play a critical role in controlling liver inflammation in ALD by regulating the expression of a variety of inflammatory genes and promoting cell-cell communication, respectively. MiR-122, a hepatocyte-specific miRNA, protects against liver inflammation and injury in ALD by inhibiting hypoxia-inducible factor 1a. TNF and IL-6 in various cytokines upregulated in ALD promote inflammation and also enhance liver regeneration. IL-22 plays a key role in preventing liver injury, promoting liver regeneration, and suppressing bacterial infection by specifically targeting hepatocytes without affecting inflammatory cells. ALD shows activation of innate immunity components such as Kupffer cells/LPS/TLR4 and complements or inhibition of innate immunity components such as natural killer (NK) cells. New serum biomarkers are under investigation to non-invasively diagnose more severe forms of ALD and to predict prognosis of patients. Through this issue, we will review the non-invasive diagnosis and biomarkers in ALD.

References

1. Chin JL, Chan G, Ryan JD. Noninvasive Assessment of Liver Fibrosis and Cirrhosis With Ultrasound-based Elastography in Alcohol-related Liver Disease. Gastroenterology 2016;150:1251-1252.
2. Cho Y, Choi YI, Oh S, et al. Point shear wave elastography predicts fibrosis severity and steatohepatitis in alcohol-related liver disease. Hepatol Int 2020;14:270-280.
3. Claria J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249-1264.
4. Fan X, McCullough RL, Huang E, et al. Diagnostic and Prognostic Significance of Complement in Patients With Alcohol-Associated Hepatitis. Hepatology 2021;73:983-997.
5. Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in alcoholic steatohepatitis. J Hepatol 2019;70:249-259.
6. Gao B, Seki E, Brenner DA, et al. Innate immunity in alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol 2011;300:G516-525.
7. Gustot T, Jalan R. Acute-on-chronic liver failure in patients with alcohol-related liver disease. J Hepatol 2019;70:319-327.
8. Israelsen M, Guerrero Misas M, Tsochatzis EA. Editorial: can quantitative fibrosis assessment be used to enhance prediction of outcomes in patients with alcohol-related liver disease? Authors' reply. Aliment Pharmacol Ther 2021;53:185-186.
9. Lackner C, Tiniakos D. Fibrosis and alcohol-related liver disease. J Hepatol 2019;70:294-304.
10. Moodley P, Dhanda AD. Editorial: can quantitative fibrosis assessment be used to enhance prediction of outcomes in patients with alcohol-related liver disease? Aliment Pharmacol Ther 2021;53:183-184.
11. Moreno C, Mueller S, Szabo G. Non-invasive diagnosis and biomarkers in alcohol-related liver disease. J Hepatol 2019;70:273-283.
12. Nguyen-Khac E, Thiele M, Voican C, et al. Non-invasive diagnosis of liver fibrosis in patients with alcohol-related liver disease by transient elastography: an individual patient data meta-analysis. Lancet Gastroenterol Hepatol 2018;3:614-625.
13. Ryu SR, Yoo JJ, Kang SH, et al. The cut-off value of transient elastography to the value of hepatic venous pressure gradient in alcoholic cirrhosis. Clin Mol Hepatol 2021;27:197-206.
14. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: From physiopathology to therapy. J Hepatol 2016;64:1403-1415.
15. Thiele M, Rausch V, Fluhr G, et al. Controlled attenuation parameter and alcoholic hepatic steatosis: Diagnostic accuracy and role of alcohol detoxification. J Hepatol 2018;68:1025-1032.

The Liver Week 2021

DAY 2: Friday, May 14, 2021 (16:30-18:00)

ROOM 5

KLTS Coordinator Session

Chairs:

Kyung-Ock Jeon (Severance Hospital)

Seung Heui Hong (Samsung Medical Center)

Latest Treatment Drugs for Hepatitis B and C and Treatment of Hepatitis D and E

Wonseok Kang

Sungkyunkwan University, Korea

Liver disease related to chronic viral hepatitis is the leading indication for liver transplantation worldwide. Viral reinfection or superinfection of the liver allograft may lead to graft failure, death, or the need for re-transplantation. Among the various types of hepatitis virus, hepatitis B (HBV) and hepatitis C virus (HCV) infection account for most of the recurrence of viral hepatitis after liver transplantation. Over the last decade, our understanding and management of HBV and HCV infection has evolved rapidly. Long term suppression of HBV replication has become successful with currently available nucleos(t)ide analogues, while HCV cure has become possible with recently developed direct-acting antiviral drugs. With recent advances in the treatment of chronic HBV and HCV infection, a significant reduction in the recurrence of HBV or HCV infection after transplantation has been achieved, leading to improvement of long-term survival. Our understanding of hepatitis D virus (HDV) or hepatitis E virus (HEV) has also changed dramatically over the past decade. Post transplantation infection with HDV or HEV frequently evolves to chronic infection with a rapid progression of fibrosis to cirrhosis. This talk will address recent advances and knowledge gaps in the clinical aspects and management of viral hepatitis in liver transplantation.

What Are the Optimal Time and Proper Indication for Simultaneous Liver-Kidney Transplantation?

Man Ki Ju

Yonsei University, Korea

No matter pre- or post-transplantation, kidney injury is associated with increased morbidity and mortality in liver transplant recipients.

As the incidence of severe kidney dysfunction has increased over the past decade, for liver transplant candidates with severe kidney dysfunction, simultaneous liver-kidney transplantation (SLKT) has emerged as an important treatment option.

However, there have been no well-defined guidelines to determine whether a kidney transplant should be offered to liver transplant candidates who have chronic kidney disease (CKD) or prolonged acute kidney injury while awaiting a liver transplant and the survival benefit of simultaneous liver-kidney transplantation (SLKT) over liver transplantation alone (LTA) is unclear from the current literature.

Rates of simultaneous liver-kidney transplantation (SLKT) have continued to increase despite lack of clear allocation guidelines and outcomes data, because kidney recovery after liver transplant alone (LTA) is difficult to predict, indications for SLK are not precisely defined. For example, candidates with hepatorenal syndrome can have kidney recovery after as much as 12 weeks on dialysis, whereas those with chronic kidney disease (CKD) may have early end-stage renal disease (ESRD) after LTA because of perioperative events and calcineurin inhibitor exposure.

During 1000 cases of liver transplantation in Severance Hospital, We experienced 16 cases of liver-kidney transplantations. In 16 cases, 14 cases was performed simultaneous liver-kidney transplantation (SLKT), 2 cases of liver after kidney transplantation (KT), and two cases of kidney after liver transplantation (LT).

In this paper, we present the consensus and guidelines of liver-kidney transplantation such as optimal time and proper indication for Liver-Kidney transplantation based on our liver-kidney transplantation experiences and recent literature review.

Latest Issues in the Liver Transplant Site

Hyung Sook Kim

Seoul ST. Mary's Hospital, Korea

Despite the outbreak of Covid 19, Organ donation has increased, 395 liver transplantations by brain deaths was done in 2020.

According to the KONOS annual report, 36 liver split transplantations were implemented in 2019.

According to the MELD score system, the number of liver transplant patients by brain death due to alcoholic liver disease still increased from 28.95% in 2015 to 42.7% in 2019.

If the hospital that decided to transplant the liver by brain death during the harvesting gives up the transplant, KONOS check up to 5 hospitals that will receive the liver, and if there is no hospital to receive the liver, proceed as organ inadequacy.

If a transplant recipient is selected, but the recipient is unable to receive a transplant due to death or worsening condition after procuring a liver from the donor, the Chairman KONOS selects the first recipient of all those waiting for a liver transplant up to Emergency 2 level.

If not selected at this time, the head of the transplant medical institution where the transplant was scheduled will select the recipient.

Efforts to reflect the various difficulties in the field are continuing.

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (08:00-08:30)

ROOM 1

Listen to the Expert

Chair:

Dong Hyun Sinn (Sungkyunkwan Univ.)

Listen to the Expert

Viral Hepatitis: The Path I have Taken as a Clinician and Researcher of Viral Hepatitis

Kwang-Hyub Han

National Evidence-Based Healthcare Collaborating Agency, Korea

DAY 3: Saturday, May 15, 2021 (08:30-09:50)

ROOM 1

KASL Symposium 4

Recent Advances in the Management of Liver Diseases

Chairs:

Il Han Song (Dankook Univ.)

Sang Hoon Park (Hallym Univ.)

ABO-Incompatible Liver Transplantations: Achievements and Remaining Questions

Jong Man Kim

Sungkyunkwan University, Korea

Introduction

In the past, adult ABO incompatible living donor liver transplantation (ABO-I LDLT) had poor graft survival and low patient survival due to hyperacute rejection and a high risk of vascular biliary complication, and it was considered a contraindication.[1-4] Susceptibility to rejection, including severe hepatic necrosis and diffuse intravascular coagulation disorder within the graft, appears to be due to the blood group antigen expressed in the vascular endothelium and bile ducts after transplantation.[5,6] Various desensitization strategies have been introduced to overcome the barrier of ABO incompatibility.[7-9] However, desensitization protocols differ at each center, and the necessity of local infusion, splenectomy, intravenous immunoglobulin (IVIG), and plasmapheresis is controversial. After the rituximab era, the outcome of ABO-I LDLT has been reported in many studies to be comparable to ABO compatible living donor liver transplantation (ABO-C LDLT).[10-13] Many centers are now trying to simplify protocols.[14-20]

Outcomes

Hyperacute rejection has not been reported in most studies since the use of rituximab. Kim et al. reported 100% patient and graft survivals and no AMR in 22 ABO-I LDLT patients with titers adjusted below 1:32 by total plasma exchange.[10] They reported five biliary complication cases. Song et al also reported that patient survival, graft survival, and biopsy proven acute rejection were not significantly different between ABO-I LDLT and ABO-C LDLT.[11] They showed that diffuse intrahepatic bile duct complications were observed in 12 cases in the ABO-I LDLT group. A recent study showed that 47 ABO-I LDLT patients who were compared to a 1:2 matched 94 ABO-C LDLT group did not show significant differences in survival and acute rejection, as well as biliary complications.[12] However, three DIHC cases occurred in the ABO-I LDLT patients and progressed to graft failure.

It is not known whether rituximab prophylaxis for desensitization affects HCC recurrence in ABO-I LDLT. Kim et al. reported that ABO incompatibility was not associated with HCC recurrence. The 1-, 2-, and 3-year disease-free survival rates in ABO-I LDLT and ABO-C LDLT groups were 90.3%, 79.7%, and 73.3% and 86.7%, 79.0%, and 75.3%, respectively P=0.96).[21] The overall patient survival rates for the same period in the ABO-I LDLT and ABO-C LDLT groups were 90.6%, 85.0%, and 81.9% and 88.0%, 83.5%, and 82.5%, respectively (P=0.77).[21] They had shown that AFP, tumor size, encapsulation and microcirculation invasion were associated with HCC recurrence except in ABO-incompatibility. Propensity score match

study had shown comparable recurrence-free survival rates and overall patient-survival outcomes between ABO-I LDLT and ABO-C LDLT groups.[22]

Conclusion

ABO-I LDLT is a very effective and safe method for extending a raw pool of liver donors. Survival outcomes are now comparable with rituximab prophylaxis and plasmapheresis. However, there is still concern about the high incidence of biliary complication especially diffuse intrahepatic biliary complications, an intractable form of biliary stenosis that can occur regardless of the isoagglutinin titer. Therefore, we need to closely follow the patient course over several months after ABO-I LDLT even in patients with very low isoagglutinin titers after ABO-I LDLT. In the future, we need to identify certain risks and precautions through studies involving immunology and adaptive mechanisms in ABO-I LDLT.

References

1. Demetris, A.J., et al., Antibody-mediated rejection of human orthotopic liver allografts. A study of liver transplantation across ABO blood group barriers. Am J Pathol, 1988. 132(3): p. 489-502.
2. Gugenheim, J., et al., Liver transplantation across ABO blood group barriers. Lancet, 1990. 336(8714): p. 519-23.
3. Farges, O., et al., The use of ABO-incompatible grafts in liver transplantation: a life-saving procedure in highly selected patients. Transplantation, 1995. 59(8): p. 1124-33.
4. Lo, C.M., A. Shaked, and R.W. Busuttil, Risk factors for liver transplantation across the ABO barrier. Transplantation, 1994. 58(5): p. 543-7.
5. Kawagishi, N. and S. Satomi, ABO-incompatible living donor liver transplantation: new insights into clinical relevance. Transplantation, 2008. 85(11): p. 1523-5.
6. Egawa, H., et al., Impact of recipient age on outcome of ABO-incompatible living-donor liver transplantation. Transplantation, 2004. 77(3): p. 403-11.
7. Ikegami, T., et al., Rituximab, IVIG, and plasma exchange without graft local infusion treatment: a new protocol in ABO incompatible living donor liver transplantation. Transplantation, 2009. 88(3): p. 303-7.
8. Egawa, H., et al., Present status of ABO-incompatible living donor liver transplantation in Japan. Hepatology, 2008. 47(1): p. 143-52.
9. Raut, V. and S. Uemoto, Management of ABO-incompatible living-donor liver transplantation: past and present trends. Surg Today, 2011. 41(3): p. 317-22.
10. Kim, J.M., et al., ABO-incompatible living donor liver transplantation is suitable in patients without ABO-matched donor. J Hepatol, 2013. 59(6): p. 1215-22.
11. Song, G.W., et al., Biliary stricture is the only concern in ABO-incompatible adult living donor liver transplantation in the rituximab era. J Hepatol, 2014. 61(3): p. 575-82.
12. Kim, J.M., et al., Case-matched comparison of ABO-incompatible and ABO-compatible living donor liver transplantation. Br J Surg, 2016. 103(3): p. 276-83.
13. Song, G.W., et al., ABO-Incompatible Adult Living Donor Liver Transplantation Under the Desensitization Protocol With Rituximab. Am J Transplant, 2016. 16(1): p. 157-70.
14. Yamamoto, H., et al., Feasibility of Monotherapy by Rituximab Without Additional Desensitization in ABO-incompatible Living-Donor Liver Transplantation. Transplantation, 2018. 102(1): p. 97-104.
15. Kim, S.H., et al., A simplified protocol using rituximab and immunoglobulin for ABO-incompatible low-titre living donor liver transplantation. Liver Int, 2018. 38(5): p. 932-939.
16. Lee, E.C., et al., A comparison of desensitization methods: Rituximab with/without plasmapheresis in ABO-incompatible living donor liver transplantation. Hepatobiliary Pancreat Dis Int, 2018. 17(2): p. 119-125.

17. Kim, J.D., et al., Single-Center Experience of ABO-Incompatible Living-Donor Liver Transplantation With a New Simplified Intravenous Immunoglobulin Protocol: A Propensity Score-Matching Analysis. Transplant Proc, 2016. 48(4): p. 1134-8.
18. Lee, J., et al., Results of ABO-incompatible liver transplantation using a simplified protocol at a single institution. Transplant Proc, 2015. 47(3): p. 723-6.
19. Lee, S.D., et al., ABO-incompatible living donor liver transplantation without graft local infusion and splenectomy. HPB (Oxford), 2014. 16(9): p. 807-13.
20. Raut, V., et al., Splenectomy does not offer immunological benefits in ABO-incompatible liver transplantation with a preoperative rituximab. Transplantation, 2012. 93(1): p. 99-105.
21. Kim, J.M., et al., ABO-incompatible Living Donor Liver Transplantation With Rituximab and Total Plasma Exchange Does Not Increase Hepatocellular Carcinoma Recurrence. Transplantation, 2018. 102(10): p. 1695-1701.
22. Yoon, Y.I., et al., Outcome of ABO-incompatible adult living-donor liver transplantation for patients with hepatocellular carcinoma. J Hepatol, 2018. 68(6): p. 1153-1162.

Management of Immune-Related Adverse Events Caused by Immune Checkpoint Inhibitors

Tae Yong Kim

Seoul National University, Korea

Recently, cancer immunotherapy is actively studied in hepatocellular carcinoma and some immune checkpoint inhibitors (ICIs) show a promising clinical outcomes. Atezolizumab and bevacizumab improved overall survival, compared with sorafenib and this combination has been introduced in real practice. As ICIs are used in practice, we experienced new adverse events of ICIs which are different from conventional chemotherapy or tyrosine kinase inhibitors. These immune-related adverse events (irAEs) could be developed in all kinds of organs in any time of treatment, it is essential to early detect and to immediately manage irAEs

Endocrinopathy are commonly observed irAE in patients who received PD-1/PD-L1 inhibitors. Among immune-related endocrinopathy, thyroid is the main involved-organ of ICIs. About 20% of patients receiving PD-1/PD-L1 inhibitors experienced thyroid dysfunctions. These thyroid dysfunctions develop in early clinical course with onset of 6 weeks after the initiation of PD-1/PD-L1. Most thyroid irAEs are asymptomatic and initial presentations seem like mild hyperthyroidism due to destruction of thyroid. And hyperthyroidism-like presentations are gradually changed into hypothyroidism during clinical course. Routine check of thyroid function is needed in patients who receive PD-1/PD-L1. And referral to endocrinologist should be considered when thyroid dysfunctions occur in patients. Most patient with mid thyroid dysfunctions can continue PD-1/PD-L1 inhibitors with symptom control (beta-blocker). Patients with hypothyroidism conversion could be managed with levothyroxine substitutions. Full recovery of thyroid function remains controversial.

Pneumonitis is the most serious and life-threatening irAEs of PD-1/PD-L1 inhibitors. Korean retrospective study which reviewed 706 cancer patients who received ICIs showed that 16 (2.3%) patients experienced ICIs induced pneumonitis (9 grade 1, 4 grade 2 and 3 grade 3). Radiologic findings are cryptogenic organizing pneumonia (COP) the most frequent, however, acute interstitial pneumonia or nonspecific interstitial pneumonia are possible. ICIs have to be immediately stopped when immune-related pneumonitis occurs in patients. Because differential diagnosis is important to exclude infectious pneumonia or other pulmonary disease, consultation to pulmonologist is needed. And immunosuppressive agents (e.g., steroid) should be started, depending on symptom and severity of pneumonitis.

Colitis is frequently observed irAE in patients receiving ICIs and diarrhea is the most frequently observed symptom in patient with immune-related colitis. Therefore immune-related colitis should be first considered, especially in patients with diarrhea who receive PD-1/PD-L1 inhibitors. However other causes could be possible, so endoscopy would be needed to differentiate other causes of diarrhea. In patients with mild

diarrhea, the withdrawal of PD-1/PD-L1 inhibitors could be enough, but in severe cases, immunosuppressive agents including steroid or infliximab should be considered.

Immune-related renal toxicity is rare but possible in patients receiving PD-1/PD-L1 inhibitors. Acute interstitial nephritis (AIN) is the most common type of irAE. Because many patients with hepatocellular carcinoma have underlying liver cirrhosis, azotemia could be developed by other causes (e.g., hepatorenal syndrome or dehydration). Kidney biopsy could be needed to differentiate other cause of azotemia. PD-1/PD-L1 inhibitors should be immediately stopped and immunosuppressive agents also should be started in severe cases.

Immune-related adrenal insufficiency is a rare, but very difficult to diagnose. Unexplained fever, fatigue and nausea sense are the most common symptoms. Therefore, we should think about the possibility of immune-related adrenal insufficiency and check rapid ACTH test to confirm adrenal insufficiency. After diagnosis of adrenal insufficiency, steroid replacement should be immediately administered. Patients with immune-related adrenal insufficiency have a trend in coexistence of other immune-related endocrinopathy, therefore thyroid function test or other endocrine test should be performed.

Cancer immunotherapy can affect all our organs including lung, thyroid, gastrointestinal tract and adrenal gland. The awareness of immune-related organ dysfunctions is important during treatment. And it is also essential to communicate with appropriate experts and to immediately administer immunosuppressive agents, depending on severity of irAE.

References

1. RS Finn, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
2. Cui TM, et al. Adverse Effects of Immune-Checkpoint Inhibitors in Hepatocellular Carcinoma. Onco Targets Ther. 2020. PMID: 33235462 Free PMC article. Review.
3. Martins F, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019. PMID: 31092901 Review.
4. C. Park, et al. Clinical insights on outcomes of corticosteroid administration in immune checkpoint inhibitor-induced pneumonitis by retrospective case series analysis. ESMO Open. 2019 Nov 28;4(6):e000575.

Early TIPS for Improving Outcomes of Acute Variceal Bleeding: Who Are the Appropriate Candidates?

Guohong Han

Fourth Military Medical University, China

Lecture Summary:

Acute variceal bleeding is a common and life-threatening complication occurring in patients with portal hypertension and is a leading cause of death in patients with cirrhosis.[1] The current recommended standard of care for acute variceal bleeding involves a combination of vasoactive drugs, prophylactic antibiotics, and endoscopic therapy.[2,3] This approach has improved patient outcomes. However, up to 10–20% of patients still experience treatment failure, requiring further intensive management. In such patients, placement of a transjugular intrahepatic portosystemic shunt (TIPS) is successful in achieving haemostasis in 90–100% of patients. However, 6-week mortality remains high (35–55%).[4] This is probably because the severity of the underlying liver disease has worsened and additional organ dysfunction may have occurred after several failed endoscopic therapy attempts.

The poor outcomes associated with the use of TIPS as a rescue treatment raises the question whether patients with predicted high-risk uncontrolled bleeding might benefit from a more aggressive therapeutic approach before treatment failure has occurred. Several factors have been proposed to identify patients with AVB who are at high risk of poor outcomes and treatment failure, such as hepatic venous pressure gradient (HVPG) more than 20 mm Hg,[5] the model for end-stage liver disease (MELD) score,[6] bacterial infection and active bleeding at endoscopy[7]. This strategy was first explored in a randomized controlled trial by Monescillo and colleagues,[8] in which patients with HVPG of 20 mm Hg or greater receiving early TIPS (within 24 h of admission) had significantly fewer treatment failures and lower mortality than those undergoing standard therapy. However, the standard therapy used in the control group was not the current standard of care and the TIPS stents were uncovered. These drawbacks, together with the difficulty of performing HVPG measurements in many centers, especially in emergency situations, encouraged Garcia-Pagan and colleagues[9] to do a subsequent multicenter randomized trial, in which patient selection was based on clinical risk factors predicting failure to control bleeding. A total of 63 patients were randomized into two arms, pharmacotherapy plus endoscopic band ligation (EBL) or TIPS. The primary outcome was failure to control bleeding or clinically significant re-bleeding within 1 year and secondary outcomes included 6-week and 1-year mortality as well as clinical endpoints such as development of portal hypertensive complications. The investigators found that Child-Pugh C patients or Child's B patients with active bleeding following initial medical and endoscopic therapy derived a survival benefit from early TIPS. Nevertheless, survival was not the primary endpoint of the study, which increased the chances of a type

I error. Indeed, the survival benefit associated with early TIPS was not confirmed in several subsequent observational studies with a similar patient population. However, a latter Chinese RCT[10] used survival as the primary end point, and confirmed that early TIPS was superior in improving transplant-free survival at 6 weeks (99% versus 84% $P = 0.04$, absolute risk difference 15%) and 1 year (86% versus 73% $P = 0.0460$) and reducing treatment failure (13% versus 38%, $P < 0.0001$). It is worth mentioning that the predominant etiology of liver disease in these cohorts was viral hepatitis [74% had chronic Hepatitis B (HBV) infection], thus providing external validation to the earlier Western studies in which the predominant etiologies have been alcohol related. This confirms beneficial effect of early TIPS across different population groups irrespective of the etiology of liver disease. It is also important to note that this study included all patients with Child–Pugh B and C disease, irrespective of active bleeding at endoscopy. Nevertheless, two large observational studies[11,12] showed that patients at high risk of failure, specifically Child C patients, would benefit from early TIPS, while the survival benefit was not consistently demonstrated in Child's B patients with active bleeding.

A recent meta-analysis of individual patient data[13] included 7 studies (3 randomized controlled trials and 4 observational studies), comprising 1327 patients (310 received early TIPS and 1017 received drugs plus endoscopy), evaluating the role of early TIPS in high-risk patients. Overall, early TIPS significantly increased the proportion of high risk patients with cirrhosis and acute variceal bleeding who survived for 1 year, compared with drugs plus endoscopy. This effect was observed in Child-Pugh B with active bleeding (CP-B+AB) patients and in patients with Child-Pugh C scores below 14 point. In keeping with previous meta-analyses, early TIPS significantly improved control of bleeding and ascites without increasing risk of hepatic encephalopathy in Child-Pugh C and CP-B+AB patients, compared with drugs plus endoscopy. When we analyzed the survival in CP-B+AB patients, mortality was clearly worse in those with a Child-Pugh score of 8 and 9 points in comparison with that "good" CP-B of 7 points. Interestingly, although early TIPS did not modify prognosis in the 7 points "good" CP-B+AB patients, it significantly improved survival in CP-B+AB with a Child-Pugh score greater than 7.

Despite studies showing survival benefit, adherence to these recommendations is low, as two recent retrospective studies[12,14] reported adherence rates of 6 and 13%, mainly due to a lack of confidence in the current data regarding an effect on survival and the lack of availability of the technique. Furthermore, within Child-Pugh C cirrhotics who are candidates for early TIPS, further research is required to further determine who would receive the most benefit. In addition, studies showing that early TIPS in Child-Pugh B patients with active bleeding do not consistently demonstrate survival benefits. On the other hand, the reported mortality risk in Child-Pugh B patients with cirrhosis and AVB varies widely among studies, ranging from 5% to 22%. This variability suggests that cohorts included in these studies belong to different prognostic subgroups. Thus, a further risk stratification for Child-Pugh B patients is warranted. A recent study showed that Chronic Liver Failure Consortium Acute Decompensation Score (CLIF-C ADs) outperforms active bleeding at endoscopy and other prognostic models for predicting 6-week and 1-year mortality in patients with Child-Pugh B cirrhosis and acute variceal bleeding.[15] With cut-off of CLIF-C ADs 48 and 56, patients with Child-Pugh B cirrhosis and acute variceal bleeding could be separated into three strata with a highly different probability of death. Thus, the CLIF-C ADs may assist with decision-making on the early use of TIPS in Child-Pugh B patients with cirrhosis and AVB. Prospective, controlled validation studies are

required to confirm these findings.

References

1. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362(9):823-832.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406-460.
3. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017;65(1):310-335.
4. Vangeli M, Patch D, Burroughs AK. Salvage tips for uncontrolled variceal bleeding. J Hepatol. 2002;37(5):703-704.
5. Moitinho E, Escorsell A, Bandi JC, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology. 1999;117(3):626-631.
6. Bambha K, Kim WR, Pedersen R, Bida JP, Kremers WK, Kamath PS. Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut. 2008;57(6):814-820.
7. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology. 2003;38(3):599-612.
8. Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology. 2004;40(4):793-801.
9. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362(25):2370-2379.
10. Lv Y, Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4(8):587-598.
11. Lv Y, Zuo L, Zhu X, et al. Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: a multicentre observational study. Gut. 2019;68(7):1297-1310.
12. Hernández-Gea V, Procopet B, Giráldez Á, et al. Preemptive-TIPS Improves Outcome in High-Risk Variceal Bleeding: An Observational Study. Hepatology. 2019;69(1):282-293.
13. Nicoară-Farcău O, Rudler M, Angrisani D, et al. Effects of Early Placement of Transjugular Portosystemic Shunts in Patients With High-Risk Acute Variceal Bleeding: a Meta-analysis of Individual Patient Data. Gastroenterology. 2021;160(1):193-205.
14. Thabut D, Pauwels A, Carbonell N, et al. Cirrhotic patients with portal hypertension-related bleeding and an indication for early-TIPS: a large multicentre audit with real-life results. J Hepatol. 2018;68:73-81.
15. Lv Y, Wang Z, Li K, et al. Risk Stratification Based on Chronic Liver Failure Consortium Acute Decompensation Score in Patients With Child-Pugh B Cirrhosis and Acute Variceal Bleeding. Hepatology. 2021;73(4):1478-1493.

Clinical Application of Liquid Biopsy as a Prognostic Biomarker in Hepatocellular Carcinoma

Soo Young Park

Kyungpook National University, Korea

Hepatocellular carcinoma (HCC) is the most frequent form of primary liver cancer worldwide.[1] Although there were major advances in diagnosis and management of HCC, there have been limitations in biomarker study in the field due to limited access to tissue sample and heterogenesity in carcinogenesis. Thus, liquid biopsy has emerged as a novel tool for assessing diagnosis and prognosis of HCC patients. In addition, liquid biopsy has advantages of simplicity and repeatability. The present session will discuss on the clinical application of liquid biopsy as a prognostic biomarker in HCC.

The liquid biopsy refers to analysis of tumor components, mostly of nucleic acids, circulating tumor cells (CTCs) and extracellular vesicles (EVs), which are released from tumors into the bloodstream or other body fluids.[2] The presence of these materials in the bloodstream has been known for many years, but its application in clinical practice significantly increased in recent a few years. Starting from antepartum fetal surveillance test to evaluate chromosomal abnormalities in high risk maternity, technology to detect cell-free DNA has been implemented in many fields in oncology.[3] With the new revolution in immuno-oncology, an obvious need is to identify patients who respond to these treatments. The first liquid biopsy to detect druggable EGFR mutations in plasma of lung cancer patients was approved by US-Food and Drug Administration (FDA) in 2016. After introduction of immuno-oncology in the management of HCC, there has been much more need for identify patients with high response rate to immune checkpoint inhibitors. Therefore, extensive researches are carried out to detect tumor mutational burden by analysis of plasma DNA derived from tumor tissue. Further, the tumor mutational burden derived from plasma DNA was predictive of response to immune checkpoint inhibition, thus removing the need for a tissue biopsy.[4] Similarly, PD-L1 expression on EVs which are reported to correlate with the tumor cell surface, could predict better response to immune checkpoint inhibition in patients with melanoma.[5] There are many other proteins EVs include. These protein-loaded EVs play roles of cell migration, invasion, and influence of immune system. Noncoding RNAs in EVs also can be used as novel serological biomarkers.[6] For example, serum exosomal levels of miR-122, miR-148a, and miR-1246 are significantly higher in HCC than those in liver cirrhosis and normal control groups.[6] Interestingly, HCC patients with liver cirrhosis treated with TACE, who had higher miR-122 after TACE/before TACE ratio had significantly longer disease-specific survival, suggesting that the exosomal miR-122 level alterations may represent a predictive biomarker in HCC patients treated with TACE.[7] Exosomal lnc-RNA may be useful as a novel diagnostic biomarker or a novel target for the treatment of HCC in the future. lncRNA TUC339 has been implicated in modulating HCC cell growth and adhesion.[8] Macrophages that take up lncRNA TUC339 increased pro-inflammatory cytokine production

and enhanced M(IL-4) markers upon IFN-γ/LPS treatment, suggesting that lncRNA TUC339 is involved in the regulation of macrophage activation and M1/M2 polarization.[9] In early stage HCC, Exosomes may be potential detection biomarkers for early-stage HCC.[10,11] Representative exosome markers for detection of HCC are CAP1, S100A4, miR-122, miR-21, miR-519d, lncRNA-FAL1, and LINC00161.[11-13] Moreover, Exosomal circular RNA PTGR1 (circPTGR1) is up-regulated in HCC and the expression of exosomal circPTGR1 is associated with poor outcomes for patients with HCC.[14]

In conclusion, liquid biopsy can be a novel, minimally-invasivel tool for biomarker discovery in HCC, with the potential to help decision-making in near future.

References

1. Villanueva A. Hepatocellular Carcinoma. N Engl J Med 2019;380:1450-1462.
2. Labgaa I, Villanueva A. Liquid biopsy in liver cancer. Discov Med 2015;19:263-273.
3. Corcoran RB, Chabner BA. Application of Cell-free DNA Analysis to Cancer Treatment. N Engl J Med 2018;379:1754-1765.
4. Wang Z, Duan J, Cai S, Han M, Dong H, Zhao J, et al. Assessment of Blood Tumor Mutational Burden as a Potential Biomarker for Immunotherapy in Patients With Non-Small Cell Lung Cancer With Use of a Next-Generation Sequencing Cancer Gene Panel. JAMA Oncol 2019;5:696-702.
5. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature 2018;560:382-386.
6. Wang Y, Zhang C, Zhang P, Guo G, Jiang T, Zhao X, et al. Serum exosomal microRNAs combined with alpha-fetoprotein as diagnostic markers of hepatocellular carcinoma. Cancer Med 2018;7:1670-1679.
7. Suehiro T, Miyaaki H, Kanda Y, Shibata H, Honda T, Ozawa E, et al. Serum exosomal microRNA-122 and microRNA-21 as predictive biomarkers in transarterial chemoembolization-treated hepatocellular carcinoma patients. Oncol Lett 2018;16:3267-3273.
8. Kogure T, Yan IK, Lin WL, Patel T. Extracellular Vesicle-Mediated Transfer of a Novel Long Noncoding RNA TUC339: A Mechanism of Intercellular Signaling in Human Hepatocellular Cancer. Genes Cancer 2013;4:261-272.
9. Li X, Lei Y, Wu M, Li N. Regulation of Macrophage Activation and Polarization by HCC-Derived Exosomal lncRNA TUC339. Int J Mol Sci 2018;19.
10. Wang H, Hou L, Li A, Duan Y, Gao H, Song X. Expression of serum exosomal microRNA-21 in human hepatocellular carcinoma. Biomed Res Int 2014;2014:864894.
11. Wang S, Chen G, Lin X, Xing X, Cai Z, Liu X, et al. Role of exosomes in hepatocellular carcinoma cell mobility alteration. Oncol Lett 2017;14:8122-8131.
12. Li C, Deng M, Hu J, Li X, Chen L, Ju Y, et al. Chronic inflammation contributes to the development of hepatocellular carcinoma by decreasing miR-122 levels. Oncotarget 2016;7:17021-17034.
13. Fornari F, Ferracin M, Trere D, Milazzo M, Marinelli S, Galassi M, et al. Circulating microRNAs, miR-939, miR-595, miR-519d and miR-494, Identify Cirrhotic Patients with HCC. PLoS One 2015;10:e0141448.
14. Wang G, Liu W, Zou Y, Wang G, Deng Y, Luo J, et al. Three isoforms of exosomal circPTGR1 promote hepatocellular carcinoma metastasis via the miR449a-MET pathway. EBioMedicine 2019;40:432-445.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

DAY 3: Saturday, May 15, 2021 (11:10-11:45)

ROOM 1

State-of-the-Art Lecture

Chair:

Sook-Hyang Jeong (Seoul National Univ.)

State-of-the-Art Lecture

Novel Insights of Translational Research in Nonalcoholic Steatohepatitis and Fibrosis

Scott L. Friedman

Icahn School of Medicine, USA

Ongoing progress in defining critical events underlying pathogenesis of steatohepatitis and fibrosis continues to yield new targets for therapy. The prevalence of non-alcoholic fatty liver disease (NAFLD) has been increasing, of which a substantial fraction of patients have non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis.[1] Accordingly, NASH is emerging as the leading indication for liver transplantation in North America and Europe. Moreover, the only feature of NASH that reliably predicts outcomes is the amount of fibrosis.[2] Therefore to be approved, any drugs tested in NASH must directly or indirectly improve fibrosis over time. One unique feature of NASH is a higher risk of hepatocellular carcinoma in non-cirrhotic patients: up to 1/3 of the HCCs arising in NASH occur before there is cirrhosis.[3] Thus, HCCs in NASH tend to be diagnosed later than in HBV and HCV, and therefore have a poorer prognosis. Moreover, NASH HCCs tend to be less responsive to newer checkpoint blockade therapies due to impaired immune function that is distinct from patients with HBV and HCV.[4] This feature imposes a key obstacle in treating HCC related to NASH, compared to other etiologies.

Progress in uncovering pathogenic determinants of fibrosis in NASH include metabolic dysregulation in hepatocytes that induce inflammation and cytokine secretion leading to cell injury and apoptosis, mitochondrial injury, followed by release of soluble mediators by injured hepatocytes.[5] These pathogenic events converge upon hepatic stellate cells, which are the primary fibrogenic cell in liver, and represent a target of new therapeutic candidates that are currently being evaluated in animal models and clinical trials.

The optimism in finding new treatments for hepatic fibrosis is based on major insights into NASH pathogenesis. Activation of myofibroblasts remains the central feature of NASH-related fibrosis. However, there are other advances that include: 1) Clarification of the sources of fibrogenic cells in different types of injury and the appreciation that stellate cells are more heterogeneous than previously thought – this conclusion is based on several studies using single cell RNA sequencing;[6-8] 2) Progressive changes in the inflammatory milieu, including chemokines, contribute to either progression or regression of fibrosis. 3) Alterations in the microbiome, which becomes less complex and has an altered composition in NASH compared to healthy controls;[9] 4) The inflammasome, an intracellular scaffold of cytokine activation, also contributes to stellate cell activation as well as to steatohepatitis pathogenesis; 5) During resolution of liver fibrosis, not only do some activated myofibroblasts undergo apoptosis, but a sizable fraction instead revert to a more quiescent phenotype, albeit with a heightened capacity to reactivate upon recurrent injury;[10,11] 6) Significant progress is being made in linking the pathogenesis of fibrosis to the accelerated risk of hepatocellular carcinoma in patients with advanced liver disease.

Fibrosis in liver follows chronic but not acute injury, and is more reversible than in other tissues including lung and kidney. In liver, reversibility has become more clear as specific therapies for liver disease have been developed, especially antivirals. Mechanisms underlying regression of fibrosis in NASH or other fibrotic liver diseases remain obscure, but recent evidence implicates a family of molecules known as "Specialized Pro-resolving Mediators" (SPM), whose sources and regulation are not yet clarified.[12] Reversibility is likely in patients in whom HBV therapy suppresses viral replication, however cirrhosis reversion has also been reported in some HCV patients following sustained viral remission. Moreover, when reversal occurs in HCV, it leads to improved clinical outcomes and reduced portal pressure. Importantly recent studies indicate that bariatric surgery associated with significant weight loss can lead to marked improvement in fibrosis and resolution of NASH.[13]

Points of attack of emerging therapies for NASH include:[5] a) Reduced hepatocellular fat content; b) Reduced inflammation and alterations in the immune response; c) Attenuation of resistance in insulin signaling and altered glucose homeostasis; d) improvement in mitochondrial function and structure with reduced oxidant stress; e) Reduce fibrogenesis and inhibition matrix synthesis; e) Resolution of fibrosis by increasing scar matrix degradation, stimulating apoptosis or inactivation of stellate cells.

There are a remarkable number of clinical trials already underway in NASH, but no drugs are approved yet. Nonetheless, there is growing optimism that new pharmacotherapies are likely to emerge within the next 3 years that will favorably alter the natural history of disease. A major impediment to progress is the lack of standardized, widely accepted non-invasive measures of disease activity and fibrosis stage.[14] This means that whereas phase 2 trials can utilize non-invasive surrogates like MRI fat fraction, MR elastography, or serum tests like ProC2, ELF or FIB-4, more advanced phase 2B and phase 3 trials will require biopsy evidence of either NASH resolution and/or a reduced fibrosis stage. Currently there are over 70 Phase 2 trials and 9 Phase 3 trials ongoing. In general, animal studies seem to be more optimistic in predicting efficacy than in human trials, for a variety of reasons. Progress, as it has been in antiviral therapy drug development, will be incremental and iterative, with continued refinements that improve trial design and outcomes. Given the capacity of the liver to resorb scar based on antiviral trials, however, emergence of effective drugs that ameliorate fibrosis in NASH is approaching, and will transform the outlook for patients with chronic tissue injury in liver.

References

1. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71:793-801.
2. Taylor RS, Taylor RJ, Bayliss S, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology 2020;158:1611-1625 e12.
3. Chayanupatkul M, Omino R, Mittal S, et al. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. J Hepatol 2017;66:355-362.
4. Pfister D, Nunez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450-456.
5. Friedman SL, Neuschwander-Tetri BA, Rinella M, et al. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908-922.
6. Xiong X, Kuang H, Ansari S, et al. Landscape of Intercellular Crosstalk in Healthy and NASH Liver Revealed by Sin-

gle-Cell Secretome Gene Analysis. Mol Cell 2019;75:644-660 e5.
7. Ramachandran P, Dobie R, Wilson-Kanamori JR, et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. Nature 2019;575:512-518.
8. Rosenthal SB, Liu X, Ganguly S, et al. Heterogeneity of hepatic stellate cells in a mouse model of non-alcoholic steatohepatitis (NASH). Hepatology 2021, in press.
9. Oh TG, Kim SM, Caussy C, et al. A Universal Gut-Microbiome-Derived Signature Predicts Cirrhosis. Cell Metab 2020;32:901.
10. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 2020; 18:151-166.
11. Liu X, Xu J, Rosenthal S, et al. Identification of Lineage-Specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution. Gastroenterology 2020;158:1728-1744 e14.
12. Musso G, Gambino R, Cassader M, et al. Specialized Proresolving Mediators: Enhancing Nonalcoholic Steatohepatitis and Fibrosis Resolution. Trends Pharmacol Sci 2018;39:387-401.
13. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. Gastroenterology 2020;159:1290-1301 e5.
14. Younossi ZM, Loomba R, Anstee QM, et al. Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. Hepatology 2018;68:349-360.

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (11:50-12:30)

ROOM 1

KASL Clinical Practice Guideline

Chair:

Dong Joon Kim (Hallym Univ.)

KASL Clinical Practice Guidelines

Yong Kyun Cho

Sungkyunkwan University, Korea

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (15:00-16:20)

ROOM 1

KASL Symposium 5

Controversial Issues Pertaining to Fatty Liver Diseases

Chairs:

Joo Hyun Sohn (Hanyang Univ.)

Yong Kyun Cho (Sungkyunkwan Univ.)

MAFLD vs. NAFLD: What's in a Name? Pros: Not Just a Name

Jacob George

The University of Sydney, Australia

Perhaps the most impactful event in the discipline of Hepatology in 2020 has been the proposal by an international expert panel to both rename and redefine non-alcoholic fatty liver disease (NAFLD). The proposed new name is metabolic (dysfunction) associated fatty liver disease (MAFLD), while the diagnostic criteria includes evidence of fatty liver in addition to one of the following: overweight/obesity, presence of T2DM, or normal weight with evidence of metabolic dysfunction. Evidence for metabolic dysregulation includes the presence of at least two metabolic risk abnormalities including elevated waist circumference, hypertension, dyslipidaemia, prediabetes or insulin resistance, and elevations in hsCRP.

The impact of the new name and definition has been transformational for the field, principally because it has addressed a more than four decade-long unmet need. As evidence of impact and outcomes, to date there have been >750 papers that have used the term, 25 editorials and commentaries and 14 letters to the editor. The proposal has been endorsed by major international (Asian Pacific Association for the study of liver, the Latin American Association for the study of the liver, a consensus from the Middle East and north Africa, and the sub Saharan Africa position statement) and national (including Spain, Turkey, Malaysia etc) liver associations. The name has received widespread endorsement from patient organisations, allied health professionals and has increased (rather than decreased) awareness of fatty liver disease among primary care physicians and specialists. In social media too, the proposal has received widespread endorsement, including 4 twitter polls that have suggested MAFLD as a more apt name for the disease that we see.

So why this widespread endorsement and why the excitement over the name change? Simply put, this is because ever since the consensus proposal, there has been an avalanche of evidence supporting the superiority of the new name and definition. For example, MAFLD better identifies patients with more advanced liver fibrosis, those at risk for cardiovascular events, and those with more advanced chronic kidney disease. MAFLD likewise, identifies patients with more severe fibrosis in hepatitis B, hepatitis C and alcohol misuse disorder, suggesting that both diseases should be addressed even after cure of hepatitis C or suppression of hepatitis B replication. In the field of cardiovascular disease, those with MAFLD have a greater risk of adverse outcomes compared to those that do not have fatty liver, while those with dual aetiology liver disease (e.g. alcohol misuse disorder and MAFLD), also have an increased risk. The latter group would be specifically excluded in the context of the NAFLD definition. Of clinical relevance also, the MAFLD definition overcomes the inherent difficulties of quantifying alcohol consumption in everyday practice. In the field of cardiovascular disease and cancer, identifying and managing MAFLD even in the context of other liver diseases will probably prevent more morbidity than a pure liver-centric approach to care. To sum up,

on the basis of this increasing evidence, the MAFLD definition has broader utility and can be applied to most healthcare settings to selectively identify and manage those at highest risk. In contrast, both for utility and applicability in practice, the NAFLD definition appears sub-optimal.

What our current in-depth understanding of MAFLD pathogenesis clearly demonstrates is that the disease is a highly complex and dynamic everchanging interactome. At any one time, the predominant pathogenic drivers will vary within the same individual, while this milieu also governs the associations and role of MAFLD with T2DM, CVD, CKD, hypertension, stroke, osteoporosis, cancer, and cognitive changes. With the framework provided by the new name and definition, we are now perfectly poised to leverage this understanding and the alignment that the new lens brings, to move forward in developing primary care-driven, patient-centred, multidisciplinary models of care for best-case management of patients with MAFLD and associated metabolic diseases. Equally, the novel framework allows for us to think innovatively and outside the box about clinical trials design, looking at them not just as a trial for MAFLD, but as trials for MAFLD and its associated metabolic diseases. With so many positive attributes stemming from the change to MAFLD, we should not lose sight of the fact that the momentum it has generated for the field gives us a once in a lifetime opportunity to transform the discipline that should be encouraged rather than emasculated.

Since its conception, both the name MAFLD and its definition has resonated with the public, patients with liver disease, allied health practitioners, physicians and with international and national liver associations, as well as policy makers. The name has resonated precisely because it's very simplicity has met a clinical need, while uptake in the scientific literature attests to its currency for clinical practice and management. As to any cons of the new name, it is hard to think of a reasoned and cogent argument. While there will be die-hard NAFLD supporters, the evidence is slowly shifting towards MAFLD.

MAFLD vs. NAFLD: What's in the Name? Cons: Premature Proposition

Ajay Duseja

Postgraduate Institute of Medical Education and Research, India

Suggestion for the change in name from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD) is not only Premature but also Confusing.

Why is it a Premature Proposition?

Ans – Because the reasons suggested for this change are Eminence based rather than Evidence based. Let us briefly look at these reasons one by one.

Reason 1 – NAFLD is a Heterogenous name

Ans – NAFLD is heterogenous because multiple pathways are involved in its pathogenesis. Changing the name from NAFLD to MAFLD will not make it homogenous.

Reason 2 – The word 'Non' in 'Non-alcoholic' trivializes the disease

Ans - There are so many diseases with prefix 'Non' like 'Non-communicable Diseases (NCD)', 'Non-Hodgkin's lymphoma (NHL)', 'Non-cirrhotic portal fibrosis (NCPF)' etc. Are these diseases less important? Are we trivializing all these diseases?

Reason 3 – The word 'non-alcoholic' is Stigmatizing

Ans – Rather than stigmatizing, the word 'non-alcoholic' is reassuring and de-stigmatizing to the patients and their care givers that their disease is not related to alcohol.

Reason 4 - No mention of metabolic risk factors in NAFLD

Ans – Metabolic risk factors are not present in all patients. Is it right to call someone as having MAFLD in the absence of metabolic risk factors? In fact, emphasis on the metabolic dysfunction may underestimate the prognostic value of hepatic steatosis itself.

Reason 5 – The diagnosis of NAFLD is based on negative criteria. Requires exclusion of alcohol and other other chronic liver diseases.

Ans – There are so many negative medical definitions. Health itself is a negative definition (absence of illness and injury). Disease (dis- ease) is a negative definition (absence of ease).

There are so many diseases which require exclusions. In fact, in the presence of multiple etiologies of hepatic steatosis, it would be difficult to assess the contribution of individual pathology.

Reason 6 – MAFLD is better than NAFLD for funding and regulatory agencies/policy makers

Ans – In fact NAFLD is better. Over last 40 years, regulatory agencies and policy makers have started understanding NAFLD and are funding its research.

There has been a progressive refinement in our understanding of pathogenesis, assessment and treatment approach and NAFLD is a much better understood terminology today than when conceived. Metabolic health (unhealth) is only one component of NAFLD. To change the name of the disease only based on its one component may force us for another change after few years when we may learn more about NAFLD. Hence, the suggestion for the change in terminology is definitely a premature proposition.

Why is this change in name from NAFLD to MAFLD confusing?

Reason 1 –Terminology of metabolic liver disease has been used conventionally for paediatric metabolic liver diseases where there is an inherited genetic defect in metabolism. Putting NAFLD in this category would be confusing to all.

Reason 2 – The proponents of MAFLD have suggested to abandon the term of 'steatohepatitis' or non-alcoholic steatohepatitis (NASH). The term NASH was given by pathologists. NASH in fact is the driver of fibrosis. Last 40 years have taught us the importance of differentiating NAFL and NASH with natural history, prognosis and treatment different in two subsets. Abandoning NASH will not only be confusing to all but would also bring sudden halt to the 4 decades of input by Pathologists.

Reason 3 - Change from NAFLD to MAFLD would also be confusing to other non-Hepatologists. Basic scientists and Radiologists have started understanding/discussing about non-invasive biomarkers/elastography/imaging in NAFLD. Similarly, Cardiologists, Endocrinologists, Gynaecologists have started doing clinical trials in NAFLD/NASH. Change in terminology is going to confuse all of them.

Reason 4 –All clinical trials look at the histology-based improvement in NASH and/or hepatic fibrosis. Distinction between NAFL and NASH has been well understood finding its place in international classification of diseases (ICD). Abandoning NASH will be confusing for the pharmaceuticals conducting clinical trials and for regulatory agencies/policy makers halting the further progress on research and drug development.

Reason 5 – Change in terminology will create confusion among Students /Researchers/ Consortia/Taskforces collating data on NAFLD and for Ethical committees for on-going and future research projects.

Reason 6 – Rather than helping, the change will create confusion for the patients and patient-driven organizations.

Reason 7 – MAFLD is applicable only to adults and is not applicable to children. So, for the same disease, the experts are suggesting two different terminologies for children and adults.

To summarize, there are no compelling reasons for this change. The change is not going to help anyone. All the progress done in last 40 years and all the efforts put in this disease may go waste and we would all have to start from scratch.

Rather than wasting our time and energy on change in terminology, we should work harder on better understanding the disease and finding pharmacological solutions for these patients. Stakeholders across the globe need to discuss and exchange ideas rather than taking a premature decision of changing the

nomenclature from NAFLD to MAFLD and creating confusion for all.

References

1. Duseja A, Taneja S. Changing Nomenclature from Nonalcoholic Fatty Liver Disease to Metabolic Dysfunction-Associated Fatty Liver Disease - Not Only Premature But Also Confusing. J Clin Exp Hepatol. 2021; 11:278-279.
2. Singh SP, Anirvan P, Reddy KR, Conjeevaram HS, Marchesini G, Rinella ME, et al. Non-alcoholic fatty liver disease: Not time for an obituary just yet! J Hepatol. 2021; 74:972-974.
3. Younossi ZM, Rinella ME, Sanyal A, Harrison SA, Brunt E, Goodman Z, et al. From NAFLD to MAFLD: Implications of a premature change in terminology. Hepatology. 2020 Jun 16. [Epub ahead of Print]
4. Ratziu V, Rinella M, Beuers U, Loomba R, Anstee QM, Harrison S, et al. The times they are a-changin' (for NAFLD as well). J Hepatol. 2020; 73:1307-1309.
5. Polyzos SA, Kang ES, Tsochatzis EA, Kechagias S, Ekstedt M, Xanthakos S, et al. Commentary: Nonalcoholic or metabolic dysfunction-associated fatty liver disease? The epidemic of the 21st century in search of the most appropriate name. Metabolism. 2020; 113:154413.
6. Kang SH, Cho Y, Jeong SW, Kim SU, Lee JW; Korean NAFLD Study Group. From nonalcoholic fatty liver disease to metabolic-associated fatty liver disease: Big wave or ripple? Clin Mol Hepatol. 2021; 27:257-269.
7. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020; 158:1999-2014.e1.

Which Is the More Appropriate Surrogate and Target? Liver Fibrosis and/or Inflammation

Vincent Wong

The Chinese University of Hong Kong, Hong Kong

Even though nonalcoholic steatohepatitis (NASH) is such a common and important condition, there is yet a registered drug for its treatment. As a result, drug development for NASH has become one of the hottest research areas in medicine. Several drugs with diverse modes of action have entered phase 3 development, with a few have already failed unfortunately. Numerous more are in phase 1 to 2 development.[1]

According to the US FDA, a drug can be registered for clinical use if it improves how a patient feels, functions, or survives. However, many a time these may not be easy to measure. For example, it would take many patients and many years of follow-up to demonstrate a survival benefit. Instead, a surrogate endpoint is a clinical trial endpoint used as a substitute for a direct measure of these outcomes. It doesn't measure the clinical benefit of primary interest in and of itself but rather is expected to predict that clinical benefit. According to the level of clinical validation, the surrogate endpoint can be a candidate endpoint, a reasonably likely surrogate endpoint, or a validated surrogate endpoint.

The US Food and Drug Administration and the European Medicines Agency have issued similar guidance on drug development for NASH. Because there is currently no treatment for NASH, this disease is considered an unmet clinical need. Therefore, drug companies can apply for conditional approval via the subpart H pathway if a drug can meet the surrogate histological endpoint of NASH resolution without worsening of fibrosis, or fibrosis improvement without worsening of NASH. The European Medicines Agency further states that if a drug is filed purely for its anti-fibrotic action, it has to demonstrate a significant improvement in not only 1 but 2 fibrosis stages. This is based on the fact that a 1-stage improvement in fibrosis can sometimes be due to chance and sampling variability during liver biopsy, and its clinical significance is thus uncertain. Finally, as these histological endpoints are not considered fully validated, even after conditional approval, the phase 3 studies need to continue for 5 to 8 years to demonstrate an improvement in long-term clinical outcomes including progression to cirrhosis and development of cirrhotic complications. A very interesting question is what would happen if a drug is conditionally approved but its efficacy on clinical outcomes falls short of statistical significance. In my opinion, many of the ongoing phase 3 trials are probably underpowered for showing a difference in clinical outcomes.

The prognostic value of liver fibrosis is firmly established. How about NASH? Over the past 10 years, there have been several longitudinal studies looking at the association between baseline histological features and clinical outcomes. The findings were largely consistent. Although the degree of lobular inflammation and hepatocyte ballooning did correlate with future liver-related events, the association became

weaker when adjusted for fibrosis stage.[2] This has led some people to suggest that we may as well look at fibrosis alone. To this end, there are a few counter arguments. First, NASH is the driving force behind fibrosis progression. It is thus not meaningful to argue which is more important. Otherwise, it would be similar to saying that fibrosis is more important than chronic hepatitis B. Second, in the natural history of NAFLD, because fibrosis is closer to the clinical outcomes than NASH and cirrhosis is in turn closer to the clinical outcomes than fibrosis, statistical methods will undoubtedly pick the closer factor as the stronger predictor. Finally, the activity of NASH has a strong correlation with fibrosis, and it is not always easy to dissect the relative effects of the two.

Now is the era of artificial intelligence (AI). A few commercially available platforms already allow us to report liver histology in a more reliable manner. Our group, in collaboration with the Southern Medical University, used dual-photon microscopy to scan over 450 unstained slides and showed that a number of automatically identified features of the fibrils could reflect the severity of liver fibrosis in patients with NAFLD.[3] That was more reliable than the pathologist's scoring. Importantly, the fibrosis features were even prognostic.

In another example, we used the PathAI system to evaluate histological slides of patients in 3 clinical trials testing the use of selonsertib for NASH.[4] This platform breaks down a histological image into tiny parts and report the proportion of the areas resembling different fibrosis stages. Again, the results of AI-assisted scoring were highly consistent, and it could even reliably detect changes in liver fibrosis.

Finally, I believe this is only the first stage. After we have demonstrated the reliability of histological features as surrogate endpoints, the next goal should be to replace them with non-invasive tests. A number of non-invasive tests of fibrosis have already been extensively evaluated in cross-sectional studies.[5] What we need is to demonstrate their role as monitoring tools for fibrosis change and the correlation with clinical outcomes.

References

1. Wong VW, Chitturi S, Wong GL, Yu J, Chan HL, Farrell GC. Pathogenesis and novel treatment options for non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol 2016;1:56-67.
2. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-1554.
3. Wang Y, Wong GL, He FP, Sun J, Chan AW, Yang J, et al. Quantifying and monitoring fibrosis in non-alcoholic fatty liver disease using dual-photon microscopy. Gut 2020;69:1116-1126.
4. Taylor-Weiner A, Pokkalla H, Han L, Jia C, Huss R, Chung C, et al. A Machine Learning Approach Enables Quantitative Measurement of Liver Histology and Disease Monitoring in NASH. Hepatology 2021.
5. Wong VW, Adams LA, de Ledinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in NAFLD and NASH - current progress and future promise. Nat Rev Gastroenterol Hepatol 2018;15:461-478.

Which Is the More Appropriate Surrogate and Target? Metabolic Factors and/or Steatosis

Dae Won Jun

Hanyang University, Korea

Non-alcoholic fatty liver disease is most hot issue in pharmaceutical company in all over the world. The global NAFLD was valued at USD 2.94 billion in 2019 and is projected to reach USD 54 billion by 2027.

The biggest change in the recent development of NAFLD drugs is the change of treatment target. At first, hepatic steatosis or hepatic fat mass had been first target for NAFLD drug development. However, as many data on the natural course of NAFLD have recently accumulated, the importance of fibrosis is gradually increasing.

In a study conducted in Sweden, liver-related mortality occurred in 7.9% of the NAFLD patient group and 1.4% of the control group during an average follow-up period of 20 years.[1] NAFLD patients with F0 or F1 had a significantly higher mortality rate compared to the control group. On the other hand, the mortality rate increased significantly in proportion to the degree of hepatic fibrosis above F2. When analyzing only NAFLD patients, compared to the F0 group, the mortality rates in the F2, F3, and F4 groups were significantly higher in proportion to the degree of hepatic fibrosis, and this trend was the same in the analysis adjusted for age, sex, diabetes, and NASH. Interestingly, patients with NASH had a somewhat higher risk of death than the control group, but mortality was similar between NAFLD and NASH.

More and more recent data suggested that main cause of death in patients with NAFLD is not liver disease mortality, but death from cardiovascular disease.[2] In the case of advanced hepatic fibrosis or more with moderate fibrosis, the mortality rate of liver disease is higher, but when fibrosis is mild, the majority of deaths originated from cardiovascular disease.

Considering that the ultimate goal of therapeutic drugs is to reduce mortality, fatty liver drugs to be developed in the future must lower the mortality rate of cardiovascular disease in fatty liver patients.

References

1. Hagstrom H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265-1273.
2. Kim D, Choi SY, Park EH, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology 2012;56:605-13.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (08:00-08:30)

ROOM 2

Listen to the Expert

Chair:

Do Young Kim (Yonsei Univ.)

Listen to the Expert

The Path I have Taken as a Clinician and Researcher with Hepatocellular Carcinoma

Joong-Won Park

National Cancer Center, Korea

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (08:30-09:50)

ROOM 2

KASL-KAHBPS-KLCA-KLTS Joint Symposium

New Perspective in Intrahepatic Cholangiocarcinoma

Chairs:

Ho Seong Han (Seoul National Univ.)
Kwang Cheol Koh (Sungkyunkwan Univ.)
Baek-Yeol Ryoo (Univ. of Ulsan)

Intrahepatic Cholangiocarcinoma: Tumour Heterogeneity and Its Clinical Relevance

Mina Komuta

International University of Health and Welfare, Japan

The diagnosis and treatment of intrahepatic cholangiocarcinoma (iCCA) are facing a new era.

The main message of my lecture is that iCCA comprises two subtypes, large duct type and small duct type, and they are totally different tumors in terms of clinical-pathological-molecular features.[1] In addition, recognizing the subtype is essential as it affects the treatment choice.

iCCA arises from cholangiocytes, that line the epithelia of the bile duct.[2] Importantly, the phenotype of cholangiocytes is different depending on the size of the bilary duct. For instance, the large bile duct is lined by mucin-producing cylindrical cholangiocytes, whereas the small bile duct is lined by mucin-negative cuboidal cholangiocytes. These differences reflect the nature of iCCA.[2] The new classification of iCCA (large duct type and small duct type) proposed by the 5th WHO classification, is based on this concept.[1] Large duct type iCCA shows mucin-producing glandular structures, which mimic the normal large bile duct. In contrast, small bile duct type iCCA shows ductular reaction-like tumor structure without mucin production and these features are similar to reactive ductules seen in nontumoral conditions.[2]

The differences are also observed in their tumor aggressiveness; large duct type is a very aggressive tumor, having perineural invasion and/or lymphatic invasion. Lymph node metastasis is also seen. On the other hand, small duct type is a less aggressive tumor and both lymphatic invasion and perineural invasion are rare.

Macroscopical features are also different: large duct type iCCA often presents as periductal infiltrating type, whereas mass-forming type is typical of a small duct type iCCA.[2]

Finally, in terms of genetic profiling, large duct type iCCA shows KRAS mutation and SMAD4 loss.[3,4] In contrast, small duct type iCCA harbours the FGFR and IDH1/2 mutations.[3,5] Importantly, the actionable genetic alternations such as FGFR fusion and IDH1/2 mutations, are seen in small duct type iCCA. In fact, the current clinical trial, ivosidenib, an oral inhibitor of the mutated IDH1 enzyme, shows efficacy in iCCA patients in terms of median progression-free survival date, and median overall survival rate.[6] FGFR inhibitors also show a good response in iCCA patients.[7,8] This data brings hope, as around 70% of iCCA patients are diagnosed at an advanced and inoperable stage.

To improve the diagnostic accuracy, it is important to understand the differential diagnosis.

Concerning large duct iCCA, a metastatic tumor, especially from pancreas, is the most important differential diagnosis. The distinction between them is often challenging and immunohistochemical examination will not always be helpful. Therefore, clinical information and imaging features are essential to reach the definitive diagnosis in this case. In contrast, small duct iCCA needs to be distinguished from combined he-

patocellular-cholangiocarcinoma (cHCC-CCA).[9] This is also challenging diagnosis because cHCC-CCA may contain small duct type iCCA as a part of tumor features. Since hepatocytic differentiation is only seen in cHCC-CCA, identification of hepatocytic differentiation will be the key to distinguish them.

Taken together, it is crucial to know that iCCA has two distinct subtypes and the pathological examination plays a key role in diagnosing iCCA and its subtype. To improve the diagnostic accuracy, it is important to understand the clinicopathological features of differential diagnosis.

In this lecture, I will explain the clinical-pathological-molecular features of iCCA and its subtypes, including the diagnostic pitfalls.

References

1. Nakanuma Y, Klimstra D, Komuta M, Zen Y. Intrahepatic cholangiocarcinoma, WHO classification of tumours of the digestive system. 5 ed. RD O, IA C, DS K, ID N, V P, M R, et al., editors. Lyon: IARC; 2019.
2. Komuta M, Govaere O, Vandecaveye V, Akiba J, Van Steenbergen W, Verslype C, et al. Histological diversity in cholangiocellular carcinoma reflects the different cholangiocyte phenotypes. Hepatology. 2012;55(6):1876-88.
3. Kendall T, Verheij J, Gaudio E, Evert M, Guido M, Goeppert B, et al. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. Liver Int. 2019;39 Suppl 1:7-18.
4. Akita M, Fujikura K, Ajiki T, Fukumoto T, Otani K, Azuma T, et al. Dichotomy in intrahepatic cholangiocarcinomas based on histologic similarities to hilar cholangiocarcinomas. Mod Pathol. 2017;30(7):986-97.
5. Jusakul A, Cutcutache I, Yong CH, Lim JQ, Huang MN, Padmanabhan N, et al. Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma. Cancer Discov. 2017;7(10):1116-35.
6. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(6):796-807.
7. Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. J Clin Oncol. 2018;36(3):276-82.
8. Mazzaferro V, El-Rayes BF, Droz Dit Busset M, Cotsoglou C, Harris WP, Damjanov N, et al. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. Br J Cancer. 2019;120(2):165-71.
9. Komuta M, Yeh MM. A Review on the Update of Combined Hepatocellular Cholangiocarcinoma. Semin Liver Dis. 2019.

Differential Diagnosis between Hepatocellular Carcinoma and Cholangiocarcinoma through Radiology

Ijin Joo

Seoul National University, Korea

Differential diagnosis of intrahepatic cholangiocarcinoma (ICC) from hepatocellular carcinoma (HCC) on imaging studies is critical as those two disease entities have different treatment strategies and prognoses. ICCs typically manifest as hepatic masses with arterial phase peripheral rim enhancement and progressive centripetal enhancement and show the target appearance on diffusion-weighted MR images, cloud-like central hyperintensity on hepatobiliary phase MR images, and ancillary features such as hepatic capsular retraction and dilatation of peripheral bile ducts. Unfortunately, atypical enhancement patterns of ICC – e.g. nonrim arterial phase hyper-enhancement - are not rare especially in chronic liver disease or liver cirrhosis, and therefore, some ICCs may mimic HCC. For this reason, avoiding a false-positive diagnosis in ICC is an important concern in the current guidelines for noninvasive diagnosis of HCC. On the other hand, HCC with atypical imaging features can also mimic ICC, which is common in scirrhous HCC or that with expression of hepatic stem cell markers.

This lecture will review the spectrum of imaging features of ICCs, challenging issues in differentiation between ICC and HCC, and how to improve the differential diagnosis.

Update of Treatment in Intrahepatic Cholangiocarcinoma: Resection and Transplantation

Gonzalo Sapisochin

University of Toronto, Canada

Update of Treatment in Intrahepatic Cholangiocarcinoma: Systemic Therapy

Hong Jae Chon

CHA University, Korea

The incidence of biliary tract cancers (BTC; cholangiocarcinoma and gallbladder cancer) is increasing, yet the prognosis remains poor. Most patients are diagnosed with advanced stages, of which less than 20% are considered resectable. Moreover, treatment options have been limited to palliative approaches, mainly focused on chemotherapy. However, the therapeutic landscape in biliary tract cancer has expanded considerably in recent years.

New chemotherapy combinations have increased the survival benefit in advanced-stage patients than standard treatments. The milestone of first-line treatment for BTC comes from the ABC-02 study that suggested the efficacy of gemcitabine–cisplatin (GemCis) chemotherapy. This regimen has since remained the standard of care, but the median overall survival is still less than 1 year. Shroff et al. demonstrated that the addition of nab-paclitaxel to standard doublet therapy (known as the GAP regimen: gemcitabine, nab-paclitaxel, and cisplatin) improves survival, even if gemcitabine and nab-paclitaxel doses were reduced by 20% from the standard dose owing to poor tolerability. Interestingly, 12 patients were converted to resectable disease and completed surgery, 2 of whom achieved a pathologically complete response. The reduced-dose triplet is now being evaluated against GemCis in the ongoing Phase III SWOG 1815 trial (NCT03768414).

Recently, the revelation of complex molecular events and their relationships with some risk factors allowed the development some very promising targeted/toxic agents to be treated alone or in combination with chemotherapy. These include fibroblast growth factor receptor (FGFR) fusions and isocitrate dehydrogenase (IDH)-1 mutation, which are each present in 10~20% of patients with intrahepatic cholangiocarcinoma. In addition, BRAFV600E mutation showed favorable efficacy with dabrafenib and trametinib combination therapy. Furthermore, along with the recent development of cancer immunotherapy, Phase III trials of GemCis and immune checkpoint inhibitor combination therapies are also underway in biliary tract cancer: pembrolizumab (NCT04003636), durvalumab (NCT03875235), M7824 (NCT04066491).

The therapeutic landscape for BTCs is blooming again, and the knowledge of their biology is still growing. The available data on chemotherapy, radiotherapy, locoregional treatments, and target therapies have added hopes to improve patient survival.

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (11:10-12:30)

ROOM 2

LCSGJ-KLCA Joint Symposium

Updates on Molecular Signatures of Hepatocellular Carcinoma

Chairs:

Jin Wook Chung (Seoul National Univ.)

Young Nyun Park (Yonsei Univ.)

Hepatocellular Carcinoma Tumor Microenvironment

Yutaka Kurebayashi

Keio University, Japan

Immune microenvironment of Hepatocellular Carcinoma (HCC) is composed of various innate and adaptive immune cells (CD4 T cell, CD8 T cell, NK cell, B cell, macrophage, dendritic cell, neutrophil, mast cell, etc.), as observed in other human tumors.[1-3] Less frequently in HCC, these immune cells form more highly ordered structure like ectopic lymphoid follicles.[4] Historically, it has been shown that tumors with increased lymphocytic or lymphoplasmacytic infiltration are associated with significantly better prognosis after surgical resection.[5,6] The current WHO classification of tumors of the liver also defines lymphocyte-rich HCC, a rare variant accounting for around 1 % of HCC.[7] Accumulating evidence also indicates the clinicopathological significance of tumor immune microenvironment in predicting therapeutic efficacy of immunotherapy.[8] Nonetheless, the combinations of immune cells forming the immune microenvironment and their association with histological findings has remained largely unclear until recently.

In this presentation, I will talk about the immune microenvironment of HCC mainly based on the results of our previous work, in which the immune microenvironment of HCC and its intratumor heterogeneity was comprehensively analyzed in 919 regions of 158 HCCs.[1,2] The immune microenvironment of HCC can be histologically classified into three distinct immunosubtypes: Immune-high (10-15%, characterized by increased T cells and extrafollicular B/plasma cell infiltration), Immune-mid (20-25%, characterized by moderate increase in T cell infiltration with little extrafollicular B/plasma cell infiltration), and Immune-low (60-70%, characterized by low infiltration of lymphocytes). Immune-high, Immune-mid, and Immune-low subtypes are associated with better to poorer prognosis in this order, and Immune-high subtype is an independent positive prognostic factor. Therefore, co-infiltration of T cells and extrafollicular B/plasma cells (lymphoplasmacytic infiltration), which is often associated with ectopic lymphoid follicle formation,[9] is considered as a histopathological hallmark of active anti-tumor immunity in HCC. Reflecting the ongoing anti-tumor immunity, PD-1 and PD-L1 expression is also significantly upregulated in the Immune-high subtype of HCC. Based on the similarities in immune cell composition and cytokine/chemokine expression pattern, Immune-high subtype may be closely associated with the active immune class defined through the gene expression analysis by Sia et al.[10] The results described above is also compatible with the study by Garnelo et al., who have also shown that co-infiltration of T and B cells in HCC is associated with better prognosis, while T cell infiltration alone without B cell infiltration is not.[11]

HCC is a well-established model of multi-step carcinogenesis;[12-14] therefore, HCC is also a suitable model for analyzing changes in immune microenvironment associated with tumor progression. For example, the

number of NK cell and macrophage infiltration and CD8/CD4 T cell ratio decrease during the progression from well-differentiated to moderately differentiated lesion of HCC.[1] On the other hand, the number of Treg increases during the progression from moderately differentiated to poorly differentiated lesion.[1] These results clearly indicate that different elements of immune microenvironment are affected at different levels of HCC progression. For intratumoral heterogeneity in the immune microenvironment of HCC, the predominant immunosubtype is prognostically important.

Of note, the Immune-high subtype is observed in 20-25% of poorly differentiated HCC or $CK19^+$ and/or $SALL4^+$ high-grade HCC (Biliary/stem subclass HCC).[15] Furthermore, patients with high-grade HCC of the predominant Immune-high subtype had significantly better prognosis. Without performing comprehensive analysis of immune microenvironment and hierarchical clustering, intratumoral density of CD3 T cells and CD79α extrafollicular B/plasma cells (≥ 100 cells/HPF CD3-positive T cells and ≥ 10 cells/HPF CD79α-positive extrafollicular B/plasma cells in ≥ 50% of tumor area) can work as a surrogate marker of Immune-high subtype. These results provide a rationale for evaluating the immune microenvironment in addition to the usual histological/molecular classification of HCC.

References

1. Kurebayashi Y, Ojima H, Tsujikawa H, Kubota N, Maehara J, Abe Y, Kitago M, et al. Landscape of immune microenvironment in hepatocellular carcinoma and its additional impact on histological and molecular classification. Hepatology 2018;68:1025-1041.
2. Kurebayashi Y, Kubota N, Sakamoto M. Immune microenvironment of hepatocellular carcinoma, intrahepatic cholangiocarcinoma and liver metastasis of colorectal adenocarcinoma: Relationship with histopathological and molecular classifications. Hepatol Res 2021;51:5-18.
3. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat Rev Cancer 2020;20:662-680.
4. Sautes-Fridman C, Petitprez F, Calderaro J, Fridman WH. Tertiary lymphoid structures in the era of cancer immunotherapy. Nat Rev Cancer 2019;19:307-325.
5. Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M. Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. Hepatology 1998;27:407-414.
6. Underwood JC. Lymphoreticular infiltration in human tumours: prognostic and biological implications: a review. Br J Cancer 1974;30:538-548.
7. WHO Classification of Tumours, 5th Edition, Digestive System Tumours. Lyon, France: International Agency for Research on Cancer, 2020.
8. Helmink BA, Reddy SM, Gao J, Zhang S, Basar R, Thakur R, Yizhak K, et al. B cells and tertiary lymphoid structures promote immunotherapy response. Nature 2020;577:549-555.
9. Calderaro J, Petitprez F, Becht E, Laurent A, Hirsch TZ, Rousseau B, Luciani A, et al. Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma. J Hepatol 2019;70:58-65.
10. Sia D, Jiao Y, Martinez-Quetglas I, Kuchuk O, Villacorta-Martin C, Castro de Moura M, Putra J, et al. Identification of an Immune-specific Class of Hepatocellular Carcinoma, Based on Molecular Features. Gastroenterology 2017;153:812-826.
11. Garnelo M, Tan A, Her Z, Yeong J, Lim CJ, Chen J, Lim KH, et al. Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma. Gut 2017;66:342-351.
12. Sakamoto M, Effendi K, Masugi Y. Molecular diagnosis of multistage hepatocarcinogenesis. Jpn J Clin Oncol

2010;40:891-896.
13. Sakamoto M, Hirohashi S, Shimosato YJHp. Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol 1991;22:172-178.
14. Ueno A, Masugi Y, Yamazaki K, Kurebayashi Y, Tsujikawa H, Effendi K, Ojima H, et al. Precision pathology analysis of the development and progression of hepatocellular carcinoma: Implication for precision diagnosis of hepatocellular carcinoma. Pathol Int 2020.
15. Tsujikawa H, Masugi Y, Yamazaki K, Itano O, Kitagawa Y, Sakamoto M. Immunohistochemical molecular analysis indicates hepatocellular carcinoma subgroups that reflect tumor aggressiveness. Hum Pathol 2016;50:24-33.

Genetic and Molecular/Immune Profiling Analyses for Hepatocellular Carcinoma

Naoshi Nishida

Kindai University, Japan

Although immune checkpoint inhibitors (ICIs) could be a key agent for the treatment of advanced hepatocellular carcinoma (HCC), previous clinical trials failed to showed the significant effect of anti-programmed cell death protein 1 (anti-PD-1) monotherapy on the treatment of HCC.[1-3] However, it is well described that a subset of the patients shows the considerable anti-tumor response on ICIs.[4] Therefore, identifying subgroups that respond well to ICIs is clinically important. To know how the effectively the anti-tumor response of this treatment can be enhanced, we explored the immunological and molecular characteristics of HCCs with programmed cell death ligand 1 (PD-L1) in patients treated with surgery as well as ICIs.

Clinical backgrounds, PD-L1 expression, and the amount of $CD8^+$ tumor infiltrating lymphocytes (TILs) were analyzed using human HCC tissues obtained from surgery. The expression of co-inhibitory receptors on tumor cells and TIMCs, respectively, were examined by immunohistochemical analysis. Somatic mutations in the cancer-associated genes and TERT promoter were determined; HCCs were classified based on the presence of gene alterations affecting the 8 oncogenic pathways. Transcriptome analysis was performed and immune status was evaluated using transcriptome-based immunogram.[5] The results were validated using dataset from the Cancer Genome Atlas. Next, HCC patients who were treated with anti-PD1 monotherapy were examined for clinicopathological backgrounds and anti-tumor responses. Tumor tissues before treatment were analyzed for the expression of immune checkpoint molecules, status of TILs, and Wnt/β-catenin related molecules.[6]

Expression of PD-L1 in HCC positively correlated with mutations of genes involving the phosphatidyl inositol 3-kinase (PI3K)-Akt pathway. Although, $CD8^+$ cells densely infiltrated in PD-L1-positive tumors, these TILs frequently expressed multiple co-inhibitory receptors. However, a subset of PD-L1-positive tumor characterized by activating mutation of PI3K-Akt pathway showed low degree of TILs. Conversely, PD-L1-negative HCCs were associated with activating mutations in the Wnt/β-catenin pathway and a small number of TILs, although expressions of co-inhibitory receptors were rare. Based on the prognostic analysis of the HCC patients who underwent anti-PD-1 monotherapy, the disease control rate (DCR) was significantly better in patients with α-fetoprotein < 400 ng/mL, negative for β-catenin/glutamate synthetase (GS) staining, high combined positive score (CPS) of programmed death-ligand 1 (PD-L1), and thig degree of TILs. Among them, negative staining of β-catenin/GS, CPS of PD-L1 $\geq$ 1, and high degree of $CD8^+$ TILs were significantly associated with longer survival in both progression-free survival (PFS) and overall survival (OS). The combination of these factors well stratified the survival of the patients on anti-PD-1 antibody in both

PFS and OS ($p < .0001$ and $p = .0048$ for PFS and OS, respectively). In addition, the immunogram revealed that tumor-carrying activating mutations in β-catenin showed downregulation of immune-related genes, especially in those related to priming and activation by dendritic cells, interferon-γ response, inhibitory molecules, and regulatory T cells; multivariate analysis showed downregulation of the genes involved in the interferon-γ response is the independent factor on the presence of the β-catenin mutation.

PD-L1-positive HCCs frequently showed inflamed phenotype; a subset of PD-L1-positive HCCs with mutation in PI3K-Akt pathway showed non-inflamed phenotype. In HCCs with dense infiltration of TILs, $CD8^+$ cells expressed multiple co-inhibitory receptors, suggesting T-cell exhaustion. On the other hands, PD-L1-negative HCCs showed mutations leading to β-catenin activation, such tumor also exhibited non-inflamed background.[7] Through the analysis of the HCC patients treated with anti-PD-1 monotherapy, the combined score including Wnt/β-catenin activation, CPS of PD-L1, and degree of $CD8^+$ TILs in HCC is revealed to be the predicting factor for the response to ICI. Constitutive activation of β-catenin can induce an immune cold phenotype with downregulation of genes involved in the immune response, especially those involved in interferon-γ response. This information should be taken into consideration for the treatment of HCC using immune checkpoint inhibitors.[6,8]

References

1. Finn RS RB-Y, Merle P, Kudo M, Bouattour M, Lim H-Y, Breder VV, Edeline J, Chao Y, Ogasawara S, Yau T, Garrido M, Chan SL, Knox JJ, Daniele B, Ebbinghaus S, Chen E, Siegel AB, Zhu AX, Cheng A-L. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2019;37:Abstract 4004.
2. Yau T PJ, Finn RS, Cheng A, Mathurin P, Edeline J, Kudo M, Han K, Harding, JJ MP, Rosmorduc O, Wyrwicz L, Schott1 E, Choo SP, Kelley RK, Begic D, Chen G, Neely J, Anderson J, Sangro B. CheckMate 459: A Randomized, Multi-Center Phase 3 Study of Nivolumab (NIVO) vs Sorafenib (SOR) as First-Line (1L) Treatment in Patients (pts) With advanced hepatocellular carcinoma (aHCC). Annals of Oncology 2019;30 (suppl_5):v851-v934. Abstract.
3. Sangro B, Sarobe P, Hervas-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021.
4. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-2502.
5. Kobayashi Y, Kushihara Y, Saito N, Yamaguchi S, Kakimi K. A novel scoring method based on RNA-Seq immunograms describing individual cancer-immunity interactions. Cancer Sci 2020;111:4031-4040.
6. Nishida N, Sakai K, Morita M, Aoki T, Takita M, Hagiwara S, et al. Association between Genetic and Immunological Background of Hepatocellular Carcinoma and Expression of Programmed Cell Death-1. Liver Cancer 2020;9:426-439.
7. Ruiz de Galarreta M, Bresnahan E, Molina-Sanchez P, Lindblad KE, Maier B, Sia D, et al. beta-Catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 Therapy in Hepatocellular Carcinoma. Cancer Discov 2019;9:1124-1141.
8. Harding JJ, Nandakumar S, Armenia J, Khalil DN, Albano M, Ly M, et al. Prospective Genotyping of Hepatocellular Carcinoma: Clinical Implications of Next-Generation Sequencing for Matching Patients to Targeted and Immune Therapies. Clin Cancer Res 2019;25:2116-2126.

Hepatocellular Carcinoma Molecular Pathological Classification and Its Practical Applications

Haeryoung Kim

Seoul National University, Korea

Hepatocellular carcinoma (HCC) is a primary liver cancer demonstrating hepatocellular differentiation. Although this definition is simple, the phenotypical and the molecular biological features of this neoplasm are heterogeneous, and there are multiple molecular subclasses and signatures of HCCs that have been identified to date in the literature. Recent studies have revealed some connections between the molecular subclasses and the morphological characteristics of HCCs, resulting in distinct histopathological variants of HCCs. Now, up to 35% of HCCs can be classified as histopathological variants of HCC, and these variants have been introduced in the recently published WHO Classification of Digestive System Tumors, 5th Edition. This classification also has practical implications both for the clinicians and the pathologists; for the clinicians, because the clinical features and outcomes of the HCCs may differ according to the subtypes and the classification may have potential therapeutic implications, and for the pathologists, because the morpho-molecular classification helps them better understand the histopathological features and provides more options for ancillary tests for diagnostic and prognostication purposes. The identification of histopathological variants of HCCs also suggests that histopathology still has an important role in HCC patient management. This talk will provide a summary of the recent morpho-molecular classification of HCC, and the practical implications of this classification will be discussed.

Hepatocellular Carcinoma Progenitor Phenotype: K19 and Hepatocellular Carcinoma

Hyungjin Rhee

Yonsei University, Korea

Keratin 19 (K19) is a marker for hepatic stem/progenitor cells.[1,2] In the normal liver, mature hepatocytes express K8 and K18, while cholangiocytes additionally express K7 and K19.[3] Although most hepatocellular carcinomas (HCCs) do not express K19 like normal hepatocytes, 10-28% of HCCs were reported to express K19, and were found to display a more invasive phenotype and poorer outcomes than those do not.[1,2,4-6] K19-positive HCCs also frequently express other markers associated with stemness, such as epithelial cell adhesion molecule (EpCAM), CD133, and c-kit/CD117.

Clinicopathologic features of HCC with K19 expression

HCC with K19 expression is defined as an HCC that demonstrates substantial (in >5% of tumor cells) immunohistochemical expression of K19.[7] HCCs with K19 expression have been associated with high serum alpha-fetoprotein (AFP) levels, chronic hepatitis B, and a more aggressive behavior, including decreased overall and recurrence-free survival, compared to K19-negative HCCs.[1,2,5,6] K19-positive HCCs show more infiltrative appearance, frequent vascular invasion, poor differentiation, fibrotic stroma, and extrahepatic dissemination.[2,5,8-11]

Molecular regulatory mechanism of K19 in HCC

In the past, a hepatic stem/progenitor cell origin was postulated for K19-positive HCCs, based on the immunohistochemical marker expression status.[1,12] However, several recent studies using lineage-tracing rodent HCC models demonstrated that K19-positive HCC cells originate from mature hepatocytes, and not from hepatic stem/progenitor cells.[13,14] In addition, K19-positive HCC cells were not observed in the early clonal expansion of rodent hepatocarcinogenesis.[15] Similarly, in the majority of K19 expression is observed in moderately or poorly differentiated advanced HCCs. Recently, K19 expression in HCC has been shown to be regulated by microenvironmental and epigenetic mechanisms. The main regulators of K19 expression include hepatocyte growth factor-MET paracrine signaling by cancer-associated fibroblast, epidermal growth factor-epidermal growth factor receptor signaling, laminin, and DNA methylation.[5,16-20]

Radiologic features of K19-positive HCC

The imaging "hallmark" of HCC is arterial phase hyperenhancement with washout in the portal venous phase image of multiphase CT or MRI; this is the diagnostic feature for patients with high-risk of HCC.[21,22]

In contrast, K19-positive HCCs often show atypical enhancement patterns, including weaker arterial phase hyperenhancement, arterial phase rim-like enhancement, and gradual enhancement in the portal venous and delayed dynamic phase.[23-26] While these atypical enhancement patterns are considered obstacles to an imaging diagnosis of HCC, they may – on the other hand – serve as clues to the diagnosis of HCCs with K19 expression. K19-positive HCCs have been associated with a decreased expression of OATP1B3 and lower signal intensity in the hepatobiliary phase, compared to K19-negative HCCs.[23,27] K19-positive HCC is associated with relatively higher ^{18}F-FDG uptake, compared with K19-negative HCC.[28]

Prognosis and treatment resistance of K19-positive HCC

K19-positive HCCs have been associated with poor outcome after curative treatment such as surgical resection, liver transplantation, and radiofrequency ablation.[1,2,4-6,10,29,30] K19-positive HCCs could show treatment resistance to transarterial chemoembolization.[10] K19-positive HCCs have shown resistance to chemotherapeutic agents, such as 5-FU, doxorubicin, and sorafenib, in *in vitro* studies.[5,30] Sorafenib resistance was associated with the gene signature of K19-positive HCC [31], and also with EMT and a hypoxic microenvironment, which are characteristics of K19-positive HCCs.[32]

References

1. Durnez A, Verslype C, Nevens F, Fevery J, Aerts R, Pirenne J, et al. The clinicopathological and prognostic relevance of cytokeratin 7 and 19 expression in hepatocellular carcinoma. A possible progenitor cell origin. Histopathology 2006;49:138-151.
2. Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, et al. Human hepatocellular carcinomas with "Stemness"-related marker expression: keratin 19 expression and a poor prognosis. Hepatology 2011;54:1707-1717.
3. Roskams T, De Vos R, Van Eyken P, Myazaki H, Van Damme B, Desmet V. Hepatic OV-6 expression in human liver disease and rat experiments: evidence for hepatic progenitor cells in man. J Hepatol 1998;29:455-463.
4. Uenishi T, Kubo S, Yamamoto T, Shuto T, Ogawa M, Tanaka H, et al. Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. Cancer Sci 2003;94:851-857.
5. Govaere O, Komuta M, Berkers J, Spee B, Janssen C, de Luca F, et al. Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. Gut 2014;63:674-685.
6. Tsuchiya K, Komuta M, Yasui Y, Tamaki N, Hosokawa T, Ueda K, et al. Expression of keratin 19 is related to high recurrence of hepatocellular carcinoma after radiofrequency ablation. Oncology 2011;80:278-288.
7. Torbenson MS, Ng IOL, Park YN, Roncalli M, Sakamoto M. Hepatocellular carcinoma. In: WHO Classification of Tumours Editorial Board, editor. Digestive system tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2019:229-239.
8. Lee Y, Park H, Lee H, Cho JY, Yoon YS, Choi YR, et al. The Clinicopathological and Prognostic Significance of the Gross Classification of Hepatocellular Carcinoma. J Pathol Transl Med 2018;52:85-92.
9. Rhee H, Chung T, Yoo JE, Nahm JH, Woo HY, Choi GH, et al. Gross type of hepatocellular carcinoma reflects the tumor hypoxia, fibrosis, and stemness-related marker expression. Hepatol Int 2020;14:239-248.
10. Rhee H, Nahm JH, Kim H, Choi GH, Yoo JE, Lee HS, et al. Poor outcome of hepatocellular carcinoma with stemness marker under hypoxia: resistance to transarterial chemoembolization. Mod Pathol 2016;29:1038-1049.
11. Zhuang PY, Zhang JB, Zhu XD, Zhang W, Wu WZ, Tan YS, et al. Two pathologic types of hepatocellular carcinoma with lymph node metastasis with distinct prognosis on the basis of CK19 expression in tumor. Cancer 2008;112:2740-2748.
12. Roskams T. Liver stem cells and their implication in hepatocellular and cholangiocarcinoma. Oncogene

2006;25:3818-3822.
13. Mu X, Espanol-Suner R, Mederacke I, Affo S, Manco R, Sempoux C, et al. Hepatocellular carcinoma originates from hepatocytes and not from the progenitor/biliary compartment. J Clin Invest 2015;125:3891-3903.
14. Shin S, Wangensteen KJ, Teta-Bissett M, Wang YJ, Mosleh-Shirazi E, Buza EL, et al. Genetic lineage tracing analysis of the cell of origin of hepatotoxin-induced liver tumors in mice. Hepatology 2016;64:1163-1177.
15. Kowalik MA, Sulas P, Ledda-Columbano GM, Giordano S, Columbano A, Perra A. Cytokeratin-19 positivity is acquired along cancer progression and does not predict cell origin in rat hepatocarcinogenesis. Oncotarget 2015;6:38749-38763.
16. Rhee H, Kim HY, Choi JH, Woo HG, Yoo JE, Nahm JH, et al. Keratin 19 Expression in Hepatocellular Carcinoma Is Regulated by Fibroblast-Derived HGF via a MET-ERK1/2-AP1 and SP1 Axis. Cancer Res 2018;78:1619-1631.
17. Yoneda N, Sato Y, Kitao A, Ikeda H, Sawada-Kitamura S, Miyakoshi M, et al. Epidermal growth factor induces cytokeratin 19 expression accompanied by increased growth abilities in human hepatocellular carcinoma. Laboratory Investigation 2010;91:262-272.
18. Govaere O, Petz M, Wouters J, Vandewynckel YP, Scott EJ, Topal B, et al. The PDGFRalpha-laminin B1-keratin 19 cascade drives tumor progression at the invasive front of human hepatocellular carcinoma. Oncogene 2017;36:6605-6616.
19. Govaere O, Wouters J, Petz M, Vandewynckel YP, Van den Eynde K, Van den Broeck A, et al. Laminin-332 sustains chemoresistance and quiescence as part of the human hepatic cancer stem cell niche. J Hepatol 2016;64:609-617.
20. Yokomichi N, Nishida N, Umeda Y, Taniguchi F, Yasui K, Toshima T, et al. Heterogeneity of Epigenetic and Epithelial Mesenchymal Transition Marks in Hepatocellular Carcinoma with Keratin 19 Proficiency. Liver Cancer 2019;8:239-254.
21. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-380.
22. Liver" EAftSot. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
23. Choi SY, Kim SH, Park CK, Min JH, Lee JE, Choi YH, et al. Imaging Features of Gadoxetic Acid-enhanced and Diffusion-weighted MR Imaging for Identifying Cytokeratin 19-positive Hepatocellular Carcinoma: A Retrospective Observational Study. Radiology 2018;286:897-908.
24. Rhee H, An C, Kim HY, Yoo JE, Park YN, Kim MJ. Hepatocellular Carcinoma with Irregular Rim-Like Arterial Phase Hyperenhancement: More Aggressive Pathologic Features. Liver Cancer 2019;8:24-40.
25. Choi JY, Kim MJ, Park YN, Lee JM, Yoo SK, Rha SY, et al. Gadoxetate disodium-enhanced hepatobiliary phase MRI of hepatocellular carcinoma: correlation with histological characteristics. AJR Am J Roentgenol 2011;197:399-405.
26. Chung GE, Lee JH, Yoon JH, Myung SJ, Lee K, Jang JJ, et al. Prognostic implications of tumor vascularity and its relationship to cytokeratin 19 expression in patients with hepatocellular carcinoma. Abdominal Imaging 2012;37:439-446.
27. Yamashita T, Kitao A, Matsui O, Hayashi T, Nio K, Kondo M, et al. Gd-EOB-DTPA-enhanced magnetic resonance imaging and alpha-fetoprotein predict prognosis of early-stage hepatocellular carcinoma. Hepatology 2014;60:1674-1685.
28. Kawai T, Yasuchika K, Seo S, Higashi T, Ishii T, Miyauchi Y, et al. Identification of Keratin 19-Positive Cancer Stem Cells Associating Human Hepatocellular Carcinoma Using 18F-Fluorodeoxyglucose Positron Emission Tomography. Clin Cancer Res 2017;23:1450-1460.
29. Nault JC, De Reynies A, Villanueva A, Calderaro J, Rebouissou S, Couchy G, et al. A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection. Gastroenterology 2013;145:176-187.
30. Kawai T, Yasuchika K, Ishii T, Katayama H, Yoshitoshi EY, Ogiso S, et al. Keratin 19, a Cancer Stem Cell Marker in Human Hepatocellular Carcinoma. Clin Cancer Res 2015;21:3081-3091.
31. Tovar V, Cornella H, Moeini A, Vidal S, Hoshida Y, Sia D, et al. Tumour initiating cells and IGF/FGF signalling contribute to sorafenib resistance in hepatocellular carcinoma. Gut 2015; doi:10.1136/gutjnl-2015-309501.
32. Zhu YJ, Zheng B, Wang HY, Chen L. New knowledge of the mechanisms of sorafenib resistance in liver cancer. Acta Pharmacol Sin 2017;38:614-622.

DAY 3: Saturday, May 15, 2021 (13:30-14:50)

ROOM 2

KASL-KLCA Joint Symposium

Technical Innovation: Approach to Liver Disease Utilizing Artificial Intelligence

Chairs:

Jin-Wook Kim (Seoul National Univ.)

Young Seok Kim (Soonchunhyang Univ.)

Technical Innovation of Artificial Intelligence in Liver Diseases From Idea to Idealization

Namkug Kim

University of Ulsan, Korea

The clinical applicable emerging technologies could depend on how to meet various unmet needs from actual clinical setting. Recent advances in engineering technology including deep learning, machine learning, informatics, clinical decision support system, and imaging biomarkers allow us to converge them beyond conventional disciplinary boundaries. Here, I will talk about new imaging technology classified as the fourth industrial revolution, especially application of artificial intelligence technology in liver diseases. Big-data analysis with deep learning in medicine including electric medical record, images, signals, etc will open a new era for decision support for liver disease treatment, survival prediction as well as diagnostic, intra-procedural imaging in hospital. I'll review technical challenges for deep learning research in medicine and our research results in Asan medical center, South Korea. In addition, for needs of diagnosis and procedures, informatics based on fully automated segmentation and detection could be provided to physicians with little additional costs.

However, in the actual clinical environment, the usability of these technologies is, however, far from satisfaction. We need to change this clinical environment with these technologies. In this talk, I will cover recent updates of artificial intelligence in the viewpoint of liver disease.

Artificial Intelligence and Clinical Application Pertinent to Liver Disease

Kwang Gi Kim

Gachon University, Korea

Liver cancer is among the most frequent types of cancerous diseases, responsible for the deaths of 745,000 patients worldwide in 2012. The liver is one of the most common organs to develop metastases and CT is one of the most common modalities used for detection, diagnosis and follow-up of liver lesions. In this work we explore a convolutional neural network for the task of liver segmentation and liver metastases detection in computed tomography (CT) examinations. CNN has proven to be a very powerful tool for semantic segmentation. The detection and delineation of the liver from abdominal 3D computed tomography (CT) images are fundamental tasks in computer-assisted liver surgery planning. However, automatic and accurate segmentation, especially liver detection, remains challenging due to complex backgrounds, ambiguous boundaries, heterogeneous appearances and highly varied shapes of the liver. To address these difficulties, we propose an automatic segmentation framework based on 3D convolutional neural network (CNN) and globally optimized surface evolution. First, a deep 3D CNN is trained to learn a subject-specific probability map of the liver, which gives the initial surface and acts as a shape prior in the following segmentation step. The quantitative validations and comparisons show that the proposed method is accurate and effective for clinical application.

Radiomics and Deep Learning: Focal Liver Disease and Tumor Detection

Woo Kyoung Jeong

Sungkyunkwan University, Korea

Radiomics is an emerging technology to mine useful features from medical imaging data, which is applied to variable fields including hepatology and oncology. Basically, it is a kind of data science defined as the high-throughput extraction of image features from radiologic images, such as X-ray, CT, MRI, ultrasound, and PET. Deep learning is also a computer technology that is in the spotlight across all fields of medical sciences. Using the technique applied to radiology, radiologists can be of great help in autosegmentation of the organs and lesions, computer-aided diagnosis, and prediction of treatment response by using medical image analysis. In this lecture, the clinical applications of these computer techniques applied to radiology-hepatology field, especially focused to detection, characterization, and estimation of treatment response of hepatic malignancies, will be addressed.

Risk Assessment and Decision Making of Hepatocellular Carcinoma Treatment through Artificial Intelligence

Gwang Hyeon Choi

Seoul National University, Korea

Hepatocellular carcinoma (HCC) is the third most common malignancy in men and seventh in women worldwide, and its incidence continues to increase. Despite significant advancements in diagnosis and treatment of HCC, its management remains a challenge. An application of artificial intelligence (AI) has improved the efficiency and accuracy of diagnosis and treatment in other tumors. And, AI approaches have been increasingly used in recent years in HCC to improve the efficiency and accuracy of diagnosis and treatment.

Despite significant advancements in diagnosis and treatment of HCC, its management remains a challenge. Risk assessment and decision making for HCC treatment is highly multifactorial, in which the physician needs to take into account multiple factors such as the stage and grade of HCC, baseline liver function, and performance status. Therefore, for HCC, an AI-based approach rather than classical biostatistical methods can help risk assessment through treatment response and prognosis prediction.

Most studies on the use of AI in the treatment of HCC are aimed to predict the response, recurrence or survival after certain treatment such as liver resection, radiofrequency ablation, transarterial chemoembolization using radiological, genetic features, or a combination of the clinical data. These studies have shown remarkable predictive power. Relatively few studies have been conducted on clinical decision support systems for HCC treatment.

AI research on HCC treatment has several limitations; small sample size, single-center data collection with lack of external validation, lack of transparency, and possibility of model overfitting. Larger collaborative study are needed and more sophisticated AI models combining radiomic and/or pathologic data with clinical features to predict the clinical outcomes and support clinical decision for HCC patients are warranted.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (11:10-12:30)

ROOM 3

KAHBPS Symposium 1

How to Achieve R0 Resection in Perihilar Cholangiocarcinoma Both Successfully and Safely

Chairs:

Chol Kyoon Cho (Chonnam National Univ.)

Yang Won Nah (Univ. of Ulsan)

Various Types of Vascular Resection and Reconstruction in Perihilar Cholangiocarcinoma

Shin Hwang

University of Ulsan, Korea

It is often difficult to achieving R0 resection of advanced perihilar cholangiocarcinoma because of the complexity in anatomic structures of the hepatic hilum and the nature of tumor invasion. If the proximal bile duct resection margin is tumor-positive, major or parenchyma-preserving hepatectomy is necessary to achieve R0 resection. For right hepatectomy, segmental resection of the right portal vein is technically demanding due to the limited length of the first-order right portal vein; thus, interposition of vein graft is often necessary. In contrast, for left hepatectomy, segmental resection of the left portal vein is feasible because of the lengthy first-order left portal vein. If the portal vein confluence is invaded, wedge resection with or without patch venoplasty can be performed. Because segmental resection and reconstruction of the right hepatic artery is often demanding, right hepatectomy is preferred in case of right hepatic artery encasement. If right hepatectomy is not allowed due to small future remnant left liver, the right hepatic artery can be transected and reconstructed with the gastroduodenal artery or right gastroepiploic artery. Experience on this type of arterial reconstruction is well accumulated along the experience of living donor liver transplantation. For parenchyma-preserving hepatectomy, resection of segment I and segment IV with bile duct resection offers very wide operative field and allows wider extent of hilar bile duct resection, thus it presents the most common type of parenchyma-preserving hepatectomy. When the portal vein is focally involved by the tumor, hilar portal vein wedge resection and roofing patch venoplasty using a autograft or allograft vein patch is a useful option. Regarding roofing patch venoplasty, it is important to make the portal vein wall defect as small as possible as well as to make the size of the vein patch either twice or three times larger than the defect size at the portal vein wall. The patch should be large enough to make the patch roof redundant. Even if the patch roof appears to be noticeably redundant at the time of operation, it is vulnerable to shrinkage due to compression of the jejunal loop and through degenerative changes of the patch per se. The availability of vein autografts or allografts facilitates combined vascular resection and reconstruction during aggressive surgery for hepatobiliary malignancies. If the reconstructed portal vein appears to be thrombogenic due to acute angulation or intimal damage, it is necessary to perform self-expandable wall stent during surgery. The surgical techniques for vascular reconstruction during aggressive resection of advanced perihilar cholangiocarcinoma are interchangeable and shared with those used for living donor liver transplantation.

Surgical Resection for Longitudinally Infiltrative Perihilar Cholangiocarcinoma

Yajin Chen

Sun Yat-Sen University, China

Transhepatic Hilar Approach for Perihilar Cholangiocarcinoma

Naohisa KURIYAMA, Haruna KOMATSUBARA, Yuki NAKAGAWA, Koki MAEDA, Toru SHINKAI, Kazuyuki GYOTEN, Aoi HAYASAKI, Takehiro FUJII, Yusuke IIZAWA, Yasuhiro MURATA, Akihiro TANEMURA, Masashi KISHIWADA, Hiroyuki SAKURAI, Shuji ISAJI, Shugo MIZUNO

Mie University, Japan

In perihilar cholangiocarcinoma (PHC), the critical aspect for curative resection is the cut margin of the remnant liver, including the hepatic artery (HA), portal vein (PV), and bile duct (BD). It is preferable to determine the resectability and possibility of reconstruction of the PV and/or HA early in the operation. To achieve this, in early 2011, we modified a primary hepatic parenchymal transection technique and developed a new operative procedure with major hepatectomy for PHC, called the transhepatic hilar approach (THA). Additionally, from an anatomical point of view, the advanced PHC easily involves the adjacent vasculatures including PV and HA. PV resection and reconstruction is frequently performed, compared with HA reconstruction, which is essential technique to achieve R0 resection.[1] This study aims to elucidate the surgical outcomes and technique of THA followed by hepatectomy for PHC.[2]

Evaluation of remnant liver function

SYNAPSE VINCENT constructs 3D image using dynamic CT (3DCT). Fusion image of 3DCT and 99mTc-GSA SPECT is reconstructed and then calculates functional remnant liver volume ratio (f-rem). F-remK (f-rem x KICG) less than 0.05 is contraindication for surgery.

Operative procedure of THA

After marking resection line along the hepatic vein using US, partial hepatic parenchymal transection to expose remnant hilar plate is performed, followed by skeletonization of HA, PV, and BD, respectively. Then, the proximal BD resection is performed to confirm a negative margin, followed by the distal BD resection and skeletonization of the hepatoduodenal ligament. Thereafter, the hepatectomy with caudate lobe is completed. THA provides us with a clear surgical view to perform reconstruction of PV in the middle of hepatectomy.

Patients

Between January 2011 and December 2020, THA followed by hepatectomy was performed for 52 patients with PHC (31 males and 21 females, median age of 69 years), of whom 31 (60%) received preoperative therapy.[3,4]

Results

Several kind of operation was underwent as following; left hepatectomy in 30, left trisectionectomy (TSN) in 2 patients, right hepatectomy in 18 patients, right TSN in 1 patient, and central bisectionectomy in 1patient, respectively. Median operation time and blood loss were 602 min and 1,634 ml. Combined vascular resection (PV alone in 17 patients, HA alone in 2 patients, PV and HA in 7 patients) was performed in 26 (50%). R0 resection excluding 3 patients with distant metastasis was achieved in 38 (78%) patients. Clavien III or higher complications occurred in 27 (52%) patients. Ninety-day hospital mortality was 1 (2%) patient. The disease-specific 5-year survival rate was 48.5% (median survival time: 52.4 months).

Conclusion

THA followed by hepatectomy for PHC is rational surgical procedure to exert practical handling of hilar plate and easily performing resection and reconstruction of the PV in the middle of hepatectomy.

References

1. Kuriyama N, Komatsubara H, Nakagawa Y, Maeda K, Shinkai T, Noguchi D, Ito T, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, Murata Y, Tanemura A, Kishiwada M, Sakurai H, Mizuno S. Impact of Combined Vascular Resection and Reconstruction in Patients with Advanced Perihilar Cholangiocarcinoma. J Gastrointest Surg. 2021 Apr 21. Epub ahead of print.
2. Kuriyama N, Isaji S, Tanemura A, Iizawa Y, Kato H, Murata Y, Azumi Y, Kishiwada M, Mizuno S, Usui M, Sakurai H. Transhepatic Hilar Approach for Perihilar Cholangiocarcinoma: Significance of Early Judgment of Resectability and Safe Vascular Reconstruction. J Gastrointest Surg. 2017;21:590-599.
3. Kuriyama N, Usui M, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, Kato H, Murata Y, Tanemura A, Kishiwada M, Sakurai H, Mizuno S, Isaji S. Neoadjuvant chemotherapy followed by curative-intent surgery for perihilar cholangiocarcinoma based on its anatomical resectability classification and lymph node status. BMC Cancer. 2020;20:405.
4. Ito T, Kuriyama N, Kozuka Y, Komatsubara H, Ichikawa K, Noguchi D, Hayasaki A, Fujii T, Iizawa Y, Kato H, Tanemura A, Murata Y, Kishiwada M, Mizuno S, Usui M, Sakurai H, Isaji S. High tumor budding is a strong predictor of poor prognosis in the resected perihilar cholangiocarcinoma patients regardless of neoadjuvant therapy, showing survival similar to those without resection. BMC Cancer. 2020;20:209.
5. Noguchi D, Kuriyama N, Nakagawa Y, Maeda K, Shinkai T, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, Tanemura A, Murata Y, Kishiwada M, Sakurai H, Mizuno S. The prognostic impact of lymphocyte-to-C-reactive protein score in patients undergoing surgical resection for intrahepatic cholangiocarcinoma: A comparative study of major representative inflammatory / immunonutritional markers. PLoS One. 2021;16:e0245946.

Real Practice of Surgical Resection Following Neoadjuvant Chemoradiation Therapy in Perihilar Cholangiocarcinoma

Gi Hong Choi

Yonsei University, Korea

Curative resection of perihilar cholangiocarcinoma (PHCC) is challenging and is accompanied by a high probability of locoregional recurrence, even after R0 resection due to the anatomical proximity of the former tumor type to hilar vascular structures and tumor extension in both radial and longitudinal directions. In this study, the necessity of neoadjuvant treatment for PHCC was addressed by comparing the recurrence patterns of PHCC and distal cholangiocarcinoma (DCC). These two tumors belong to extrahepatic cholangiocarcinoma, however surgical procedures for radical resection are different because the hilar vessels should be isolated from the bile duct and peritumoral tissue for PHCC and DCC can usually be removed by *en bloc* resection (PD or pylorus-preserving PD) without dissecting the distal bile duct and peritumoral tissue. and investigating the efficacy of concurrent chemoradiotherapy (CCRT) before surgery in locally advanced PHCC.

Accordingly, we hypothesized that these differences in anatomical location and surgical procedures might lead to different patterns of recurrence; specifically, we hypothesized that PHCC would have higher locoregional and peritoneal seeding recurrence rates than DCC. We further hypothesized that neoadjuvant treatment to reduce the tumor burden before surgery would increase the R0 resection rate and decrease recurrence after curative resection in patients with PHCC. Since the introduction and establishment of CCRT for pancreatic cancer in our institute, CCRT has been selectively applied as the first-line treatment for patients with initially unresectable or borderline resectable PHCC, which has allowed some patients to receive curative resection through either tumor shrinkage or downstaging.

We first compared recurrence patterns after R0 resection of PHCC (n=204) and DCC (n=258). Second, patients who underwent resection of PHCC (n=132) were divided into a CCRT group (n=28) and upfront resection group (n=104). Perioperative outcomes and long-term survival were compared between the two groups, and prognostic factors for disease-free survival (DFS) and overall survival (OS) were determined.

Recurrence rate was higher in the PHCC group than the DCC group (64.7% vs 48.1%, $P<.001$), mainly due to locoregional and peritoneal recurrence. CCRT was associated with a higher proportion of R0 resections (92.9% vs 73.1%, $P=.027$) and less locoregional recurrence (3.6% vs 19.2%, $P=.044$) than upfront resection. Two groups showed comparable median DFS (CCRT vs resection, 19.0 vs 15.0 months, $P=.561$) and OS (34.1 vs 27.1, $P=.651$). R0 resection, initial carbohydrate antigen 19-9 level >37 U/mL, initial bilirubin level >3 mg/dL, and poor tumor differentiation were independent prognostic factors for both DFS and OS.

Meanwhile, inpatient hospital mortality in the CCRT group was high (7 patients, 25%). The primary

cause of mortality was liver failure after aggressive surgical resection. Due to extensive tumor involvement, most cases required extensive radical hepatectomy, resulting in liver failure. However, most (92.8%) inpatient hospital mortality (n=14) occurred in the early period of inexperience between 2004 and 2011. As preoperative multimodality treatment protocols have been optimized and surgical experience has accumulated over time, mortality and morbidity rates have decreased dramatically. The other limitation is that various chemotherapeutic regimens were used for CCRT according to each oncologist's preferences while three-dimensional conformal external beam radiotherapy was administered relatively uniformly. These heterogeneous chemotherapy regimens may make it difficult to verify the role of CCRT in the outcomes of these patients, which means that a well-designed prospective study is strongly required.

In conclusion, PHCC showed more locoregional and peritoneal recurrence than DCC, which indicates that neoadjuvant treatment for PHCC may be useful. Through tumor downstaging, CCRT of patients with locally advanced PHCC provided a higher R0 resection rate and lower loco-regional recurrence than up-front resection. These findings should be confirmed in a well-designed prospective study.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (13:30-14:50)

ROOM 3

KAHBPS Special Lecture

Chairs:

Hee Chul Yu (Jeonbuk National Univ.)

Sang-Jae Park (National Cancer Center Korea))

KAHBPS Special Lecture

Solving the Equations of Portal Flow, Liver Regeneration, and Posthepatectomy Liver Failure

Eric Vibert

Paris-Sud University, France

Clinicopathological Characteristics of Intraductal Papillary Neoplasm of the Bile Duct (IPNB): Surgeons' Point of View

Keiichi Kubota

Dokkyo Medical University, Japan

IPNB is defined as an intraductal growing tumor covered by well-differentiated papillary neoplastic epithelium with fine fibrovascular cores in the intra- and extra-hepatic bile ducts. IPNB is now subclassified into two types according to similarity to intraductal papillary mucinous neoplasm of the pancreas (IPMN): Type 1 IPNB is histologically similar to IPMN, typically develops in the intrahepatic bile ducts, and contains macroscopic mucin components. Type 2 IPNB has a more complex histological architecture with irregular papillary branching or with foci of solid-tubular components, typically involves the extrahepatic bile ducts, and is frequently associated with invasive cancers. In this presentation, clinicopathological characteristics of the two types are discussed on the basis of the data of Japan-Korea collaborative study, with special attention to the surgical outcome.

There were 520 patients with Type 1 IPNB and 174 with Type 2 IPNB. Liver dysfunction, jaundice, fever, and abdominal pain were more frequently observed in patients with type 2 IPNB. The levels of AST, ALT, ALP, γ-GTP, T. Bil, CEA and CA19-9 were significantly higher in patients with Type 2 than in those with Type 1. On comorbidity, cholecystolithiasis and choledocholithiasis were more frequently observed in patients with Type 1 IPNBs than in those with Type 2 IPNBs. Although there were no significant differences in the incidences of anomalous junction of pancreato-biliary ducts and clonorchiasis between patients with Type 1 and Type 2 IPNBs, their incidences were higher than reported rates up-to-now. Type 1 IPNB was more frequently located in the intrahepatic bile duct than Type 2, whereas Type 2 was more frequently located in the distal bile duct than Type 1 IPNB ($P<0.001$). Mucobilia was more frequently observed in patients with Type 1 IPNB than in those with Type 2 IPNB. Type 1 IPNBs were more frequently resected by hepatic resection than Type 2 IPNBs. Sectionectomy and bigger hepatectomy were employed for resecting Type 1 IPNB. Some patients required hepato-pancreatoduodenectomy. Bile duct resection was also performed in a few patients. While Type 2 IPNBs were more frequently extirpated by PD than Type 1 IPNB. On the bile duct margin, there were no significant differences in the cancer positivity of proximal and distal bile duct margins between Type 1 and Type 2 IPNBs. Furthermore, the positive or negative bile duct margins did not influence not only the cumulative survival rates, but also the cumulative disease-free survival rates. No significant differences in the incidences of recurrence sites were noted between the Type 1 and Type 2 IPNBs. Lymph node metastasis was observed more frequently in patients with Type 2 IPNB than in those with Type 1 IPNB. On tumor differentiation, low or intermediate grade dysplasia, high grade dysplasia and IPNB with an associated invasive carcinoma were observed in 7.4%, 31.6% and 61%, respectively.

Univariate analysis showed that age, type, CEA level and tumor location in the distal bile duct were

significant factors associated with cumulative survival rates. Multivariate analysis demonstrated that age, Type 2 and tumor location in the distal bile duct were significantly associated with cumulative survival rates. There were significant differences in 5-year cumulative survival rates (75.2% vs 50.9%; P <0.0001) and 5-year cumulative disease-free survival rates (64.1% vs 35.3%; P <0.0001) between Type 1 and Type 2 IPNB. In patients without cancer invasion, cumulative survival rates and cumulative disease-free survival rates were significantly better in Type 1 than in Type 2.

In summary, IPNBs are classified into two types, the two types have different clinical characteristics and overall survival and disease-free survival, Type 1 IPNBs are resected mainly by hepatic resection, while Type 2 IPNBs are extirpated by PD and hepatic resection, extent of lymph node resection should be same for Type 1 and Type 2 IPNB, and inflammation in the bile duct may be associated with development of IPNB.

References

1. Kubota K, Jang JY, Nakanuma Y, et al. Clinicopathological characteristics of intraductal papillary neoplasm of the bile duct: a Japan-Korea collaborative study. J Hepatobiliary Pancreat Sci 2020; 27: 581-597.
2. Nakanuma Y, Uesaka K, Kakuda Y, Intraductal papillary neoplasm of bile duct: Updated clinicopathological characteristics and molecular and genetic alterations. J Clin Med 2020; 9: 3991. doi: 10.3390/jcm9123991. PMID: 33317146
3. Matsumoto T, Kubota K, Hachiya H, et al. Impact of tumor location on postoperative outcome of intraductal papillary neoplasm of the bile duct. World J Surg 2019; 43: 1313-1322.

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (15:00-16:20)

ROOM 3

KAHBPS Symposium 2

Critical Thinking for Surgical Treatment of Metastatic Liver Tumor

Chairs:

Kyung Sik Kim (Yonsei Univ.)

Ki-Hun Kim (Univ. of Ulsan)

Oncologist's View of Determining Optimal Timing of Hepatectomy

Myung Ah Lee

The Catholic University of Korea, Korea

In solid tumor, metastasis means that cancer may spread by lymphatics or blood stream whole body leading to disseminated disease. Even there is only single tumor in single organ metastasis in imaging study, this is not real single metastasis. However, in colorectal cancer, there are subset of patients with resectable synchronous disease. In these patients, we can expect cure with 5-year survival rate ranging 27-73%. Surgical resection of primary tumor and metastatic lesion can be standard treatment in colorectal cancer. Recently, liver resection for liver metastasis is tried in other solid tumor in selected cases.

For colorectal cancer, staged operation or simultaneous resection are tried according to location, size, numbers, and other patient factors. The multidisciplinary team should make decision for operation timing and sequence based on each patient' status. In staged operation, it can reduce the operation morbidity comparing to simultaneous resection and resect right patients for liver resection during the chemotherapy treatment course. For simultaneously resection before chemotherapy, it may reduce the need for two major operation and avoid chemotherapy related hepatic injury, leading the postoperative liver failure. In one meta-analysis, there is no differences between simultaneous resection and staged operation in morbidity or mortality. Cost effectiveness and the length of hospital day is better in simultaneous resection group than staged operation. If the liver metastasis is limited and not required cytoreduction, simultaneous resection may be considered.

However, this is limited to resectable liver metastasis. If the patient has potentially resectable but not expecting R0 resection or borderline resectable, systemic chemotherapy should be done before surgery. Decision for chemotherapy or surgery first may be made based on these factors: 1) characteristics of primary cancer, such as advanced, location, genetic profiles, or other prognostic factors 2) disease status of liver metastasis such as size, numbers, margin status 3) presence of extrahepatic disease 4) tumor burden such as tumor marker elevation, 5) disease free interval if the liver metastasis is recurrent disease. 6) expected response of systemic chemotherapy. If the systemic chemotherapy is first done, it should be used with the goal of resection. There is strong correlation between response rate and clinical outcome. Higher response should be obtained by systemic treatment but not overtreatment. It may result in loss of resectability window or treatment limiting toxicity. Some chemotherapy agent can induce liver dysfunction, leading to increasing postoperative morbidity even achieving high response rate. The treatment duration can also affect perioperative morbidity.

In other cancers, local treatments including liver resection are tried. However, there is insufficient evidence to support yet. Some cancers can develop recurrent disease rapidly after local treatment unless systemic control is not done. We should consider the characteristics of primary cancer even if the lesion is

limited only to liver. Patients are limited selection for metastasectomy. Moreover, further study should be explored for these cancers.

References

1. Ejaz A, Semenov E, Spolverato G, et al. Synchronous primary colorectal and liver metastasis: impact of operative approach on clinical outcomes and hospital charges. HPB 2014; 16: 1117–1126.
2. van der Pool AE, de Wilt JH, Lalmahomed ZS et al. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. Br J Surg 2010; 97: 383–390.
3. Pawlik TM, Rodriguez-Bigas MA, Monson J RT et al. Timing of Surgical Resection for Curative Colorectal Cancer with Liver Metastasis. Ann Surg Oncol 2018; 25: 32–37.
4. Vallance AE, Meulen JV, Kuryba A, et al. The timing of liver resection in patients with colorectal cancer and synchronous liver metastases: a population-based study of current practice and survival. Colorectal Dis 2018; 20(6) :486-495.
5. Chow FC, Chok KS. Colorectal liver metastases: An update on multidisciplinary approach. World J Hepatol 2019;11(2): 150-172.
6. Bale R, Putzer D, Schullian P. Local Treatment of Breast Cancer Liver *Cancers* 2019; *11(9):* 1341
7. Symonds LK, Cohen SA. Use of perioperative chemotherapy in colorectal cancer metastatic to the liver. Gastroenterology Report 2019; 7(5): 301–311.

The Effects of Chemotherapy Associated Liver Injury (CALI) on Outcomes Following Hepatectomy

Jai Young Cho

Seoul National University, Korea

Recent improvement of surgical care and surgical technique, and increased experience of liver transplantation contributed to aggressive hepatic resection for colorectal liver metastasis (CRLM) including massive hepatic resection after portal vein embolization, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), and two-stage hepatectomy. For initially unresectable extensive metastasis, some portion of patients with Stage IV could be converted to resectable disease after chemotherapy. However, there are still several unsolved issues regarding diagnosis and treatment of liver metastasis from colorectal cancer.

Despite the documented benefits of neoadjuvant chemotherapy in patients with CLM, there are a number of detrimental side-effects that require consideration. In particular, there are a number of chemotherapy related complications which may impair the hepatic parenchyma, thus influencing outcome following resection, including steatosis, chemotherapy-associated steatohepatitis (CASH) and sinusoidal obstruction syndrome (SOS).

In patients with resectable colorectal cancer liver metastasis (CRLM), liver resection is currently considered the best strategy for achieving long-term survival, with 5-year survival rates ranging from 40 to 53 %. There are several options for the treatment of resectable synchronous liver metastases, including staged versus simultaneous resection, and alternative perioperative chemotherapeutic regimens. The benefits of staged resection in terms of perioperative complications and oncological outcomes are still controversial when compared with simultaneous resection, but the patient must undergo two major operations, resulting in a longer hospital stay and greater hospital costs. In the last decade, the mortality and morbidity rates of colorectal and liver surgery have decreased owing to the advances in surgical devices, surgical techniques, ablation techniques, anesthetic techniques, and postoperative care. Thus, simultaneous resection has become widely accepted. However, it is not recommended if simultaneous resection is necessary for treating rectal cancer or in patients undergoing extensive liver resection, because it may increase the risk of perioperative complications. Although several studies have demonstrated the safety of simultaneous liver resection for CRLM, these studies did not evaluate the outcomes of simultaneous major liver resection (MLR) and colorectal surgery specifically in patients who had undergone rectal surgery. Therefore, it is very important for surgeons to predict and reduce potential risks for combined surgery with colorectal surgery.

Surgical Treatment of Metastatic Neuroendocrine Tumors

Jan Lerut

Université Catholique de Louvain, Belgium

Gastro-entero-pancreatic NETs are often diagnosed at an advanced stage. Fortunately the metastatic disease remains for a long time confined to the liver. This “window of opportunity” is of particular interest for the surgical treatment of NET liver metastases (LET-LM). Primary tumour R0 resection followed by liver resection may indeed nowadays represent a curative option for many of these patients. Partial RO liver resection is unfortunately only possible in a minority of patients as indeed detailed pathologic examination of the resected specimen often reveals many more lesions than those identified by state of the art imaging. During the last years the place of total hepatectomy (read Liver transplantation -LT) in the treatment of NET-LM has gained more and more attention in the literature. Especially the European Liver Transplant Registry and the Milan National Tumour Institute experiences, identified several factors as a prerequisite for success: R0 resection of the primary, presence of a well differentiated, low-grade tumour[Ki-67 < 5 –10 %]; primary tumour localization within the portal venous drainage area; tumour burden < 50 % of liver volume; age < 55 years; response to pre-LT treatment with somatostatin analogues and m-Tor inhibitors; stable or controlled disease for ≥ 6 months and avoidance of multi-visceral transplantation. When adhering to these strict selection criteria ,LT compared very well to all other surgical and non-surgical approaches in terms of time to progression and survival as shown by the 5-year OS and DFS rates of 97 and 85%.

Time has thus come to recognize LT as a valuable treatment for NET-LM. Living donor LT (LDLT) ,using small grafts (seen absent portal hypertension), will without any doubt play a major role in the treatment of NET-LM as this procedure allows in particular to time optimally this intervention sticking thereby to the principles of basic oncology, namely controlling the “factors tumour and time.”. Detailed analysis of larger transplant experiences is needed to further improve our knowledge and to optimise the use of a scarce organ resource in this disease.

To Do or Not To Do?: Non-Colorectal Liver Metastasis

Sae Byeol Choi

Korea University, Korea

Liver resection is considered standard treatment for patients with colorectal liver metastases (CRLM), with 5-year overall survival rates of 50% or more.[1,2] In addition, it is accepted as a treatment option in patients with neuroendocrine liver metastases (NELM), with 5-year survival ranging from 60 to 80%. Liver resection for metastasis from other malignancy is still controversial.[3,4]

Selected patients with non-CRLM, non-NELM may also be potential candidates for surgical treatment, since several studies demonstrated an association with improved survival after liver resection.[5-7] Due to advancement of chemotherapeutic agents as well as surgical technique, indications for liver resection are expanding.

In one study for 51 patients with NCNNLM, the histology of primary tumors was classified as adenocarcinoma (n = 16), sarcoma (n = 4), squamous cell carcinoma (n = 4), melanoma (n = 16), gastrointestinal stromal tumor (n = 9), and adrenocortical carcinoma (n = 2). One-, three-, and five-year overall survival rates were 85%, 52%, and 38%, respectively. The median overall survival was 37 (95%CI, 25 to 49) months.[8]

In gastric cancer liver metastasis (GCLM), the 5 year survival rate was approximately 30% after hepatectomy. Surgical treatment is considered to be a feasible option for GCLM. The number of metastatic liver tumors, the level of CA19-9, and the patient age to be prognostic indicators for the surgical treatment of GCLM.[9] As a liver-targeted therapy, in select patients with GCLM, liver resection and RFA showed satisfactory and comparable short- and long-term results. Thus, systemic chemotherapy may not be the only therapeutic option for patients with liver metastasis, and possible liver-directed treatment options for such patients should be considered on an individual basis.[10]

In breast cancer liver metastasis (BCLM), liver resection was also a therapeutic option although BCLM have long been considered as a systemic disease because of the hematological route of dissemination. By contrast, there is a growing evidence in the literature for satisfactory longterm results after a combination of chemotherapy and liver resection, with 5-year survival reaching 40% in some series.[11,12] The best results after the resection of BCLM are obtained after applying selection criteria based on small metastases (<4-5 cm), minor hepatectomy, radical resection (ideally R0, or R1), stable disease (ideally in regression) after neoadjuvant therapy, and a delay between primary and secondary lesions longer than 1 or 2 years (reflecting a favorable oncologic context).[13]

Liver resection can be a safe and effective way of treating non-CRLM if clinically indicated at experienced centers where multidisciplinary adjuvant treatments are available. It can be considered more frequently as part of the multidisciplinary care for selected patients with good outcomes. All patients with liver metas-

tases should be discussed in a multidisciplinary tumor board, including an expert liver surgeon in order to offer the best possible treatment.

References

1. House MG, Ito H, Gonen M, et al: Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. J Am Coll Surg 210:744-52, 752-5, 2010
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al: Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 25:4575-80, 2007
3. Mayo SC, de Jong MC, Pulitano C, et al: Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol 17:3129-36, 2010
4. Sarmiento JM, Heywood G, Rubin J, et al: Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 197:29-37, 2003
5. Adam R, Chiche L, Aloia T, et al: Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. Ann Surg 244:524-35, 2006
6. Ruys AT, Tanis PJ, Nagtegaal ID, et al: Surgical treatment of renal cell cancer liver metastases: a population-based study. Ann Surg Oncol 18:1932-8, 2011
7. van Walsum GA, de Ridder JA, Verhoef C, et al: Resection of liver metastases in patients with breast cancer: survival and prognostic factors. Eur J Surg Oncol 38:910-7, 2012
8. Aghayan DL, Kalinowski P, Kazaryan AM, et al: Laparoscopic liver resection for non-colorectal non-neuroendocrine metastases: perioperative and oncologic outcomes. World J Surg Oncol 17:156, 2019
9. Kawahara K, Makino H, Kametaka H, et al: Outcomes of surgical resection for gastric cancer liver metastases: a retrospective analysis. World J Surg Oncol 18:41, 2020
10. Guner A, Son T, Cho I, et al: Liver-directed treatments for liver metastasis from gastric adenocarcinoma: comparison between liver resection and radiofrequency ablation. Gastric Cancer 19:951-60, 2016
11. Abbott DE, Brouquet A, Mittendorf EA, et al: Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. Surgery 151:710-6, 2012
12. Mariani P, Servois V, De Rycke Y, et al: Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. Eur J Surg Oncol 39:1377-83, 2013
13. Golse N, Adam R: Liver Metastases From Breast Cancer: What Role for Surgery? Indications and Results. Clin Breast Cancer 17:256-265, 2017

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

DAY 3: Saturday, May 15, 2021 (08:30-09:50)

ROOM 4

Publication Forum

Chairs:

Yoon Jun Kim (Seoul National Univ.)

Seung Up Kim (Yonsei Univ.)

Tips to Write a Paper and Get It Published in High Impact Journals

W. Ray Kim

Stanford University, USA

Sharing Experience in Handling High Impact Journal

Yoshiyuki Ueno

Yamagata University, Japan

It is one of the vital activities for every researcher to share his/her experiences. In most cases, it is done by publishing as an article. Of course, in some cases, it also could be done through media press release or simply in personal SNS. However, being as a member of scientific community, most researchers pay significant respects for academic journals, preferentially published by academic societies. The central dogma contains 1) fair peer review process, 2) clear and distinct editorial policies, and 3) appropriate publication handling. Under these dogmata, each academic society-based journal has their own scopes. Reading scientists, or audience, pay their intellectual curiosity according to these characteristic features of journals. So, it is a matter of course that we expect different contents journals by journals. For example, we anticipate quite different articles published in New England Journal of Medicine and those in Journal of Clinical Investigation. This is also applicable that Gut published different articles compared to Gastroenterology. Thus, authors who want to publish their findings need to pay sufficient respects to each submitting journals. These 'respects' practically means several aspects, needless to say preparing the manuscript in required format by each journal. The violation of required format usually gives significant negative impression towards the manuscript, leading to editorial kick without external review process. The excellent manuscript prepares each section according to the journal's scope and audience. The discussion section should be described in the viewpoints of journals' readers. Thus, the manuscript which apparently submitted and adjusted to different journal without any modifications to submitted journal policy is usually considered to be less priority to the journal. This also could be resulting in editorial kick without review. In contrast, the manuscript which describe findings just fits to journal" policy and audiences' interests attracts editorial boards member and will be given full consideration for possible publication. The academic society-based journal in general wants to establish its own position in academic fields. This in not simply reflecting the journal impact factor (IF). IF is one of the journals performance indicators, not the only one. Editorial board usually pay other performance indication, too, such as citation number, submission number, etc. It is ideal to establish win-win relationship between journal and authors. To achieve this goal, it is most important that both sides pay significant respects to each other, which could be appreciated in fair and clear manner. Today, most established journals have their own scope and missions. To successfully publish your important research, it also very important to understand the each journal's scope before submission. It is always first important step to communicate with editorial office.

Long Journey of CMH to Be an International Journal

Yoon Jun Kim

Seoul National University, Korea

The journal, *Clinical and Molecular Hepatology* (CMH), is entering a new era of its journey. Twenty-seven years ago, the journal started its journey, by publishing 10 review articles in Korean and one original article in English at year 1995. The language policy has been changed to English-only in year 2010, and the journal's title has been changed from *Korean Journal of Hepatology* to CMH in 2012. The Journal was indexed in Medline since 2002, SCOPUS since 2010, Directory of Open Access Journals (DOAJ) since 2017, and Emerging Source Citation Index (ESCI) in year 2017. In 2019, the Journal was indexed in the Science Citation Index Expanded (SCIE). By being indexed in the SCIE, CMH has taken another leap toward a premier journal in the field of hepatology, a home for quality research, reviews, and commentaries.

Further Step to be a Valuable Journal

Seung Up Kim

Yonsei University, Korea

Clinical and Molecular Hepatology (*CMH*) has entered a new era of its journey at the end of 2019, when CMH was indexed in the Science Citation Index Expanded (SCIE). The recent impact factor increased up to 3.9 in 2020 and is estimated around 4.8 in 2021. CMH has taken another leap toward a premier journal in the field of hepatology, a home for quality research, reviews, and commentaries.

CMH is an international, peer-reviewed, open- access journal published quarterly in English. *CMH* aims to share advanced and latest knowledge, trend, and understanding of hepatobiliary diseases, to provide a wide open academic forum for active debate and discussion among clinical doctors, translational researchers, and basic scientists, and to improve public health through a multidisciplinary approach, especially in resource-limited Asia-Pacific area with high prevalence of B viral infection and hepatocellular carcinoma. In addition, *CMH* gives priority to epidemiological studies of hepatobiliary diseases in East Asia, North Asia, Southeast Asia, Central Asia, South Asia, Southwest Asia, Pacific, Africa, Central Europe, Eastern Europe, Central America, and South America.

The active and passionate local and international members of *CMH* editorial board are very sure that the journal will continue to grow and improve to be a premier journal in the field of hepatology.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (13:30-14:50)

ROOM 4

Essential Hepatology for Clinicians

Chairs:

Se Hyun Cho (The Catholic Univ. of Korea)

Chang Hyeong Lee (Daegu Catholic Univ.)

Typical Histological Findings Pertaining to Parenchymal Liver Diseases

Baek Hui Kim

Korea University, Korea

Nowadays, many parenchymal diseases are characterized and diagnosed based on clinical features, serologic and radiologic studies. Histopathologic examination of liver biopsy alone can provide limited diagnostic information about the patient. Nevertheless, pathologic diagnosis of liver parenchyma can give critical information about the diagnosis, activity, and staging of disease in some patients with proper clinical information. Microscopically visible response of the liver to injury is very limited regardless of the cause of injury. Sometimes, liver histology shows confusing overlapping disease pattern, and unrecognizable changes in early phase or after recovery phase of disease. Pathologists should interpret these response patterns in combination with clinical information to reach out accurate diagnosis.

The pathologic diagnosis of parenchymal liver disease depends on the combination of several histopathologic patterns, including cellular infiltrate, lobular damage, ductal damage, steatosis, and fibrosis. Viral hepatitis usually characterized by portal infiltration of lymphocytes, with variable lobular damages. Fibrosis of viral hepatitis usually begins from portal and periportal spaces, and extends to central area. Steatosis in viral hepatitis is more common in chronic hepatitis C, and fibrotic nodule size is more variable in chronic hepatitis C. In autoimmune hepatitis, inflammatory infiltrates tend to be composed of plasma cells, and are located more in interface of portal and hepatic parenchyma, which together with regenerating hepatocytes forming rosettes-like appearance. Fibrosis of autoimmune hepatitis is also portal space centered pattern. Steatohepatitis shows variable degree of cytoplasmic steatosis, either non-alcoholic or alcoholic hepatitis. Cirrhotic liver can show decreased contents of fat-containing hepatocytes. Balloon cells or Mallory bodies can be seen in non-alcoholic and alcoholic steatohepatitis, Wilson's disease, and sometimes in chronic hepatitis C and drug induced hepatitis. Characteristically, fibrosis of steatohepatitis (alcoholic, non-alcoholic, and Wilson's disease) are observed in zone 3 area making pericellular fibrosis pattern in early stage. Primary biliary cholangitis is characterized by florid ductal damage with infiltration of lymphocytes in epithelium. Portal area can be heavily infiltrated by plasma cells. Chronic primary biliary cholangitis can be diagnosed by loss of bile duct in portal area. Bile duct/ductular reaction is accompanied in primary biliary cholangitis. Primary sclerosing cholangitis involves comparatively large bile ducts, and these large ducts are not easily contained in needle biopsy. Onion-ring like periductal fibrosis is characteristic features of primary sclerosing cholangitis, but also can be observed in bile duct obstruction of other causes. Drug-induced liver injury can show any pattern of liver injury depending on which drug is ingested, such as cholestasis, parenchymal necrosis, steatosis, and fibrosis. History taking is most important part in the diagnosis of drug-induced liver injury. Many cases of drug-induced liver injury show non-specific

hepatic parenchymal damage with cholestatic pattern. Wilson's disease associated hepatitis is usually steatohepatitis, but copper staining is not helpful in the diagnosis.

Many hepatic parenchymal diseases show nearly normal or minimal changes and most diseases show no pathognomonic histologic features. Accurate clinical information and communication between clinician and pathologist can make hepatic parenchymal biopsy more valuable.

Radiological Assessment of Hepatic Steatosis and Fibrosis

So Yeon Kim

University of Ulsan, Korea

Clinical needs for noninvasive quantification of hepatic fat has spurred the development of promising imaging techniques in diagnosis and monitoring of hepatic fat. The wide accessibility and relatively lower cost make US an attractive imaging technique. To overcome low accuracy of conventional US, quantitative US-based methods are being developed based on assessment. Among them, the controlled attenuation parameter (CAP) method based on transient elastography implemented by FibroScan® (EchosensTM, Paris, France; approved by FDA in 2013), is the most widely used US-based approach. A methodological limitation of US-based methods estimating liver fat content, including CAP, is that there are many other liver pathologies such as hepatitis, hemochromatosis or fibrosis which can also affect sound waves in the same manner. Computed tomography (CT) is a widely available imaging method capable of providing objective assessment of liver fat content. The X-ray attenuation of triglycerides is lower than normal liver parenchyma, leading to lower attenuation of the liver, expressed in Hounsfield units, in the presence of hepatic steatosis. Recently adopted dual-energy CT has shown disappointingly lower accuracy than single-energy CT. CT provides a more objective assessment of hepatic steatosis than US, but a less accurate assessment than magnetic resonance imaging (MRI) or MR spectroscopy (MRS). An important drawback of CT is use of ionizing radiation, limiting the use of repeated examinations. CT voxel-based attenuation values are confounded by other factors, including the presence of glycogen, iron, copper, and iodine. MRS and chemical shift MRI can serve as confounder-corrected methods capable of quantifying proton density fat-fraction (PDFF). PDFF correlates with the percentage of liver fat content as measured using pathologic fat content. To standardize PDFF as a quantitative imaging biomarker (QIB) across different platforms and improve its value, standardization and practicality the Quantitative Imaging Biomarkers Alliance (QIBA) PDFF group has been recently established. MRI-PDFF is emerging as an increasingly accepted quantitative biomarkerof liver fat, and will continue to transform clinical diagnostic algorithms and drug discovery trials for new treatments in the coming years.

Liver fibrosis should be assessed in all individuals with chronic liver disease as it predicts the risk of future liver-related morbidity and thus need for treatment, monitoring and surveillance. Imaging-based elastographic methods including US and MRI have been increasingly used. Elastography techniques take advantage of the physical properties of liver fibrosis that make the liver 'stiffer' by quantifying 'sheer wave' velocity or tissue displacement generated by an ultrasonic or physical impulse. Vibration-controlled transient elastography (VCTE or Fibroscan) and MR elastography (MRE) use a mechanical driver to generate the sheer wave and measure its velocity using sonographic Doppler or MR techniques, respectively. Point sheer wave elastography (pSWE or acoustic radiation force impulse) and two-dimensional SWE (2D-SWE)

use high frequency sonographic impulses for sheer wave generation VCTE was the first elastography technique to be commercialized and thus has had extensive validation and evaluation of its strengths and limitations in comparison with other methods. Liver stiffness measurement (LSM) by VCTE may be increased by acute hepatitis and cholestasis, respiration, congestive cardiac failure, recent food and excess alcohol ingestion and increasing body mass index (BMI). Cut-offs are variable between aetiologies of liver disease and not universally accepted within causes of liver disease, MRE examines whole sections of liver and thus is less prone to sampling error and has a low technical failure rate. Obesity, hepatic inflammation and degree of steatosis does not impact on accuracy in NAFLD, however, increased LSMs are observed with hepatic inflammation in chronic viral hepatitis B and C.

Understanding underlying physics and technical limitations of these imaging methods to quantify liver fat and fibrosis helps physicians interpret results more accurately and apply proper treatment for patients.

The Practical Process of Enlisting, Allocation, and Operation of Liver Transplantation

Young Rok Choi

Seoul National University, Korea

Liver transplantation (LT) is a highly effective treatment for end-stage liver disease or hepatocellular carcinoma. Nevertheless, the supply had not reached the demand for LT. While the number of decease liver donors was 7.54 per million in Korea, the living donation was the world 1st, 22.9 per million in Korea. The annual number of LT reached the only ¼ of the waiting list. Therefore, physician/surgeon/pediatrics should know the details to enlist a patient for deceased donor LT not to lose patients' survival chance. Patients without underlying liver disease have a high probability of dying, if they do not receive a liver transplant within seven days, they can be registered with the highest priority. A patient with fulminant hepatic failure with a hepatic coma of grade 3 or higher within eight weeks can be registered as status one if one of the following three is accompanied; Ventilation therapy or renal replacement therapy, PT INR >2 or higher. In addition, status 1 is possible in cases of primary non-function or severe liver damage within seven days after liver transplantation or in hepatic arterial thrombosis and an-hepatic status. In the case of aggravation of Wilson's disease-related liver disease, PELD>25 in the case of children with one of the following; ventilatory respiration, massive bleeding (RBC transfusion ≥30 ml/kg), renal failure, loss of consciousness (GCS<10).

From status 2 to status 5, the patient can be enlisted according to the MELD/PELD scores. Patients with HCC within Milan criteria may receive an additional score of up to 25 points, and the following findings must be described in the results of the radiologic examination within six months prior to enlisting; no extra-hepatic spread, no major portal vein tumor thrombosis.

Patients, who are waiting for a brain-death organ with a weight equivalent to 0.5 to 2 times the weight of a brain death person, become the candidates for receiving the deceased liver organ. Their status, the deceased donor organ's procurement region, and blood type will be the main factors to be allocated with the deceased donor's liver.

To maintain their statue, relisting is essential. Status 1 can only be registered once in a lifetime. A patient with status one can be relisted once within seven days after enlisting. In other words, a patient is registered as a status one once for up to 14 days in a lifetime. Status 2,3 needs relisting within seven days after enlisting.

The five-year survival rate was 68.5 years in DDLT compared to 81.1 in LDLT.

Drug-Induced Liver Injury: Update and Clinical Application

Eun Young Cho

Wonkwang University, Korea

Introduction

Almost all drug metabolism occurs in the liver and kidneys. The so-called "detoxification" process is one of the key roles of the liver and usually occurs in two phases, primarily in hepatocytes. Phase I is a reaction to increase the water solubility of a fat-soluble substance and at the same time convert it into a substrate to be used in phase II reaction, which in turn converts the substrate into a compound with higher water solubility by binding to a specific substance in the body. The representative enzyme involved in the phase I reaction is an enzyme system called cytochrome P-450 that has an oxidative function and can process several different substances due to various homologous enzymes. The phase II reaction is the conversion of substances with functional groups such as hydroxyl, amino, carboxyl, epoxide, and halogen into a form that is more water-soluble and easier to be released outside the body via a process called conjugation.

These detoxification processes are essential metabolic actions that protect the human body from various foreign substances, and some drugs exert their pharmacological action through this detoxification process. However, in some cases, intermediate metabolites generated during this process are toxic to the liver, leading to drug-induced liver injury (DILI), a relatively rare but important liver disease that can lead to acute liver failure. In this lecture, I tried to introduce the updated content related to DILI.

Epidemiology

According to a European population-based study, the annual incidence of DILI ranges from 2.3 to 13.9 per 100,000 population.[1-3] The highest incidence of DILI reported is 19 per 100,000 inhabitants per year, with a steady increase in the age-standardized incidence.[4] In addition, in a U.S. population–based study, the yearly incidence of DILI was found to be approximately 3/100,000 residents.[5] Taken together, these studies have shown that DILI, both in its intrinsic and idiosyncratic forms, is the most common cause of acute liver failure (ALF) in developed countries. A previous study showed that the incidence rate of any drug-induced ALF was 1.61 events per 1,000,000 person-years (95% CI, 1.06-2.35), and the incidence rate for acetaminophen-induced ALF was 1.02 events per 1,000,000 person-years (95% CI, 0.59–1.63).[6] There are, however, differences in the causative agent of DILI depending on the region. In Western countries, it is caused by prescription medication, whereas in Asia, it is caused by traditional, complementary, and dietary supplements.[7,8]

DILI type and characteristics of each type

Traditionally, DILI is classified into intrinsic or direct hepatotoxicity and idiosyncratic hepatotoxicity. How-

ever, recently, indirect hepatotoxicity has also been added to the classification.[9] Intrinsic hepatotoxicity is defined as liver injury caused by the toxicity of the drug itself. It is predictable and reproducible in animal models and is characterized by a dose-dependent effect and short latency (1–5 days).[10] Idiosyncratic hepatotoxicity cannot be predicted and it is not dose-dependent or reproducible in animal models. The R-ratio can be used to differentiate it into hepatocellular, cholestatic, and mixed types.[11] Indirect hepatotoxicity is not caused by direct toxicity or specific reactions of the drug itself, but by the medication action. It may exacerbate existing liver disease. These three types of drug-induced hepatotoxicity can be classified into several phenotypes based on their clinical characteristics.[12]

Factors involved in DILI development,

Factors affecting the incidence and severity of DILI include age (children, >60 years), sex, dosage, genetic factors (e.g., *HLA* gene, *CYP2E1*, *NAT2* slow acetylator), concomitant drug use, excessive alcohol use, nutritional status (obesity, fasting), preexisting liver disease (hepatitis B and C), and other medical disorders (e.g., diabetes, psoriasis, HIV, renal failure, and organ transplantation). Therefore, it is necessary to obtain a thorough medical history and check for these risk factors.

Diagnostic tools for DILI and models evaluating its severity

The diagnosis process of DILI is complex and requires a careful approach. Since there is confusion with other acute and chronic liver diseases, a process to exclude this diagnosis is necessary. In other words, other causes that can cause liver injury, such as viral hepatitis, alcoholic liver disease, and autoimmune hepatitis, need to be evaluated. At the same time, it is necessary to obtain an accurate and detailed medical history, in particular, to confirm the relevance of drug use. It is important to characterize the liver injury, and the R-ratio* may be helpful in diagnosis. Based on this, an algorithm for a step-by-step approach for the diagnosis of DILI was recently proposed in the EASL Guidelines.[13] In addition, various diagnostic tools for evaluating causality related to DILI have been developed. Among them, the most commonly used is the Roussel Uclaf Causality Assessment Method (RUCAM). The RUCAM scale is divided into seven categories that can be somewhat complicated: time to onset from the beginning of the drug/herb intake, course of ALT after cessation of the treatment, risk factor, concomitant use of drug/herb, search for alternative causes, previous hepatotoxicity of the drug/herb, response to unintentional re-exposure.[12] As diagnostic tools that can be used relatively simply, the clinical diagnostic scale, the structured expert opinion process,[14] and standard diagnostic methods obtained by modifying the RUCAM scale in Japan have also been introduced.[15] LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/) can aid in the diagnosis of DILI by providing comprehensive information on drugs, herbs, or food products. There is also the Drug Induced Liver Injury Rank (DILIrank) Dataset (https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset), a simple search method for drug liver toxicity. The DILIrank consists of 1,036 FDA-approved drugs that are divided into four classes according to their potential for causing DILI. Meanwhile, liver biopsy is not necessary for diagnosing DILI, but it may be useful to rule out other causes of liver injury and to assess the extent of inflammation and liver damage.[16]

It is important to evaluate the prognosis of patients to identify those who can progress to liver failure

early because there are no specific agents for the treatment of most DILIs. The representative prognostic evaluation tool is Hy's law. Hy's law is generally defined as an elevated ALT or AST level three-fold or more than the normal upper limit in hepatocellular-type liver injury. In addition, it also includes a serum total bilirubin level greater than 2× the normal upper limit. If it corresponds to Hy's law, it is possible that the fatality rate is more than 10%; therefore, careful monitoring is necessary.

Best practices for the management of DILI

The most important step in the treatment of DILI is the discontinuation of the suspected drug and avoidance of re-exposure. In most cases, it spontaneously improves without the need for any treatment, which can be an important criterion in causality assessment.[13,17,18] However, in some cases, even though the drug is discontinued, the condition may progress to acute liver failure or death. Therefore, close follow-up is important, even after stopping the use of the suspected drugs.[13] The use of special agents may be helpful in some situations of DILI. Cholestyramine can be used to treat acute liver injury caused by leflunomide and chronic cholestasis caused by terbinafine.[19] Carnitine improves fatty acid absorption and β-oxidation by regulating mitochondrial acetyl-CoA levels, resulting in liver injury caused by valproic acid.[20,21] N-acetylcysteine (NAC) is a well-known treatment for liver injury caused by acetaminophen. Early use of NAC has been reported to prevent progression to severe hepatic encephalopathy or deterioration of renal function.[22] In addition, the combination of NAC and prednisolone may be helpful in patients with severe idiosyncratic DILI.[23] Ursodeoxycholic acid can be used in patients with chronic cholestasis due to DILI, but its efficacy has not yet been proven. Liver transplantation remains the primary treatment option for ALF caused by DILI.[28]

Conclusions

DILI is an important clinical problem and a cause of ALF. It is a diagnosis of exclusion and requires a meticulous process of evaluation and a high index of clinical suspicion to attribute a potential agent as the cause of the liver injury. Suspicious drugs should be stopped immediately, and NAC or steroids may be used as treatments depending on the type of drug that causes liver injury, but in most cases, there is no specific treatment. Therefore, efforts to avoid prescribing drugs known to cause liver injury, and additional studies on models evaluating the severity of DILI are needed. In addition, if a drug that causes liver injury is identified, it should be reported to well-established networks to help acquire and pool more information.

References

1. Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002;36:451-455.
2. De valle MB, Av klinteberg V, Alem N, Olsson R, Björnsson E. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. Aliment Pharmacol Ther 2006;24:1187-1195.
3. de Abajo FJ, Montero D, Madurga M, Rodriguez LAG. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004;58:71-80
4. ES Björnsson, OM Bergmann, HK Björnsson, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419-1425.e3

5. Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, et al. The incidence of drug-and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the state of Delaware. Drug Saf 2017;40:783-787.
6. DS Goldberg, KA Forde, DM Carbonari, et al. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. Gastroenterology 148:1353-1361.e3 2015
7. Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug induced liver injury at an Asian center: a prospective study. Liver Int 2007;27:465-474.
8. Shen T, Liu Y, Shang J, Xie Q, Li J, Yan M, et al. Incidence and etiology of drug-induced liver injury in mainland China. Gastroenterology 2019;156:2230-2241.
9. Hoofnagle JH, Björnsson ES. Drug-Induced Liver Injury - Types and Phenotypes. N Engl J Med 2019;381:264-273.
10. Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 1999.
11. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323-1330.
12. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
13. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol 2019;70:1222-1261.
14. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology (Baltimore, Md) 2010;51:2117-2126.
15. Takikawa H, Onji M. A proposal of the diagnostic scale of drug-induced liver injury. Hepatol Res 2005;32:250-251.
16. Kleiner DE. The histopathological evaluation of drug-induced liver injury. Histopathology 2017;70:81-93.
17. Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. Int J Mol Sci 2015;17.
18. Yang H, Guo D, Xu Y, et al. Comparison of Different Liver Test Thresholds for Drug-Induced Liver Injury: Updated RUCAM versus Other Methods. Front Pharmacol 2019;10:816.
19. Mallat A, Zafrani ES, Metreau JM, Dhumeaux D. Terbinafine-induced prolonged cholestasis with reduction of interlobular bile ducts. Dig Dis Sci 1997;42:1486-1488.
20. Lheureux PER, Penaloza A, Zahir S, Gris M. Science review: Carnitine in the treatment of valproic acid-induced toxicity – what is the evidence? Crit Care 2005;9:431.
21. Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. Clin Toxicol (Philadelphia, Pa) 2009;47:101-111.
22. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137:856-864, 64.e1.
23. Borlak J, van Bömmel F, Berg T. N-acetylcysteine and prednisolone treatment improved serum biochemistries in suspected flupirtine cases of severe idiosyncratic liver injury. Liver Int 2018;38:365-376.
24. Piotrowicz A, Polkey M, Wilkinson M. Ursodeoxycholic acid for the treatment of flucloxacillin-associated cholestasis. J Hepatol 1995;22:119-120.
25. Katsinelos P, Vasiliadis T, Xiarchos P, et al. Ursodeoxycholic acid (UDCA) for the treatment of amoxycillin-clavulanate potassium (Augmentin)-induced intra-hepatic cholestasis: report of two cases. Eur J Gastroenterol Hepatol 2000;12:365-368.
26. Ranucci G, Cirillo F, Della Corte C, Vecchione R, Vallone G, Iorio R. Successful use of ursodeoxycholic acid in nodular regenerative hyperplasia of the liver. Ann Pharmacother 2011;45:e20.
27. Wree A, Dechêne A, Herzer K, et al. Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury. Digestion 2011;84:54-59.
28. Grek A, Arasi L. Acute Liver Failure. AACN Adv Crit Care 2016;27:420-429.

The Liver Week 2021

DAY 3: Saturday, May 15, 2021 (15:00-16:20)

ROOM 4

Associate Course

Chairs:

Soo Hyung Ryu (Inje Univ.)

Won Hyeok Choe (Konkuk Univ.)

Interpreting More Than You Know: Liver Disease-Related Testing

Yang Hyun Baek

Dong-A University, Korea

Liver disease-related tests, the so-called "liver function tests" or "liver chemical tests", can be useful in the evaluation and management of patients with liver disorders. These tests have the potential to identify liver disease, distinguish among types of liver disorders, predict the severity and progression of liver dysfunction, and monitor response to therapy. These tests include total and direct bilirubin, albumin, prothrombin time, and the serum enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). Interpretation of these results need to perform a careful history taking and physical examination. Herein, I review commonly used 'liver disease-related test' and provides a framework for interpreting them.

서 론

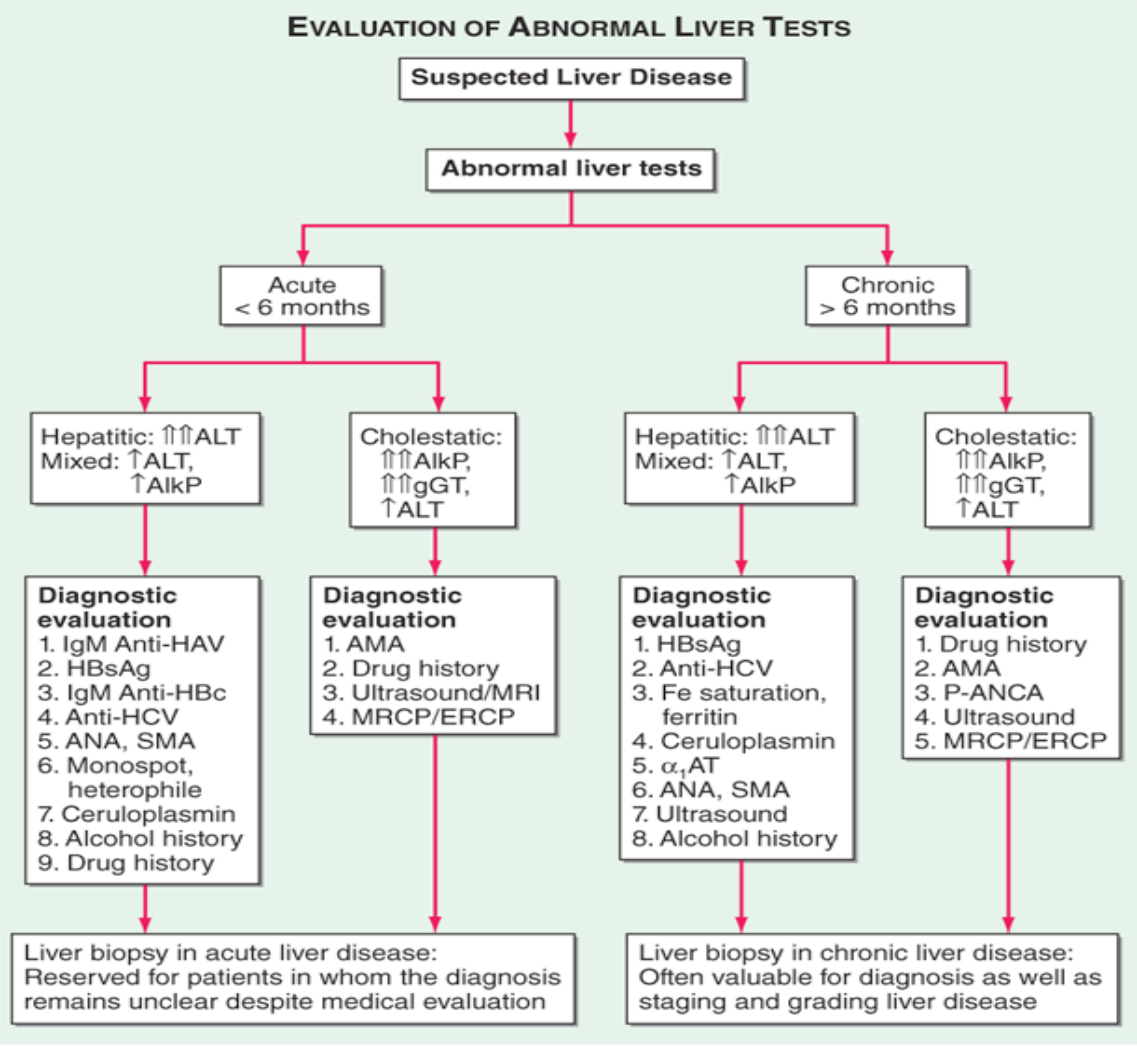
병원을 방문한 환자의 기본 검사에는 일반적으로 간기능 검사가 포함되어 있고 건강 검진의 보편화에 따라 우리는 다양한 간기능 검사 이상을 보이는 환자를 진료실에서 접하게 된다. 엄밀히 따지자면 '간기능 검사'라는 용어는 잘못된 표현으로 이러한 검사를 통해 간기능의 정도를 평가하기는 어려우며 간질환 계통의 감별, 간 손상 정도의 예측 및 치료 반응의 평가 등을 확인하는데 이용할 수 있다. 또한 간질환이 아닌 경우에도 상승 가능하므로 이러한 검사의 의미를 이해하는 것은 매우 중요하다. 간질환에 대한 생화학 검사 중 아미노 전이효소는 일반적으로 간세포 손상을 반영하는 지표이나 이러한 효소는 간 외의 다른 장기에서도 발견되어 간질환이 아닌 경우에서도 상승이 가능하며, ALP와 r-GTP는 담즙 정체형 손상을 의미하고, 알부민과 프로트롬빈 시간은 간의 합성능을 반영, 빌리루빈은 간의 배설능을 의미한다. 본문에서는 좀 더 구체적으로 각 항목의 의미를 알아보고 어떤 질환들을 감별해 나가야 하는지 알아보고자 한다.

Evaluation of abnormal liver tests

간질환이 의심되는 환자에서 시행하는 생화학적 검사에는 bilirubin, albumin, AST, ALT, ALP, GGT등이 포함되어 있으며 결과에 따라 간세포형, 담즙 정체형, 혼합형의 간 손상을 유추할 수 있고 다음과 같은 알고리즘에 따라 감별할 수 있다(Figure 1).

Aminotransferase

AST와 ALT는 간에서 당신생에 관여하는 아미노전이효소이다. AST는 간세포의 세포질과 마이토콘드리아 모두에 존재하는 반면 ALT는 세포질에만 존재한다.[2] 이러한 효소는 간세포 손상시 혈액으로 나오게 되며 간세포 손상의 원인으로는 약물, 알코올, 바이러스, 허혈성 손상, 자가면역성 질환, 윌슨병, 혈색소증, 비알코올 지방간질환과 같은 다양한 원인이 있다. (Table 1) AST는 간 뿐만이 아니라 심장근육, 골격근, 신장, 뇌, 췌장, 폐, 백혈구와 적혈구에서도 존재하며 ALT는 주로 간과 신장에 존재한다.[3] 따라서 아미노전이효소는 다양한 간 외 원인에 의해서도 상승할 수 있으며 특히 AST 단독 상



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Figure 1. Evaluation of abnormal liver tests[1]

승시 lactate dehydrogenase, creatine kinase 등의 검사와 함께 도움을 받을 수 있다.

환자가 아미노전이효소의 상승으로 방문한 경우 재검을 통해 상승 유무를 재확인하고 면밀한 병력 청취를 시행하여 간과 간 외 원인의 가능성을 추정하고, 흔한 간질환의 원인을 감별해나가야 한다. 병력 청취시 알코올 섭취, 약물, 건강식품 등의 보조제, 마약 남용, 문란한 성생활, 동성애, 문신, 피어싱, 수혈, 거주 환경, 급성 바이러스 간염의 전구 증상, 대사 질환의 가능성, 가족력 등에 대해 확인이 필요하다.[4] 또한 드문 원인에 대한 가능성도 고려해야 하며 이를 통해서도 원인 감별이 어려울 경우 조직검사를 고려한다.[5]

AST:ALT ratio는 효소 상승의 원인을 해석하는데 도움이 된다. 일반적으로 AST/ALT ratio가 1이하인 경우는 만성 간질환, 지방간인 경우가 흔하고 AST/ALT ratio가 1 이상인 경우 간경변, 알코올성 간질환, 근육 조직이나 용혈 등에 의한 간 외 원인에 의한 상승 가능성을 생각해 볼 수 있다. 특히, AST/ALT ratio가 2배 또는 3배 이상 상승할 경우 알코올성 간질환의 가능성을 좀 더 고려해볼 수 있다.[4] 간경변의 경우 만성 간질환이지만 AST/ALT ratio가 1 이상인 이유는 pyridoxine 결핍과 불량한 영양 상태로 인해 ALT가 낮기 때문이다.[6] 아미노전이효소가 1000 이상으로 상승한 경우에는 바이러스성

간염, 독성간염, 허혈성 간손상을 고려할 수 있고 드물지만 자가면역성 간염, Budd-Chiari증후군, 급성 담도 폐쇄 시에도 급격한 상승을 보일 수 있다.[5]

Table 1. Causes of Elevated Serum Aminotransferase levels[5]

Causes of Elevated Serum Aminotransferase levels	
Mild	**ALT > AST** Hepatic Chronic viral hepatitis Non-alcoholic fatty liver disease Medication and toxin α1-antitrypsin deficiency Autoimmune hepatitis Non-hepatic Celiac disease Hyperthyroidism **AST > ALT** Hepatic Alcohol related liver disease Cirrhosis Non-hepatic Hypothyroidism Macro-AST Myopathy Strenuous exercise
Severe	**Hepatic** Acute bile duct obstruction Acute Budd-Chiari Syndrome Acute viral hepatitis Ischemic hepatitis Hepatic artery ligation Medication/toxin Wilson disease **Non-hepatic** Acute rhabdomyolysis

Alkaline Phosphatase

ALP는 간에 특이적인 효소는 아니며 간, 뼈, 백혈구, 태반, 장과 신장에 존재한다. ALP의 상승은 빠른 골대사, 수유, 임신과 관련한 변화에서 보일 수 있다. 30세 이후 ALP는 점차적으로 상승하여 60세에는 정상의 1.5배 정도까지 상승할 수 있다. 또한 ALP상승은 지방식 이후에 상승할 수 있어 금식시에 검사하는 것을 권장하며, O형과 B형을 가진 사람에서 생리적으로 상승할 수 있다. 전기영동검사는 ALP 상승의 기원을 확인하는데 좋은 방법이나 일반적으로 많이 사용되지 않고 GGT를 추가로 검사하는 것은 간에서 기인한 상승인지를 감별하는데 도움이 된다.[3,7] ALP와 GGT가 동시에 상승되어 있다면 담즙 정체성 또는 침윤성 간질환을 고려하여 이에 대한 검사를 시행해야 하지만 아미노전이효소와 함께 ALP가 상승한 경우는 간세포성 질환에서 더 흔히 관찰된다.[8] ALP가 간질환에서 상승하는 것은 담도계에 체류되는 경우보다 합성이 증가한 경우가 많아 담관 폐쇄 이후 상승하기까지는 1-2일 정도 시간이 걸릴 수 있고 반감기가 약 7일 정도라서 담관 폐쇄가 호전된 이후 ALP 정상까지는 수일이 걸릴 수 있다. 담즙 정체와 침윤성 간질환에 대한 검사는 영상 검사를 기본으로 한다. 영상 검사에서 담관 확장이 관찰된다면 MRCP, ERCP, EUS등을 시행할 수 있고 담관 확장이 없는 경우, 특히 젊

은 여성의 경우, anti-mitochondrial antibody검사를 시행해 볼 수 있다.[9,10]

Table 2. Causes of Cholestatic liver enzyme elevations in adults[5]

Intrahepatic Causes of Cholestatic Liver enzyme Elevations in Adults
Drugs
Primary biliary cholangitis
Primary sclerosing cholangitis
Granulomatous liver disease
Idiopathic adult ductopenia
Infiltrative disease
Intrahepatic cholestasis of pregnancy
Total parenteral nutrition
Graft-versus-host disease
Sepsis
Extrahepatic Causes of Cholestatic Liver enzyme Elevations in Adults
Choledocholithiasis
Immune-mediated duct injury
Malignancy
Infection
Pancreatitis
Pancreatic pseudocyst

Gamma glutamyl transpeptidase

GGT는 간, 신장, 췌장, 비장, 심장, 폐와 뇌에 존재한다. GGT는 간담도계 질환 외에도 알코올, phenytoin, phenobarbital, carbamazepine, antiretroviral drug, warfarin, 당뇨, 만성 폐쇄성 폐질환, 심근 경색, 췌장 질환, 신부전에서도 상승할 수 있다. 그러나 골질환에서는 상승하지 않기 때문에 ALP 상승시 담즙 정체형 간질환을 감별하기 위한 검사로 이용될 수 있다. 하지만 GGT는 항상 ALP와 함께 상승하지는 않으며 progressive familial intrahepatic cholestasis (PFIC)와 benign recurrent intrahepatic cholestasis (BRIC) type 1,2에서는 GGT상승 없이 ALP 만 상승을 보인다.

AST:ALT ratio 2배 이상 상승하면서 GGT상승시 일반적으로 알코올 간질환을 시사하여 간질환이 없는 경우에도 잠재적인 알코올 섭취를 의미할 수 있다. 또한 GGT는 비알코올 지방간에서도 상승할 수 있다.[11] 증상 없이 GGT만 단독으로 상승한 경우 수개월 간격으로 모니터를 시행하면서 다른 수치의 이상이 동반된다면 초음파나 CT를 고려해 볼 수 있고 필요시 간 조직검사를 시행해 볼 수 있다.

Bilirubin

빌리루빈은 heme의 분해 산물이다. 매일 약 4 mg/kg의 빌리루빈이 생성되며 약 80%는 적혈구의 헤모글로빈 분해로, 나머지는 전신에 존재하는 myoglobin과 cytochrome과 같은 hemoprotein의 분해로 생성된다. 빌리루빈의 대사는 세망내피계에서 시작된다. Heme은 biliverdin으로 전환되고 biliverdin은 biliverdin reductase에 의해 bilirubin으로 전환된다. 세망내피계에서 형성된 빌리루빈은 지용성이므로 혈액에서 운반되기 위해 알부민과 결합하여 이동한 후 간내 space of Disse에서 알부민과 분리되어 간세포내로 이동 후 UDP glucuronyl transferase에 의해 conjugation이 일어난다. Conjugated bilirubin은 multiple drug resistance-associated protein 2 (MRP2)에 의해 canalicular membrane을 통해 이동한다. 담즙으로 분비되어 소장 말단과 대장에 도달하면 B-glucuronidase를 가진 박테리아에 의해 가수분해되어 unconjugated bilirubin이 되고 bacteria에 의해 환원되어 무색의 urobilinogen이 된다. Urobilinogen은 산화되어 오렌지 색깔을 가진 urobilin으로 분비되거나 간문맥으로 재흡수된다.[5]

conjugated bilirubin이 상승한 경우 Dubin-Johnson syndrome, Rotor's syndrome과 같은 간 분비능의 유전성 질환을 고려할 수 있고 unconjugated bilirubin만 상승한 경우 용혈, 조혈 기능 장애, 혈종, 근손상, Gilbert syndrome, Crigler-Najjar syndrome과 같은 conjugation 장애를 보이는 유전성 질환의 가능성이 있다. 병력 청취, 비장 비대 유무, 헤모글로빈 수치가 진단에 도움이 될 수 있다. .

Albumin

알부민은 간에서 합성되는 단백질로 혈장 삼투압의 75%를 차지한다. 정상적으로 성인에서 하루에 15 g이 합성되나 알부민이 감소하거나 희석되어 혈중 수치가 떨어지면 두 배로 합성될 수 있다. 알부민의 반감기는 14-21일로 일반적으로 급성 간손상보다는 간경화에서 진행성 손상의 지표가 되기도 하며 간질환의 가능성이 낮은 사람에서 알부민은 선별 검사로서의 유용성은 매우 낮다. 알부민의 합성은 간에서 이루어지지만 영양 상태, 삼투압, 전신 감염, 호르몬 등에 의해 조절을 받기 때문에 저알부민혈증을 보일 경우 간질환 외에도 영양실조, 단백소실성 위장병증, 신증후군, 만성 염증성 질환이나 호르몬 불균형 등도 감별을 해야 한다.[5]

Prothrombin time

Factor VIII을 제외한 응고 인자들은 간에서 생성된다. 프로트롬빈 시간은 응고인자 II, V, VII, X를 이용한 외인성 경로를 통해 prothrombin에서 thrombin으로 전환되는데 걸리는 시간을 측정한 것이다. Factor VII은 반감기가 6시간으로 가장 짧기 때문에 프로트롬빈 시간은 간 합성능의 급성 변화에 대한 신뢰도 있는 지표로서 급성 간부전의 중증도와 예후를 평가하는데 유용하다. 프로트롬빈 시간은 합성능의 80%가 소실될 때까지 변화를 잘 보이지 않으며 프로트롬빈 시간의 연장은 간경화나 진행성 간부전에서 주로 관찰된다. 그러나 프로트롬빈 시간은 간경화에서 감소되는 단백질 C와 S와 같은 항응고인자를 고려하지 않기 때문에 간경변에서 출혈의 위험도를 나타내는 좋은 지표는 아니다. 프로트롬빈 시간은 간의 합성능이 감소된 상황 외에도 factor II, VII, XI, X 에 필요한 비타민 K결핍증, 파종성 혈관내 응고에서도 지연될 수 있고 factor VIII를 측정함으로써 간질환과 파종성 혈관내 응고를 감별할 수 있다.

프로트롬빈 시간은 10-14초 사이로 보통 측정되지만 검사에 이용되는 thromboplastin reagent에 따라 변동이 있을 수 있어 특정 실험실에서 사용되는 시약의 international sensitivity index (ISI)에 기초하여 프로트롬빈 시간의 값이 표준화된 INR로 보고된다. INR와 계산 공식은 다음과 같다:

$$INR = \text{patient's prothrombin time/mean control prothrombin time}^{ISI}$$

INR은 MELD score에 포함되며 급성, 그리고 만성 간부전과 간이식의 적응증을 판단하는 예후 지표로 이용된다.

맺음말

본문에서 간질환과 관련된 검사의 임상적 의미와 감별해야 할 질환들에 대해 살펴보았다. 이러한 검사들은 각 질환을 진단하기보다는 간질환의 범주를 결정하는데 도움이 되며 어떤 방향으로 진단을 진행해나가야 할지에 대한 정보를 제공하는 역할을 하므로 구체적인 병력 청취와 신체 진찰이 함께 이루어져야 한다. 따라서 임상의들은 이러한 검사의 의미를 정확하게 이해하고 체계적인 접근을 시행해 나가야 하겠다.

References

1. Harrison's Principles of Internal Medicine 20th Edition.
2. Swastik Agrawal, Radha K Dhiman, Jimmy K Limdi. Evaluation of abnormal liver function tests. Postgrad Med J 2016;92:223-234.

3. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342:1266–1271.
4. Schreiner AD, Rockey DC. Evaluation of abnormal liver tests in the adult asymptomatic patient. Curr Opin Gastroenterol 2018l;34:272-279.
5. Sleisenger and Fordtrans' Gastrointestinal and liver disease.11th Edition.
6. Dufour DR, Lott JA, Nolte FS, et al. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clin Chem 2000;46:2027–2049.
7. Dufour DR, Lott JA, Nolte FS, et al. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clin Chem 2000;46:2027–2049.
8. Trauner M, Boyer JL. Cholestatic syndromes. Curr Opin Gastroenterol 2002;18:314–329.
9. Goldberg DM, Martin JV. Role of gamma-glutamyl transpeptidase activity in the diagnosis of hepatobiliary disease. Digestion 1975;12:232–246.
10. Rosalki SB, Tarlow D, Rau D. Plasma gamma-glutamyl transpeptidase elevation in patients receiving enzyme-inducing drugs. Lancet 1971;2:376–377.
11. Pitisuttithum P, Chan WK, Goh GB, Fan JG, Song MJ, Charatcharoenwitthaya P, et al. Gamma-glutamyl transferase and cardiovascular risk in nonalcoholic fatty liver disease: The Gut and Obesity Asia initiative. World J Gastroenterol. 2020;26:2416-2426.

Associate Course

Seems Complicated but Actually Quite Simple: Antiviral Therapy

Young Youn Cho

Chung-Ang University, Korea

About 70% of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) are associated with chronic hepatitis B (CHB) infection in Korea. Antiviral agents with high resistance barriers have markedly reduced the cumulative incidence of CHB related LC and HCC. Direct acting antivirals (DAAs) have been recently introduced for chronic hepatitis C (CHC) treatment. The new DAAs have a very high cure rate (sustained virological response) of 95-99%. The goal of this review is to summarize the Korean guidelines for CHB and CHC treatment.

서론

국내 간경변증과 간암 사망의 70% 정도는 B형간염과 연관되어 있을 것으로 생각될 정도로 B형간염은 국내 간질환의 주요한 원인이다.[1] 항바이러스제가 널리 사용되기 이전 한국인 만성 B형간염에서의 연구 결과를 보면 B형간염에서 간경변증으로 진행되는 5년 누적 발생률은 23%이었고 간암의 5년 누적 발생률은 3%였다.[2] 하지만 항바이러스제의 도입 이후 간경변증의 5년 누적 발생률은 5.3%, 간암의 5년 누적 발생률은 0.8%로 감소하였다.[3]

C형간염은 B형간염바이러스에 이어 우리나라 만성 바이러스간염의 두 번째 흔한 원인이다. 최근에 C형간염의 치료에서 혁명적인 변화가 생겨서 경구 항바이러스제(direct acting antivirals, DAA)를 이용한 치료가 활발해졌으며, 최근 사용하고 있는 DAA는 95% 이상의 완치율을 보이고 있다.[1]

이번 강의에서는 대한간학회의 가이드라인을 중심으로 B형간염과 C형간염 치료의 핵심적인 내용을 다룰 계획이다.

B형간염의 치료

1. 자연 경과

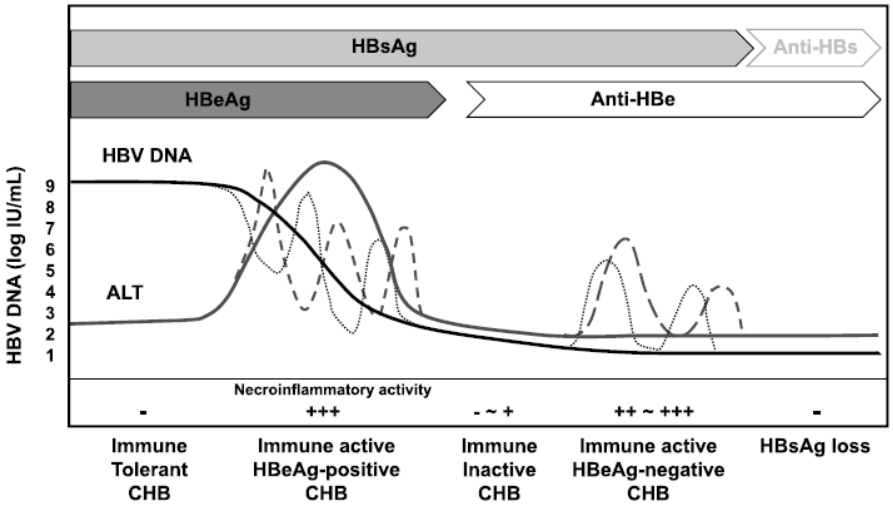


그림 1. 만성 B형간염의 자연경과(대한간학회 진료 가이드라인, 2018)

2. 치료

만성 B형간염의 궁극적인 치료의 목적은 간경변증과 간세포암종 발생을 예방하여 생존율을 향상시키는 것이다. 대표적인 치료 적응증은 아래와 같다.[4]

(1) 혈청 HBV DNA ≥20,000 IU/mL 인 HBeAg 양성 간염 또는 혈청 HBV DNA ≥2,000 IU/mL 인 HBeAg 음성 간염의 경우, ALT가 정상 상한치의 2배 이상

(2) 혈청 HBV DNA ≥2,000 IU/mL인 대상성 간경변증

비대상성 간경변증이나 간암의 경우 혈청 HBV DNA가 검출되면, ALT와 관계없이

(3) 내성발현에 대해 유전자 장벽이 높은 약제로 엔테카비어, 테노포비어DF, 테노포비어AF, 베시포비어가 있으며 초치료 환자의 경우 이러한 경구약제로 치료를 시작한다. 규칙적인 약제 복용에도 바이러스 돌파가 발생할 경우에는 항바이러스제 내성검사 후 구제 치료를 고려한다. 과거에 유전자 장벽이 낮은 약제로 치료를 시작한 경우 구제요법을 복잡하게 시행한 과거력을 보이는 경우가 있어서 이러한 환자의 치료 경과를 이해하기 위해서는 구제요법에 대한 대략적인 이해가 필요하다. 현재 추천되고 있는 약제는 아래 표 1과 같다.[4]

표 1. 약제 내성의 구제 치료

Resistance	Preferred	Alternative
Lamivudine/Telbivudine/ Clevudine resistance	1. Change to tenofovir††	1. Add tenofovir† 2. Add adefovir
Entecavir resistance	1. Change to tenofovir† 2. Add tenofovir†	1. Add adefovir
Adefovir resistance	1. Change to tenofovir† 2. Change to entecavir+tenofovir†	1. Add entecavir
Tenofovir resistance	1. Add entecavir	
Multi-drug resistance	1. Change to entecavir+tenofovir††* 2. Change to tenofovir†	

*Preferred for heavily pretreated patients (e.g. including entecavir+adefovir resistance).
†Tenofovir disoproxil fumarate or tenofovir alafenamide fumarate.

항바이러스제는 대부분의 경우 중단을 고려하지 않는다. 하지만 HBsAg 소실이 이루어진 환자에서는 치료를 종료할 수 있고, HBeAg 양성 만성 B형간염 환자에서 HBV DNA가 검출되지 않고, HBeAg이 소실된 환자의 경우 선택적으로 치료를 종료할 수 있다.[4]

C형간염

1. 자연경과

C형간염바이러스에 감염된 환자 중 55~89%가 만성 간염 상태로 이행하며, 이들 중 2~24%가 20년 이상 경과 후 간경변증으로 진행한다.[1]

2. 치료

대개의 경우 선별검사로 HCV 항체를 검사하며, HCV 항체 양성 환자에서 HCV RNA를 검사하여 C형간염을 확진한다. 항바이러스 치료를 위해 HCV 유전자형 검사와 간경변증에 대한 평가가 필수적이다.[5]

HCV RNA가 검출되는 거의 모든 환자는 치료의 대상이 되며 현재는 대부분의 환자에게 새롭게 개발된 경구 항바이러스제인 direct acting antivirals(DAA)를 사용하게 된다. 국내에 승인된 약제는 여러 종류가 있고 과거에는 치료 약제 선택이 상당히 복잡하였으나, 현재는 초치료로 ledipasvir/sofosbuvir(하보니), glecaprevir/pibrentasvir(마비렛) 두 약제만을 사용하기 때문에 치료 옵션이 매우 간단해졌다. DAA는 다양한 약제와 약물상호작용을 유발할 수 있으므로 반드시 치료 전 사용하고 있는 모든 약제에 대하여 상호작용 여부를 확인해야 한다. 약물 상호작용에 대한 정보는 www.hep-druginteractions.org 에서 확인할 수 있다.

과거에 많이 사용하였던 daclatasvir와 asunaprevir 병합요법의 경우 치료 전 HCV의 내성 관련 치환(resistance-associated substitution, RAS)이 있는 경우 치료 성적이 좋지 않았기 때문에 치료 전 L31 혹은 Y93 변이가 있는지를 확인하여 치료 여부를 결정하였다.

치료 종료 시점 HCV RNA가 검출되지 않는 상태를 치료종료 바이러스 반응(end-of-treatment response, ETR)이라 정의한다. 치료 종료 12주 또는 24주째 혈중 HCV RNA가 검출되지 않는 상태를 지속바이러스반응(sustained virological response, SVR)로 정의한다.

References

1. 대한간학회. 한국인 간질환 백서. 2013
2. 이광재, 한광협, 전재윤, 문영명, 이상인, 박인서 등. 장기간의 추적관찰에 따른 만성 B형 간염의 자연경과. 대한소화기학회지 1997;29:343-351.
3. Lim SY, Kim JH. The epidemiology of hepatitis B virus infection in Korea Korean J Intern Med 2019;34(5):945-953.
4. 대한간학회. 만성 B형간염 진료 가이드라인. 2018
5. 대한간학회. 만성 C형간염 진료 가이드라인. 2017

Information of Welfare Service for the Patients with Liver Disease

Kyung Ae Lee

Hallym University Sacred Heart Hospital, Korea

Hospitals with a general hospital level or higher are required to have one or more social welfare workers (Article 28-2-6 of the Enforcement Regulation of the Medical Act), and social workers working in hospitals or medical institutions are called medical social workers. The medical social workers establish a system of cooperation with the clinical department of each hospital, and help to solve the social and emotional internal problems that may cause the patient's disease or interfere with the treatment during the treatment process. The medical social workers provide the suitable social welfare services for solving the problems so that the patients can return to the local community and perform their social functions normally (Frnaces Upham (1960)). Hallym University Medical Center's social work team has also established a collaboration system (Figure 1) with each clinical department, and counseling for patients with liver diseases (hepatitis, cirrhosis, liver failure, hepatocellular carcinoma, liver transplantation, etc.) has been increasing over the past 5 years (Table 1).

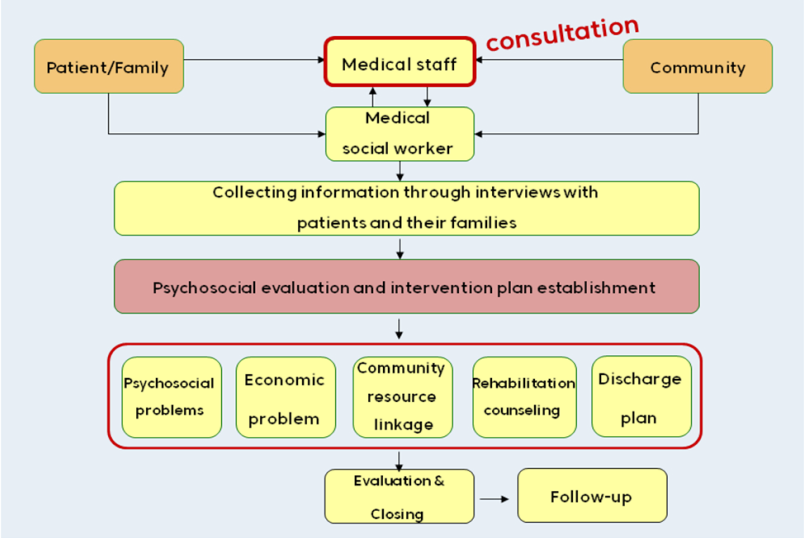


Figure 1. Social work team cooperation consult system

Table 1. Status of Intervention in Gastroenterology in HUMC (Recent 5 Years)

	2016	2017	2018	2019	2020
Intervention status	700	759	811	773명	823명
Liver disease	218(31.1%)	230(30.3%)	260(32.0%)	273명(35.3%)	294명(35.7%)

Liver disease is prone to complications such as cirrhosis and liver cancer in the 40s and 50s when their economic activity is active, It is not easy to solve without multifaceted resources because the treatment period is prolonged, When consulting with patients with liver disease, many patients complain of psychological, emotional, socio-economic difficulties due to various factors such as a decrease in income (disruption), an increase in expenditure, burden of care, and a change in role. "Is there any way to get help with medical bills?", "I'm so unsure of what to do now, is there a place where I can get help?" We get a lot of questions.

In fact, the government prepares and implements various welfare policies such as health, housing, and education according to the life cycle and household situation for the vulnerable social group, However, Access to information on welfare support benefits is not easy because the welfare policies are operated by different institutions, Therefore, it is very important for medical social workers to collect social welfare information that is helpful to patients with liver disease and their families, and to provide with customized social welfare services to the target client by listing support standards, application methods, institutions and personnel in charge (Figure 2).

Figure 2. Welfare information for patients with liver disease[1]

Welfare information for patients with liver disease can be categorized into chronic liver disease, severe liver disease, and alcoholic liver disease prevention and management program, medical expenses support

1 Source: Table of contents of the 2020 welfare information booklet for liver disease patients. The Korean Liver Association and Abbvie have been publishing welfare information booklets for liver disease patients as a social contribution activity since 2017, and by integrating welfare information scattered by institutions, liver disease prevention and management programs, medical expenses support programs, livelihoods: It contains information on non-support programs, disability and daily life support.

program, living expenses support program, and disability and daily life support.

First, medical expenses support projects include hepatitis C drug expenses, surgery and hospitalization treatment expenses, and nursing expenses support. National and private medical expenses support programs such as the Asan Foundation, Korea Medical Support Foundation, and World Vision are utilized. In addition, Each hospital has its own sponsorship fund to support the expenses like outpatients, examination fees, and drug fees unsupported by national and private medical expenses support projects. Such medical expense support provides treatment opportunities so that patients can start treatment well, and sometimes helps to maintain them without dropping out.

Second, in the case of a living expenses support project, emergency living expenses, housing expenses, and education expenses are provided through the National Basic Livelihood Security System, the second-class protection system, and emergency welfare support programs for patients with liver disease and their families who are experiencing economic difficulties due to diseases or other reasons. Etc. By evaluating the target's income, property, and criteria for those who are obligated to support them, we provide support to support temporary and long-term livelihoods, helping patients with liver disease and their families who need help in crisis situations such as sudden difficulty in living to get out of a crisis situation.

Third, among patients with liver disease, if sequel disorders remain due to liver cirrhosis, hepatocellular carcinoma treatment, or liver transplantation that progressed to Child-Pugh B~C, the disorder can be registered according to the judgment time. Depending on the degree of disability, disability is classified into severe disability and mild disability. There are medical expense support for the disabled, disability allowance and disability pension. In addition, if elderly patients 65 years of age or older have difficulty performing their daily life independently (hygiene management, meals, cheating, moving, etc.), the elderly long-term care insurance system, which provides caring services, can be used.

In addition, medical social workers support psycho-emotional support programs for patients with liver disease and their families who experience family conflict, disconnection from society, helplessness, alienation, and depression due to role change. For patients with liver disease, short-term counseling is carried out to improve motivation for change by utilizing various counseling techniques for stopping drinking, and support to maintain stopping drinking long-term by linking A.A (Alcoholics Anonymous) meetings. In addition, not only in hospital, but also in the place where the person in need of care after discharge from the hospital lived, they can enjoy services that meet their individual needs and live in harmony with the local community. Discharge support activities are also underway so that they can receive care services.

References

1. Korean Association for the Study of the Liver(2020), Welfare Information for Liver Disease Patients in 2020.
2. Jang, Soo Mi, Rhee, Yung Seon, Lee, In Jeong, Lim, Jung Won, Choi, Gyong Aw, Han, In Young(2020),Social Work in Health Care. Seoul:Hakjisa.
3. Korean Association for the Study of the Liver(www.kasl.org)
4. Bokjiro (www.bokjiro.go.kr)

Associate Course

Realizing Your Dream of Becoming the Best Clinical Research Coordinator a Reality

Sunyoun Youn

Asan Medical Center, Korea

The size of the drug pipeline in the global pharmaceutical industry was 17,737 in 2020, an increase of 9.6% from the previous year, and the recent trend shows an increase in the average annual growth rate at 7.6%. Korea's market share in global clinical trials was about 3.25% in 2019, ranking 8th in the global market. Korea ranked 3rd in the world based on the clinical trial standards of unitary states, and by city, Seoul ranked first in the world for three consecutive years from 2017 to 2019.

Although high mobility makes it difficult to accurately estimate the total number of domestic CRC personnel, the number of CRCs in Korea in 2017 appeared to be 3,711 to 3,817, according to KoNECT's [2017 CRC Personnel Status Survey and Career Change Analysis in Korea] conducted in 28 institutions. The numerical growth is prominent compared to 1,633 people in 2009 and 1,773 people in 2010.

In addition to the growth of the global pharmaceutical industry, Korea's market share in global clinical trials and the CRC personnel are also growing at a great speed. With the growth of clinical trials in Korea, not only has the number of CRC personnel increased, but also the competence of CRC has become significant more than ever.

CRC refers to a person who possesses the experience and knowledge related to the conduct of research and protection of study participants. CRCs perform tasks under the delegation of Principal Investigator (PI) based on the relevant guidelines for GCP and related laws.

CRC performs diverse tasks throughout the entire clinical trial from start to the closure of the study. CRC traditionally performed the role as clinical trial coordinator, educator, counselor, providers of direct nursing, and spokespersons for the study subject. As the size and standard of global clinical trials continue to increase, the role of CRCs has expanded to Administrator, project manager, data manager, educator, quality assurance manager, alliance manager. Hence, as they are offered the opportunities to serve various roles in diverse fields, they must possess the necessary competencies and qualities accordingly.

If one completes the standard education for CRC to obtain the basic competencies in clinical trial, then participate in various educational programs to gain professional knowledge and acquire domestic and international certification, this CRC would be capable of performing tasks internationally.

Next, it is important to broaden one's vision by constantly paying attention to the international statuses and trends of clinical trials so that the CRC does not fall behind in the rapidly changing clinical trial environment. It is also crucial to maintain smooth communication and close relationships with various relevant departments. Most importantly, the "ethical principles in clinical trials" must be fully understood when conducting a clinical trial with human research participants. Prior to the rapid enrollment of the performed

clinical trial and successful study results, the CRC must not forget the safety and ethics of the clinical trial participants.

If a CRC with professional commitment and a sense of ethics constantly studies and possesses diverse experiences with a broadened clinical trial vision, then the dream of becoming the best CRC is certainly never a challenging goal.

References

1. ICH GCP E6(R2)
2. KONECT, [2020] Statistics of Information on Korean Clinical Trial Industry
3. KONECT, Result Report_CRC Personnel Status Survey and Career Change Analysis in Korea
4. KONECT, White Paper of Korean Clinical Trial
5. KFDA, Understanding the Ethical Standards in Clinical Trials

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

DAY 2: Friday, May 14, 2021 (10:00-11:00)

ROOM 1

Plenary Session 1

Chairs:

Byung Ik Kim (Sungkyunkwan Univ.)
Han Chu Lee (Univ. of Ulsan)
Chul Soo Ahn (Univ. of Ulsan)

PS 1-1

Nucleos(t)ide Analogue Treatment Is Associated with Lower Risk of Extrahepatic Malignancy In Chronic Hepatitis B Patients: A Landmark Study Using Nationwide Claim Data

Dong Hyeon Lee[1,2], Sung Won Chung[1], Goh Eun Chung[3], Misook Kim[4], Boram Yang[4,5], Joon Yeul Nam[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea; [3]Department of Internal Medicine Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea; [4]Medical research collaborating center, Seoul National University Hospital, Seoul, Korea; [5]Chungnam National University, College of Pharmacy, Daejeon, Korea

Aims: Epidemiologic studies suggested that chronic hepatitis B virus (HBV) infection is a risk factor for various primary extrahepatic malignancy as well as liver cancer. Although nucleos(t)ide analogues (NAs) against HBV could reportedly reduce the risk of hepatocellular carcinoma (HCC), whether NAs could reduce the risk of extrahepatic malignancy is still unclear.

Methods: We conducted an 18-month landmark study using the nationwide claim data from the National Health Insurance Service of Korea. Patients who were diagnosed with chronic hepatitis B (CHB) in 2012–2014 (n = 90,944) and age, sex, socioeconomic status, and areas of habitat matched-controls from general population (n = 685,436) were included. CHB patients were further classified into NA-treated (n = 6,539) or NA-untreated CHB groups (n = 84,405). The inverse probability treatment weighting analysis was applied for balancing study groups. The primary outcome was the development of overall extrahepatic malignancy. The development of liver cancers (HCC and intrahepatic cholangiocarcinoma) and death were considered as competing events. We additionally analysed extrahepatic malignancy incidence at different landmark points (12-month and 24-month) as a sensitivity analysis.

Results: During the study period (median = 47.4 months), 30,413 patients (3.9%) developed extrahepatic malignancy. The NA-untreated CHB group had significantly higher risk of overall extrahepatic malignancy than both the NA-treated CHB group (adjusted sub-hazard ratio [aSHR] = 1.27, 95% confidence interval [CI] = 1.11–1.45, *P*=0.003) and the control group (aSHR = 1.22, 95% CI = 1.18–1.26, *P*<0.001), while there was no difference between the NA-treated CHB group vs. the control group (NA-treated vs. control, aSHR = 0.96, 95% CI = 0.84–1.09, *P*=0.55). In both 12-month and 24-month landmark analyses, the NA-untreated CHB group had significantly higher risk of overall extrahepatic malignancy than both the NA-treated CHB group (aSHR = 1.22, *P*=0.002; aSHR = 1.22, *P*=0.002, respectively) and the control group (aSHR = 1.24, *P*<0.001; aSHR = 1.20, *P*<0.001, respectively).

Conclusions: CHB patients without NA treatment have higher risk of extrahepatic malignancy, which can be attenuated with NA treatment.

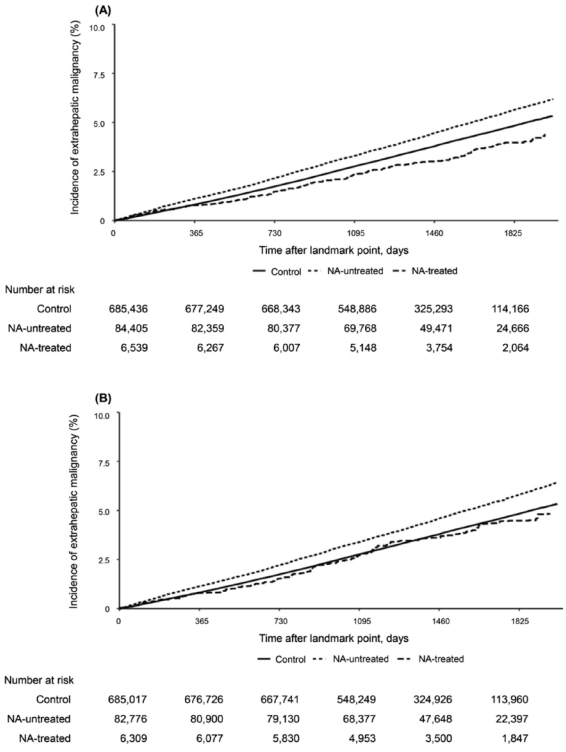


Figure: Cumulative incidence of extrahepatic malignancy (18-months landmark) (A) Before inverse probability treatment weighting (IPTW) analysis, (B) after IPTW analysis

Keywords: Chronic hepatitis B, Nucleos(t)ide analogue, Extrahepatic malignancy

PS 1-2

Cost-Effectiveness and Health-Related Outcomes of One-Time Screening and Treatment for Hepatitis C in Korean Population: A Pilot Project for Hepatitis C Screening

Young Chang[1], Hye Won Lee[2], Nathaniel Smith[3], Rob Blissett[3], Do Young Kim[2*], Jae Young Jang[1*]

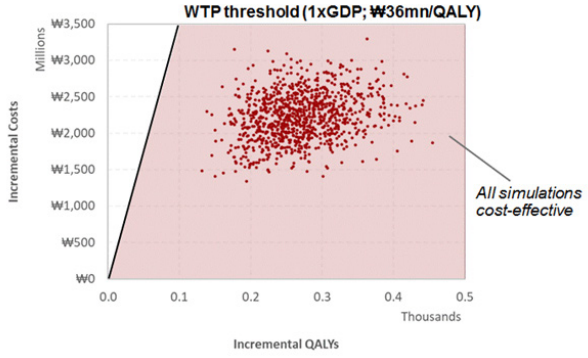
[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Gilead Sciences Korea Ltd, Seoul, South Korea; [4]Maple Health Group LLC, New York, NY, USA

Aims: As a part of a pilot project for early detection of hepatitis C patients in Korea, hepatitis C screening was temporarily performed in 56-year-old general population in Korea. This study investigated the cost-effectiveness of one-time screening and treatment strategy for hepatitis C patients as compared to no screening or risk-based screening strategies.

Methods: From September 1, 2020 to October 31, 2020,

56-year-old general Korean population received hepatitis C virus (HCV) antibody (Ab) tests at the national general health checkup, followed by HCV RNA tests for HCV Ab-positive subjects as a confirmatory test. To model different screening and treatment strategies for hepatitis C patients, a Markov disease progression model with screening and treatment decision tree was used. The screening strategies included "Scree-all", "Risk-based screening", and "No screening" strategies followed by treatment. Treatment strategies included 8 or 12 weeks of ledipasvir/sofosbuvir and 8 weeks of glecaprevir/pibrentasvir. Model inputs were primarily sourced from the results of the hepatitis C screening pilot project, and from published literature.

Results: A total of 133,705 subject, 104,918 subjects received hepatitis C screening test with acceptability of screening rate of 78.47%. Of the 104,918 examinees, 792 cases (0.75%) were positive for HCV Ab and 189 cases (0.18%) were positive for HCV RNA, resulting in HCV RNA positivity in persons with HCV Ab of 23.86%. The acceptability of treatment is estimated to be 70.34% based on the results of the survey. In cost-effective analyses, the screen-all strategy led to the lowest rates of advanced liver disease events. When screening with the screen-all strategy, compared to the no-screening strategy, compensated cirrhosis was expected to decrease by 50%, decompensated cirrhosis by 48%, hepatocellular carcinoma by 49%, liver transplantation by 43%, and death by 49%. The incremental cost-effectiveness ratio (ICER) of the screen-all strategy compared to the no screening strategy was ₩8,164,704/quality-adjusted life-year (QALY), which was much lower than the cost-effectiveness threshold of gross domestic product per capita, ₩35,831,274. When compared with the risk-based strategy, the screen-all strategy was consistently cost-effective with ICER of ₩7,965,201/QALY. In both deterministic and probabilistic sensitivity analyses, the cost-effectiveness of the screen-all strategy over the no screening or risk-based screening strategies was robust in all situations (Figure 1).



Conclusions: Screening all 56-aged Korean population once followed by effective treatment is expected to reduce the incidence of adverse liver disease and is cost-effective when compared with risk-based screening or no screening.

Keywords: Hepatitis C, Screening, Cost-effective

PS 1-3

Minimally Invasive Living Donor Liver Transplantation: Pure Laparoscopic Explant Hepatectomy and Graft Implantation Using Upper Midline Incision

Kyung-Suk SUH, Suk Kyun HONG, Kwangpyo HONG, Eui Soo HAN, Su young HONG, Sanggyun SUH, Jeong-Moo LEE, YoungRok CHOI, Nam-Joon YI, Kwang-Woong LEE

Surgery, Seoul National University Hospital, Korea

Aims: Minimally invasive approaches have increasingly been applied in surgeries and have even recently been used in live donor hepatectomy. We have developed a safe and reproducible method for minimally invasive living donor liver transplantation (LDLT), which consists of pure laparoscopic explant hepatectomy and graft implantation using an upper midline incision.

Methods: From March 2020 to June 2020, minimally invasive LDLT was attempted in five patients. Explant hepatectomy was performed using the pure laparoscopic method, and graft implantation was performed using an upper midline incision.

Results: The procedure was completed in three of the five patients. The first two patients required open conversion due to bleeding. In the three successful procedures, the time required to remove the liver was 285, 180, and 166 min, respectively, and the total operative time was 640, 575, and 499 min, respectively. All patients recovered well, and the duration of hospital stay was 30, 26, and 15 days, respectively.

Conclusions: According to the data of the present study, minimally invasive LDLT in properly selected recipients is a feasible and safe procedure when performed by a highly experienced surgeon and transplantation team. Further studies with larger series are needed to confirm the safety and feasibility.

PS 1-4

Roles of Intrahepatic Inflammation-Induced IgA+PD-L1-high Macrophages in Development and Immunotherapy of Hepatocellular Carcinoma

Pil Soo Sung[1,2,*], Dong Jun Park[1,*], Sung Woo Cho[1], Gil Won Lee[1], Pu Reun Rho[1], Jung Hoon Cha[1], Eun Sun Jung[3], Sung Hak Lee[4], Jaejun Lee[5], Hyun Yang[5], Jeong Won Jang[1,2], Si Hyun Bae[1,5], Jong Young Choi[1,2], Jaegyoon Ahn[6], Seung Kew Yoon[1,2,*]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [2]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [3]Department of Hospital pathology, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea; [4]Department of Hospital pathology, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [5]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea; [6]Department of Computer Science & Engineering,

Incheon National University, Incheon, South Korea

Aims: Immunoglobulin A (IgA) neutralizes pathogens to prevent infection at mucosal sites. Serum levels of IgA were also reported to increase according to the progression of liver fibrosis in non-alcoholic steatohepatitis (NASH). Here, we investigated the roles of inflammation-induced, intrahepatic $IgA^{+}PD\text{-}L1^{high}$ macrophages in development and immune checkpoint inhibitor (ICI) treatment of hepatocellular carcinoma (HCC).

Methods: ELISA of IgA and immunohistochemial staining of IgA, CD3, CD68, and PD-L1 were performed with patients' samples. Multi-color flow cytometry was performed with mononuclear cells isolated from surgical and biopsy specimens. *In vitro* differentiation of macrophages, stimulation of them with coated IgA, and RNA sequencing was performed. Mice model representing acute hepatitis, liver fibrosis, and HCC was used to observe the role of intrahepatic IgA^{+} macrophages.

Results: Serum IgA levels are significantly higher in patients with HCC than chronic liver diseases ($P<0.001$), and predicted the fibrosis progression and HCC development ($P<0.001$, AUROC = 0.70). Immunohistochemical staining of IgA in the patient liver revealed the strong positivity of IgA in macrophages and the frequency of IgA^{+} cells reflected serum levels of IgA. Intrahepatic IgA^{+} macrophages expressed higher levels of PD-L1 and HLA-DR than IgA^{-} macrophages. RNA sequencing demonstrated that stimulation of coated IgA complex to M2-polarized macrophages caused their activation and upregulation of PD-L1. Anti-PD-L1 treatment IgA-stimulated macrophages enhanced T cell functionality during co-culture. The number of intrahepatic IgA+ macrophages increased in the liver fibrosis mouse model, not in the acute hepatitis model. *In vivo* blockade of IgA signalling using soluble FcαRI peptide or treatment of anti-PD-L1 resulted in the decreased syngeneic tumor volume and decreased the number of IgA^{high} tumor-infiltrating macrophages. Blockade of YAP/TAZ signalling resulted in the attenuated IgA-mediated upregulation of PD-L1 in macrophages both *in vitro* and *in vivo*.

Conclusions: Serum IgA level predicts the development of HCC and reflects the intrahepatic infiltration of $IgA^{+}PD\text{-}L1^{high}$ macrophages. These cells dismantle anti-tumor immune responses to HCC. YAP inhibitor and anti-PD-L1 may target these cells.

Keywords: Hepatocellular carcinoma, Immunoglobulin A, Macrophage, PD-L1

DAY 3: Saturday, May 15, 2021 (10:00-11:00)

ROOM 1

Plenary Session 2

Chairs:

Kwan Soo Byun (Korea Univ.)
Joon Hyeok Lee (Sungkyunkwan Univ.)
Hyeon Kook Lee (Ewha Womans Univ.)

PS 2-1

Diagnostic Performance of Magnetic Resonance Imaging, Vibration-Controlled Transient Elastography and Controlled Attenuation Parameter in Predicting Steatohepatitis in NAFLD Patients

JiHwan Lim[1], Sun Young Yim[1], Ki Choon Sim[2], Na Yeon Han[2], Tae Hyung Kim[1], Young Sun Lee[1], Yoo Jin Lee[3], Tak-Kyoon Ahn[1], Hye Sung Cho[4], Young Dong Yoo[4], Young Kul Jung[1], Yeon Seok Seo[1], Ji Hoon Kim[1], Hyung Joon Yim[1], Dong Sik Kim[4], Soon Ho Um[1]

[1]Department of Internal Medicine, Korea University School of Medicine; [2]Department of Radiology, Korea University School of Medicine; [3]Department of Pathology, Korea University School of Medicine; [4]Department of Hepatobiliary Surgery, Korea University School of Medicine

Aims: The number of nonalcoholic fatty liver disease (NAFLD) patients have been increasing and it is emerging as important cause of chronic liver injury in Korea. NAFLD ranges from benign nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) where NASH includes progressive fibrosis. Liver biopsy is the gold standard method for the diagnosis of NASH and although there are no reliable non-invasive means of differentiating NAFLD from NASH, noninvasive models that correlate with individual histologic parameters have been developed. The aim of the current study was to examine the diagnostic accuracy of magnetic resonance imaging (MRI) and transient elastography (TE) in classifying fibrosis while MRI-derived proton density fat fraction (PDFF) and controlled attenuation parameter (CAP) in classifying degree of steatosis as well as the possibility of combination imaging modalities in predicting NASH.

Methods: We retrospectively reviewed database of 213 patients who had undergone liver MRI and TE from November 2017 to February 2021 and cross-sectional analysis was performed in 113 patients who had underwent both imaging study and liver biopsy. The radiologist and pathologist were blinded to clinical and pathology/imaging data, respectively. A systematic NAFLD activity score (NAS) was scored using NASH Clinical Research Network. The Area Under the Receiver Operating Characteristics (AUROCs), sensitivity, and specificity of MRI and TE were analyzed according to degree of steatosis and fibrosis. Further analysis was performed to observe if combination of imaging analysis could detect presence of NASH using linear regression analysis.

Results: Out of 113 patients, 78 patients (69%) were male, mean body mass index was 29.3±4.8 kg/m^2 and presence of diabetes and hypertension were observed in 32.7% and 27.4%, respectively. The proportion of patients with probable NASH (NAS 3,4) and definite NASH (NAS ≥ 5) were 40.7% and 23%, respectively. The correlation between MRI-PDFF and CAP was moderate (r = 0.57, *P*<0.001). The AUROCs of MRI-PDFF and CAP were 0.905 (CI 0.856-0.964, *P*<0.001) and 0.739 (CI 0.644-0.835, *P*<0.001), respectively in detecting advanced steatosis (score ≥3, steatosis >33%). MRI-PDFF provided significantly more reliable fat content measurement than did CAP for every degree of steatosis. The AUROC values for MRI-PDFF and TE were 0.936 vs 0.563 for steatosis grade ≥1 and 0.922 vs 0.92 for steatosis grade ≥2 (*P*=0.005 and *P*<0.001, respectively). In predicting degree of liver fibrosis, the correlation between MRE and TE was also moderate (r=0.631, *P*<0.001). MRE identified patients with advanced fibrosis (F ≥3) with an AUROC 0.973 (0.924-0.994, *P*<0.001) and TE identified with an AUROC 0.946 (0.885-0.981, *P*<0.001). The predictive efficacy between MRE and TE did not differ in predicting any degree of liver fibrosis. Since there is no imaging modality that can exactly predict degree of NASH, next we analyzed whether the diagnostic ability of combined modalities improved. The predictive efficacy significantly increased when MRI-PDFF was added to MRE alone (AUROC; 0.869 vs 0.619, *P<0.001) in identifying both definite NASH (NAS ≥5) and probable NASH (NAS 3-4) (AUROC; 0.823 vs 0.602,* *P*<0.001). However, the predictive ability did not improve for the combination of TE and CAP. In multivariate analysis, there was significant correlation between MRE and degree of hepatocyte ballooning in addition to degree of fibrosis (both, *P*<0.001).

Conclusions: MRI-PDFF have higher diagnostic performance in non-invasive detection of liver steatosis than TE but no significant difference was observed in identifying degree of liver fibrosis. Furthermore, combination of MRE and MRI-PDFF enabled detection of NASH in NAFLD patients with high diagnostic efficacy. Our result presents the possibility of non-invasive method in predicting NASH and could possibly reduce the need for liver biopsy following further validation in a larger cohort.

Keywords: NAFLD, NASH, MRE, MRI-PDFF, Fibrosis

PS 2-2

The Artificial Intelligence-Driven Model for Prediction of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients: Derivation and Validation Using 13,508 Patients from Asian and Caucasian Cohorts

Hwi Young Kim[1*], Pietro Lampertico[2*], Joon Yeul Nam[3*], Hyung-Chul Lee[4*], Seung Up Kim[5], Yeon Seok Seo[6], Han Ah Lee[6,7], Soo Young Park[8], Young-Suk Lim[9], Eun Sun Jang[10], Eileen L. Yoon[7,11], Hyoung Su Kim[12], Sung Eun Kim[13], Sang Bong Ahn[14], Jae-Jun Shim[15], Soung Won Jeong[16], Yong Jin Jung[17], Joo Hyun Sohn[18], Yong Kyun Cho[19], Dae Won Jun[11], George N. Dalekos[20], Ramazan Idilman[21], Vana Sypsa[22], Thomas Berg[23], Maria Buti[24], Jose Luis Calleja[25], John Goulis[26], Spilios Manolakopoulos[27], Harry LA Janssen[28], Myoung-jin Jang[29], Yun Bin Lee[3], Yoon Jun Kim[3], Jung-Hwan Yoon[3], George V. Papatheodoridis[30], Jeong-Hoon Lee[3**]**

[1]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea; [2]Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei

University College of Medicine, Seoul, South Korea; [6]Department of Internal Medicine, Korea University Anam Hospital, Korea University College; [7]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea; [8]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea; [9]Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Centre, Seoul, Korea; [10]Departments of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea; [11]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea; [12]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea; [13]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang-si, Republic of Korea; [14]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University College of Medicine, Seoul, Republic of Korea; [15]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea; [16]Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea; [17]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center; [18]Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri-si, Republic of Korea; [19]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [20]Department of Medicine and Research Laboratory of Internal Medicine, National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Larissa, Greece; [21]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkey; [22]Department of Hygiene, Epidemiology & Medical Statistics, Medical School of National and Kapodistrian University of Athens, Athens, Greece; [23]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; [24]Hospital General Universitario Vall Hebron and Ciberehd, Barcelona, Spain; [25]Hospital U Puerta de Hierro, IDIPHIM CIBERehd, Madrid, Spain; [26]4th Department of Internal Medicine, Aristotle University of Thessaloniki Medical School, General Hospital of Thessaloniki "Hippokratio", Thessaloniki, Greece; [27]2nd Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Hippokratio", Athens, Greece; [28]Liver Clinic, Toronto Western & General Hospital, University Health Network, Toronto, ON, Canada; [29]Medical Research Collaboration Center, Seoul National University Hospital, Seoul, Republic of Korea; [30]Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens "Laiko", Athens, Greece

*These four authors contributed equally to this work as co-first authors.
**These two authors contributed equally to this work as co-corresponding authors.

Aims: Several risk scores have recently been developed to predict risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). Our aims were to develop and validate an artificial intelligence-assisted prediction model for HCC risk and compare it with previous models.

Methods: Using gradient boosting machine (GBM) algorithm, a model was developed from 6,051 chronic hepatitis B patients on entecavir or tenofovir therapy from 4 hospitals in Korea. Additional two external validation cohorts were independently established: Asian (5,817 patients from 14 Korean centers) and Caucasian PAGE-B cohorts (1,640 from 11 Western centers). The primary outcome was HCC development.

Results: In the derivation cohort and two validation cohorts, cirrhosis was present in 26.9%–50.2% at baseline. A model using 10 parameters at baseline was derived and showed a good prediction performance (c-index, 0.79). This model showed significantly better discrimination function than previous models (PAGE-B, modified PAGE-B, REACH-B, and CU-HCC) in both Asian (c-index, 0.79 vs. 0.64–0.74; all $P<0.001$) and Caucasian validation cohorts (c-index, 0.81 vs. 0.57–0.79; all $P<0.05$ except modified PAGE-B [$P=0.22$]). Calibration plot showed calibration function was also satisfactory. When the patients were grouped into 4 risk groups, the minimal risk group (11.2% of Asian cohort and 8.8% of Caucasian cohort) showed <0.5% of HCC risk during 8 years of follow-up (Fig. 1A and 1B).

Fig. 1A

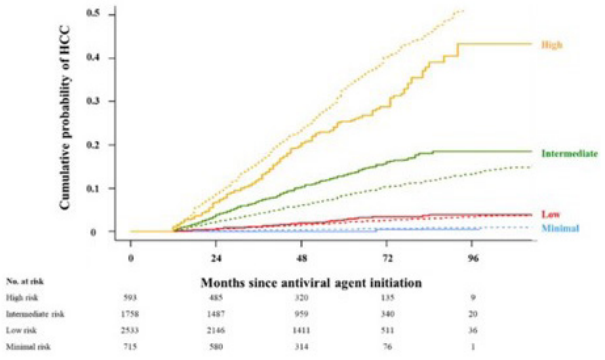


Fig. 1B

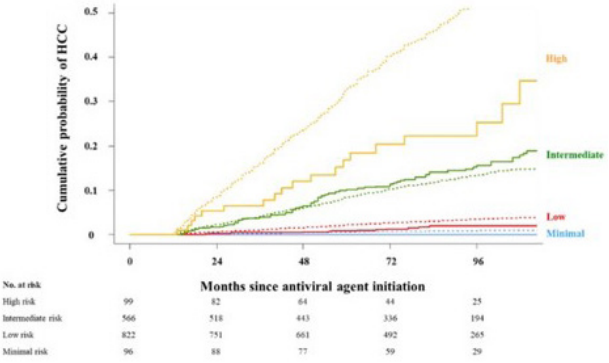


Figure 1. The expected versus the observed HCC development according to PLAN-B model in the (A) and (B) Caucasian validation cohorts. Thick lines represent the observed HCC development and dottedlines represent the expected HCC development.

Conclusions: This GBM-based model provides the best prediction power for HCC risk in Asian as well as Caucasian patients with CHB under entecavir or tenofovir treatment.

Keywords: Hepatocellular carcinoma, Chronic hepatitis B, Ma-

chine learning, Prediction model

PS 2-3

ADV Score Is a Quantifiable Prognostic Prediction Model for Surgical Resection of Hepatocellular Carcinoma: A Korea-Japan Collaboration Validation Study with 10,606 Patients

Shin Hwang[1], Masaki Kaibori[2], Jong-Man Kim[3], Kyung Sik Kim[4], Bum-Soo Kim[5], Yang-Seok Ko[6], Myunghee Yoon[7], Sung-Su Yoon[8], Yo-Han Park[9], Collaboration of the Korea, Japan Society of Hepatobiliary Pancreatic Surgery

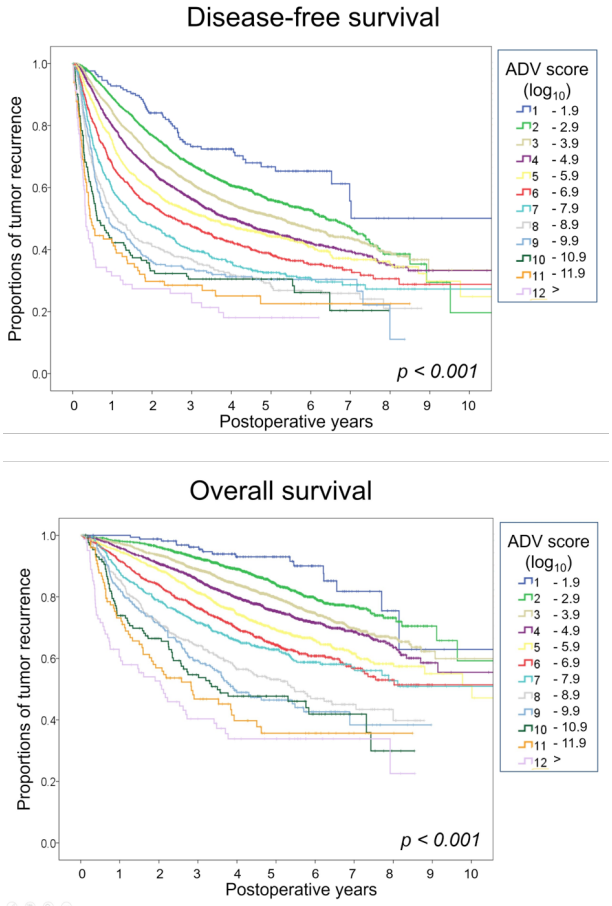
[1]Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center; [2]Kansai Medical Center, Japan; [3]Samsung Medical Center, Sungkyunkwan University; [4]Yonsei University College of Medicine; [5]Kyung Hee University; [6]Chonnam National University; [7]Pusan National University; [8]Yeungnam University; [9]Pusan Paik Hospital, Inje University

Aims: We previously demonstrated that multiplication of α-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP) and tumor volume (TV) (ADV score, expressed in log10) is an integrated surrogate marker of post-resection prognosis for hepatocellular carcinoma (HCC). This study aimed to validate the ADV score as a quantifiable biomarker for oncological aggressiveness of HCC on its prognostic impact following resection of HCC.

Methods: A multicenter validation cohort with 10,606 patients (4,900 [46.2%] from Korea and 5,706 [53.8%] from Japan) was established through the Korea-Japan collaboration study groups managed by the Korea and Japan Society of Hepatobiliary Pancreatic Surgery.

Results: In the Korean cohort, disease-free survival (DFS) and overall survival (OS) rate at 5 years were 66.7% and 93.0% in ADV score <2log; 56.0% and 84.1% in ADV score 2.0-2.9log; 51.0% and 79.7% in ADV score 3.0-3.9log; 45.7% and 75.3% in ADV score 4.0-4.9log; 44.4% and 69.4% in ADV score 5.0-5.9log; 38.4% and 64.3% in ADV score 6.0-6.9log; 32.6% and 62.9% in ADV score 7.0-7.9log; 28.7% and 53.2% in ADV score 8.0-8.9log; 30.4% and 46.5% in ADV score 9.0-9.9log; 30.5% and 47.7% in ADV score 10.0-10.9log; 22.5% and 35.7% in ADV score 11.0-11.9log; and 18.1% and 33.8% in ADV score ≥12log, respectively (both *P*<0.001). The ADV-score dependent DFS and OS rates in the Japanese cohort were very similar with those of the Korean cohort. Consequently, the overall study cohort also revealed similar ADV-score dependent DFS and OS rates. Multiplication of AFP and DCP (AD score) and TV were independent risk factors for DSF and OS. The 5-year DFS and OS rates were visualized according to AD score and TV as like weather prediction diagrams.

Conclusions: This high-volume international validation study revealed that the preoperative ADV score is a reliable surrogate biomarker for quantifiable prediction of post-resection prognosis in the Korean and Japanese patients with HCC.



Keywords: Hepatocellular carcinoma, Tumor biology, Resection, Recurrence

PS 2-4

Activation of Metabotropic Glutamate Receptor 5 Ameliorates Liver Fibrosis through Cytotoxicity of NK Cells against Hepatic Stellate Cells

Won-Mook Choi[1,2], Tom Ryu[1], Jun-Hee Lee[1], Young-Ri Shim[1], Myung-Ho Kim[1], Hee-Hoon Kim[1], Ye Eun Kim[1], Keungmo Yang[1], Kyurae Kim[1], Sung Eun Choi[1], Min Jung Kim[1], Won Kim[3], Seok-Hwan Kim[4], Hyuk Soo Eun[5], Won-Il Jeong[1,6]

[1]Laboratory of Liver Research, Graduate School of Medical Science and Engineering, KAIST, Daejeon, Republic of Korea, [2]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea, [4]Department of Surgery, Chungnam National University, College of Medicine, Daejeon, Republic of Korea, [5]Department of Internal Medicine, Chungnam National University, School of Medicine, Daejeon, Republic of Korea, [6]Biomedical Research Center, KAIST, Daejeon, Republic of Korea

Aims: The crucial roles of metabotropic glutamate receptor 5 (mGluR5) in hepatic stellate cells (HSCs) have been revealed in

various studies. However, the mechanism that associates glutamate metabolism and mGluR5 in liver fibrosis remains unclear. Here, we suggest activation of mGluR5 in natural killer (NK) cells ameliorates liver fibrosis by increasing cytotoxicity through interferon-γ (IFN-γ) production in the liver.

Methods: 2-week injection of carbon tetrachloride (CCl_4) were conducted in wild type mice, mGluR5 knockout (KO) mice or NK cell-specific mGluR5 KO mice. Pharmacologic activation of mGluR5 was done by CHPG. In addition, NK cells in liver were isolated by magnetic-activated cell sorting and cytotoxicity assay was measured with calcein-acetoxymethyl assay.

Results: CCl_4-induced Liver fibrosis was more aggravated in mGluR5 KO mice with significantly decreased frequency of NK cells compared to WT mice. Consistently, NK cell-specific mGluR5 KO mice had worsening of liver fibrosis with decreased IFN-γ production in CCl_4 induced fibrosis model. *In vitro*, activation of mGluR5 in NK cells significantly increased the expression of anti-fibrosis related genes such as *Ifng*, *Prf1* and *Klrk1*. In vivo, pharmacologic activation of mGluR5 alleviated CCl_4-induced liver fibrosis by restoration of NK cell cytotoxicity. In human liver, activation of mGluR5 increased the cytotoxicity of NK cells dervied from healthy liver, but not from cirrhotic liver with reduced mGluR5 expression in NK cells.

Conclusions: mGluR5 has crucial roles in ameliorating liver fibrosis by enhancing NK cell cytotoxicity, which could be a potential therapeutic target for liver fibrosis.

Keywords: Fibrosis, Glutamate, Vesicular glutamate transporter, Natural killer cell

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

DAY 3: Saturday, May 15, 2021 (13:30-14:50)

ROOM 1

KASL Plenary Session

Chairs:

Oh Sang Kwon (Gachon Univ.)

Tae Hun Kim (Ewha Womans Univ.)

KP 1-1

Gut Microbiome and Metabolomic Signatures in Alcoholic Liver Disease

Raja Ganesan, Haripriya Gupta, Ye Rin Choi, Hyeong Seop Kim, Sang Jun Yoon, Yoseph Asmelash Gebru, Satya Priya Sharma, Dong Joon Kim, Ki Tae Suk

Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

Aims: Alcoholic liver disease (ALD) is strongly associated with intestinal dysbiosis and elevated systemic levels of gut-derived bacterial products. Identifying microbiome-derived metabolic signatures is challenging in ALD due to the complex patterns that have long-term effects on the development of ALD. We evaluated a feature of the gut-microbiota and microbiome-derived metabolic signatures in patients with ALD.

Methods: A prospective cohort study was carried out between April 2017 and March 2020. Stool samples (healthy control [HC, n=108], alcoholic fatty liver [AFL, n= 25], alcoholic hepatitis [AH, n=80], alcoholic cirrhosis [AC, n=80]) were collected for the metagenomics by 16S rRNA sequencing and metabolites profiles by using GC-MS and LC–MS methods. Score plot analysis and pattern recognition analysis were performed to find metabolic characteristics between groups.

Results: Compared with HC, relative abundance of Proteobacteria was increased and Bacteroidetes was decreased in ALD groups (AFL, AH, and AC) (P<0.001). Also, Fusobacteria was seen to be increased only in AH group (P<0.0001). Metabolites in ALD patients underlines the importance of biosynthesis of secondary metabolites (P<0.05) and microbial metabolic potential regulations. Totally, 103 metabolites are quantified and screened. Supervised OPLS-DA model classified alcohol exposure that has AFL, 17%; AH, 23.2%; AC, 31.7% of metabolic discrimination, amplified from AFL to AC. An indole 3-propionic acid, indole-3-acrylic acid, indole-3-lactic acid, hexadecanedioic acid, propionate, and stercobilin has significantly decreased. The palmitoylcarnitine, 8-hydroxyquinoline, and acetylcholine (**P<0.01) are significantly increased. The pathways of linoleic acid metabolism, histidine metabolism, fatty acid degradation, and glutamate metabolism were closely related with alcoholic liver metabolism and gut microbiota dysbiosis.

Conclusions: This microbial dysbiosis is associated with microbiomes and metabolomics functionalities as lipid, carbohydrate, and amino acids metabolism including short chain fatty acids synthesis that has linked to preserved cell function. An indole-3-propionic acid altered which may filed to potent neuroprotective as antioxidant molecules. Our finding with metabolomics reports provides that pathways of linolenic acid metabolisms and histone metabolism were identified as biomarkers metabolisms for clinical intervention.

Keywords: ALD, Microbiome, Metabolic discriminations, Targeted therapy

KP 1-2

Impact of Expanding Antiviral Treatment Criteria at a Population Level in the Republic of Korea: A Modeling Analysis

Young-Suk Lim[1], Sang Hoon Ahn[2], Jae-Jun Shim[3], Homie Razavi[4], Devin Razavi-Shearer[4], Dong Hyun Sinn[5]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2] Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Kyung Hee University Hospital, Seoul, Republic of Korea, [4]CDA Foundation, Lafayette, Colorado, United States, [5]Samsung Medical Center, Seoul, Republic of Korea

Aims: HBV is a major disease burden in the Republic of Korea. Current antiviral treatment for HBV decreases disease progression, however, cannot eradicate the virus. Antiviral treatment is offered for a subset of chronic HBV infected individuals. This study examined the impact of expanding treatment criteria on the future disease burden at the population level.

Methods: A dynamic country-level transmission and disease burden model was calibrated to Korean data and estimated the HBV disease progression and mortality. Three scenarios were developed and compared to the Base case which maintained the current eligibility requirements and treatment levels. An economic analysis was also conducted.

Results: Through 2035, expanding the current guidelines to include all cirrhotic individuals and treating 70% of everyone eligible would result in averting 4,300 cases of decompensated cirrhosis, 13,000 cases of HCC, and would save 11,800 lives. Reducing the ALT restriction to the ULN and treating 70% of those eligible would result in averting 7,200 cases of decompensated cirrhosis, 26,700 cases of HCC, and would save 23,300 lives. Treating 70% of individuals a viral load ≥2,000 IU/mL would result in averting 9,800 cases of decompensated cirrhosis, 43,300 cases of HCC, and would save 37,000 lives. All scenarios were highly cost-effective through 2035.

Conclusions: Expanding treatment criteria in Korea would result in almost 12,000 lives saved, but by fundamentally shifting the guidelines this number can be doubled or tripled. As many of these individuals are of working-age the ICER for all scenarios were below the GNI per capita.

Keywords: HBV, Treatment Criteria, Modeling, Epidemiology

KP 1-3

An External Validation of FibroScan-AST Score (FAST) for Non-Invasive Identification of Patients at Risk of Progressive Non-Alcoholic Steatohepatitis

Jae Seung Lee[1], Hye Won Lee[1], Jun Yong Park[1], Do Young Kim[1], Sang Hoon Ahn[1], Soo Young Park[2], Jae Young Jang[3], Young Eun Chon[4], Chun Kyon Lee[5], Seung Up Kim[1*]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea; [3]Department of Internal

Medicine, College of Medicine, Soonchunhyang University, Seoul, Korea; [4]Department of Internal Medicine, CHA Bundang Medical center, CHA Universtiy, Seongnam, Korea; [5]Department of Internal Medicine, National Health Insurance Cooperation, Ilsan Hospital, Goyang, Korea

Aims: An identification of nonalcoholic steatohepatitis (NASH) that is associated with increased risk of progression to cirrhosis and hepatocellular carcinoma is a major priority in patients with non-alcoholic fatty liver disease (NAFLD). We validated the predictive value of FibroScan-aspartate aminotransferase (AST) score (FAST) and other non-invasive fibrosis surrogates in diagnosing NASH.

Methods: This multicenter retrospective study recruited a total of 157 participants who underwent transient elastography (TE) and liver biopsy for suspicion of NAFLD. FAST was calculated using liver stiffness (LS), controlled attenuated parameter (CAP), and AST. The c-index were calculated for NAFLD activity score (NAS) ≥5 or NAS ≥4 with fibrosis ≥2 (NASH-NAS4F2), NASH by Fatty Liver Inhibition of Progression algorithm (FLIP-NASH) and severe disease in Steatosis-Activity-Fibrosis score by histologic activity ≥3 and/or fibrosis ≥3 (severe SAF).

Table. The c-index for progressive NASH

	c-index	*p* value	95% CI	
NAS≥5 (n=69, 43.9%)				
FAST score	0.697	<0.001	0.614	0.779
LS (kPa)	0.642	0.002	0.555	0.729
APRI	0.704	<0.001	0.621	0.787
CAP (dB/m)	0.513	0.784	0.422	0.604
NFS	0.606	0.023	0.518	0.695
FIB-4	0.617	0.012	0.528	0.706
FLIP-NASH (n=118, 75.2%)				
FAST score	0.769	0.000	0.678	0.860
LS (kPa)	0.718	<0.001	0.619	0.818
APRI	0.744	0.000	0.651	0.837
CAP (dB/m)	0.573	0.175	0.462	0.684
NFS	0.685	0.001	0.577	0.793
FIB-4	0.683	0.001	0.580	0.786
Severe SAF (n=77, 49.0%)				
FAST score	0.767	<0.001	0.692	0.842
LS (kPa)	0.762	<0.001	0.687	0.837
APRI	0.732	<0.001	0.653	0.811
CAP (dB/m)	0.453	0.310	0.362	0.544
NFS	0.733	<0.001	0.656	0.811
FIB-4	0.735	<0.001	0.656	0.813
NAS≥5 + (NAS≥4 and histologic fibrosis≥2) (n=79, 50.3%)				
FAST score	0.715	<0.001	0.634	0.795
LS (kPa)	0.716	<0.001	0.635	0.797
APRI	0.687	<0.001	0.604	0.771
CAP (dB/m)	0.521	0.656	0.429	0.613
NFS	0.665	<0.001	0.580	0.750
FIB-4	0.658	0.001	0.572	0.744

NASH, non-alcoholic steatohepatitis; CI, confidence interval; NAS, non-alcoholic fatty liver disease(NAFLD) activity score; FAST, FibroScan- aspartate aminotransferase(AST); LS, liver stiffness; APRI, AST to platelet ratio index; CAP, controlled attenuated parameter; NFS, NAFLD fibrosis score; FIB-4, fibrosis-4; FLIP, fatty liver inhibition of progression algorithm; SAF, steatosis-activity-fibrosis score

Results: The median age and body mass index of the study population (90 [57.3%] male and 67 [42.7%] female) was 42.0 years and 29.2 kg/m^2, respectively. Hypertension and diabetes mellitus were identified in 36 (22.9%) and 46 (29.3%) patients, respectively. The median LS, CAP, FAST, NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4), and AST to platelet ratio index (APRI) were 8.7 (interquartile range [IQR] 6.5–11.8) kPa, 312.0 (IQR 275.5–337.5) dB/m, 0.542 (IQR 0.327–0.696), -2.389 (IQR -3.470 – -0.901), 0.978 (IQR 0.665–1.664), and 0.608 (IQR 0.350–0.952), respectively. The c-index of FAST for NAS ≥5 (n=69 [43.9%]), NASH-NAS4F2 (n=79 [50.3%]), FLIP-NASH (n=118 [75.2%]), and severe SAF (n=109 [69.4%]) were 0.697, 0.769, 0.767 and 0.791, respectively (all *P*<0.001), whereas the c-index of LS was 0.642, 0.718, 0.762, and 0.716, respectively and those of APRI was 0.704, 0.744, 0.732 and 0.687, respectively (all *P*<0.05). Other fibrosis surrogates showed lower c-index compared to FAST.

Conclusions: FAST score is useful non-invasive surrogate for the identification of patients at high risk of progressive NASH.

Keywords: Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Fibrosis

KP 1-4

Sarcopenia and Myosteatosis are Independent Predictors for Long-Term Mortality in Korean Liver Cirrhosis Patients

Han Ah Lee[1,2], Jeong-Ju Yoo[3], Jihwan Lim[1], Young-Sun Lee[1], Young Kul Jung[1], Ji Hoon Kim[1], Hyung Joon Yim[1], Sang Gyune Kim[3], Jong Eun Yeon[1], Kwan Soo Byun[1], Yeon Seok Seo[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea

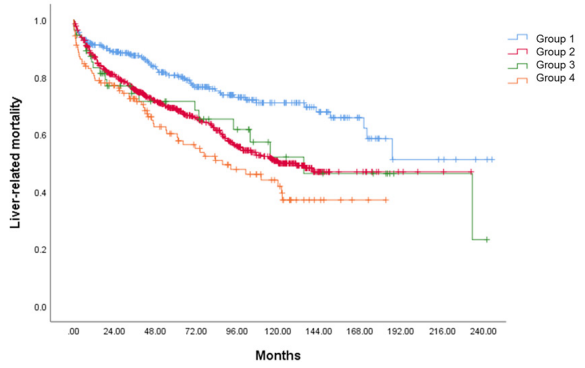
* This study was supported by "The Research Supporting Program" of The Korean Association for the Study of the Liver.

Aims: Muscle depletion in liver cirrhosis is characterized by both sarcopenia and myosteatosis. We investigated the clinical significance of these muscular abnormalities in prognosis of patients with liver cirrhosis.

Methods: Patients with liver cirrhosis were retrospectively enrolled from 2 academic teaching hospitals. Skeletal muscle area and attenuation indexes were assessed by computed tomography scan using the third lumbar vertebra skeletal muscles. Sarcopenia and myosteatosis were defined using previously validated cutoffs.

Results: A total of 1,329 patients were included. Male was predominant (n=942, 70.9%), and the etiology of cirrhosis was alcohol in 697 (52.4%) and hepatitis B in 415 (31.2%), and others in 144 patients (10.8%). Sarcopenia was present in 864 (65.0%), 181 (14.9%) had myosteatosis. During a median follow-up period of 53.3 months, 479 patients (36.0%) had liver-related mortality or liver transplant. Patients with sarcopenia (119.8 vs. 233.5 months, *P*<0.001) and myosteatosis (103.5 vs. 170.0 months, *P*=0.011) had worse median survival than those who had not. When patients were classified into four groups (group 1, no muscular abnormality; group 2, sarcopenia; group

3, myosteatosis; group 4, both sarcopenia and myosteatosis), the median survival was significantly different between group 2 and group 4 (*P*=0.042). (Figure). In multivariate analyses, presence of sarcopenia (hazard ratio [HR] 1.284, 95% confidence interval [CI] 1.019-1.617, *P*=0.034) and myosteatosis (HR 1.306, 95% CI 1.006-1.694, *P*=0.045), alcohol drinking (HR 1.527, 95% CI 1.241-1.878, *P*<0.001), lower albumin (HR 0.632, 95% CI 0.536-0.746, *P*<0.001) and sodium levels (HR 0.978, 95% CI 0.958-0.998, *P*=0.031), and higher MELD score (HR 1.063, 95% CI 1.043-1.084, *P*<0.001) were significant predictors for mortality.



Conclusions: Sarcopenia and myosteatosis are independently associated with a higher long-term mortality in liver cirrhosis. Previous definition of muscle depletions should be modified in Asian patients with liver cirrhosis.

Keywords: Sarcopenia, Myosteatosis, Cirrhosis, Mortality

KP 1-5

Cancer Associated Fibroblast Derived SPP1 Is the Potential Therapeutic Target of Sorafenib and Lenvatinib Resistance in Hepatocellular Carcinoma

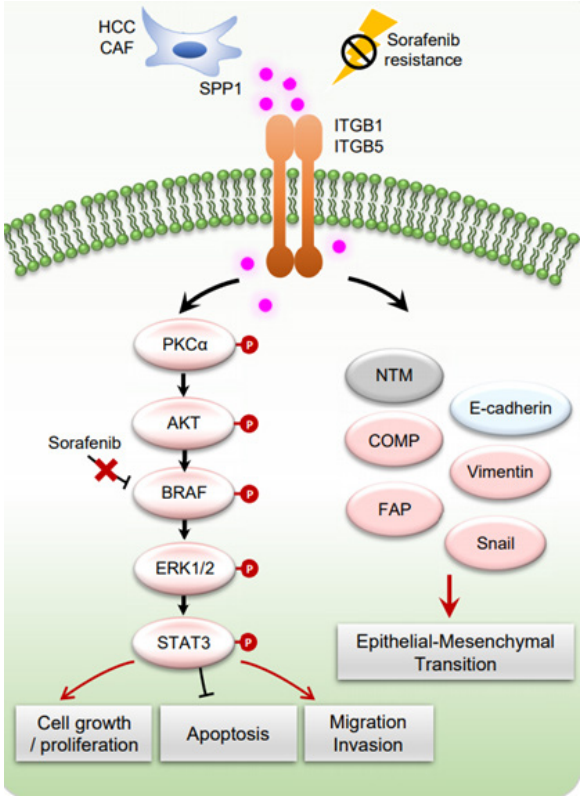
Hye Ri Ahn[1,2], Jung Woo Eun[1], Jung Hwan Yoon[3,4], Geum Ok Baek[1], Moon Gyeong Yoon[1], Ju A Son[1,2], Soon Sun Kim[1], Jae Yeon Cheong[1], Hyo Jung Cho [1]*

[1]Department of Gastroenterology, Ajou University School of Medicine, Suwon, South Korea; [2]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, South Korea; [3]Laboratory of Oncogenomics, Department of Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Functional RNomics Research Center, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Cancer-associated fibroblasts (CAFs) have been considered as an important player inducing chemo-resistance, however the mechanism of CAF-medicated chemo-resistance remains unclear in hepatocellular carcinoma (HCC). This study aimed to identify the mechanism of CAF-medicated sorafenib/lenvatinib resistance and a novel therapeutic starategy to overcome sorafenib/lenvatinib resistance.

Methods: CAFs and para-cancer fibroblasts (PAFs) were isolated from HCC tissues and adjacent non-tumor tissues and cultured. Transcriptome sequencing data of 9 pair of CAFs and PAFs were generated and analyzed to identify a novel therapeutic target of chemo-resistance. *In vitro* and *in vivo* study was performed to validate the selected target and its mechanism. In advanced HCC cohort (n=42), plasma SPP1 expression level prior to sorafenib/lenvatinib administration was measured and progression free survival (PFS) and overall survival (OS) according to plasma SPP1 level was analyzed using Kaplan-Meier analysis.

Results: Co-culture of CAFs and HCC cells significantly enhanced chemo-resistance of HCC cells against sorafenib and lenvatinib both *in vitro* and *in vivo*. In systematic integrative analyses of CAFs/PAFs transcriptome sequencing data and publicly available gene expression data, CAF-derived SPP1 was selected as a candidate molecule inducing sorafenib/lenvatinib resistance. In mechanism study, CAF-derived SPP1 increased phosphorylation of PKC and leading subsequent activation of RAF-ERK1/2-STAT3 in HCC cells. It resulted sorafenib/lenvatinb resistance. SPP1 inhibition via SPP1 blocking peptide or aptamer restored CAF-induced sorafenib/lenvatinib resistance *in vitro* and *in vivo* HCC mouse model. In addition, patients with high plasma SPP1 prior to sorafenib/lenvatinib treatment showed significantly poor PFS (*P*=0.005) and poor OS (*P*=0.041).



Conclusions: CAF-derived SPP1 enhances sorafenib/lenvatinib resistance through alternative activation of RAF-ERK1/2-STAT3 via PKC phosphorylation. Inhibition of CAF-derived SPP1 is a potent therapeutic strategy to overcome sorafenib/lenvatinib resistance. Plasma SPP1 level prior to treatment would be a promising biomarker for predicting sorafenib/lenvatinib response in patients

with advanced HCC.

Keywords: HCC, CAF, Chemo-resistance, SPP1

KP 1-6

Clinical Aspect of Coronavirus Disease 2019 (COVID-19) on HBV Infected Patient

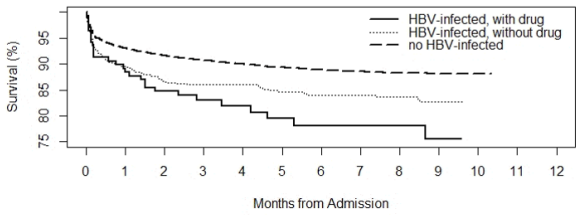
Young Kul Jung[1], Gi Hyeon Seo[2], Tae Hyung Kim[1], Sun Young Yim[3], Young-Sun Lee[4], Ji Hoon Kim[4], Yeon Seok Seo[3], Hyung Joon Yim[1], Jong Eun Yeon[4], Kwan Soo Byun[4], Soon Ho Um[3]

[1]Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Korea; [2]Health Insurance Review and Assessment Service, Seoul, South Korea; [3]Department of Internal Medicine, Korea University Anam Hospital, Seoul, Korea; [4]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea

Aims: In the presence of liver disease, several reports announced liver disease and cirrhosis are risk factors in COVID infection and poor outcomes. However, there is no large data to report the clinical course of COVID-19 patients with chronic hepatitis B virus (HBV) infection. In this study, we aimed to report the clinical course of COVID-19 patients with HBV infection and provide a reference for clinical treatment of patients. And also to know whether the use of antiviral agents had an effect on the clinical course.

Methods: We performed a nationwide population-based cohort study using the Korean Health Insurance Review and Assessment database. Claim records were screened for 19,160 individuals who diagnosed by test of COVID-19 until November 2020.

Results: Of the 19,160 patients diagnosed with COVID-19, 675 (3.5%) patients had HBV infection. Among them, 138 (20.4%) patients were receiving antiviral therapy for the purpose of treating hepatitis B. The Mean age was 52.6 years for corona infection patients and 59.3 years for HBV infected patients, and HBV infected patients were elderly and they showed that concomitant diseases such as diabetes and hypertensive lung disease were relatively high compared with non HBV infected patients(P<0.001). During the observation period (about 10 months), 1,524 (8.2%) of COVID-19 patients died, and 91 with HBV-infected the hepatitis B patients died caused by COVID-19 (13.5%) (P<0.001). Out of 675 HBV infected patients, hospital stay was 19.9 days, of which 85 patients (12.6%) were admitted to the intensive care unit, 13 patients (1.9%) had liver failure, 54 patients (8%) had acute respiratory failure, and had acute renal failure. 34 (5%) were shown. When the overall risk of mortality was classified into all patients, HBV infected patients with antiviral drugs, and HBV infected patients without antiviral drug, the Crude odd ratio (OR) was 1.72 (95% confidence interval, 1.39-2.11), respectively. ; P<0.001), 1.96 (95%CI, 1.30-2.87; P=0.001) showed that HBV infected patient group had a high risk of death when exposed to COVID-19. However, after age, sex, and comorbid diseases were corrected, the adjusted OR was 0.97 (95%CI, 0.76-1.23; P=0.823) and 1.01 (95%CI, 0.63-1.59; P=0.952), respectively and it indicated no difference in mortality risk compared to other patients. In addition, there was no difference in intensive care unit admission or hospital stay after correction.



Conclusions: In COVID-19 infected patients with chronic liver disease or cirrhosis caused by HBV infection, they showed a slightly higher mortality rate than with other disease. However, In the case of patients treated with anti-viral agent from HBV infection, it can be seen that mortality rate from COVID-19 does not increase further if there is no cirrhosis or comorbidity.

Keywords: Covid-19, HBV, Liver disease, Risk factor

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

DAY 2: Friday, May 14, 2021

Free Paper Session 1

FP-001~FP-006	Basic
FP-007~FP-014	Viral Hepatitis
FP-015~FP-022	NAFLD, AIH, others
FP-023~FP-030	Liver Cancer, Basic
FP-031~FP-038	Liver Cancer, Clinical
FP-039~FP-046	Liver Transplantation

Friday, May 14, 2021, 08:40-09:40

1. Basic

FP-001

Discovery of Novel Pyrimidine-Based Capsid Assembly Modulators as Potent Anti-HBV Agents

WooChan Kim[1#], Jung-Ah Kang[2#], Minji Park[3], Pyeong-Hwa Jeong[1], Yoon Jun Kim[4], Yuri Cho[3*], Sung-Gyoo Park[5*], Yong-Chul Kim[1*]

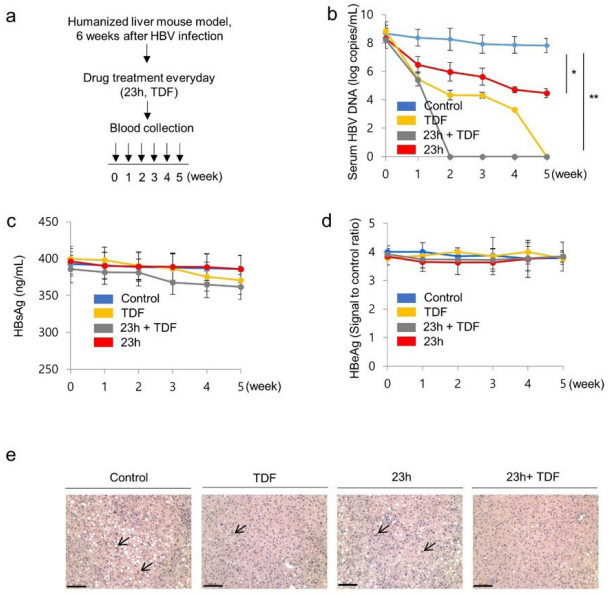
[1]School of Life Science, Gwangju Institute of Science and Technology(GIST), Republic of Korea; [2]Bionanotechnology Research Center, Korea Research Institute of Bioscience & Biotechnology (KRIBB), Daejeon, Republic of Korea; [3]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea; [4]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [5]College of Pharmacy, Seoul National University, Seoul, Republic of Korea

Aims: Core assembly modulators of viral capsid proteins have been developed as an effective treatment of chronic hepatitis B virus (HBV) infection. In this study, we synthesized novel potent pyrimidine derivatives as core assembly modulators, and their antiviral effects were evaluated *in vitro* and *in vivo* biological experiments.

Methods: We screened the synthesized derivatives for their ability to inhibit HBV replication in HBV-expressing HepG2.2.15 cells. Immunoblot analysis of HBV capsid assembly with Cp149-containing suspensions was performed to confirm the anti-HBV efficacy of the synthesized derivatives. Molecular docking was performed by using CDOCKER interfaced with Accelrys Discovery Studio 3.5. The co-crystal structure of the Y132A mutant HBV capsid (VCID 8772) in complex with NVR-010-001-E2 was downloaded from the protein data bank (PDB code: 5E0I, resolution: 1.95 Å). 2-Week *in vivo* repeated toxicity for mice was tested on 5 weeks old BALB/c male mice. Human liver-chimeric urokinase-type plasminogen activator-severe combined immunodeficiency (uPA/SCID) mice were used for evaluating *in vivo* anti-HBV efficacy.

Results: One of the synthesized derivatives, compound 23h (R^1 = $MeSO_2$, R^2 = 1-piperidin-4-amine, R^3 = 3-Cl-4-F-aniline) displayed potent inhibitory effects in the *in vitro* assays (52% inhibition in the protein-based assay at 100 nM and an IC_{50} value of 181 nM in the serum HBV DNA quantification assay). Moreover, treatment with compound 23h for 5 weeks significantly decreased serum levels of HBV DNA levels (3.35 log reduction) in a human liver-chimeric uPA/SCID mouse model, and these effects were significantly increased when 23h was combined with Tenofovir, a nucleotide analog inhibitor of reverse transcriptase used for the treatment of HBV infection. No significant toxicity was observed with 2-weeks of oral treatment of 23h in BALB/c mice.

Conclusions: In conclusion, novel 2,4,6-substituted pyrimidine derivatives were synthesized and optimized as potent modulators of HBV core assembly through structure/activity relationship (SAR) and structure-property relationship (SPR) studies. The results of the current study indicated that, compound 23h (R^1 = $MeSO_2$, R^2 = 1-piperidin-4-amine, and R^3 = 3-Cl-4-F-aniline) is the most optimized modulator of HBV capsid assembly. Dramatic pharmacological efficacy of compound 23h *in vitro* and *in vivo* has moved forward the discovery program of new anti-HBV drug to preclinical studies.



Keywords: Hepatitis B virus, Capsid Assembly Modulator, Chronic hepatitis B, Pyrimidine

FP-002

A Fist-In-Class Small Molecule Targeting 17-Beta-Hydroxysteroid Dehydrogenase 13

Ji Won Choi, Jin Woo Jung, Chanwoo Park, Yang Hun Tae, Seung-chul Lee, Jiyeon Park, Hyeim Jo, Seong-Il Choi, Somyi Park, Donghyun Ko, Dong-Kyu Kim

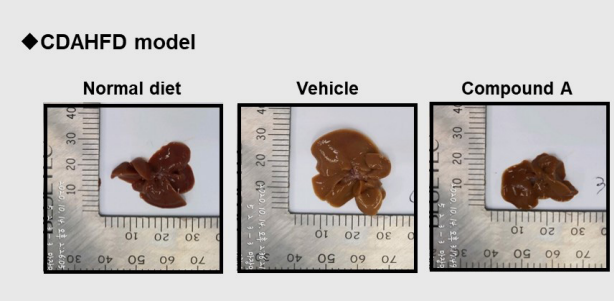
Research institute, HK inno.N Corporation, Seoul, Korea

Aims: Human genetic studies identified an association of single nucleotide polymorphisms in the hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) gene with non-alcoholic fatty liver disease (NAFLD) and HCC development. Recently, the study of human liver lipidome and transcriptome revealed that a loss-of-function variant in HSD17B13 increase hepatic phospholipids, especially phosphatidylcholines and phosphatidylethanolamines, and decrease fibrosis. Thus, we tried to approach to make a HSD17B13 protein (17-beta-hydroxysteroid dehydrogenase 13, 17β-HSD13) inhibitor, as a first-in-class small molecule, and identified a potent 17β-HSD13 inhibitor, Compound A.

Methods: To determine the *in vitro* enzyme potency, Compound A was assessed using NAD/NADH-Glo™ assay. *In vitro* cell ef-

ficacy of Compound A were determined by measuring mRNA expression of alpha-smooth muscle actin (alpha-SMA) after treatment with tumor growth factor-beta (TGF-beta) in both normal and HSD17B13-overexpressed LX-2 hepatic stellate cells. C57BL/6 were given either a normal diet or choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for 14 weeks. After 7 weeks of being fed CDAHFD, mice were administered orally with Compound A for 7 weeks. Mice plasma were analyzed by Biochemistry Analyzer and NAFLD activity score (NAS) and liver fibrosis stage were graded by pathologist

Results: Compound A inhibits the 17β-HSD13 and significantly decreased mRNA level of alpha-SMA in normal and HSD17B13-overexpressed LX-2 cells. In CDAHFD model, Compound A improved lipid profiling, decreased alanine aminotransferase, lactate dehydrogenase, and liver to body weight ratio. Especially, administration of Compound A dramatically recovered liver morphology and significantly decreased NAS in CDAHFD-fed mice.



Conclusions: Compound A, a first-in-class oral small molecule targeting 17β-HSD13, decreased the NAS and recovered liver function in CDAHFD model. It is suggested that Compound A could be a potent therapeutic agent for the treatment of non-alcoholic steatohepatitis.

Keywords: 17-Beta-Hydroxysteroid Dehydrogenase 13, 17β-HSD13, NAFLD, CDAHFD

FP-003

Intestinal Catecholamine/Hepatic Growth Differentiation Factor 15 Axis as a Homeostatic Keeper in Alcoholic Liver Disease

Hee-Hoon Kim[1], Young-Ri Shim[1], Won Kim[2], Won-Il Jeong[1]*

[1]Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Republic of Korea; [2]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul 07061, Republic of Korea

Aims: Metabolic stress caused tumor necrosis factor-alpha (TNF-α)-dependent hepatic sympathetic neuropathy, which further caused a metabolic and immunologic disturbance. However, the compensatory mechanisms for hepatic sympathetic homeostasis have not been investigated. Here, we demonstrate that chronic alcohol consumption increases intestinal catecholamine influx to the liver, which induces the expression of a novel neurometabolic regulator, Growth differentiation factor 15 (GDF15), to restore the hepatic metabolic and immunologic homeostasis.

Methods: C57BL/6J wild type, hepatocyte-specific GDF15 knockout ($GDF15^{\Delta HEP}$) and β-adrenergic receptor (ADRB) 1/2 double knockout (DKO) mice were fed with isocaloric (Pair) or 4.5 % of ethanol containing diet (EtOH) for 8 weeks. Different doses of ethanol, β-agonist, and lipopolysaccharide (LPS) were used *in vitro* cell culture and *in situ* closed liver perfusion. RNA-sequencing, qRT-PCR, western blot, and immunostaining were performed.

Results: Chronic alcohol consumption induced TNF-α production of Kupffer cells (KC), which indicated the loss of sympathetic nerve. As a compensatory mechanism, the catecholamine levels of the cecum and portal blood of EtOH-fed mice were increased compared to those of Pair-fed mice. In RNA-sequencing analysis of liver tissues of Pair- and EtOH-fed mice, *Adrb2* expression was significantly elevated in EtOH-fed mice among catecholamine receptors. Interestingly, ADRB2 activation of EtOH-treated hepatocytes through β-agonist enhanced GDF15 production *in vitro* and *in situ* closed liver perfusion, which facilitated ADRB2-dependent suppression of LPS-primed inflammatory KCs to ameliorate alcoholic liver injury. Consistently, *in vivo,* $GDF15^{\Delta HEP}$ or ADRB1/2 DKO mice showed increased liver damage and fat accumulation compared to those of control mice after chronic ethanol consumption. Finally, plasma catecholamine and GDF15 levels were increased in alcoholic patients compared to the healthy donor.

Conclusions: Our findings suggest that the gut-liver axis through catecholamine and GDF15 acts as metabolic and immunologic homeostatic keepers in chronic alcohol consumption by suppressing inflammation and fat accumulation, which could be potential therapeutic targets.

Keywords: Alcoholic Inflammation, Gut-Liver Axis, Neuro-metabolism, Sympathetic signaling

FP-004

Association between Serum TNF-α and Sarcopenia in Liver Cirrhosis

Ji Won Han[1,#], Da In Kim[2,#], Hee Chul Nam[1], Do Seon Song[2,*]

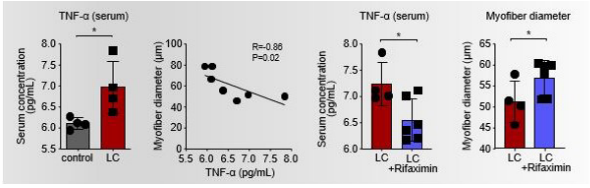
[1]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Sarcopenia occurs frequently and is an independent prognostic factor in patients with liver cirrhosis (LC). However, the association between LC-related systemic inflammation and sarcopenia needs to be elucidated.

Methods: Sprague-Dawley rats were treated with thioacetamide (TAA) or saline control. Rifaximin was administered to TAA-treated rats to determine its effects on sarcopenia and sys-

temic inflammation. ELISA was performed to measure inflammatory mediators in the rat serum. RT-PCR was performed to measure the molecular expression in each tissue. Serum TNF-α level, liver stiffness (LS), and L3 skeletal muscle index (L3SMI) were measured in 60 patients with chronic liver disease (CLD).

Results: LC and sarcopenia were successfully induced in TAA-treated rats. Serum TNF-α level was significantly higher in the LC group than in the control and correlated with myostatin expression and weight and myofiber diameter of muscle. Furthermore, the expression of intestinal tight junctional molecules such as occludin and ZO-1 was reduced in the LC group and associated with serum TNF-α level and degree of sarcopenia. In patients with LS≧7 kPa or sarcopenia, serum TNF-α level was significantly increased. Of note, the value of L3SMI was inversely correlated with serum TNF-α level in patients with LS≧7 kPa. TNF-α was reduced by rifaximin, which might be linked to the reduced expression of muscular MuRF1 and myostatin and improvement of myofiber diameter within muscle tissues.



Conclusions: These results imply that TNF-α is associated with LC-related sarcopenia. Rifaximin might be effective in reducing TNF-α level and improving sarcopenia in LC, but these results need to be validated in future studies.

Keywords: Sarcopenia, Liver cirrhosis, TNF-α, Rifaximin

FP-005

Diagnostic Performance of mRNA Panel as Potential Marker for Recurrence of Hepatocellular Carcinoma

Ju A Son[1,2], Hye Ri Ahn[12], Geum Ok Baek[1], Moon Gyong Yoon[1], Hyo Jung Cho[1], Soon Sun Kim[1], Jung Woo Eun[1,*], Jae Yeon Cheong[1,*]

[1]Department of Gastroenterology, Ajou University School of Medicine, Suwon, South Korea; [2]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, South Korea

Aims: Hepatocellular carcinoma has high rate of recurrence of up to 60% to 70% in patients who underwent liver resection. Therefore, it is urgently needed to identify reliable biomarker for early diagnosis of HCC recurrence. In this study, we aimed to investigate diagnostic gene signatures for recurrence of HCC.

Methods: 85 HCC tissue samples from recurrence and non-recurrence patients who underwent hepatectomy were analyzed using two different platforms, microarray and RNA-sequencing. Five candidate genes were finally selected by integrative analysis of gene expression profiles. In validation cohort (N=57), expressions of selected five gene candidates were measured using quantitative real-time PCR. Also, diagnostic performances of these genes for recurrence status of HCC were evaluated. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic values of gene candidates. Moreover, univariate and multivariate Cox regression analyses were used to identify independent prognostic factors of recurrence.

Results: Six genes among 19 core recurrent gene signatures showed good diagnostic performances for HCC recurrence (AUC>=0.8). Finally, five candidate markers for HCC recurrences, *CETN2*, *HMGA1*, *MPZL1*, *RACGAP1*, and *SNRPB* were selected, and these markers were markedly upregulated in patients with recurrent HCC in validation cohort. ROC analysis showed the combination of *HMGA1* and *MPZL1* is a potent diagnostic biomarker for recurrence HCC (AUC=0.807), with a greater accuracy than combination of other markers and serum AFP. Also, the patients in the high expression of *CETN2*, *HMGA1*, and *RACGAP1* showed significantly poor OS and DFS. According to Cox regression analysis, serum AFP and *RACGAP1* had significant impact on overall survival. Meanwhile, platelet, microvascular invasion, and *HMGA1* had significant impact on disease-free survival.

Conclusions: Consequently, combination of *HMGA1* and *MPZL1* is a promising diagnostic marker for recurrence HCC. Moreover, *HMGA1* and *RACGAP1* might be a potential biomarker in diagnosis and assessment of prognosis of recurrence of HCC.

Keywords: HCC, Recurrence, Gene signiture, Biomarker

FP-006

Prominent Portal T Cell Infiltration, Rather than Ductulitis, Is an Indicator of Corticosteroid Response in Chronic Hepatic GVHD after Allogeneic Stem Cell Transplantation

Pil Soo Sung[1,2*], Soon Kyu Lee[1,2], Ji Won Han[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Graft-versus-host-disease (GVHD) is a major complication after allogeneic hematopoietic SCT (alloHSCT). Among major organ-specific chronic GvHDs, the chronic hepatic GvHD has not been studied in detail. In this study, we investigated the clinical and histological characteristics of biopsy-confirmed, chronic hepatic GVHD.

Methods: Twenty-nine patients with biopsy-confirmed, chronic hepatic GVHD patients were enrolled. Immunohistochemical staining for CD3, CD68, CD38, CD20, and CK19 was performed to identified immune cell types infiltrated in the inflamed livers. Responses to corticosteroid, ruxolitinib, or other immunosuppressant treatments were evaluated. For some patients, flow cytometry was performed with biopsy specimens

to identify the activation status of CD8 T cells and regulatory T cells. Biochemical response to treatment was defined as bilirubin normalization + ALP<1.5 × ULN + AST < 1.5 × ULN (Paris-II criteria in PBC was adopted).

Results: Pathologically, two separate patterns of chronic hepatic GVHD were identified: hepatitic variant GVHD (n = 13) and cholestatic variant GVHD (n = 16). In hepatitic variant GVHD, periportal areas demonstrated mixed inflammation including T cells (CD3+), macrophages (CD68+), and plasma cells (CD38+) with prominent necroinflammatory foci. T cells is a main population infiltrated in portal area. In cholestatic variant GVHD, dutulitis and ductopenia was identified. Median ALT was significantly higher in patients with hepatitic variant, although median ALP and GGT was higher in patients with cholestatic variants. In patients with hepatitic variant, biochemical responses to corticosteroid were noted in 10 patients (10/13, 77%), although biochemical responses to corticosteroid were noted in 9 patients with (9/16, 56%) in cholestatic variant. Flow cytometry detected activated intrahepatic CD8 T cells, M1 macrophages, and non-suppressive regulatory T cells in patients with severe inflammation. Three patients in cholestatic variant died from hepatic failure, and one patient in cholestatic variant underwent liver transplantation. The explant showed diffuse necrosis of hepatocytes with extensive CK19+ bile ductules proliferation and fibrosis.

Conclusions: Histological evaluation of chronic hepatic GVHD is useful in predicting the responses to corticosteroids. Hepatitic variants with portal T cell infiltration respond well to steroid treatment and show better prognosis.

Keywords: Hepatic GVHD, T cell, Corticosteroid, Liver failure

Friday, May 14, 2021, 11:10-12:30

2. Viral Hepatitis

FP-007

A Clinico-Epidemiological Study of Acute Hepatitis in Korea: A Prospective Multicenter Study

Chan Young Jeong[1], Gwang Hyeon Choi[1], Byung Seok Lee[2], Young Seok Kim[3], Youn Jae Lee[4], In Hee Kim[5], Sung Bum Cho[6], Jae Hyun Yoon[7], Kyung-Ah Kim[8], Choi Dae Hee[9], Woo Jin Chung[10], Hyun-Jin Cho[11], Seong Kyun Na[12], Sook-Hyang Jeong[1]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea; [2]Departments of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea; [3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [4]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea; [5]Department of Internal Medicine, Jeonbuk National University Hospital, Jeonju, Republic of Korea; [6]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [7]Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea; [8]Departments of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang Republic of Korea; [9]Departments of Internal Medicine, Kangwon National University Hospital, Chunchon, Republic of Korea; [10]Departments of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea; [11]Departments of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea; [12]Departments of Internal Medicine, Jeju National University Hospital, Jeju, Republic of Korea

Aims: This study aimed to analyze etiology and clinical characteristics of acute hepatitis in South Korea in 2020.

Methods: We prospectively enrolled 249 with acute hepatitis diagnosed by AST > 200 IU/L without history of underlying chronic hepatitis in 12 university hospitals from March 2020 to November 2020. Clinical data as well as a detailed questionnaire survey results on the risk factors for acute hepatitis were collected and entered into the common case report forms.

Results: A total 216 patients with acute hepatitis showed a median age of 45 year with male proportion of 44%. The causes of acute hepatitis were viral hepatitis (n=79, 36.6%), toxic hepatitis (n=94, 43.1%), crytogenic (n=25, 11.5%), and autoimmune hepatitis (n=14, 6.4%). Among the patients with viral hepatitis, hepatitis A virus (HAV) was attributable to 76% (n=60), HEV 11% (n=7), HCV 4% (n=3), and HBV 3% (n=2), with other systemic viral infections: Epstein-Barr virus (EBV) 8% (n=5), and Cytomegalovirus 3% (n=2). Among the patients with toxic hepatitis, prescribed drugs were attributable to 47% and other health supplement to 53% including oriental medicine and diet pills. The most common prescribed drug was acetaminophen (9%) followed by antibiotics (6%) and antihelminthics (5%). The cryptogenic hepatitis showed a mixed features of viral and toxic hepatitis with lower level of ALT and total bilirubin levels. Only one toxic hepatitis patient underwent liver transplantation, while remaining others recovered.

Conclusions: In 2020, the major etiologies of acute hepatitis in Korea were toxic hepatitis and viral hepatitis. Among the hepatitis viruses, HEV is emerging to be the 2nd most common etiology, and more than half of toxic hepatitis were attributable to health supplements, which should be aware to reduce disease burden of acute liver disease.

Figure 1. Patient flowgram

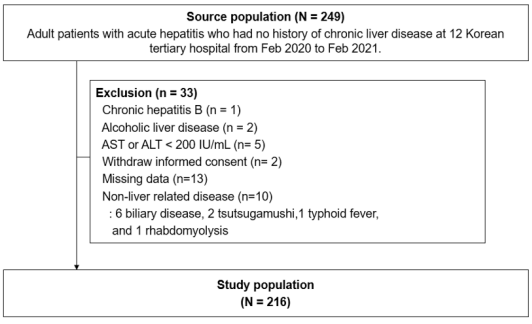
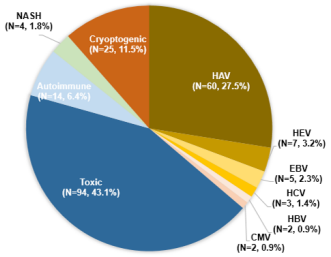


Figure 2. Proportion of acute hepatitis according to etiology



* CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus

Keywords: Acute hepatitis, Viral hepatitis, Toxic hepatitis, Cryptogenic hepatitis

FP-008

The Outcomes of Entecavir, Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamide in Treatment-Naïve Patients with Chronic Hepatitis B Infection

Hye Yeon Chon[1], Sang Hoon Ahn[2], Yoon Jun Kim[3], Jung-Hwan Yoon[3], Jeong-Hoon Lee[3], Dong Hyun Sinn[4], Seung Up Kim[2]

[1]Department of Internal Medicine, Konyang University College of Medicine, Daejeon, Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [4]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Antiviral therapy for chronic hepatitis B (CHB) reduced the risk of hepatocellular carcinoma (HCC) development. The outcomes of entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) were compared in patients with CHB.

Methods: Between 2017 and 2019, treatment-naïve patients with CHB treated with ETV, TDF, and TAF were recruited from three Korean tertiary institutes. The cumulative incidences of HCC and orthotopic liver transplantation (OLT) or mortality were calculated and compared using Kaplan-Meier analysis before and after trimatch.

Results: A total of 2,082 patients (1,064 treated with ETV, 629 with TDF, and 389 with TAF) were recruited. During follow-up period (median 20.9 months), 43 patients developed HCC, whereas 66 developed OLT or mortality. Before trimatch, the cumulative incidence of HCC was statistically similar among patients treated with three antiviral agents (P=0.340). However, the cumulative probability of OLT or mortality development in patients treated with ETV or TDF was significantly higher than that of patients treated with TAF before trimatch (all P<0.05). On multivariate analysis, male gender (hazard ratio [HR]=2.990) and older age (HR=1.044) were independently associated with an increased risk of HCC development (all P<0.05), whereas higher platelet count (HR=0.993) was independently associated with a decreased risk (P<0.05). The type of antiviral agents did not significantly influence the risk of HCC and OLT or mortality development (all P>0.05). After trimatch, no significant difference in the cumulative probability for HCC and OLT or mortality according to antiviral agents was found (all P>0.05).

Conclusions: The outcomes of ETV, TDF, and TAF on the risk of HCC and OLT or mortality were statistically similar in treatment-naïve patients with CHB.

Keywords: Antiviral therapy, Hepatocellular carcinoma, Chronic hepatitis B virus

FP-009

Association of Concurrent Fatty Liver with Hepatocellular Carcinoma and Mortality in Patients with Chronic Viral Hepatitis

Mi Na Kim[1,2*], Kyungdo Han[3*], Juhwan Yoo[4], Yeonjung Ha[1], Young Eun Chon[1], Ju Ho Lee[1], Seong Gyu Hwang[1]

[1]Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [2]Clinical and Translational Hepatology Laboratory, Seongnam, Republic of Korea; [3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea; [4]Department of Biomedicine & Health Science, the Catholic University of Korea, Seoul, Korea

Aims: Population-based data are lacking whether concurrent fatty liver influences HCC or mortality risk in chronic hepatitis B or C virus infection. We aimed to investigate the impact of concurrent fatty liver on HCC incidence and all-cause mortality in patients with chronic hepatitis B or hepatitis C using a nationwide cohort.

Methods: We included 57,385 patients with chronic hepatitis B or hepatitis C who underwent health examinations provided by the National Health Insurance Service of South Korea in 2009. Patients were divided into three groups according to fatty liver index (FLI) as follows: 1) no fatty liver, FLI <30, 2) grade 1 (G1) fatty liver, 30≤ FLI <60, 3) grade 2 (G2) fatty liver, FLI >60. Patients were followed up to death or December 31, 2018. Using Cox proportional-hazards regression modeling, we estimated the risks of HCC and all-cause mortality according to the FLI groups.

Results: During a median of 8.4-years of follow-up, we documented 3,496 HCC cases and 4,146 deaths. Risks of HCC and mortality increased with worsening fatty liver (all P for trend <0.0001). Compared to the patients with no fatty liver (n = 35,018), the multivariate-adjusted hazard ratios (aHRs) for HCC were significantly increased in the patients with G1 fatty liver (n = 14544) (aHR = 1.50, 95% confidence interval [CI] = 1.38–1.64) and G2 fatty liver (n = 7823) (aHR = 1.88, 95% CI = 1.67–2.12). The risk of mortality significantly increased in the patients with G1 fatty liver (aHR = 1.53, 95% CI = 1.41–1.66) and G2 fatty liver (aHR = 2.16, 95% CI = 1.94–2.42), compared to the patients with no fatty liver.

Conclusions: Concurrent fatty liver was associated with signifi-

cantly increased risks of HCC incidence and mortality in chronic viral hepatitis. Given the increasing prevalence of fatty liver, our study results suggest the importance of assessment and management of fatty liver for reducing the risks of HCC and mortality in chronic viral hepatitis.

Keywords: Chronic viral hepatitis, Fatty liver, Hepatocellular carcinoma, Mortality

FP-010

Association between Daily Aspirin Therapy and Hepatocellular Carcinoma According to Metabolic Risk Factor Burden in Patients with Chronic Hepatitis B

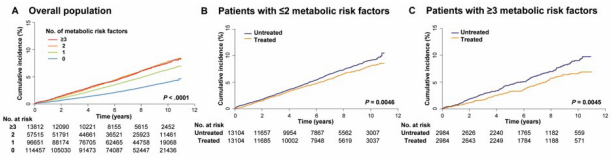
Cheol-Hyung Lee[1*], Yun Bin Lee[2*], Hyemi Moon[3*], Eun Ju Cho[2], Jeong-Hoon Lee[2], Su Jong Yu[2], Yoon Jun Kim[2], Juneyoung Lee[3,4], Jung-Hwan Yoon[2]

[1]The Armed Forces Medical Command, Seongnam, Republic of Korea; [2]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Department of Biostatistics, College of Medicine, Korea University, Seoul, Republic of Korea; [4]BK21 FOUR R&E Center for Learning Health Systems, Korea University, Seoul, Republic of Korea

Aims: Several studies have provided evidence supporting chemopreventive effect of aspirin against hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients. Recently, we demonstrated that daily aspirin use was associated with reduced HCC risk in non-cirrhotics with CHB, but not in cirrhotics. To identify better candidates for daily aspirin therapy, we investigated the association of aspirin use with HCC risk according to metabolic risk factor burden, which is an independent risk factor of HCC, among non-cirrhotics with CHB.

Methods: We collected baseline data on metabolic risk factors, including obesity, high blood pressure, hypercholesterolemia, and diabetes, in 282,611 adult non-cirrhotics with CHB using the Korean National Health Insurance Service database. The study patients were stratified according to the number of metabolic risk factors, after which propensity score-matched cohorts were generated to balance baseline characteristics between aspirin users and nonusers. The risk of HCC was analyzed, accounting for competing risks.

Results: In overall population, 11,024 patients developed HCC during a median follow-up period of 7.4 years. The cumulative incidences of HCC rose with increasing metabolic risk factor burden (*P*<.0001; panel A). Among patients with ≤2 metabolic risk factors (13,104 pairs), the cumulative incidences of HCC in aspirin users were significantly lower than in nonusers *(P*=.005; panel B); however, aspirin use was not associated with lower HCC risk after multivariable adjustment (adjusted hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.84–1.03; *P*=.18). Among patients with ≥3 metabolic risk factors (2,984 pairs), aspirin users showed significantly lower cumulative HCC incidences compared to nonusers (*P*=.005; panel C) and aspirin use was associated with 28% reduced risk of HCC (adjusted HR, 0.72; 95% CI, 0.57–0.91; *P*=.006).



Conclusions: In this Korean nationwide cohort study, daily aspirin use was associated with reduced risk of HCC in non-cirrhotic CHB patients with higher burden of metabolic risk factors.

Keywords: Liver cancer, Metabolic syndrome, HBV, Survival, Bleeding

FP-011

Cost-Effectiveness of Universal One-Time Screening for Hepatitis C in the Korean Population: from a Societal Perspective

Hye-Lin Kim[1], Kyung-Ah Kim[2], Hwa Young Choi[3], Gwang Hyeon Choi[4], Eun Sun Jang[4], Moran Ki[3], Sook-Hyang Jeong[4]

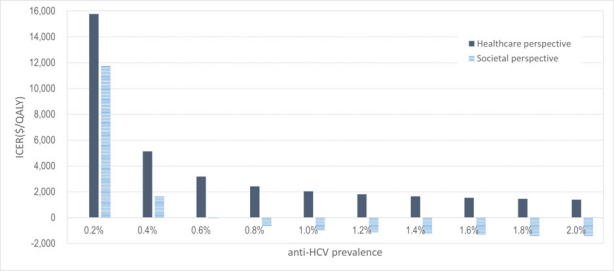
[1]College of Pharmacy, Sahmyook University, Seoul, Republic of Korea; [2]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; [3]Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Republic of Korea; [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

Aims: Since the introduction of direct-acting antivirals (DAA) achieving over 95% of sustained virological response (SVR) rates, active detection of hepatitis C virus (HCV) infection is important to eradicate HCV. This study aimed to evaluate the cost-effectiveness of universal screening versus no screening in the Korean population from a societal perspective as well as the healthcare system perspective.

Methods: A published hybrid decision-tree plus Markov model was applied to compare the expected costs and quality-adjusted life-years (QALY) between universal 1-time HCV screening and no screening strategy. Population aged 40-65 years was simulated with the model over a lifetime, from both of healthcare system perspective and societal perspective. Input parameters were obtained from analyses of National Health Insurance claims data, Korean HCV cohort data, or from a literature review. We estimated incremental cost-effectiveness ratio (ICER) and HCV-related health events.

Results: From a healthcare system perspective, the HCV screening strategy had an ICER of $3,538/QALY in the population with 0.6% of an anti-HCV prevalence. Being far less than the willingness-to-pay threshold of $25,000/QALY, the universal screening program was cost-effective compared to no screening strategy. From a societal perspective including productivity loss cost by premature death due to liver disease, the screening became more cost-effective as the $1,303/QALY of ICER. The most influential parameters on cost-effectiveness were the screening

cost, anti-HCV prevalence, and acceptability of DAA treatment. However, all ICERs under various conditions were estimated less than the threshold in the sensitivity analysis. If anti-HCV prevalence is over 0.18~0.19%, the screening strategy could be cost-effective from both analytic perspectives. Moreover, this simulation showed that screening could prevent 19 HCV-related deaths and 15 hepatocellular carcinomas per 100,000 screened persons.



Conclusions: Universal 1-time HCV screening in the Korean population aged 40-65 years would be highly cost-effective and reduce HCV-related clinical events compared with no screening.
Keywords: Hepatitis C, Screening, Cost-effectiveness, Societal perspective, Healthcare system perspective

FP-012

Real-World Effectiveness and Safety of SOF/LDV for Patients with Chronic Hepatitis C in Taiwan

Ching-Chu Lo[1], Pin-Nan Cheng[4], Chi-Yi Chen[6], Chung-Feng Huang[2,3], Hsing-Tao Kuo[7], Kuo-Chih Tseng[5], Yi-Hsiang Huang[8], Chi-Ming Tai[9,10], Cheng-Yuan Peng[11], Ming-Jong Bair[12,13], Chien-Hung Chen[14], Ming-Lun Yeh[3,15], Chih-Lang Lin[16], Chun-Yen Lin[17,18], Pei-Lun Lee[19], Lee-Won Chong[20,21], Chao-Hung Hung[14,22], Te Sheng Chang[22], Jee-Fu Huang[3,23], Chi-Chieh Yang[24], Jui-Ting Hu[25], Chih-Wen Lin[26], Chun-Ting Chen[27,28], Chia-Chi Wang[29],-Wei-Wen Su[30], Tsai-Yuan Hsieh[28], Chih-Lin Lin[31], Wei-Lun Tsai[32], Tzong-Hsi Lee[33], Guei-Ying Chen[34], Szu-Jen Wang[35], Chun-Chao Chang[36,37], Lein-Ray Mo[38], Sheng-Shun Yang[39], Wen-Chih Wu[40], Huang Chia-Sheng[41], Chou-Kwok Hsiung[42], Chien-Neng Kao[43], Pei-Chien Tsai[2], Chen-Hua Liu[44], Mei-Hsuan Lee[45], Chun-Jen Liu[44], Chia-Yen Dai[2,3], Wan-Long Chuang[2,3], Han-Chieh Lin[8], Jia-Horng Kao[44], Ming-Lung Yu[2,3], on behalf of TACR investigators

[1]Division of gastroenterology, department of Internal medicine, St. Martin De Porres Hospital, Chiayi, Taiwan; [2]Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]School of Medicine and Hepatitis Research Center, College of Medicine, and Center for Cancer Research and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]Division of Gastroenterology and Hepatology,Department of Internal Medicine, National Cheng Kung University Hospital,College of Medicine, National Cheng Kung University, Tainan, Taiwan; [5]Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi; School of Medicine, Tzuchi University, Hualien, Taiwan; [6]Division of Gastroenterology and Hepatology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Taiwan; [7]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi Mei Medical Center, Yongkang District, Tainan 710, Taiwan; [8]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital; Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [9]Department of Internal Medicine, E-Da Hospital, Kaohsiung, Taiwan; [10]School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan; [11]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital; School of Medicine, China Medical University, Taichung, Taiwan; [12]Division of Gastroenterology, Department of Internal Medicine, Taitung Mackay Memorial Hospital, Taiwan; [13]Mackay Medical College, New Taipei City, Taiwan; [14]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan; [15]Department of Internal Medicine, Kaohsiung Municipal Siaogang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [16]Department of Gastroenterology and Hepatology, Keelung Chang Gung Memorial Hospital, Taiwan; [17]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, Taiwan; [18]Graduate Institute of Biomedical Science, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [19]Chi Mei Medical Center, Liouying Division of Gastroenterology and Hepatology,Department of Internal medicine; [20]Division of Hepatology and Gastroenterology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; [21]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan; [22]Division of Hepatogastroenterology, Department of Internal Medicine, ChiaYi Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan; [23]Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [24]Department of gastroenterology, Division of internal medicine, Show Chwan Memorial Hospital, Taiwan; [25]Liver center, Cathay General Hospital, Taiwan; [26]Division of Gastroenterology and Hepatology, E-Da Dachang Hospital, and School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan; [27]Division of Gastroenterology, Department of Internal Medicine Tri-Service General Hospital Penghu Branch, National Defense Medical Center, Taipei, Taiwan; [28]Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [29]Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and School of Medicine, Tzu Chi University, Taiwan; [30]Department of Gastroenterology and Hepatology, Changhua Christian Hospital, Taiwan; [31]Department of Gastroenterology, Renai branch, Taipei City Hospital, Taipei, Taiwan; [32]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Taiwan; [33]Division of Gastroenterology and Hepatology, Far Eastern Memorial Hospital, Taiwan; [34]Penghu Hospital, Ministry of Health and Welfare, Taiwan; [35]Division of Gastroenterology, Department of Internal Medicine, Yuan's General Hospital, Taiwan; [36]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital, Taiwan; [37]Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taiwan; [38]Division of Gastroenterology, Tainan Municipal Hospital, Taiwan; [39]Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [40]Wu Wen-Chih Clinic, Taiwan; [41]Yang Ming Hospital, Taiwan; [42]Chou Kwok

Hsiung Clinic, Taiwan; [43]National Taiwan University Hospital Hsin-Chu Branch, Taiwan; [44]Hepatitis Research Center and Department of Internal Medicine, National Taiwan University Hospital; [45]Institute of Clinical Medicine, National Yang-Ming University

Aims: TASL HCV Registry (TACR) is a nationwide registry program organized and supervised by Taiwan Association for the Study of the Liver (TASL), which aims to setup the database and biobank of patients with chronic hepatitis C (CHC) in Taiwan. The present study aimed to evaluate the treatment outcome of sofosbuvir (SOF)/ledipasvir (LDV) in Taiwanese CHC patients in TACR.

Methods: All patients enrolled in the 48 study sites of TACR registry between 2017 to 2020 were included in this analysis. The primary objective was to evaluate the antiviral efficacy of SOF/LDV as measured by the proportion of subjects with sustained viral response 12 weeks after end-of treatment (SVR12).

Results: A total of 5644 SOF/LDV+ ribavirin treated CHC patients with available SVR12 from 48 sites were included in this analysis. The mean age was 61.4 years, and female accounted for 54.4% of the population. The dominant viral genotypes were GT1 (50.8%) and GT2 (39.2%). Overall, 18.2% patients had baseline HCV RNA ≥6,000,000 IU/ml. 1529 (27.1%) patients had liver cirrhosis, including 201 (3.6%) with liver decompensation, 484 (8.6%) had preexisting hepatocellular carcinoma (HCC) before SOF/LDV treatment and 499 (8.8%) had hepatitis B virus dual infections. The overall SVR12 was 98.6%, 98.4%, 100%, 100% and 98.7% among those with GT1, GT2, GT4, GT5 and GT6, respectively. Factors associated with treatment failure with GT2 were DAA adherence < 80% (odds ratio [OR]/95% confidence intervals [CI]: 132.1/11.7-1492.5, *P*<0.0001), end of treatment HCV RNA viral load > 15 IU/ml (OR/CI: 16 (5.69-45.0, *P*<0.0001), baseline HCV RNA viral load ≥ 6,000,000 IU/ml (OR/CI: 2.07/1.02-4.19, *P*=0.044) and active HCC (OR/CI: 3.26/1.12-9.45, *P*<0.03). The incidence of any adverse events was 14.2%; fatigue was the most common adverse event occurring in ≥ 5% of patients.

Conclusions: SOF/LDV is effective and safe in treating CHC patients in real-world setting of Taiwan. The result could be explicitly generalized to patients with GT1, GT2, GT4, GT5 and GT6 regardless of the cirrhosis.

Keywords: HCV, DAA, Real world, Sofosbuvir/Ledipasvir

FP-013

Effect of Direct-Acting Antivirals for Hepatitis C Virus-Related Hepatocellular Carcinoma Recurrence and Death after Curative Treatment

Soon Sun Kim[1], Young-Hwan Ahn[1], Heirim Lee[2,3], Hyo Jung Cho[1], Jae Youn Cheong[1], Bumhee Park[2,3]

[1]Department of Gastroenterology, Ajou University School of Medicine, Suwon; [2]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon; [3]Office of Biostatistics, Medical Research Collaborating Center, Ajou Research Institute for innovative Medicine, Ajou University Medical Center, Suwon

Aims: Since the report of an unexpected high rate of hepatocellular carcinoma (HCC) recurrence after direct-acting antiviral (DAA) therapy, whether DAA should be prescribed to patients with hepatitis C virus (HCV)-infected HCC has been debated. Our study aimed to elucidate the benefit or harm of DAA therapy on HCC recurrence after curative therapy in Korean patients.

Methods: We retrospectively enrolled 1021 patients with HCV-infected HCC who underwent radiofrequency ablation (RFA), liver resection, or both as the first treatment modality from January 2007 to December 2016 and without history of HCV therapy before HCC treatment from a nationwide database, the Korea Health Insurance Review and Assessment. The impact of HCV treatment on HCC recurrence and all-cause mortality was investigated using the Cox proportional hazard model and landmark analysis (180 d or 365 d after HCC treatment).

Results: Among 1021 patients, 912 (89.3%) received RFA, 105 (10.5%) received liver resection, and two (0.2%) underwent combination therapy with RFA and liver resection for the first HCC treatment. After the first HCC treatment, 77 (7.5%) were treated with DAA, 14 (1.4%) were treated with interferon-based therapy and 930 (91.1%) did not receive HCV therapy. DAA therapy was an independent protective parameter for HCC recurrence (hazard ratio [HR], 0.037; 95% confidence interval [CI], 0.005–0.261; *P*<0.001) after adjustment for sex, age, diabetes, liver cirrhosis, and HCC treatment modality. After applying the landmark analysis, DAA therapy was still an independent prognostic factor for lower HCC recurrence rate (HR, 0.04; 95% CI, 0.006–0.289; *P*=0.001 for landmarks at 180 d after HCC treatment and HR, 0.05; 95% CI, 0.007–0.354; *P*=0.003 for landmarks at 365 d after HCC treatment). Furthermore, DAA therapy was associated with lower all-cause mortality in both multivariate Cox proportional hazards (HR, 0.044; 95% CI, 0.006–0.313; *P*=0.002) and landmark (HR, 0.049; 95% CI, 0.007–0.349; *P*=0.003 for landmarks at 180 d and HR, 0.063; 95% CI, 0.009–0.451; *P*=0.006 for landmarks at 365 d) analysis.

Conclusions: DAA therapy after curative HCC treatment can decrease HCC recurrence and all-cause mortality compared with interferon-based therapy or no antiviral therapy. Therefore, clinicians should positively consider employing DAA therapy after curative HCC treatment in patients with HCV-related HCC.

Keywords: Carcinoma, Hepatocellular, Antiviral agents, Risk factors, Hepatitis C, Chronic, Recurrence

FP-014

Long-Term Oncologic Outcomes of Liver Resection for Hepatocellular Carcinoma in Adolescents and Young Adults: A Multicenter Study from A Hepatitis B Virus-Endemic Area

Yong-Kang DIAO[1], Jun-Wei LIU[1], Wan Yee LAU[3], Xin-Ping FAN[4], Ting-Hao CHEN[5], Ya-Hao ZHOU[6], Wei-Min GU[7], Hong WANG[8], Jie

LI[9], Ying-Jian LIANG[10], Tian YANG[1,2]

[1]Hepatobiliary Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), China; [2]Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), China; [3]Faculty of Medicine, The Chinese University of Hong Kong, China; [4]General Surgery, Pingxiang Mining Group General Hospital, China; [5]General Surgery, Ziyang First People's Hospital, China; [6]Hepatobiliary Surgery, Pu'er People's Hospital, China; [7]General Surgery, The Fourth Hospital of Harbin, China; [8]General Surgery, Liuyang People's Hospital, China; [9]Hepatobiliary Surgery, Fuyang People's Hospital, China; [10]Hepatobiliary Surgery, The First Affiliated Hospital of Harbin Medical University, China

Aims: Hepatocellular carcinoma (HCC) is common among adolescents and young adults (AYAs) with chronic hepatitis B virus (HBV) infection in areas with endemic HBV. We sought to characterize clinical features and long-term oncologic outcomes among AYAs versus older adults (OAs) who underwent liver resection for HCC.

Methods: Patients undergoing curative-intent liver resection for HCC were identified using a Chinese multicenter database; patients were categorized as AYA (aged 13-39 years) versus OA (aged ≥ 40 years). Patient clinical features, perioperative outcomes, overall survival (OS) and time-to-recurrence (TTR) were evaluated and compared. Multivariable Cox-regression analyses were performed to identify the impact of age relative to the risk factors associated with OS and TTR.

Results: Among 1,952 patients with HCC who underwent resection, 354(22.2%) were AYAs. AYAs were less likely to have cirrhosis or portal hypertension yet were likely to have advanced tumor pathological characteristics than OAs. Although major hepatectomy was more often performed in the AYA group, postoperative morbidity and mortality were comparable between the AYA and OA groups. Compared with OAs, the AYAs had a comparable OS (median: 88.8 vs. 93.2 months, *P*=0.305) but a decreased TTR (median: 35.6 vs. 50.7 months, *P*=0.029). After adjustment for other confounding factors on multivariable analyses, young age (<40 years) was independently associated with poorer TTR (hazard ratio: 1.35, 95% confidence interval: 1.08-1.69, *P*=0.009) but not OS (*P*=0.15).

Conclusions: Compared with OAs, AYAs had a higher incidence of recurrence following liver resection among Chinese patients with HCC, suggesting that enhanced surveillance for postoperative recurrence may be required among AYAs.

Keywords: Hepatocellular carcinoma, Hepatectomy, Adolescents and young adults, Overall survival, Time-to-recurrence

FP-015

Efficacy of Sodium Glucose Co-Transporter 2 Inhibitor on a Progression of Nonalcoholic Steatohepatitis in a Murine Steatohepatitis Model

Young Chang[1], Jae Young Jang[1]*, Sukmin Kang[1], Soung Won Jeong[1], Jeong-Ju Yoo[3], Sae Hwan Lee[2], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2], So Young Jin[4]

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea, [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea, [4]Department of Pathology, Soonchunhyang University College of Medicine, Seoul, Korea

Aims: Sodium glucose cotransporter 2 (SGLT2) inhibitors, an antidiabetic drug, have shown positive effects in diabetes and cavdiovascular diseases. It is unclear whether SGLT2 inhibition could exert a beneficial effect on nonalcoholic steatohepatitis (NASH)-associated liver fibrosis and hepatocellular carcinoma.

Methods: We examined the protective effect of SGLT2 inhibitor, empagliflozin, in a murine NASH model. The choline-deficient, amino acid-defined diet (CDAA) containing 58% fat (palm oil) by calories was formulated, and the diets were administered to 8-week-old male C57Bl/6J mice for up to 24 weeks. A total of 21 mice were divided into two groups, the control group and the SGLT2 inhibitor group, and 35mg/kg/day of empagliflozin was administered to the SGLT2 inhibitor group. Five animals in each group were treated for 12 weeks, and the remaining five in the control group and six in the SGLT2 inhibitor group were treated for 24 weeks.

Results: There was no significant difference in mean body weight between the control and treatment group after 12 weeks (24.19 g vs. 23.91 g; *P*=0.65). Laboratory findings, including serum aspartate transaminase, alanine transaminase, creatinine, glucose, and triglyceride, also showed no statistical differences between groups (all *P*>0.1). When hepatic fibrosis was assess by Sirius red staining, the area of collagen deposition was smaller in the SGLT2 inhibitor group (Figure 1). Moreover, 12 weeks of SGLT2 inhibitor treatment downregulated the expression of various fibrosis-related proteins in the liver compared to the control, indicating that SGLT2 inhibitor treatment attenuated hepatic fibrosis (Figure 2). After 24 weeks, the inhibitory effect of SGLT2 inhibitor on hepatic fibrosis was consistently observed as downregulated fibrosis-related proteins. However, multiple hepatic tumors developed in both groups without significant differences in tumor number and size (Figure 3).

Conclusions: High fat-CDAA feeding in C57Bl/6J mice was identified as a suitable model of NASH developing robust fibrosis

and hepatic tumor within 24 weeks. SGLT2 inhibitor showed the potential to attenuate hepatic fibrosis in the progression of NASH, whereas administration of SGLT2 inhibitor alone was insufficient to suppress the development of hepatic tumors.

Figure 1. The area of collagen deposition (Sirius-red) was smaller in (A) the SGLT2 inhibitor group than in (B) the control group.

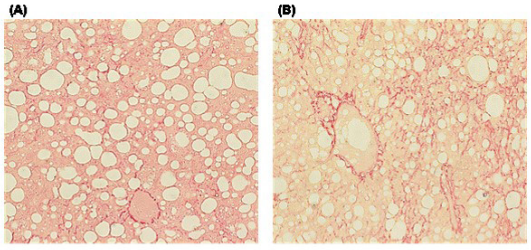


Figure 2. Both after (A) 12 weeks and (B) 24 weeks, SGLT2 inhibitor treatment downregulated the expression of various fibrosis-related proteins in the liver compared to the control.

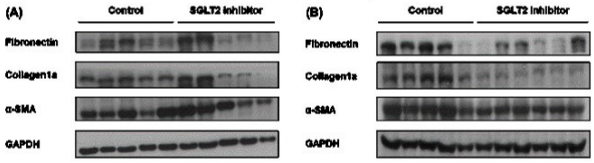
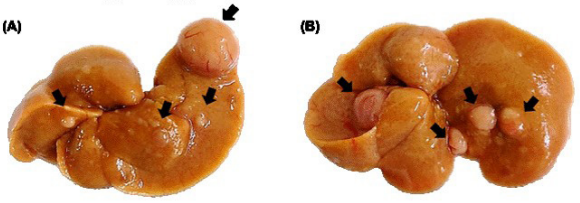


Figure 3. Multiple hepatic tumors developed in both groups without significant differences in tumor number and size. (A) control, (B) SGLT2 inhibitor treated



Keywords: SGLT2 inhibitor, Nonalcoholic steatohepatitis, Hepatic fibrosis, Hepatocellular carcinoma

FP-016

Exogenous 8-Hydroxydeoxyguanosine Prevents Liver Fibrosis through the Inhibition of Rac1-NADPH oxidase Signaling in a Nonalcoholic Steatohepatitis Model

Seung Kak Shin[1*], Hye Jeong Cho[1], Hyosang Hwang[1], Dong Hae Chung[2], Oh Sang Kwon[1], Yun Soo Kim[1], Ju Hyun Kim[1]

[1]Department of Internal Medicine, [2]Department of Pathology, Gachon University College of Medicine, Gil Medical Center, Incheon, Republic of Korea

Aims: Recently, the importance of Rac1-NADPH oxidase (NOX) signaling in liver fibrosis, and the exogenous 8-hydroxydeoxyguanosine (8-OHdG) as an inhibitor of Rac1 activity were suggested. The aim was to evaluate the effects of the 8-OHdG in a non-alcoholic steatohepatitis (NASH) model.

Methods: C57BL/6N mice were fed normal chow diet for 12 weeks (G1, n=5), FPC (rich in fructose, palmitate, and cholesterol) diet for 12 weeks (G2, n=6), and FPC diet + CCl_4 [0.2 μl (0.32 μg)/g of body weight] for 12 weeks (G3, n=7), and FPC diet + CCl4 for 12 weeks treated with 8-OHdG (60 mg/kg/day by gavage, G4, n=7). Pathologic evaluations were made based on the NASH Clinical Research Network score. Hepatic fibrotic contents were quantified by hydroxyproline assay. *In vitro* study, LX-2 cells were exposed to conditioned media (CM) from palmitate-treated hepG2 cells.

Results: The fibrosis stages were higher in G3 than G2 (2.3±0.5 vs. 0.2±0.4, *P*=0.016). Exogenous 8-OHdG treatment (G4) reduced the fibrosis stages compared with G3 (1.6±0.5 vs. 2.3±0.5, *P=0.023). The hydroxyproline levels (μg/g liver tissue) in G1, G2, G3 and G4 were 213.0±34.4, 367.4±86.8, 480.7±128.4, and 361.3±102.3, respectively. The 8-OHdG also reduced the hydroxyproline levels (P*=0.006). Meanwhile, nonalcoholic fatty liver diseases activity scores (NAS) were not different between G3 (8.0±0.0) and G4 (8.0±0.0). The 8-OHdG treatment reduced the mRNA expressions of TGF-β (*P*=0.02), α-SMA (*P*=0.04), TIMP-1 (*P*=0.04) and collagenIα (*P*<0.001) in LX-2 cells exposed to CM from palmitate-treated hepG2 cells. The increases of DCF fluorescence intensities, and the relative band densities of GTP-bound Rac1 and NOX-2 in LX-2 cells exposed to CM from palmitate-treated hepG2 cells were attenuated by 8-OHdG treatment.

Conclusions: These results suggest that 8-OHdG prevents liver fibrosis through the inhibition of Rac1-NADPH oxidase signaling, highlighting 8-OHdG as a potential therapeutic agent for prevention and treatment of NASH with liver fibrosis.

Keywords: Nonalcoholic steatohepatitis, Liver fibrosis, 8-hydroxydeoxyguanosine, Rac1

FP-017

Diagnosis of Fatty Liver Using BIA: Comparison with Abdominal Ultrasound and CAP Score of Transient Elastography

Jin Wook Choi, Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, SoonChunHyaung University Bucheon Hospital

Aims: Abdominal ultrasound (USG) or recently introduced CAP score of transient elastography (TE) can be used for the diagnosis of fatty liver. However, there is a disadvantage that USG and TE can be performed only in specialized medical institutions. The aim of this study was to evaluate whether bioelectrical impedance analysis (BIA), which can be easily used by the general public, can be used as reliable tool in diagnosis of fatty liver.

Methods: A total of 249 patients who underwent all three following test, TE, BIA, and USG were enrolled. The correlation between fat mass measured by BIA, CAP score of TE and fatty liver grade measured by USG was analyzed. In addition, the cut-off value of BIA, which can predict fatty liver grade measured by USG or CAP score, was calculated.

Results: As fatty liver grade measured by USG increase, the absolute body fat mass in BIA increased, significantly (normal: 16.2 ± 6.7, Gr I: 21.3 ± 9.3, Gr II: 28.8 ± 10.1, Gr III: 29.9 ± 10.3 kg, p-value < 0.001). In addition, CAP score of TE and the absolute

body fat mass in BIA showed a positive correlation. The cut-off value of the absolute body fat mass that can predict the grade of fatty liver was as follows; any grade of fatty liver 20.85kg, fatty liver Gr II 22.85kg, fatty liver Gr III 24.05kg (sensitivity of 77.4% and specificity of 75.5%). And the cut-off value of the absolute body fat mass that can predict CAP score was as follows; over 230 dB 20.02kg, over 260 dB 23.65kg, over 290 dB 23.65kg (sensitivity of 68.2% and specificity of 85.5%).

Conclusions: The absolute body fat mass measurement through BIA has a significant correlation with fatty liver grade measured by USG or the CAP score. Therefore, BIA can be used as a reliable tool in diagnosing fatty liver.

Keywords: Abdominal ultrasound, Transient elastography, Bioelectrical impedance analysis, Fatty liver

FP-018

The Role of Genetic and Epigenetic Factors in Disease Development and Progression in Nonalcoholic Fatty Liver Disease

Soo Min Bang[1], Young-Sun Lee[1], Jeong-An Gim[2], Yoonseok Lee[1], Se Ryun Bae[1], Young Kul Jung[1], Ji Hoon Kim[1], Yeon Seok Seo[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Soon Ho Um[1], Kwan Soo Byun[1]

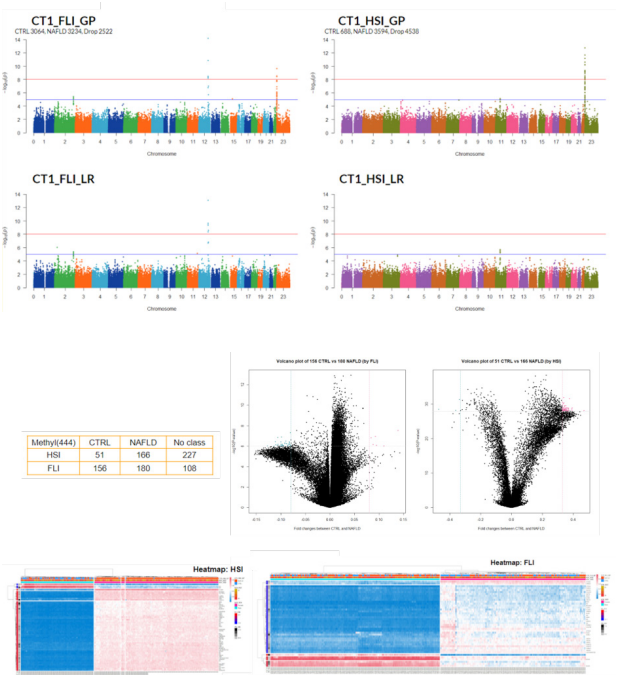
[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea; [2]Medical Science Research Center, Korea University College of Medicine, Seoul, South Korea

Aims: Nonalcoholic fatty liver disease (NAFLD) is chronic and progressive liver disease with high prevalence of about 30% of the general population. This study evaluated the role of genetic and epigenetic factors in the development and progression of NAFLD using the Korean Genome Epidemiology Study (KoGES).

Methods: The KoGES is consisted with more than 10,000 participants from Ansan and Anseoung city from 2001. After excluding chronic viral hepatitis and alcohol abusers, 8840 patients were analysed genome wide association study (GWAS). 444 patients were analysed DNA methylation and 50 patients were reanalysed DNA methylation 5 years later. Participants with the fatty liver index(FLI) > 60 were classified into NAFLD group, whereas participants with FLI < 30 were classified into control group.

Results: In GWAS data, 3234 and 3064 participants were classified into NAFLD group and control group, respectively. In chromosome 12, CCDC63, HECTD4, OAS3, and MYL2 genes showed significantly different patterns between controls and NAFLD participants based on FLI. In chromosome X, six SNPs of intergenic regions showed significance as a P-value of 5E-08 or less. In DNA methylation data, 180 and 156 participants were classified into NAFLD group and control group, respectively. FLI value has correlation patterns for 13 probes with r2 greater than 0.12.

Conclusions: Here, we demonstrate that GWAS and DNA methylation profiles showed significant difference between NAFLD group and control group. Our results suggest that GWAS and DNA methylation level and clinical variables can be used for the clues for molecular pathways in NAFLD.



Keywords: NAFLD, GWAS, DNA methylation

FP-019

Effects of PNPLA3, TM6SF2 and SAMM50 on the Development and Severity of Nonalcoholic Fatty Liver Disease in Children

Kyung Jae Lee[1], Jin Soo Moon[2], Nan Young Kim[3], Jae Sung Ko[2]

[1]Department of Pediatrics, Hallym University Sacred Heart Hospital, Anyang, Korea; [2]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea; [3]Hallym Institute of Translational Genomics & Bioinformatics, Hallym University Medical Center, Anyang, Republic of Korea

Aims: Several genetic variants have been reported to increase the risk of non-alcoholic fatty liver disease (NAFLD). To assess the effect of the genetic variants on pediatric NAFLD in general and overweight population.

Methods: We recruited the 228 pediatric NAFLD patients and 225 controls (69 overweight and 156 normal weight). We genotyped 4 variants of *PNPLA3* (rs738409), *TM6SF2* (rs58542926) and *SAMM50* (rs2073080, rs3761472). All participants underwent anthropometric measurements, blood cell count, liver function test. For overweight populations we measured abdominal circumference, blood pressure, fasting glucose, insulin and lipid profile. We evaluated the degree of steatosis based on the ultrasound and noninvasive fibrosis scores

Results: Risk alleles of 4 variants independently increased suscep-

tibility to NAFLD in general population (OR 1.99~ 3.26, *P*<0.05) and overweight population (OR 2.22~ 22.94, *P*<0.05). Other independent risk factors were body mass index Z score (BMI-Z) and male gender in general population and fasting insulin and male sex in overweight population. These variants also increased alanine aminotransferase, sonographic grade of steatosis, fibrosis scores regardless of age, sex, body mass index and metabolic features. Impact of genetic variants on the risk of NAFLD was greater in the overweight population than general population.

Conclusions: *PNPLA3*, *TM6SF2* and *SAMM50* are associated with development and severity of pediatric NAFLD in general and overweight population.

Keywords: Non-alcoholic fatty liver disease, Patatin-like phospholipase domain-containing 3, Transmembrane 6 superfamily member 2, Samm50

FP-020

The Association between Breastfeeding and Non-Alcoholic Fatty Liver Disease in Parous Women: A Nationwide Cohort Study

Yewan Park[1,2*], Dong Hyun Sinn[1*], Joo Hyun Oh[3], Myung Ji Goh[1], Kyunga Kim[2,4], Wonseok Kang[1], Yong-Han Paik[1], Moon Seok Choi[1], Joon Hyeok Lee[1], Kwang Cheol Koh[1], Seung Woon Paik[1], Geum-Youn Gwak[1]

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Digital Health, SAIHST, Sungkyunkwan University, Seoul, Korea; [3]Department of Internal Medicine, Eulji General Hospital, Eulji University School of Medicine, Seoul, South Korea; [4]Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea

Aims: Breastfeeding has multiple effect on maternal health outcomes. However, the effect of breastfeeding on non-alcoholic fatty liver disease (NAFLD) in parous women is not clear.

Methods: A total of 6,893 Korean parous women, aged 30 to 50 years, who participated in the Korean National Health and Nutrition Examination Survey were assessed for association between breastfeeding and NAFLD. The duration of lactation was calculated by dividing total lactation period by the number of breastfed children. NAFLD was defined by hepatic steatosis index (HSI).

Results: Of the 6,893 women, 1,049 (15.2%) had NAFLD. The prevalence of NAFLD was 18.3%, 13.3%, 14.4%, and 15.8%, for women with a breastfeeding period of 0-1 month, ≥1 to <6 months, ≥6 to <12 months, ≥12 months, respectively. In fully-adjusted model, breastfeeding (≥1 month) was related with reduced NAFLD prevalence (odd ratio (OR) 0.67, 95% confidence interval (CI) 0.51-0.88, adjusted for metabolic, socioeconomic and maternal risk factors). The fully-adjusted OR (95% CI) decreased with an increase in a breastfeeding duration: 0.70 (0.50-0.97), 0.65 (0.46-0.90), and 0.62 (0.45-0.85) for women with ≥1 to <6 months, ≥6 to <12 months and ≥12 months breastfeeding duration, respectively, compared to women with 0-1 month of breastfeeding duration. The association was observed in all pre-defined subgroup analyzed, and was greater for women with younger age at menarche (<13 years).

Conclusions: Breastfeeding showed protective association with NAFLD in later life in parous women, suggesting potential maternal benefits of breastfeeding on NAFLD.

Keywords: Non-alcoholic liver disease, Breastfeeding, Breastfeeding duration

FP-021

Metabolic Dysfunction Associated Fatty Liver Disease Identifies Patients with Cardiovascular Disease Risk Better than Nonalcoholic Fatty Liver Disease

Ho Soo Chun[1,2], Jae Seung Lee[3], Hye Won Lee[3], Beom Kyung Kim[3], Jun Yong Park[3], Do Young Kim[3], Sang Hoon Ahn[3], Yong-ho Lee[4], Ji-Hye Kim[5], Minjong Lee[1,2], Seung Up Kim[3]

[1]Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, South Korea, [2]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, South Korea, [3]Department of Internal Medicine and Yonsei Liver Center, Yonsei University College of Medicine, Seoul, South Korea, [4]Department of Internal Medicine Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, South Korea, [5]Department of Health Promotion, Yonsei University Health System, Seoul, South Korea

Aims: Cardiovascular disease (CVD) is the main cause of mortality in subjects with non-alcoholic fatty liver disease (NAFLD). We investigated the association between CVD risk and metabolic dysfunction associated fatty liver disease (MAFLD) or NAFLD and the influence of significant liver fibrosis on CVD risk.

Methods: Subjects who underwent a comprehensive medical check-up between 2014 and 2019 were recruited. Significant liver fibrosis was defined using NAFLD fibrosis score or BARD score. Predicted CVD risk was calculated using the 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator of 2013 ACC/AHA guidelines.

Results: Of the study population (n=78,762), 27,047 (34.3%) and 24,036 (30.5%) subjects had MAFLD and NAFLD, respectively. A total of 1,084 (4.0%) and 921 (3.8%) subjects had previous CVD history in MAFLD and NAFLD subgroups, respectively. The prevalence of previous CVD history and high ASCVD risk score (>15%) were significantly higher in MAFLD or NAFLD group with significant liver fibrosis than in the other groups (all *P*<0.001). In multivariate analysis, MAFLD was independently associated with previous CVD history after adjusting for confounders (odds ratio=1.088-1.387, all *P*<0.05), whereas NAFLD was not (all *P*>0.05). Adjusted odds ratios for high ASCVD risk score were significantly higher in MAFLD than in NAFLD group (all *P*<0.001). Significant liver fibrosis was independently associated with previous CVD history and high ASCVD risk score in both MAFLD and NAFLD subgroups (all *P*<0.05).

Conclusions: MAFLD might better identify subjects with CVD risk than NAFLD. Fibrosis assessment might be helpful for detailed prognostication in subjects with MAFLD or NAFLD.

Keywords: Non-alcoholic fatty liver disease, Metabolic dysfunction associated fatty liver disease, Cardiovascular disease, Liver fibrosis

FP-022

Metabolic Dysfunction-Associated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study

Hye Won Lee[1-3], Hokyou Lee[4], Hyeon Chang Kim[4], Seung Up Kim[1-3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea; [4]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea

Aims: The association between nonalcoholic fatty liver disease (NAFLD) and colorectal cancer (CRC) has been controversial. Using the new consensus-driven definition, we evaluated the association of metabolic dysfunction-associated fatty liver disease (MAFLD) with the risk of developing CRC.

Methods: From a nationwide health screening database, we included 8,933,017 participants (48.6% male) aged 40-64 years between 2009 and 2010. Participants were categorised by presence of fatty liver disease (FLD)—NAFLD and MAFLD, separately—and by the combination of the two definitions: Neither-FLD, NAFLD-only, MAFLD-only, or Both-FLD. The primary outcome was the development of CRC.

Results: Among the participants, 2,517,330 (28.2%) had NAFLD and 3,337,122 (37.4%) had MAFLD, while 2,465,151 (27.6%) met both NAFLD and MAFLD definitions. Over a median follow-up period of 10.1 years, 60,888 new CRC cases developed. NAFLD and MAFLD were each associated with a significantly higher risk of developing CRC. When the Neither-FLD group was the reference, multivariable-adjusted hazard ratios (95% confidence interval) for CRC were 1.16 (1.06-1.28) in the NAFLD-only group, 1.18 (1.16-1.20) in the Both-FLD group, and 1.32 (1.28-1.35) in the MAFLD-only group. The presence of advanced liver fibrosis further increased CRC risk in each FLD group.

Figure 1. Prevalence of previous CVD history and high ASCVD risk score according to fibrotic burden evaluated using NAFLD fibrosis score in subjects with MAFLD (A and B) and those with NAFLD (C and D). The prevalence of previous CVD history and high ASCVD risk score were highest in subjects with MAFLD or NAFLD and significant liver fibrosis, medium in subjects with MAFLD or NAFLD, but without significant liver fibrosis, and lowest in subjects without MAFLD or NAFLD (all p<0.001).

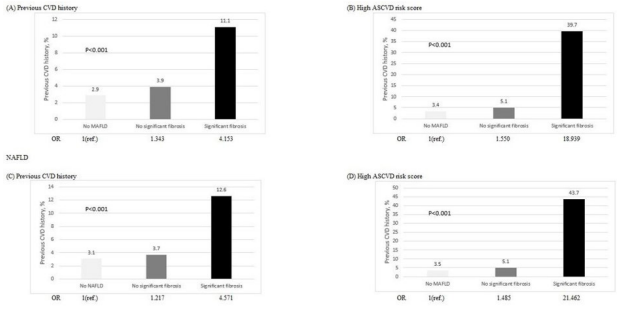
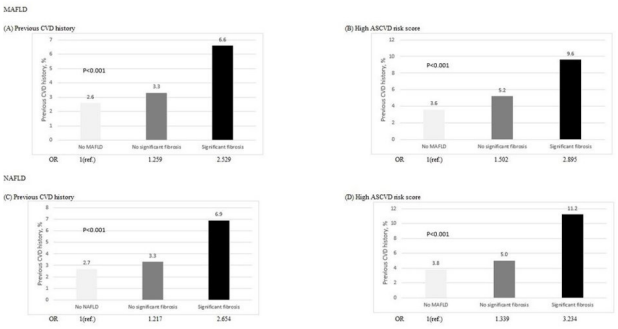


Figure 2. Prevalence of previous CVD history and high ASCVD risk score according to fibrotic burden evaluated using FAST score in subjects with MAFLD (A and B) and those with NAFLD (C and D). The prevalence of previous CVD history and high ASCVD risk score were highest in subjects with MAFLD or NAFLD and significant liver fibrosis, medium in subjects with MAFLD or NAFLD, but without significant liver fibrosis, and lowest in subjects without MAFLD or NAFLD (all p<0.001).



Conclusions: FLD was associated with a higher risk of CRC development. CRC risk was higher in the presence of MAFLD, especially when accompanied by liver fibrosis.

Keywords: MAFLD, NAFLD, Liver fibrosis, Volorectal cancer

Friday, May 14, 2021, 15:00-16:20

4. Liver Cancer,Basic

FP-023

RalA Is Negatively Regulated by RalGAPA2 and Positively Regulated by Specific Transcription Factors to Exert Its Oncogenic Functions in HCC

Lu Tian, Karen Man Fong Sze, Lu Qing Zhao, Charles Shing Kam, Daniel Wai Hung Ho, Lo Kong Chan, Irene Oi Lin Ng

Department of Pathology, The University of Hong Kong

Aims: Directly downstream of Ras, the Ras-like (Ral) small GTPases RalA and RalB are proto-oncogenes which cycle between the active GTP-bound and inactive GDP-bound forms. The equilibrium of Ral activity is precisely controlled and RalGTPase activating protein (RalGAP) complex is responsible for its negative regulation. Currently, the role of Ral upregulation and relevance of RalGAPA2 inactivation-mediated Ral activation in cancers remains unclear. We aimed to examine the clinical significance, functional implications, and underlying mechanisms of RalA signaling in HCC development.

Methods: By RNA-sequencing and qPCR, the mRNA expression levels of RalA and RalGAPA2 were detected in HCC samples followed by clinicopathological correlation analysis. RalA and RalGAPA2 knockdown and overexpressing HCC cells were generated for functional characterization *in vitro* and *in vivo*. Transcription regulation of RalA was examined by luciferase reporter and ChIP assays. The therapeutic effect of RBC8, a Ral-specific inhibitor, was examined.

Results: Our in-house and TCGA RNA-seq data revealed a stepwise increase of RalA throughout HCC carcinogenesis, with significant association with more aggressive tumor behavior and poorer prognosis. Consistently, knocking down RalA attenuated

HCC cell proliferation and migration *in vitro*, and tumorigenicity and metastasis *in vivo*. RalA upregulation was driven by copy number gain and transcriptional activities of SP1 and ETS2. On the other hand, RalGAPA2 knockdown increased RalA activity and promoted intrahepatic and extrahepatic metastasis *in vivo*. Consistently, RalGAPA2 downregulation was observed in patients' HCCs and correlated with poorer prognosis. Of note, Ral inhibition by RBC8 suppressed oncogenic functions in a dose-dependent manner and sensitized HCC cells to sorafenib treatment, with underlying enhanced inhibition of mTOR signaling.

Conclusions: Our results provide new biological insights on the dysregulation of RalA signaling through dual mechanisms in supporting pro-oncogenic functions in HCC. Targeting RalA might serve as a potential alternative therapeutic approach alone or in combination with currently available therapy.

Keywords: HCC, Ral GTPase, RalGAP complex, RBC8

FP-024

SMAC-Survivin Apoptotic "Switch" Is Regulated Through the PI3K- Src-p at the α1- Na/K-ATPase in NASH Related Hepatocellular Carcinoma: Studies in-vitro/vivo and in Humans

Juan SANABRIA

Surgery, Marshall and Case Western reserve University, USA

Aims: Hepatocellular Carcinoma (HCC) is the second and fastest-growing cause of cancer related mortality worldwide. Our group has described the signaling properties of the α1-Na/K-ATPase (NKA) providing a pathway for organogenesis during cell development. We hypothesized that during hepatocarcinogenesis, regulation of Src-phosphorylation at the α1-subunit of the NKA causes an imbalance of the Smac/DIABLO-Survivin apoptotic signaling process, favoring cell division and tumorigenesis.

Methods: Expression of Cav-1/Smac/Survivin proteins was performed on immuno-stained HCC cell lines (Hep3 & SNU475), and livers from a NASH-HCC rodent model, and humans. Furthermore, signaling pathway studies were explored in-vitro guided by RNA sequencing. Selective blockage of Src- phosphorylation at its kinase domain was performed by administration of a synthetic peptide (33aa=pNaKtide, developed from N domain of Na/K-ATPase). Significant differences among groups were accepted at $P<0.05$ using ANOVA/t-test.

Results: α1-NKA/Src-p inhibition promoted apoptosis of cell lines, and receptor' IC50 drove concomitantly both, Survivin's downregulation and SMAC's upregulation expressions (dose-related, $P<0.01$). In-vivo, liver tumor burden was significantly lower in animals treated with pNaKtide ($P<0.01$), and the expressions of Cav-1/Survivin were significantly higher in liver tumor tissue from non-treated when compared to treated animals ($P<0.01$). A similar pattern of Cav-1 and survivin expressions was noted in tumors from patients with NASH±HCC when compared to liver tissue from healthy subjects or subjects with liver metastases ($P<0.05$). In-vitro, Src-p at the α1-NKA activates PI3K/Akt dependent and independent to EGFr/Grb2 pathways.

Conclusions: α1-NKA/Src-p in Caveola regulates Survivin/SMAC expressions which in turn modulate a cellular "switch" from apoptosis to cell division involving two signaling pathways.

FP-025

Circulating Exosomal LncRNA-ATB Promotes Myopenia in Human Hepatocellular Carcinoma

Yu Rim Lee[1], Gyeonghwa Kim[2], Won Young Tak[1], Se Young Jang[1], Young Oh Kweon[1], Jung Gil Park[3], Min Kyu Kang[3], Hye Won Lee[4], Young Seok Han[5], Jae Min Chun[5], Keun Hur[2], Soo Young Park[1]

[1]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea; [2]Department of Biochemistry and Cell Biology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, Daegu, South Korea; [3]Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, South Korea; [4]Department of Pathology, Keimyung University School of Medicine, Daegu, South Korea; [5]Department of Surgery, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea

Aims: Sarcopenia frequently occurs in advanced cancer patients and is related to poor prognosis, while the detailed mechanism that promotes sarcopenia remains to be elucidated. A recent study from our research group revealed the prognostic significance of circulating exosomal non-coding RNAs (miRNA-21 and lncRNA-ATB) in HCC patients. We therefore determined the clinical significance of myopenia in HCC patients, and the possible mechanisms related to circulating exosomal non-coding RNAs.

Methods: HCC patients between October 2014 and September 2015 at Kyungpook National University Hospital, Daegu, South Korea were enrolled for this prospective study. Serum samples and CT scan were assessed from all these patients prior to definitive treatment. Psoas muscle mass index (PMI) was evaluated using CT imaging. Exosomes were extracted from serum samples using the ExoQuick Exosome Precipitation Solution. Non-coding RNAs were isolated from exosomes using the miRNeasy serum/plasma micro kit.

Results: A total of 78 patients were enrolled in this study. Decreased PMI was related to cancer stage (both TNM stage and BCLC stage) and other prognostic factors, including the T stage, lymph node, and distant metastasis (all $P<0.05$). Multivariate analysis using the Cox regression test identified that low PMI was an independent predictor of mortality (HR=2.281, 95% CI=1.176–4.422, $P=0.015$), along with larger tumor size, lymph node, and distant metastasis. The overall survival and progression-free survival were significantly lower in patients with low PMI (log-rank test: both $P<0.05$). Circulating exosomal lncRNA-ATB expression negatively correlated with PMI, and higher exosomal lncRNA-ATB was identified as independent predictor

of myopenia (OR=3.786, 95% CI=1.107–12.942, *P*=0.034).
Conclusions: Circulating exosomal lncRNA-ATB might be a novel biomarker and therapeutic targets for both disease progression and myopenia in HCC patients.
Keywords: Hepatocellular carcinoma, Myopenia, Circulating biomarker, Exosome, lncRNA

FP-026

Extracellular Vesicle-Derived Polymeric Immunoglobulin Receptor (pIgR) Activates PDK1/Akt/GSK3β/β-Catenin Signaling to Drive Cancer Stemness and Tumorigenesis in Hepatocellular Carcinoma

Samuel Wan Ki Wong[1,*], Sze Keong Tey[1,*], Janice Yuen Tung Chan[1], Xiaowen Mao[1], Yi Gao[3], Judy Wai Ping Yam[1,2]
*Contributed equally

[1]Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong; [2]State Key Laboratory of Liver Research (The University of Hong Kong), Hong Kong; [3]Department of Hepatobiliary Surgery II, ZhuJiang Hospital, Southern Medical University, Guangzhou, Guangdong, P. R. China

Aims: The involvement of hepatocellular carcinoma (HCC)-derived extracellular vesicles (EVs) in tumour microenvironment is discussed in recent years but their role in modulating cancer stemness thus facilitating progression of HCC remains unclear. Therefore, we aim to identify key components of HCC-derived EVs crucial to cancer progression.
Methods: Proteomic profiling identified polymeric immunoglobulin receptor (pIgR) to be progressively increased in circulating EVs along HCC development. Various functional assays were performed on cells pre-incubated with late-HCC patient EVs and anti-pIgR antibody while similar assays were repeated with pre-treatment with pIgR-enriched EVs collected from stable pIgR overexpressing cells established by CRISPR synergistic activation mediators. The target of pIgR in recipient cells were identified through western blotting and real-time polymerase chain reaction, with corresponding inhibitor used to block and delineate the downstream pathway. Lastly, anti-pIgR antibody and sorafenib were co-administrated into BALB/cAnN-nu mice subcutaneously injected with patient derived xenograft and growth of tumours were monitored.
Results: Late-HCC patient EVs and pIgR-enriched EVs both potently enhanced cancerous and cancer stemness properties in functional assays which in turn was inhibited by anti-pIgR antibody, implicating the crucial role of EV-pIgR in HCC. EV-pIgR was found to activate β-catenin through PDK1/AKT/GSK3β signaling resulting in the expansion of cancer stem cell (CSC) populations, and enhancement of proliferation, survival and metastatic potential of HCC cells. Inhibitors of Akt and β-catenin significantly dampened the promoting capacity of EV-pIgR on oncogenic phenotypes of the recipient cells. Co-administration of anti-pIgR antibody and sorafenib significantly reduce the tumorigenicity of patient-derived xenograft that expresses pIgR, suggesting the application of pIgR as a therapeutic target for HCC.
Conclusions: This study identified and demonstrated the pivotal functional role and clinical significance of EV-pIgR in HCC. The findings also provide insights into a novel therapeutic option to inhibit the growth of CSC population and cancer progression in HCC.
Keywords: Hepatocellular Carcinoma, Extracellular vesicles, Polymeric immunoglobulin receptor, Cancer stemness

FP-027

Significance of Telomerase Reverse Transcriptase Gene and Telomere Length with Clinical Phenotype of Hepatocellular Carcinoma

Jeong Won Jang[1,3,#], Jin Seoub Kim[2,3,#], Hye Seon Kim[2,3], Soon Kyu Lee[1,3], Hee Chul Nam[1,3], Pil Soo Sung[1,3], Chang Min Kim[4], Jin Young Park[4], Si Hyun Bae[1,3], Jong Young Choi[1,3], Seung Kew Yoon[1,3]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]The Catholic University Liver Research Center, The Catholic University of Korea, Seoul, Republic of Korea; [4]CbsBioscience Inc., Daejeon, Republic of Korea

Aims: Telomerase reverse transcriptase (TERT) mutations are reportedly the most frequent somatic genetic alterations in hepatocellular carcinoma (HCC). An integrative analysis of TERT-telomere signal during hepatocarcinogenesis is lacking. This study aimed to investigate the clinicopathological association and prognostic value of *TERT* gene alterations and telomere length in HCC patients undergoing hepatectomy as well as transarterial chemotherapy (TACE).
Methods: TERT promoter mutation, expression and telomere length were analyzed in 305 tissue samples by Sanger sequencing and real-time PCR, respectively. Protein-protein interaction (PPI) networks were examined to identify a set of genes interacting with *TERT*.
Results: The PPI networks identified eight key TERT-interacting gene sets, such as *CCT5, TUBA1B, mTOR, RPS6KB1, AKT1, WHAZ, YWHAQ,* and *TERT*. Among these, *TERT* was the strongest differentially expressed gene. *TERT* promoter mutations were more frequent, TERT expression was significantly higher, and telomere length was longer in tumors versus non-tumors. *TERT* promoter mutations were most frequent in HCV-related HCCs and less frequent in HBV-related HCCs. *TERT* promoter mutations were associated with higher TERT levels and longer telomere length and were an independent predictor of worse overall survival after hepatectomy. TERT expression was positively correlated with tumor differentiation and stage progression, and independently predicted worse progression-free survival after TACE. Telomere length was marginally associated with survival in TACE-treated patients, but not in those undergoing

hepatectomy.
Conclusions: The TERT-telomere network has a crucial role in the development and progression of HCC. TERT-telomere abnormalities might serve as useful biomarkers for HCC, but the prognostic values may differ with tumor characteristics and treatment.
Keywords: Telomere, TERT, Biomarkers, Treatment outcome

FP-028

Clinical and Biological Implications of Cell Cycle-Related Gene Fusions and Mutations in Resectable Hepatocellular Carcinomas

Jihyun An[1], Ji-Hye Oh[2], Wonkyung Kim[2], Bora Oh[2], Yoo-Jin Oh[2], Chang Ock Sung[3], Ju Hyun Shim[4]

[1]Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Gyeonggi, Republic of Korea; [2]Asan Institute for Life Science, Asan Medical Center, Seoul, Republic of Korea; [3]Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Uncontrolled proliferation induced by cell cycle deregulation is a hallmark of cancer cells. This study aimed to explore fusional and non-fusional aberrations related to the cell cycle, and investigate their prognostic relevance in a surgical series of hepatocellular carcinomas (HCCs).
Methods: Based on high-resolution transcriptomic data for 206 early-stage HCC samples obtained after curative hepatectomy at Asan Medical Center, South Korea, we fully characterized distinct patterns of fusion events using STAR-Fusion. The presence of the fusion transcripts was subsequently confirmed by Sanger sequencing. We also identified non-fusional genetic aberrations deregulating the cell cycle in the same cohort. Prognostic effects of genomic events were evaluated by competing risks regression analyses.
Results: We identified a total of 89 gene fusion events in 49 samples, including 77 novel and 7 recurrent fusion transcripts. The cell cycle-related gene fusions, *ERRFI1-CCNE1, UPF3A-CDC16*, and *ITM2B-RB1*, were observed in different tumors (n=4). Notably, the *UPF3A-CDC16* fusions recurrently detected in two samples harbored biallelic loss of function of *CDC16,* together with abnormally high levels of *cyclin B1* and *Ki-67*. We additionally found that a sub-category of 17 cell cycle gene aberrations other than gene fusions were present in 61 (29.6%) of the 206 patients. These fusional and non-fusional subgroups were enriched for gene sets related to cell proliferation, and were associated with poorer outcomes for cancer-specific death, when compared to non-affected individuals (adjusted hazard ratios [95% confidence intervals], 16.86 [5.37-52.88] and 2.58 [1.30-5.09], respectively).
Conclusions: We have provided a comprehensive overview of fused and mutated cell-cycle genes that confer a negative effect on tumor behavior in early HCCs. Our clinical and biological insights may serve as the basis for better-tailored cares for patients with the disease.
Keywords: Liver cancer, Fusion, Genomics, Cell cycle

FP-029

Immunotherapy Biomarker-Based Classification and Its Potential Clinical Usefulness in Hepatocellular Carcinoma

Jihyun An[1], Ji-Hye Oh[2], Wonkyung Kim[2], Bora Oh2, Yoo-Jin Oh[2], Chang Ock Sung[3], Ju Hyun Shim[4]

[1]Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Gyeonggi, Republic of Korea; [2]Asan Institute for Life Science, Asan Medical Center, Seoul, Republic of Korea; [3]Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Programmed cell death ligand-1(PD-L1) expression has not served as a predictive marker for immunotherapy targeting the checkpoint in patients with hepatocellular carcinoma (HCC). The cross-talk among various intrinsic or extrinsic immune-related composites within the tumor microenvironment could play a role in the PD-L1 regulation. Here, we explored the dynamic interplay between PD-L1 expression and other predefined predictors of response to checkpoint inhibitors in HCC, and classified the tumors based on potential responsiveness to the therapy.
Methods: This study included the Asan genomic cohort of 206 HCC patients receiving primary hepatectomy who had both whole exome sequencing and RNA sequencing datasets. PD-L1 expression was evaluated by immunohistochemical assay using the 22C3 antibody with a Combined Positive Score (CPS) cut-off of 1%. Tumor mutational burden (TMB), neoantigen load, and T-cell inflamed phenotype were measured using genomic data.
Results: PD-L1 positivity was observed in 29 (14.1%) of the 206 patients. Genesets related to immune system and proliferation were highly enriched in the PD-L1-positive group with no difference in clinical and pathological data. PD-L1 expression was significantly correlated with T cell-inflamed phenotype, as was not with neoantigen or TMB. We next constructed a novel Immuno-responsive classification of HCC by PD-L1 and TMB that were mutually exclusive: C1, +/+; C2, +/-; C3, -/+; and C4, -/-, respectively for PD-L1 and TMB. Most immune cell types were highly infiltrated in the C1 and C2 groups with the relative abundance of Immune-checkpoint genes. Survival outcomes were also better in the two subclasses.
Conclusions: Our immunogenomic analysis uncovered potential immuno-responsive HCC subtypes with distinct patterns of targetable immune biology. Tailored studies of patients treated with immunomodulators are needed for future clinical use of the classification.
Keywords: Immunotherapy, Liver cancer, Response, Genomics

FP-030

Preferential Expression of Programmed Death-Ligand 1 Protein in Tumor-Associated Macrophages and Its Potential Role in Immunotherapy for Hepatocellular Carcinoma

Dong Jun Park[1], Pil Soo Sung[1,2], Gil Won Lee[1], Sungwoo Cho[1], Sung Min Kim[1], Byung-Yoon Kang[1], Wonhee Hur[1], Hyun Yang[1,3], Soon Kyu Lee[1,2], Sung Hak Lee[6], Eun Sun Jung[4], Chang Ho Seo[5], Joseph Ahn[5], Ho Joong Choi[5], Young Kyoung You[5], Jeong Won Jang[1,2], Si Hyun Bae[1,3], Seung Kew Yoon[1,2,*]

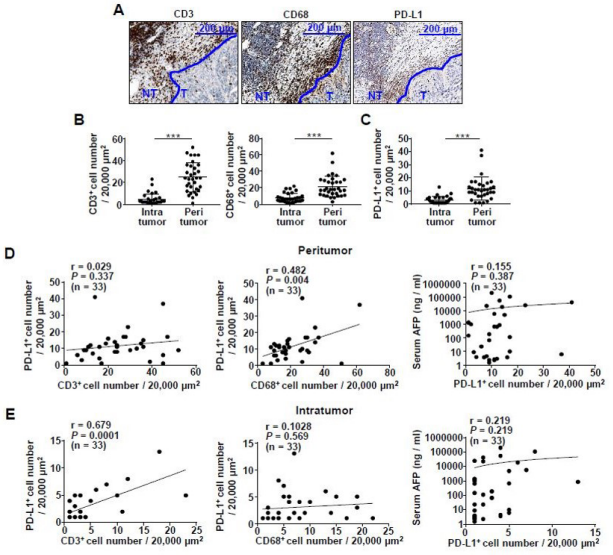
[1]The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Internal Medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [4]Department of Hospital Pathology, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [5]Department of Surgery, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [6]Department of Clinical Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Immune checkpoint inhibitors (ICIs) are used for the treatment of various cancers. However, ICI monotherapy has not demonstrated a robust efficacy against hepatocellular carcinoma (HCC). Tumor-associated macrophages (TAMs) exhibit the M2-phenotype, and their frequency is known to be associated with poor prognosis of HCC, although the function and phenotypes of TAMs in human HCC tissues have not been clearly characterized. Programmed death-ligand 1 (PD-L1) in tumor cells may directly suppress exhausted PD-1$^+$ T cells. However, the importance of PD-L1 expressed in TAMs remains unclear. In this study, we focused on the infiltration and PD-L1 expression of TAMs in the TME of HCC.

Methods: *In vitro* experiments, anti-PD-L1–treated M2 macrophages were co-cultured with activated T cells to evaluate the role of PD-L1-expressing TAMs in anti-PD-L1 treatment. For *in vivo* experiments, an immunogenic syngeneic HCC mouse model was established to determine the frequency and role of tumor-infiltrating T cells and TAMs. Peripheral blood mononuclear cells (PBMCs) were obtained from eight patients with unresectable HCC before and 4 weeks after nivolumab treatment. Immunohistochemical staining and multicolor flow cytometry were performed on liver tissues and PBMCs of patients with HCC.

Results: Immunohistochemical staining for PD-L1 as well as for the CD3 and CD68 demonstrated that T cells and PD-L1–expressing TAMs were infiltrated in both intratumoral and peritumoral tissue of patients with HCC. The number of peritumoral TAMs positively correlated with PD-L1 expressing cells and PD-L1 protein co-localized with CD68, suggesting that PD-L1 was mainly expressed in TAMs rather than T cells or tumor cells in HCC (P<0.05). *In vitro* experiments confirmed that T-cell functionality (INF-γ and TNF-α production) significantly increased when M2 macrophages were treated with anti-PD-L1. In syngeneic Hepa1-6 mouse model, TAMs expressed high levels of PD-L1. In this model, tumors with anti-PD-L1 treatment showed significantly smaller diameter that those with IgG treatment. After anti-PD-L1 treatment, intra-tumoral CD8$^+$ T cells showed higher expression of activation markers and the frequency of TAMs was significantly reduced, suggesting that the decreased size of the tumors after anti-PD-L1 treatment resulted from the reinvigoration of CD8$^+$ T cells. Three of the eight enrolled patients responded to anti-PD-1 treatment. Increased frequency of Ki-67-positive CD4$^+$ and CD8$^+$ T cells was noted in nivolumab-responder PBMCs obtained after 4 weeks of treatment.

Conclusions: Targeting PD-L1-expressing macrophages in HCC may be used as a strategy to enhance the effectiveness of immunotherapy.



Keywords: Hepatocellular carcinoma, Tumor-associated macrophages, PD-L1, Nivolumab

Friday, May 14, 2021, 16:30-17:50

5. Liver Cancer,Clinical

FP-031

Changes in General and Central Obesity Are Associated with Hepatocellular Carcinoma: A Nationwide Longitudinal Study

Mi Na Kim[1,2*], Kyungdo Han[3*], Juhwan Yoo[4], Yeonjung Ha[1], Young Eun Chon[1], Ju Ho Lee[1], Seong Gyu Hwang[1]

[1]Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [2]Clinical and Translational Hepatology Laboratory, Seongnam, Republic of Korea; [3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea;

[4]Department of Biomedicine & Health Science, the Catholic University of Korea, Seoul, Korea

Aims: Obesity is the major risk factor for hepatocellular carcinoma (HCC). However, whether there is an association of changes in obesity status with HCC has not been assessed. We investigated the long-term impact of changes in general and central obesity on the risk of HCC in a large, population-based, longitudinal cohort.
Methods: We screened 7,221,479 subjects who underwent health examinations provided by the National Health Insurance Service of South Korea in 2009 and 2011; 6,789,472 subjects were finally enrolled. Patients were classified according to whether there was any change in obesity status, as follows: 1) maintained normal body mass index (BMI) or waist circumference (WC), 2) incident obesity, 3) reversed obesity, and 4) persistent obesity.
Results: During a median 6.4-year follow-up, we documented 9,952 HCC cases. Compared to participants who maintained a normal BMI (n = 4,173,640), the multivariate-adjusted hazard ratios (aHRs) for HCC were significantly increased in the incident (aHR = 1.10, 95% confidence interval [CI] = 1.01–2.10) and persistent (aHR = 1.28, 95% CI = 1.23–1.34) general obesity groups. Compared to participants who maintained a normal WC, participants with incident or persistent central obesity showed a significantly increased risk of HCC (aHR = 1.19, 95% CI = 1.11–1.27, and aHR = 1.33, 95% CI = 1.26–1.40, respectively). Participants with reversed general or central obesity did not show an increased risk of HCC compared to those who maintained a normal BMI and WC.
Conclusions: Participants with persistent or incident obesity had a higher risk of HCC compared to those who maintained a normal BMI or WC. Taken together, these findings indicate the importance of strategies for preventing and reversing obesity to reduce the incidence of HCC.
Keywords: Hepatocellular carcinoma, Obesity, Body mass index, Waist circumference

FP-032

Incidence Rates of Hepatocellular Carcinoma Does Not Increase in Patients with Old Age or Medicare Group: A Nationwide 10-Years Analysis and Projection

Young Eun Chon[1], Sung Yong Park[2], Han Pyo Hong[3], Donghee Son[4], Eileen Yoon[5], Soon Sun Kim[6], Sang Bong Ahn[7], Soung Won Jeong[8*], Dae Won Jun[5*]

[1]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam; [2]Big Data Center, National Health Insurance Service, Wonju, [3]Big Data Center, Department of Statistics, Yonsei University Wonju College of Medicine, Wonju, [4]Biostatistical Consulting and Research Lab, Medical Research Collaborating Center, HanyangUniversity; [5]Department of Internal Medicine, School of Medicine, Hanyang University, Seoul; [6]Department of Gastroenterology, Ajou University School of Medicine, Suwon; [7]Department of Internal Medicine, Eulji University College of Medicine, Seoul; [8]Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea

Aims: Comprehensive analyses on changes in hepatocellular carcinoma (HCC) incidence rate are important for planning the future management of HCC. This study aimed to analyze the trend of nationwide HCC incidence rate over 10 years and to predict the incidence rate in 2028.
Methods: Data of newly diagnosed HCC patients between 2008 and 2018 were obtained from Korean National Health Insurance Service database, which 97.2% of the total Korean population is enrolled. Age-standardized incidence rates were calculated to compare the changes in HCC incidence rate according to different age groups, sex, income levels, and regions.
Results: A total of 127,426 patients were newly diagnosed with HCC between 2008 and 2018. An annual average number of new HCC cases were 11,584, with a crude incidence rate of 22.4 per 100,000 person-years, and an age-standardized rate (ASR) of 17.3 per 100,000 person-years. From 2008 to 2018, the ASR of HCC incidence significantly decreased in the entire cohort (21.7→13.9 per 100,000 person-years), and in the following age groups (0-29, 30-59, and 60-79 years), but that of the 80+ years significantly increased (58.7→62.3 per 100,000 person-years, average annual percent change [AAPC], +9.4%, P<0.001). In contrast to the significant reductions of ASR of HCC incidence in other income groups, that of the medical care group (lowest income group), did not show significant reduction from 2008 to 2018 (27.9→25.5 per 100,000 person-years; AAPC, -1.4%, P=0.202). The predicted ASR of HCC incidence is estimated as 12.0 per 100,000 person-years in 2028.
Conclusions: In Korea, the ASR of HCC incidence has been gradually decreasing over 10 years. However, it is not decreasing in the elderly or in those with medicare group. A customized HCC control strategies are required according to age and income groups.
Keywords: Age-standardized rate, Incidence, Hepatocellular carcinoma, Korea, Prediction

FP-033

Controlled Attenuation Parameter Value and The Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Under Antiviral Therapy

Joo Hyun Oh[1*], Hye Won Lee[2,3*], Dong Hyun Sinn[1*], Jun Yong Park[2,3], Beom Kyung Kim[2,3], Seung Up Kim[2,3], Do Young Kim[2,3], Sang Hoon Ahn[2,3], Wonseok Kang[1], Geum-Youn Gwak[1], Moon Seok Choi[1], Joon Hyeok Lee[1], Kwang Cheol Koh[1], Seung Woon Paik[1], Yong-Han Paik[1]

[1]Department of Medicine, Nowon Eulji Medical Center, Eulji University School of Medicine; [2]Department of Internal medicine, Yonsei University College of Medicine, [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Controlled attenuation parameter (CAP) can evaluate hepatic steatosis in patients with chronic hepatitis B (CHB).

However, prognostic implications of CAP value remain unclear. We evaluated the association between CAP values and the risk of hepatocellular carcinoma (HCC) in patients with CHB under antiviral therapy and maintained virologic response.

Methods: A total of 1,823 CHB patients who were taking nucleos(t)ide analogue and showing suppressed hepatitis B virus replication (≤20 IU/mL) were analyzed. The primary outcome was incident HCC during follow-up. Patients were grouped into those with and without advanced chronic liver disease (ACLD) (liver stiffness measurement cutoff: 10 kPa), and those with and without hepatic steatosis (CAP cutoff: 222 dB/m).

Results: During 6.4 years of follow-up (interquartile range: 4.0-7.2 years), 127 patients (7.0%) newly developed HCC. Among patients with ACLD (n=382), the cumulative HCC incidence rate was lower for those with CAP ≥ 222 (11.0% at 5 years) than those with CAP <222 (24.0% at 5 years, *P*=0.002), and was an independent factor associated with HCC. When CAP value was further stratified, the cumulative HCC incidence rate decreased in dose-dependent manner according to an increase in CAP value (24.0%, 13.9%, 12.8% and 6.0% at 5 years for those with CAP <222, 222-246, 247-273 and ≥274, respectively). Among patients without ACLD (n=1,441), there was no significance difference in HCC risk according to CAP value (HCC incidence rate: 3.3% and 4.0% at 5 years for those with CAP <222 and CAP ≥222, *P*=0.20).

Conclusions: Among CHB patients under antiviral therapy showing suppressed HBV replication, low CAP value predicted higher risk for HCC among ACLD patients, indicating that CAP value has a prognostic implication in this population.

Keywords: Transient elastography, Controlled attenuation parameter, Chronic hepatitis B, Hepatocellular carcinoma

FP-034

Imaging Findings of Liver MRI with Liver-Specific Contrast and the Risk of Hepatocellular Carcinoma

Jong-In Chang[1], Dong Hyun Sinn[1], Woo Kyung Jeong[2], Wonseok Kang[1], Geum-Youn Gwak[1], Yong-Han Paik[1], Moon Seok Choi[1], Joon Hyeok Lee[1], Kwang Cheol Koh[1], Seung-Woon Paik[1]

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Departments of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Liver magnetic resonance imaging (MRI) with liver-specific contrast is used to characterize liver lesions but is also known to correlate with liver function. However, the prognostic role of liver MRI findings for the prediction of hepatocellular carcinoma (HCC) is largely unexplored.

Methods: A total of 200 patients aged 40 years or older with chronic liver disease, who underwent gadoxetic acid-enhanced liver MRI between 2011 and 2015 were analyzed. The MRI findings were retrospectively reviewed by an independent radiologist blinded to clinical information and were categorized into three groups: normal, high-risk features, and high-risk nodules. High-risk features were defined as multiple cirrhotic (regenerative) nodules and confluent fibrosis and high-risk nodules were defined by LR-3 or LR-4 nodules based on the Liver Reporting & Data System version 2018. The primary outcome was the development of HCC within 3 years from liver MRI evaluation.

Results: HCC was diagnosed in 23 patients (11.5%) during a mean 27.6 months of follow-up. Among 84 patients with normal MRI findings, there was no HCC development within 3 years from liver MRI evaluation. Among 65 patients with high-risk features, HCC was diagnosed in 7 patients, with a cumulative incidence rate of HCC of 0%, 2.2%, and 15.3% at one, two, and three years. Among 51 patients with high-risk nodules, HCC was diagnosed in 16 patients, with a cumulative incidence rate of HCC of 19.0%, 31.7%, and 37.2% at one, two, and three years, respectively. In multivariable analysis, MRI findings were independent factors associated with HCC development.

Conclusions: The incidence of HCC was different based on the baseline MRI findings. Our study suggested that MRI findings might be used to stratify future HCC risk of individuals at risk of developing HCC.

Keywords: Hepatocellular carcinoma, Liver MRI, Surveillance

FP-035

Whole Blood Viscosity Is a Biomarker for the Extrahepatic Metastases and Survival in Patients with Treatment-Naïve Hepatocellular Carcinoma

Ji Won Han, Soon Kyu Lee, Pil Soo Sung, Hee Chul Nam, Jeong Won Jang, Jong Young Choi, Seung Kew Yoon

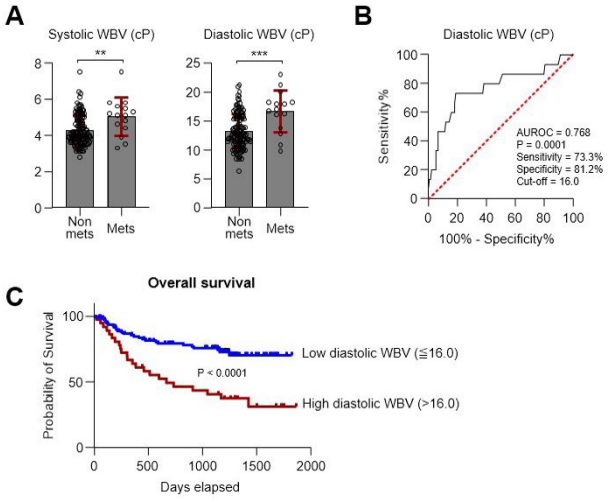
Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Aims: Whole blood viscosity (WBV) is increased in cancer patients and associated with the advanced stage with systemic metastases, which might be due to the enhancement of adhesion of circulating tumor cells to the vascular structure. However, its clinical relevance in hepatocellular carcinoma (HCC) is still unclear.

Methods: We enrolled 148 treatment-naïve HCC patients with preserved liver function (Child-Pugh score ≦ 7) who diagnosed with HCC between January 2016 to December 2017 at Seoul St. Mary's hospital. Systolic and diastolic WBV was examined by automated scanning capillary tube viscometer.

Results: The median observation time was 1,110 days. Extrahepatic metastases were observed in 15 patients (11.3%) at diagnosis. Portal vein tumor thrombosis (PVTT), tumor size, tumor number, and systolic/diastolic WBV were factors associated with extrahepatic metastases. Systolic WBV (mean ± SD, 5.0 ± 1.0 cP vs. 4.3 ± 0.8 cP) and diastolic WBV (16.6 ± 3.6 cP vs. 13.3 ± 3.0 cP) were significantly increased in patients with metastases compared to patients without metastases. Multivariate logistic regression revealed that high diastolic WBV over 16 cP is an in-

dependent factor associated with metastases. Interestingly, patients who developed extrahepatic metastases (n = 20, 15.0%) during observation period among patients without metastases at diagnosis (n = 133) had higher diastolic WBV (14.5 ± 2.9 cP vs. 13.0 ± 2.9 cP) initially. Patients with high diastolic WBV had poor survival, and multivariate cox regression revealed that high diastolic WBV is an independent risk factor for the poor survival (HR = 3.4, *P*<0.001) along with the Child B and PVTT.



Conclusions: We firstly showed that high WBV is a biomarker for extrahepatic metastases and poor survival in patients with treatment-naïve HCC with preserved liver function. Future prospective, larger study is needed to validate our results.

Keywords: Blood viscosity, Hepatocellular carcinoma, Metastasis

FP-036

Biomarkers for Locally Advanced Hepatocellular Carcinoma Patients Treated with Liver-Directed Combined Radiotherapy

Seung Yeun Chung[1,2], Kyoung-Jin Kim[1], Jinsil Seong[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Republic of Korea; [2]Department of Radiation Oncology, Ajou University School of Medicine, Republic of Korea

Aims: In the era of biomarker-driven cancer therapy, robust biomarkers for hepatocellular carcinoma (HCC) have not been well-defined. In this hypothesis-generating study, we investigated biomarkers that can be incorporated to predict treatment outcomes in patients with locally advanced HCC who are administered liver-directed combined radiotherapy (LDCRT).

Methods: Ninety-nine patients with HCC who were treated with conventional fractionation LDCRT between July 2016 and October 2018 were enrolled in this prospective single-arm study. Clinical outcomes and possible serum biomarkers, including sPD-L1, IL-10, IL-6, cfDNA, ITIH4, and IFN-γ, were analyzed. The primary endpoint was disease progression, and additional endpoints were local failure-free rate, intrahepatic failure-free rate, and lung metastasis-free rate.

Results: The median follow-up period was 18.7 months. The one-year progression-free rate was 38.2%. Increasing baseline sPD-L1 per pg/mL, previous treatment history, PIVKA-II > 1629 mAU/mL, and multiple tumors were the adverse factors for progression based on multivariate analysis. Survival tree analysis revealed three prognostic groups for progression, in which patients with multiple lesions and baseline sPD-L1 ≥ 41.07 pg/mL showed the worst outcomes. For dynamic changes in biomarker levels, sPD-L1 fold change and cfDNA fold change values were unfavorable factors for progression.

Conclusions: Baseline sPD-L1, sPD-L1 fold change, and cfDNA fold change values showed the highest potential as biomarkers for predicting post-treatment progression after LDCRT in HCC patients. By incorporating clinical factors, these biomarkers may be useful for devising a biomarker-driven treatment paradigm in locally advanced HCC.

Keywords: Hepatocellular carcinoma, Radiotherapy, Biomarker, Tumor progression

FP-037

Machine Learning Based Pattern Recognition Software to Predict 5-Year Recurrence Risk after Surgical Resection in Hepatocellular Carcinoma Patients: A Multicenter Study

Youn I Choi[1], Seung Kak Shin[1], Young Jae Kim[2], Kwang Gi Kim[2], Young Kul Jung[3], Tae Hyung Kim3, Bo Hyun Kim[4], Oh Sang Kwon[1], Yun Soo Kim[1], Ju Hyun Kim[1]

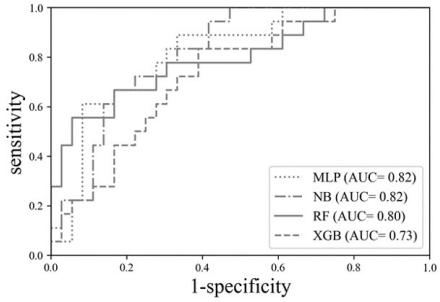
[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea; [2]Department of Biomedical Engineering, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea; [4]Division of Gastroenterology, Department of Internal Medicine, Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea

Aims: Even there is growing unmet need in personalized risk prediction among post-operative status of hepatocellular patients (HCC), there have been lacking data on highly reliable clinical decision support system (CDSS). Herein, we developed, and validated the machine learning (ML) based pattern recognition system to predict the recurrence risk among patients who underwent surgical resection for HCC in harmonious with clinical, laboratory, and imaging radiomics.

Methods: We retrospectively reviewed HCC patients who were surgically resected, and cured from three university hospitals (GMC, KAH, and NCC) in Korea during January 2014 to June 2019. Pre-operative clinical, laboratory, computed tomography (CT) radiomics (102 features from CT images), and 5-yearrecurrence outcome data were gathered. Though permutation feature importance methods, features which loaded on ML mod-

el were selected by removing values in priority of low average. GMC data were used as training/test set (n=293), and KAH, and NCC data as external validation set (n=126). ML models we used were multilayer perceptron (MLP), Gaussian Naïve Bayes (NB), XGBoost, and Random Forest(RF), and which function was evaluated using area under the receive operating curves (AUROC).

Results: Of 419 enrolled patients, during median 10.2 year of follow up period, incidental 147 cases of HCC recurrence cases were developed. Among ML models, XGB method showed best performance to predict 5-year risk of HCC recurrence with AUCs of 0.66 (95% CI (95% CI 0.57 to 0.74). In subgroup analysis for HCC<5 cm in size, NB model yielded AUROC of 0.89 (95% CI 0.74 to 0.97) with statistical significance.



Abbreviation: AUROC, area under the receive operating curves; ML, machine learning; HCC, hepatocellular carcinoma; MLP, multilayer perceptron; Gaussian Naïve Bayes (NB), Random Forest(RF)

Figure 1. AUROC of ML based predication model among HCC<5 cm patients

Conclusions: ML based prediction model for HCC recurrence risk among surgically resected HCC patients could be used to identify at risk HCC recurrence especially less than 5 cm in size, and enable physicians to close follow up based on patients' level estimation through ML algorithm.

Keywords: Machine learning, Hepatocellular carcinoma, Recurrence, Prediction model

FP-038

Kinetics of the Neutrophil-Lymphocyte Ratio during PD-1 Inhibition as a Prognostic Factor in Advanced Hepatocellular Carcinoma

Won-Mook Choi[1], Ji Yoon Kim[1], Jonggi Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Young-Suk Lim[1], Han Chu Lee[1], Changhoon Yoo[2], Min-Hee Ryu[2], Baek-Yeol Ryoo[2], Kang Mo Kim[1]

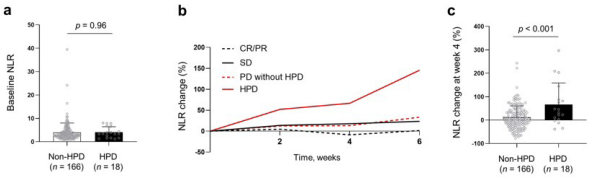
[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Programmed death-1 (PD-1) inhibitors such as nivolumab have improved survival outcomes and produced durable responses in advanced hepatocellular carcinoma (HCC). However, predictive biomarkers to identify suitable patients for these treatments are still lacking. Here, we evaluated the relationship between the baseline and kinetics of the neutrophil-lymphocyte ratio (NLR) and clinical outcomes in nivolumab-treated HCC patients.

Methods: All consecutive HCC patients treated with nivolumab between July 2017 and June 2020 were screened for the eligibility. The NLRs were calculated before and at 2, 4, and 6 weeks after treatment. Survival outcomes were compared based on the baseline and kinetics of NLR. We additionally analyzed the association between the baseline and dynamic changes in the NLR with hyperprogression (HPD).

Results: Among the 194 included cases, most patients were male (82.0%) and had a Child-Pugh class A disease (70.6%). Patients with a baseline NLR ≥3 (hazard ratio [HR] 2.46; 95% CI 1.63–3.71) had a poorer overall survival compared to patients with baseline NLR <3. During the treatment, the NLR increased rapidly in the patients developing HPD and only a ΔNLR at 4 weeks was predictive of HPD. Indeed, the risk of HPD increased by 20% for every 20% increase in the ΔNLR at 4 weeks, and a ΔNLR >75% at this timepoint had an 86.1% accuracy for predicting HPD. Accordingly, an NLR increase at 4 weeks (HR 1.79; 95% CI 1.19–2.68) was associated with an increased risk of death, especially among patients with a baseline NLR ≥3.

Fig. Analysis of NLR dynamic changes in nivolumab-treated HCC patients according to the tumor response (*n* = 184). (a) Baseline NLR with non-HPD and HPD. (b) NLR percent change dynamics. (c) Percent change in the NLR at week 4 in non-HPD and HPD cases.



Conclusions: The baseline and on-treatment kinetics for the NLR are effective prognostic indicators in nivolumab-treated patients with HCC. This may help to guide patient selection and on-treatment strategies for immunotherapies in advanced HCC.

Keywords: Liver Cancer, Immune Checkpoint Inhibitor, Dynamic Changes, Prognosis, Hyperprogression

Friday, May 14, 2021, 16:30-17:50

6. Liver Transplantation

FP-039

Stepwise Development of Robotic Donor Right Hepatectomy According to the Anatomical Variations in the Hilum and The Graft Volume

Hye Yeon YANG[1], Seoung yoon RHO[1], Seung Soo HONG[1], Dai Hoon HAN[1], Jae Geun LEE[2], Dong Jin JOO[2], Jin Sub CHOI[1], Gi Hong CHOI[*1]

[1]Surgery, Yonsei University College of Medicine, Korea; [2]Transplanta-

tion surgery, Yonsei University College of Medicine, Korea

Aims: Initial strict selections of donor without anatomical variations are recommended for minimally invasive living donor liver transplantation (LDLT) program because the donor safety is the most paramount. In this study, we introduced our stepwise development of robotic donor LDLT from donors with from favorable to unfavorable anatomies.
Methods: From Apr. 2016 to Oct. 2020, 80 donors received robotic donor right hepatectomy. All donors were divided according to the variations of the portal vein and bile duct and the graft volume (>800 cc). Donors who had at least one variable that satisfy beyond the three extended criteria were defined as 'unfavorable group'. The proportion of variations was analyzed according to the four periods and perioperative outcomes were compared between favorable and unfavorable group.
Results: Among 80 cases, portal vein variation and bile duct variation were observed 10 cases and 22 cases, respectively. Donors who had graft weight more than 800 g were 22 cases. Unfavorable group donors were 8 cases in 1st and 2nd period, respectively. In 3rd period, 9 donors were unfavorable group. In recent 20 cases, 14 donors were unfavorable group. Comparing the perioperative outcomes between favorable and 'unfavorable group, there were no significant differences regarding total operative time, warm ischemic time, estimated blood loss and postoperative complication.
Conclusions: Stepwise development of robotic donor right hepatectomy showed comparable perioperative outcomes in donor with the anatomical variations in the hilum and larger graft volume and seems to a reasonable way for a safe and successful minimally invasive LDLT program.

FP-040

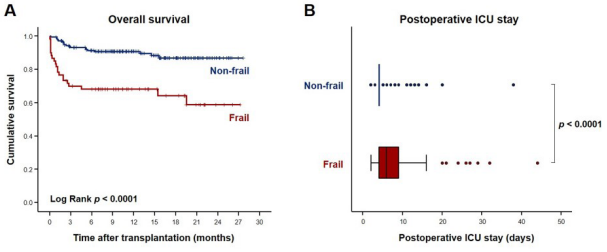
Pre-transplant Functional Status Predicts Postoperative Morbidity and Mortality after Liver Transplantation in Patients with Cirrhosis

Jihye Kim[1*†], Won Hyuk Chang[2*], Dong Hyun Sinn[1], Geum-Yeon Gwak[1], Yong-Han Paik[1,3], Moon Seok Choi[1], Joon Hyeok Lee[1], Kwang Cheol Koh[1], Seung Woon Paik[1], Jong Man Kim[4], Wonseok Kang[1,3**]**

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Physical and Rehabilitation Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea; [4]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[†]Current affiliation: Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Aims: Frailty has been recognized as a predictor of outcomes among patients on the transplant waitlist. This study aimed to investigate whether pre-transplant frailty can predict postoperative morbidity and mortality after liver transplantation in patients with cirrhosis.
Methods: We retrospectively reviewed a total of 282 consecutive patients who underwent liver transplantation between September 2018 and July 2020 at a tertiary hospital in Korea. Physical frailty at baseline was assessed by Short Physical Performance Battery (SPPB) and patients were categorized into two groups: frail (SPPB <10) and non-frail (SPPB ≥10). Primary outcome was postoperative mortality (overall survival [OS]) and secondary outcomes included postoperative intensive care unit (ICU) stay and 30-day complication rate.
Results: After excluding 40 patients (10 pediatric cases; 17 without liver cirrhosis; 13 with missing data), 242 patients were finally analyzed. The median age was 57 years, and patients with underlying hepatocellular carcinoma was 138 (57.0%). Among the cohort, 60 (24.8%) were classified as frail and 182 (75.2%) non-frail. The frail group had more female patients (55.0% vs. 45.0%; *P*<0.001) and a higher proportion of unfavorable features (Child-Pugh class C, 70.0% vs. 26.9%; MELD score ≥30, 65.0% vs. 13.1%; hepatorenal syndrome, 51.7% vs. 11.0%; preop-ICU stay, 45.0% vs. 4.4%). OS was shorter in the frail group as compared with the non-frail group (9.3 vs 11.6 months; *P*<0.001). Postoperative ICU stay was longer in the frail group (median 6 days, interquartile range [IQR] 2 – 44 days) than in the non-frail group (median 4 days, IQR 2 – 38 days; *P*<0.001), and the 30-day complication rate was higher in the frail group than in the non-frail group (78.3% vs. 21.7%; *P*=0.008). Frailty was an independent risk factor for death (adjusted hazard ratio, 2.39; 95% confidence interval, 1.02 – 5.60; *P*=0.044) after adjustment for body mass index, MELD score, preoperative ICU care, and history of HCC.



Conclusions: Pre-transplant frailty assessment using SPPB provides an important prognostic information for clinical outcomes in patients with cirrhosis undergoing liver transplantation.
Keywords: Frailty, Liver transplantation, Cirrhosis, Prognosis

FP-041

Preoperative Prediction Score of Hepatocellular Carcinoma Recurrence in Living Donor Liver Transplantation: Validation of SNAPP Score Developed at Asan Medical Center

Seok-Hwan KIM[1,2], Deok-Bog MOON[*2]

[1]Surgery, Chungnam National University Hospital, Korea; [2]Division of Hepatobiliary and Liver Transplantation, Department of Surgery, Asan Medical Center, Korea

Aims: The previously proposed scoring systems are not readily available due to the lack of simplicity for predicting hepatocellular carcinoma (HCC) recurrence. We aimed to develop and validate the new score system, which can predict HCC recurrence after living donor liver transplantation (LDLT) by using morphologic and biologic data.
Methods: Predictors for HCC recurrence after LDLT were developed (n = 627) and validated (n = 806) in 1433 patients who could collect information to date between 2007 and 2016 at Asan Medical center (AMC) to create the SNAPP score [tumor Size and Number, alpha-fetoprotein (AFP), vitamin K absence-II (PIVKA-II), positron emission tomography (PET)].
Results: On logistic regression based on 3-year recurrence-free survival, the SNAPP factors were independently associated with HCC recurrence. The SNAPP score was highly predictive of HCC recurrence (C statistic, 0.920), and 5-year post-LT recurrence rates were significantly different between low, intermediate, and high SNAPP score groups. The performance of the SNAPP score (C-index [95%CI], 0.840 [0.801-0.876]) on predicting tumor recurrence after LDLT was better than that of the NYCA, the RETREAT, and the MoRAL score.
Conclusions: The SNAPP score provides excellent prognostication after LDLT for HCC patients. Hence, we can help voluntary patients' decisions about whether to undergo LDLT or not.

FP-042

Cross-Match as an Immuno-Oncological Risk Factor for Hepatocellular Carcinoma Recurrence and Inferior Survival after Living Donor Liver Transplantation: A Call for Further Investigation

Cheng-Maw HO, Rey-Heng HU, Yao-Ming WU, Ming-Chih HO, Po-Huang LEE

Department of Surgery, National Taiwan University Hospital, Taiwan

Aims: The success of immunotherapy for patients with hepatocellular carcinoma (HCC) suggest that immune dysregulation occurs in HCC patients. This warrants an immuno-oncological risk assessment in the platform of liver transplantation.
Methods: This retrospective single-center study analyzed risk factors for—particularly cross-matching performed through conventional complement-dependent cytotoxicity cross-match tests—and the outcomes of HCC recurrence following living donor liver transplant.
Results: A total of 71 patients were included. The median follow-up period was 29.1 months. Seventeen (23.9%) patients had posttransplant HCC recurrence, and their 1-, 3-, and 5-year survival rates were 70.6%, 25.7%, and 17.1%, respectively, which were inferior to those of patients without HCC recurrence (87.0%, 80.7%, and 77.2%, respectively [P< 0.001]). In addition to microvascular invasion, positive cross-match results for B cells at 37°C (B- 37°C) or T cells at 4°C (T- 4°C) was associated with inferior overall survival in multivariable analysis after adjustment for tumor status beyond Milan criteria and elevated alpha-fetoprotein levels. Rejection alone cannot be the mechanism underlying the effects of positive cross-match results on patient outcomes. Adjusted survival curves suggested that positive cross-match B- 37°C or T- 4°C was associated with inferior recurrence-free and patient survival, but the robustness of the finding was limited by insufficient power.
Conclusions: Additional large-scale studies are required to validate positive cross-match as an immuno-oncological factor associated with HCC recurrence and inferior patient survival.

FP-043

Performance of Artificial Intelligence in Predicting Survival Following Deceased Donor Liver Transplantation: Retrospective Study Using Multi-Center Data from the Korean Organ Transplant Registry (KOTRY)

Young-Dong YU[1], Kwang-Sig LEE[2], Hye-Sung JO[1], Dong-Sik KIM[1]

[1]Surgery, Korea University Anam Hospital, Korea; [2]AI center, Korea University College of Medicine, Korea

Aims: Although the Model for End-stage Liver Disease (MELD) score is commonly used to prioritize patients awaiting liver transplantation, previous studies have indicated that MELD score may fail to predict well for the postoperative patients. Similarly, other scores (D-MELD score, Balance of risk score) that have been developed to predict transplant outcome have not gained widespread use. These scores are typically derived from linear statistical models. The aim of this study was to compare the performance traditional statistical models with machine learning approaches in predicting survival following liver transplantation using multi-center data.
Methods: Data came from 785 deceased donor liver transplant recipients enrolled in the Korean Organ Transplant Registry (KOTRY, 2014~2019). Five machine learning methods and 4 traditional statistical models were compared for the prediction of survival.
Results: Of the machine learning methods, random forest (RF) yielded the highest area under the receiver operating characteristic curve (AUC-ROC) values (1 month = 0.89, 3 month =0.92, 12 month = 0.87) for predicting survival. The AUC-ROC values of Cox regression analysis was 0.76, 0.85 and 0.80 for 1month, 3month and 12 month posttransplant survival, respectively. However, the AUC-ROC values of the MELD, D-MELD and BAR score were all below 0.70.
Conclusions: Machine learning algorithms such as random forest was superior than the conventional cox regression model and previously reported survival scores in predicting 1 month, 3month 12 month survival following liver transplantation. Therefore, artificial intelligence may have significant potential in providing assistance with clinical decision making during liver

transplantation including matching donors and recipients.

FP-044

Modified Charlson Comorbidity Index as a Pre-Operative Selection Tool for Liver Transplantation in Elderly Patients

Jiho CHOI, YoungRok CHOI*, Su Young HONG, Sanggyun SUH, Kwangpyo HONG, Eui Soo HAN, Jeong-Moo LEE, Suk kyun HONG, Nam-Joon YI, Kwang-Woong LEE, Kyung-Suk SUH

Surgery, Seoul National University College of Medicine, Korea

Aims: Liver transplantation is an effective treatment for end-stage liver disease and hepatocellular carcinoma. The number of elderly patients who undergo liver transplantation is increasing. Although it has been known that the overall outcome in elderly patients is no different from the younger ones, there is no tool to predict the prognosis of elderly patients. Therefore, we hypothesized that Modified Charlson Comorbidity Index (CCI), which includes 5 comorbidities, can predict the outcome of elderly patients.

Methods: We conducted a retrospective study of 155 patients over 65 years old who underwent liver transplantation at Seoul National University Hospital from August 2011 to May 2019. Modified CCI score (MODIFIED CCI) including coronary disease, Chronic Obstructive Pulmonary Disease, Diabetes Mellitus, connective tissue disease, and renal insufficiency was calculated. Then, recipients were subcategorized into 2 groups; low MODIFIED CCI group (0-1), and high MODIFIED CCI group (2-5)). Proportional hazards analysis was performed to determine the independent effect of each variable on post-transplantation (TPL) survival using Modified CCI, age at transplantation, gender, Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, and 5-Factor Modified Frailty Index.

Results: There were 41 patients in the high MODIFIED CCI group. The high MODIFIED CCI group showed significantly lower 1-, 3- month, and 1, 3, 5-year survival than the low MODIFIED CCI group. In the Cox regression, the Modified CCI (HR=2.409), gender (HR=0.447), and MELD score (HR=1.107) remained

Conclusions: Survival after LT is diminished in patients with preoperative high MELD and modified CCI score >1. The Modified CCI can be used

FP-045

Salvage Living Donor Liver Transplantation for Hepatocellular Carcinoma Recurrence after Hepatectomy: Quantitative Prediction Using α-Fetoprotein – des-γ-Carboxyprothrombin – Tumor Volume (ADV) Score

Shin Hwang, Gi-Won Song, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Sung-Gyu Lee

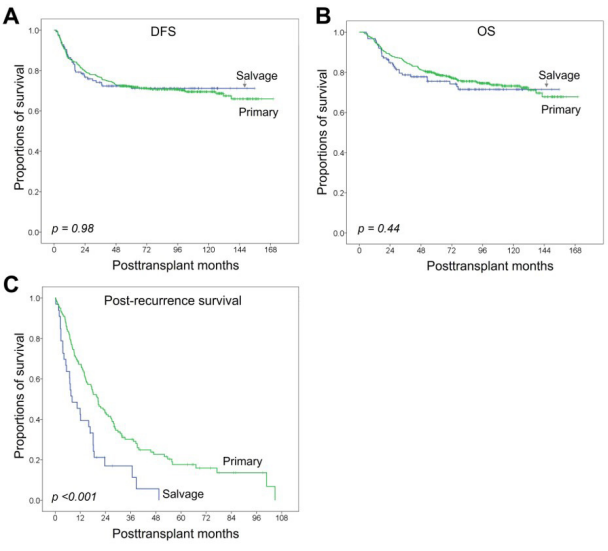
Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

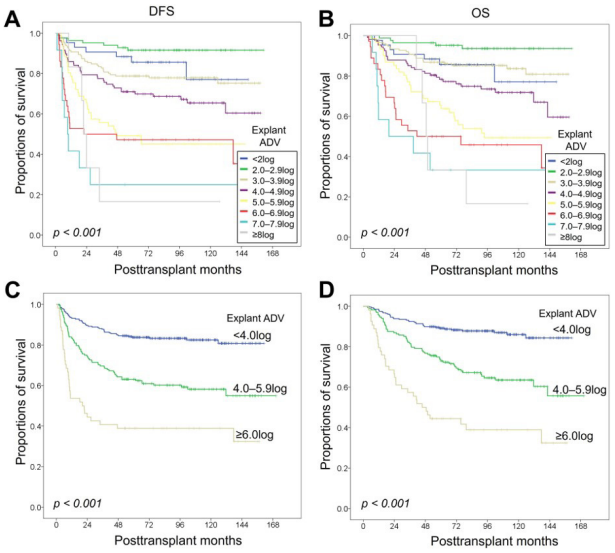
Aims: Salvage liver transplantation is a definite treatment for recurrent hepatocellular carcinoma (HCC) after hepatectomy. ADV score is calculated by multiplying α-fetoprotein and des-γ-carboxyprothrombin concentrations and tumor volume. Prognostic accuracy of ADV score was assessed in patients undergoing salvage living donor liver transplantation (LDLT) and their outcomes were compared with patients undergoing primary LDLT.

Methods: This study was retrospective single-center case-controlled study. Outcomes were compared in 125 patients undergoing salvage LDLT from 2007 to 2018 and in 500 propensity score-matched patients undergoing primary LDLT.

Results: In patients undergoing salvage LDLT, median intervals between hepatectomy and tumor recurrence, between first HCC diagnosis and salvage LDLT, and between hepatectomy and salvage LDLT were 12.0, 37.2, and 29.3 months, respectively. Disease-free survival (DFS, *P*=0.98) and overall survival (OS, *P*=0.44) rates did not differ significantly in patients undergoing salvage and primary LDLT. Pretransplant and explant ADV scores were significantly predictive of DFS and OS in patients undergoing salvage and primary LDLT (*P*<0.001). DFS after prior hepatectomy (*P*=0.52) and interval between hepatectomy and LDLT (*P*=0.82) did not affect DFS after salvage LDLT. Milan criteria and ADV score were independently prognostic of DFS and OS following salvage LDLT, and prognosis of patients within and beyond Milan criteria could be further stratified by ADV score.

Conclusions: Risk factors and post-transplant outcomes were similar in patients undergoing salvage and primary LDLT. ADV score is surrogate biomarker for post-transplant prognosis in salvage and primary LDLT recipients. Prognostic model incorporating ADV scores can help determine whether to perform salvage LDLT.





Keywords: Hepatectomy, Tumor marker, Neoadjuvant therapy, Tumor biology

FP-046

The Impact of Immuneosuppressants on Gut Microbiome of Long-Term Stable Patients after Liver Transplantation

Soon Kyu Lee[1], Joo Yeon Jhun[2], Mi-La Cho[2], Ho Joon Choi[3], Young Kyoung You[3], Pil Soo Sung[1], Jeong Won Jang[1], Seung Kew Yoon[1], Jong Young Choi[1*]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Rheumatism Research Center, Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Dysbiosis of gut microbiota in the end-stage liver disease is dramatically recovered after liver transplantation (LT). However, under the effect of immunosuppressants (IS), gut microbial balance in the long-term LT setting has not been elucidated. In this study, we examined the gut microbial balance in the long-term LT patients.

Methods: A total of 16 long-term LT patients and 20 healthy volunteers were consecutively enrolled in our study. Included LT patients had normal liver function without history of rejection and underwent LT more than 5 years ago. Healthy controls have no medical diseases including metabolic and alcoholic disease. Fecal specimens were collected in each patient and we compared the microbial composition of LT patients to healthy controls.

Results: The mean age of LT patients was 61.6 years and the mean time from LT was 11.7 years. Of 16 included LT patients, 9 patients (56.2%) were male and 13 patients (81.2%) underwent living-donor LT. Tacrolimus was used in 13 patients with the median dose of 2.3mg and the other 3 patients received cyclosporine. The diversity and richness of gut microbiome were similar between the LT and healthy groups. However, compared with the healthy group, the LT group showed reduction in potentially beneficial families including Akkermansiaceae, Bifidobacteriaceae and Ruminococcaceae, whereas increases in potentially pathogenic family Bacteroidaceae. At species level, Bifidobacterium longum, Akkermansia muciniphila, Faecalibacterium prausnitzii were decreased in the LT group compared to the healthy group.

Conclusions: In the long-term stable LT patients, gut microbial imbalance is still noted and it may be attributable to IS. Further studies evaluating the effects of gut microbial imbalance on the immune cellular homeostasis of the long-term LT patients are needed.

Keywords: Liver transplantation, Immunosuppressant, Gut mirobiome, Gut dysbiosis

DAY 3: Saturday, May 15, 2021

Free Paper Session 2

FP-047~FP-054	Alcohol, Liver Cirrhosis
FP-055~FP-062	Liver Cancer, Clinical
FP-063~FP-070	Surgery, Technical Issues
FP-071~FP-078	Liver Cancer, Clinical
FP-079~FP-086	Biliary and Pancreatic Disease

Saturday, May 15, 2021, 08:30-09:50

7. Alcohol, Liver Cirrhosis

FP-047

Estimation of Fibrosis and Steatosis of Liver Using Electrochemical Impedance Spectroscopy on A Needle: A Preliminary Result

Hee Joon KIM[1], Jong Hyun LEE[2], Jin Hwan KIM[2], Yang Seok KOH[1], Chol Kyoon CHO[1]

[1]Division of HPB Surgery, Department of Surgery, Chonnam National University Medical School, Korea; [2]School of Mechanical Engineering, Gwangju Institute of Science and Technology (GIST), Korea

Aims: Preoperative estimation of the liver function is mandatory for safe hepatectomies and successful liver transplantations. Aim of this study is to evaluate the diagnostic and predictive value of electrochemical impedance in estimation of the degree of fibrosis and steatosis of the liver.

Methods: A specialized electrochemical impedance spectroscopy on a needle(EoN) for measurement of tissue impedance was designed and made in Gwangju Institute of Science and Technology(GIST). The electrical impedances for nine resected liver parenchyma were measured at two different points of each specimens in the frequency range of 100Hz to 1Mhz. The electrical impedance were analyzed comparing to pathologic grading of fibrosis and steatosis.

Results: The nine specimens were diagnosed with one of fibrosis grade 0, two of fibrosis grade 1, one of fibrosis grade 2, three of fibrosis grade 3, and two of fibrosis grade 4. Of these data, one preoperative portal vein embolization case, and one preoperative chemotheraphy were excluded. The specimens with higher fibrosis grade have shown the significantly higher impedance value. The fibrosis grade was significantly correlated to electrical impedance in all current frequency range (P<0.001~0.022, R=0.341~0.753, R2=0.1335~0.566). The highest correlation coefficient was observed at the current frequency of 735703Hz (P<0.001, R=0.753, R2=0.566). Macrosteatosis was significantly correlated to electrical impedance in the current frequency from 100 to 544Hz (P<0.001, R=-0.583, R2=0.340).

Conclusions: The electrical impedance of liver parenchyma was significantly correlated to fibrosis and steatosis. This study have shown the possibility of preoperative quantification of hepatic fibrosis and steatosis using the electrical impedance spectroscopy on a needle.

FP-048

Diagnostic Efficacy of Serum Asialo α1-Acid Glycoprotein Levels for Liver Fibrosis and Cirrhosis in CHB Compared to Healthy Subjects: A Prospective Study

Yoon Seok Lee, Young-Sun Lee, Ji Hoon Kim, Sun Young Yim, Young Kul Jung, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Soon Ho Um, Kwan Soo Byun

Department of Internal Medicine, Korea University College of Medicine

Aims: Serum Asialo α1-Acid Glycoprotein (AsAGP) is a novel biomarker specific for liver fibrosis. However, there is no prospective study to investigate diagnostic performance of AsAGP for fibrosis burden compared with healthy control. The aim of this study to evaluate the diagnostic efficacy of serum AsAGP level in differentiating chronic hepatitis and cirrhosis.

Methods: A total of 206 subjects (68 healthy controls, 70 chronic hepatitis B, 68 hepatitis B related liver cirrhosis) were prospectively enrolled. Liver cirrhosis was classified based on liver stiffness levels (>11 kilopascal) measured by transient elastography (FibroScan).). Only the cases that satisfies all the following criteria were enrolled as healthy control; absence of fatty liver in sonography, HTN, DM We compared serum AsAGP level between the three groups and evaluated diagnostic performance differentiating chronic hepatitis and cirrhosis.

Results: Serum AsAGP level was significantly different between heathy control, chronic hepatitis and liver cirrhosis (1.04 ± 0.31 μg/ml, 1.12 ± 0.34 μg/ml, 1.51 ± 0.43 μg/ml respectively; ANOVA P<0.001). Serum AsAGP level was positively correlated with liver stiffness (r= 0.46, p-value<0.001). We performed area under the receiver operating characteristics (AUROC) for evaluating diagnostic efficacy of AsAGP between three groups. AUROC of Healthy control versus cirrhosis was 0.943 (P<0.001). The optimal cut-off level was 1.056 μg/ml (sensitivity 88.24 %, specificity 86.76 %). AUROC of Healthy control versus chronic hepatitis was 0.842, P<0.001). The optimal cut-off level was 0.918 μg/ml (sensitivity 90%, specificity 70.59%). AUROC of chronic hepatitis versus cirrhosis was 0.788, P<0.001). The optimal cut-off level was 1.442 μg/ml (sensitivity 67.65%, specificity 91.43%). In multivariate analysis, serum AsAGP level was the independent predictor of cirrhosis (odds ratio 1.58, p-value <0.0001)

Conclusions: Serum AsAGP level in patients with cirrhosis was significantly higher than healthy controls and chronic hepatitis. AsAGP level showed a good diagnostic performance in predicting liver cirrhosis and chronic hepatitis which suggests a potential role as a biomarker for liver fibrosis.

Keywords: Liver cirrhosis, Biomarker

FP-049

Lactobacillus and Pediococcus Attenuates the Progression of Alcoholic Liver Disease by Improving Inflammation

Hyeong Seop Kim[1], Mi Ran Choi[1], Ye Rin Choi[1], Ji Ye Hyun[1], Min Kyo Jeong[1], Hee Jin Park[1], Jung A Eom[1], Byeong Hyun Min[1], Sang Jun Yoon[1], Haripriya Gupta[1], Yoseph Asmelash[1], Raja Ganesan[1], SatyiaPriya Sharma[1], Eun Ju Park[1], Sung Min Won[1], Sang Hak Han[2], Dong Joon Kim[1†], Ki Tae Suk[1†]

[1]Institute for Liver and Digestive Diseases, Hallym University College

of Medicine, Chuncheon, South Korea; [2]Department of pathology, Hallym University College of Medicine, Chuncheon, South Korea

Aims: Alcoholic liver disease (ALD) is a leading cause of liver-related deaths and closely related with gut-microbiome. The inflammation due to microbiome-derived endotoxemia is main etiology of ALD progression. We evaluated the effects of *Lactobacillus* and *Pediococcus* on ALD progression in mice model.

Methods: Eight weeks male C57BL/6J mice were separated into 5 groups (n=10/group; control, ALD [Lieber-De Carli liquid diet+5% EtOH], and 3 ALD+strains [10^9 CFU/g for 12 weeks; *L. helveticus*, *L. lactics*, and *P. pentosaceus*). Liver/body weight ratio, pathology, quantitative PCR analysis of mRNA levels of markers for inflammation and fibrosis, and inflammation enzyme via western blot were examined.

Results: Increase liver weight in ALD group was significantly decreased by the supplementation of *L. lactics*, and *P. pentosaceus*. In the pathology, *L. helveticus* supplementation effectively ameliorated elevated liver inflammation and grade in EtOH group. EtOH induced deterioration in pro/anti-inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, and IL-10) was improved in the ALD+strain groups. Expression of Col1α1 and Cox-2 was increased in EtOH and downregulated in *L. helveticus*, *L lactics*, and *P. pentosaceus*

Conclusions: *L. helveticus*, *L. lactics*, and *P. pentosaceus* have therapeutic effects on inflammation of ALD. Preclinical or clinical studies are needed for the evaluation of detailed mechanism study.

Keywords: Alcoholic Liver Disease, Inflammation, Lactobacillus, Pediococcus

FP-050

Impact of Previous Acute Decompensation on Tolerance to Acute-on-Chronic Liver Failure

Eileen L. Yoon[1], Do Seon Song[2], Hee Yeon Kim[2], Chang Wook Kim[2], Jin Mo Yang[2], Young Kul Jung[3], Hyung Joon Yim[3], Baek Gyu Jun[4], Jung Gil Park[5], Young Chang[6], Jeong-Ju Yoo[6], Sang Gyune Kim[6], Soung Won Jeong[6], Jae Young Jang[6], Seong Hee Kang[7], Moon Young Kim[7], Ki Tae Suk[8], Dong Joon Kim[8], Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

[1]Department of Internal Medicine, Hanyang University College of Medicine; [2]Department of Internal Medicine, The Catholic University of Korea; [3]Department of Internal Medicine, Korea University; [4]Department of Internal Medicine, Inje University; [5]Department of Internal Medicine, Yeungnam University; [6]Department of Internal Medicine, Soonchunhyang University; [7]Department of Internal Medicine, Yonsei University Wonju College of Medicine; [8]Department of Internal Medicine, Hallym University College of Medicine

Aims: Acute-on-chronic liver failure (ACLF) is known to be associated with decreased tolerance to inflammatory response. We aimed to evaluate the impact of previous acute decompensation (AD) on the tolerance to ACLF.

Methods: Cirrhosis patients who were admitted with acute deterioration in 47 academic hospitals were prospectively enrolled during 2015~2019. Patients were divided into two groups without previous AD (1st event) and with previous AD (Recurrent event) at index admission. Development of ACLF within 28 days from the enrollement were collected. Liver transplant free survival was evaluated. ACLF was defined by the EASL CLIF-C definition.

Results: A total of 1,670 cirrhosis patients were enrolled and followed up for 15.8±10.0 months (3.0-48.6). Three fourths of those patients were male and mean age was 55 years old. Half of them (N=837) experienced index admission as a 1st event. Seventy percent of those patients were due to chronic alcohol use. Patients without previous AD were younger, presented more with ascites and jaundice, higher WBC, and sodium levels compared to the patients with previous AD. CRP, MELD, and CLIF-C Organ failure score were not different between two groups. ACLF within 28 days was more frequent in the patients with previous AD than in those without previous AD (26.9% vs. 21.7%, *P*=0.014). However, the survival of these patients with ACLF were 24.8 months (95% C.I 19.2-30.5) in those without previous AD and 16.5 months (95% C.I 13.4-19.6) in those with previous AD, which were not different between two groups.

Conclusions: ACLF is more frequent in the decompensated cirrhosis patients with previous AD. Additionally, the survival of patients who experienced ACLF were not different regardless of previous AD. Further studies would be needed to clarify the possibility of decreased tolerance to ACLF in cirrhosis patients without previous AD.

Keywords: Acute-on-chronic liver failure, Tolerance, Inflammation, Decompensation

FP-051

Hepatopulmonary Syndrome Is Related to the Development of Acute-on-Chronic Liver Failure and Poor Prognosis in Cirrhotic Patients

Han Seul Ki[1*], Moon Young Kim[1,2,3*], Seong Hee Kang[1,2], Ki Tae Suk[4], Soon Koo Baik[1,2,3]

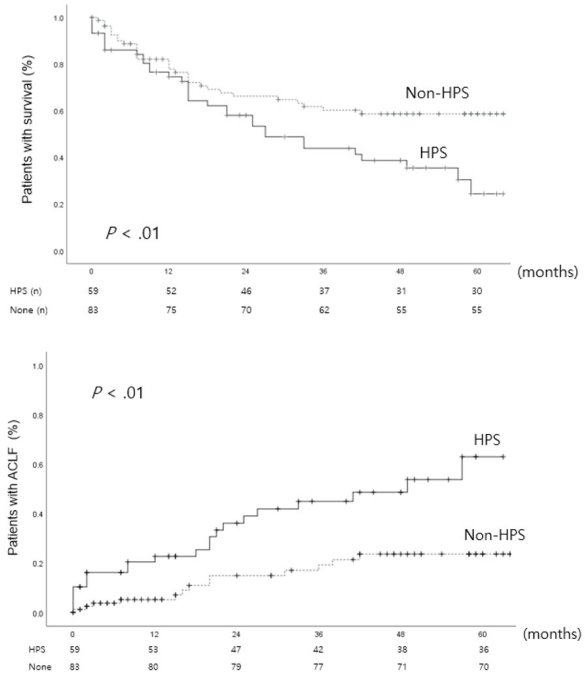
[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [2]Regeneration Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [3]Cell Therapy and Tissue Engineering Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [4]Department of Internal Medicine, Hanllym University College of Medicine, Chuncheon, South Korea

* These authors contributed equally to this work.

Aims: Long-term prospective data on hepatopulmonary syndrome (HPS) from a large number of patients, especially in Asian patients, are lacking. We evaluated the long-term prognosis, specifically the development of acute-on-chronic liver failure (ACLF), of HPS and related factors.

Methods: A total of 142 patients with cirrhosis who underwent

saline-agitated contrast echocardiography for the diagnosis of HPS were enrolled and observed prospectively.



Results: The median follow-up period was 27 months. A total of 59 patients (41%) were diagnosed with HPS (24 grade 1, 23 grade 2, 12 grade 3). Thirty-eight and 37 patients died in the HPS and non-HPS groups, respectively (*P*<.01). The 5-year survival rate was 47% in the HPS group and 62% in the non-HPS group. In the Cox proportional hazards model, HPS and Model for End-stage Liver Disease (MELD) score≥18, and Child–Turcotte–Pugh (CTP) class B/C were significant risk factors for mortality after adjusting for other risk factors (HPS hazard ratio [HR] = 1.9, *P*=.01; MELD score≥18 HR = 2.3, *P*<.01; CTP class B/C HR = 2.9, *P*<.01). Compared to that in non-HPS group, the HPS group had a significantly higher incidence of ACLF during follow-up (*P*<.01) and more frequently presented with lung involvement of ACLF (*P*=.03).

Conclusions: In the long-term follow-up cohort, patients with HPS showed poorer prognosis than that of patients without HPS. HPS was a risk factor for ACLF development independent of hepatic dysfunction, and lung involvement was common.

Keywords: Hepatopulmonary syndrome, Cirrhosis, Portal hypertension, Cirrhosis complications

FP-052

A Model to Predict Survival in Patients Undergoing Portosystemic Shunt Embolization

Seo Yeon Yoo, Won-Mook Choi, Young-Suk Lim

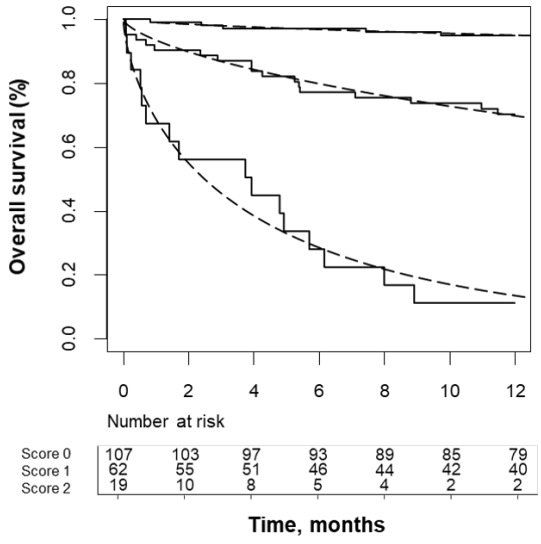
Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Portosystemic shunt embolization (PSSE), such as plug-assisted (PARTO) and balloon-occluded retrograde transvenous obliteration (BRTO), is a potentially effective treatment for hepatic encephalopathy and gastric varix in patients with cirrhosis. However, some of the patients undergoing PSSE rapidly progress to hepatorenal syndrome and hepatic failure. Therefore, identifying the patients who would be benefited by the procedure is important. The aim of this study was to develop a prognostic model to accurately predict the survival of the patients after PSSE.

Methods: A historical cohort of 188 consecutive patients who received PARTO, BRTO, or other forms of PSSE between January 2005 and May 2020 at Asan Medical Center, Seoul, Korea were analyzed by a Cox proportional hazard model to develop a prediction model for overall survival.

Results: Median survival of the included patients was 19.7 months, and 1-year survival rate was 79%. Total bilirubin and International Normalized Ratio (INR) were the two only independent baseline factors that were significantly associated with the overall survival of the patients. A simple risk prediction score model ("Bilirubin-INR score") was developed assigning 1 point for ≥3 mg/dL of total bilirubin and for ≥1.3 of INR, respectively. Harrell's C-index of the Bilirubin-INR score for predicting 1-year survival was 0.834 (95% confidence interval, 0.765–0.904), which was comparable to the MELD score (*P*=0.64) and the Child-Pugh score (*P*=0.30), and indicated excellent discrimination performance. The estimated survival rate stratified by the Bilirubin-INR score was in high concordance with the observed survival rate, indicating excellent calibration performance.

Conclusions: The novel Bilirubin-INR score, which is easier to calculate than MELD or Child-Pugh Score, may help identify a proper indication for PSSE in cirrhotic patients with hepatic encephalopathy or gastric varix associated with portosystemic shunt.



Keywords: BRTO, Cirrhosis, Gastric varix, Hepatic encephalopathy, PARTO, Portosystemic shunt, Shunt embolization

FP-053

Elevated Transaminase Level at Admission as a Independent Predictor for Mortality in Coronavirus Disease 2019

Hea-Eun Kim, Jae-Won Park, Sang-Mi Jang, Chan-Young Jeong, Gwang-Hyeon Chio, Eun-Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim

Department of Internal Medicine, Seoul National University Bundang Hospital

Aims: Coronavirus disease 2019 (COVID-19) is a systemic disease which may involve liver, but the relationship between liver injury and mortality or disease severity is unclear. Herein, we aimed to evaluate the clinical characteristics of COVID-19 patients with liver injury and the prognostic value of abnormal liver tests in patients with COVID-19.

Methods: We retrospectively included 156 COVID-19 patients over 18 years old who were admitted to our tertiary referral center. Hospitalization criteria included patients with underlying diseases or severe symptoms requiring intensive care. Clinical features and survival of patients were compared according to the liver tests. Multivariate logistic regression model was used to analyze the risk factors for disease severity.

Results: Overall, 100 patients (64.1%) developed systemic inflammatory response syndrome (SIRS) and thirteen patients (8.3%) died during hospitalization. Forty-nine patients (31 %) showed elevated transaminases (TAs) at admission and twenty patients (13 %) presents elevated total bilirubin. Patients with elevated TAs had a higher ratio of male sex (76 % vs 25 %, $P<0.05$), a higher chance of developing SIRS (74 % vs 48 %, $P<0.05$), a higher rate of severe pulmonary infiltration (64 % vs 56 %, $P<0.05$) and higher mortality rate (18.4 % vs 3.7 %, $P<0.05$). Multivariate logistic regression analysis showed that the elevated TA level was an independent predictor of mortality (odds ratio: 24.661, 95% confidence interval: 3.7-161.0), along with hypertension, chronic lung disease, coagulopathy and renal dysfunction .

Table 3. Multivariate logistic regression analysis of patients with coronavirus disease 2019

	Regression coefficient	Odds ratio (95% CI)	*P value*
Age	0.033	1.033 (0.957 - 1.116)	0.403
Sex	-1.618	0.198 (0.035 - 1.133)	0.069
Severe pneumonia	0.078	1.081 (0.133 - 8.785)	0.942
Diabetes Mellitus	-0.285	0.752 (0.119 - 4.741)	0.092
Hypertension	2.536	12.628 (1.258 - 126.812)	<0.05
Dyslipidemia	1.104	3.015 (0.204 - 44.519)	0.645
Cardiovascular disease	-0.465	0.628 (0.080 - 4.907)	0.196
Chronic respiratory disease	3.936	51.191 (4.305 - 608.751)	<0.05
WBC count	0.019	1.019 (0.920 - 1.130)	0.716
Hemoglobin	-0.113	0.893 (0.574 - 1.388)	0.614
Platelet	-0.007	0.993 (0.980 - 1.007)	0.323
Elevated aminotransferase group	3.205	24.661 (3.777 - 161.001)	<0.05
Total bilirubin	-1.066	0.344 (0.042 - 2.831)	0.321
PT INR	3.273	26.381 (1.775 - 392.069)	<0.05
Cr	0.236	1.266 (0.989 - 1.622)	0.061

Conclusions: Elevated TA level at hospital admission was associated with grave disease course and predictive of in-hospital mortality in patient with severe COVID-19.

Keywords: Liver injury, Covid19, Mortality

FP-054

A Nationwide Study of Pyogenic Liver Abscess in Korea: Incidence, Mortality and Temporal Trends during 2007-2017

Tae Kyu Lee, Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, SoonChunHyaung University Bucheon Hospital

Aims: The epidemiology of pyogenic liver abscess (PLA) continues to change but few population-based studies have been conducted in Korea. This study investigated the epidemiology and clinical outcomes of PLA patients in current 11 years

Methods: We used the Health Insurance Review and Assessment Service data between 2007 and 2017. The annual incidence rates, demographic data, underlying diseases, complications, and mortality rates were analyzed using the data.

Figure 1

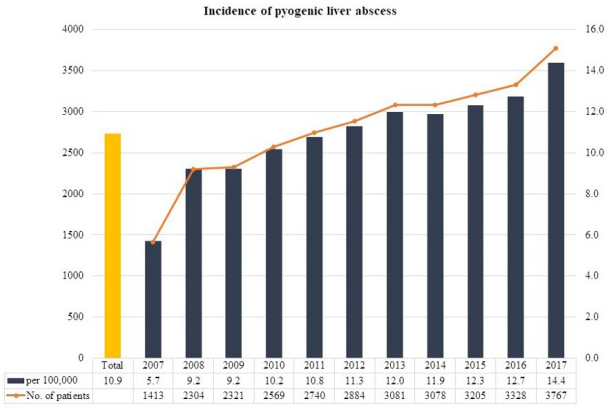
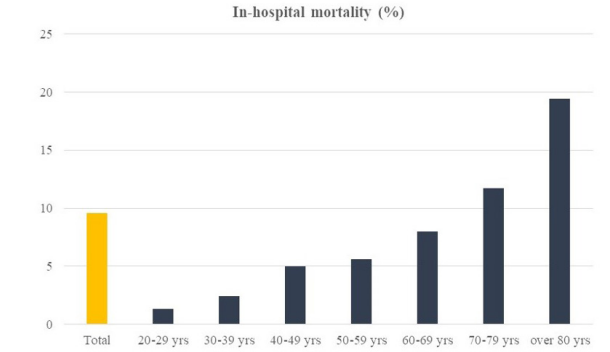


Figure 2



Results: The annual incidence of PLA for all age groups was 10.9 per 100,000 population. The incidence was gradually increased in Korea from 5.7 per 100,000 in 2007 to 14.4 per 100,000 in 2017. In patients with liver abscess, the rates of diabetes and malignancy were 37.24 and 26.5%, respectively. Metastatic infection was reported in 1.74% of patients and endophthalmitis was most common. In-hospital mortality was 9.6%, and there

was no significant change in mortality during the observation period. The mortality rate tends to increase with age, but the mortality rate is greatly affected by the accompanying diseases, especially cancer. Mortality was associated with older age, female, diabetes, malignancy, chronic kidney disease in multivariate analysis.

Conclusions: The incidence of PLA is rapidly increasing in Korea and in-hospital mortality has not changed so far. In particular, patients with comorbidity such as old age, cancer, diabetes have a high in-hospital mortality, so clinical attention is required.

Keywords: Liver abscess, Hepatic abscess, Epidemiology, Incidence, Mortality, Trends, Nationwide study, Korea

Saturday, May 15, 2021, 11:10-12:30

8. Liver Cancer,Clinical

FP-055

Prediction of Microvascular Invasion via Gadoxetic acid-Enhanced MRI in Hepatocellular Carcinoma: The Implication of Planning Extent of the Hepatectomy

Hyeo Seong HWANG[1], Heejin BAE[2], Mi-Suk PARK[2], Dai Hoon HAN[1], Gi Hong CHOI[*1], Kyung Sik KIM[1], Jin Sub CHOI[1]

[1]Department of Surgery, Yonsei University College of Medicine, Korea; [2]Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Korea

Aims: The purpose of this study was to identify predictive factors for microvascular invasion (MVI) in hepatocellular carcinoma (HCC) using clinical factors and imaging findings of magnetic resonance imaging (MRI), to divide the patients into a subgroup with similar prognosis and finally to evaluate whether the extent of hepatectomy can affect long-term outcomes in the subgroup.

Methods: A total of 410 patients with surgically resected single HCC (≤ 5cm) who underwent preoperative gadoxetic acid-enhanced MRI were included. Significant predictive factors for MVI were identified via univariate and multivariate analysis and used to divide the patients into low and high-risk groups. In the subgroup, long-term outcomes were analyzed after the minor versus major hepatectomy.

Results: Four variables were independently associated with MVI: alpha-fetoprotein ≥ 400 ng/ml (P=0.021), tumor size ≥ 3 cm (P<0.001), non-smooth tumor margin (P<0.001) and arterial peritumoral enhancement (P=0.001). Patients with a combination of three or more factors were classified as the high-risk group (n = 103), which showed worse prognosis than the low-risk group (n=307) (P<0.001). While the extent of hepatectomy was not associated with prognosis in the low-risk group, major hepatectomy significantly improved disease-free survival (P<0.011) and decreased early intrahepatic recurrence (<2 years) (P=0.005) than minor hepatectomy in the high-risk patients.

Conclusions: The patients who had a combination of three or more predictive factors for MVI showed worse prognosis after hepatectomy for HCC and major hepatectomy improved long-term outcomes in these high-risk patients.

FP-056

Comparison of Overall Survival between Surgical Resection and Radiofrequency Ablation for Early Hepatitis B-Related Hepatocellular Carcinoma after Adjusting Antiviral Treatment

Moonhaeng Hur[1], Jeong-Hoon Lee[1], Ju Yeon Kim[1], Ji Hoon Hong[1], Min Kyung Park[1], Hee Jin Cho[1], Ji Hye Kim[1], Minseok Albert Kim[1], Joon Yeul Nam[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Dong Ho Lee[2], Jeong Min Lee[2], Suk Kyun Hong[3], Nam-Joon Yi[3], Kwang-Woong Lee[3], Kyung-Suk Suh[3], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [2]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [3]Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea

Aims: It is still controversial whether surgical resection provides superior overall survival for early hepatocellular carcinoma (HCC) compared to radiofrequency ablation (RFA). In this study, we aimed to compare the two potentially curative treatments (resection vs. RFA) after adjusting for antiviral treatment-related factor.

Methods: This retrospective study included 761 patients who underwent surgical resection (n=567) or RFA (n=194) as an initial treatment for hepatitis B virus-related HCC patients at very-early or early stage between 2006 and 2016 at a single referral center. Primary and secondary endpoints were OS and recurrence-free survival (RFS), respectively.

Results: The RFA group had smaller mean tumor size (1.7 vs. 3.9 cm), but higher proportion of cirrhotic patients (85.6% vs. 63.1%) than the resection group (both P<0.01). In the entire cohort, during 81.0 (interquartile range, 62.3–107.1) months of follow-up, there was no difference in both OS (resection vs. RFA: hazard ratio [HR]=2.073, 95% confidence interval [CI]=0.858–5.008, P=0.11) and RFS (HR=0.699, 95% CI=0.488–1.003, P=0.052) between two groups after inverse probability of treatment weighting (IPTW). In an IPTW-balanced subgroup of patients with single HCC of <3 cm (256 and 167 patients treated with resection and RFA, respectively), the use of antiviral treatment was independently associated with longer OS (adjusted HR [aHR]=0.282, 95% CI=0.104–0.766, P=0.01) and RFS (aHR=0.565, 95% CI=0.383–0.835, P<0.01). After adjustment for the antiviral treatment, RFA was not independently associated with either OS (aHR=2.151, 95% CI=0.708–6.532, P=0.18) or RFS (aHR=0.716, 95% CI=0.507-1.010, P=0.06). There was

no difference in both OS (aHR=0.522, 95% CI=0.058–4.724, *P*=0.56) and RFS (aHR=1.116, 95% CI=0.738–1.688, *P*=0.60) between patients treated with tenofovir vs. entecavir.

Conclusions: RFA may provide comparable OS to resection in the treatment for very-early or early HCC, although RFS is marginally shorter than the resection group after adjusting the antiviral treatment.

Keywords: Hepatocellular carcinoma, Surgical resection, Radiofrequency ablation, Nucleos(t)ide analogue

FP-057

The Effectiveness of Transarterial Radioembolization for Large Single Nodular Hepatocellular Carcinoma: A Comparison to Surgical Resection

Jihye Kim[1,2,*], Ju Yeon Kim[1,*], Jeong-Hoon Lee[1,], Dong Hyun Sinn[2,**], Moon Haeng Hur[1], Ji Hoon Hong[1], Min Kyung Park[1], Hee Jin Cho[1], Na Ryung Choi[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Hyo Cheol Kim[3], Nam-Joon Yi[4], Kwang-Woong Lee[4], Kyung-Suk Suh[4], Dongho Hyun[5], Hee Chul Park[6], Jong Man Kim[7], Jung-Hwan Yoon[1]**

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Radiology, Seoul National University College of Medicine, Seoul, Korea; [4]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea; [5]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [7]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: The optimal treatment for large hepatocellular carcinoma (HCC) is still controversial due to a high risk of recurrence even after surgical resection. This study aimed to compare long-term outcomes of surgical resection vs. recently introduced novel internal (transarterial radioembolization, TARE) and external (proton beam therapy, PBT) radiatiotherapies in patients with large single nodular HCC.

Methods: We conducted a retrospective analysis on a total of 565 patients who were initially treated with either surgical resection (the resection group, n=500) or radiotherapies (TARE or PBT; the radiotherapy group, n=65) for large (≥5 cm) single nodular HCC at two referral centers in Korea. Patients with Child-Pugh-Turcotte class B/C, Eastern Cooperative Oncology Group ≥1, major portal vein invasion and/or extrahepatic metastasis at baseline were excluded. Primary outcome was overall survival (OS) and secondary outcomes included time-to-intrahepatic progression and time-to-progression (TTP).

Results: The resection group had younger age (median, 60 vs. 69 years), lower prevalence of cirrhosis (30.2% vs. 43.1%), and smaller tumor size (median, 7.0 cm vs. 9.5 cm) (all *P*<0.05). During follow-up (median, 35.9 months), OS (39.7 vs. 19.6 months, *P*=0.016), the median time-to-intrahepatic progression (21.7 vs. 11.0 months, *P*<0.001) and TTP (18.1 vs. 10.4 months, *P*=0.045) were longer in the resection group than in the radiotherapy group by a crude analysis. After employing inverse probability of treatment weighting (IPTW), the resection group showed significantly longer time-to-intrahepatic progression (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.32–0.90; *P*=0.019), while TTP (HR, 0.71; 95% CI, 0.43–1.18; *P*=0.185) and OS (HR, 0.50; 95% CI, 0.22–1.15; *P*=0.103) were comparable. The resection group showed independently lower risk of intrahepatic tumor progression (adjusted HR, 0.55; 95% CI, 0.35–0.87; *P*=0.010).

Conclusions: Surgical resection showed a comparable OS and TTP to TARE or PBT for large single nodular HCC despite of a significant benefit in time-to-intrahepatic tumor progression.

Keywords: Hepatocellular carcinoma, Transarterial radioembolization, Proton beam therapy, Resection

FP-058

Models for Tumor Recurrence after Liver Transplantation Can Predict Early Recurrence after Curative Liver Resection in Solitary Hepatocellular Carcinoma

Sung Joon Kim[1], Jong Man Kim[2], Gyu-Seong Choi[2], Nam-Joon Yi[3], Kwang-Woong Lee[3], Kyung-Suk Suh[3], Jae-Won Joh[2]

[1]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea

Aims: Hepatocellular carcinoma (HCC) is the third highest cause of cancer mortality worldwide. Although various treatment choices have been developed for HCC, liver resection (LR) is known as the curative treatment option along with liver transplantation. Despite remarkable advances in diagnosing and treatment modalities of HCC, the high incidence of recurrence remains a major challenge in HCC. Early recurrence is associated with poor prognosis in hepatectomy patients. Models for tumor recurrence after liver transplantation (MoRAL) to predict the HCC recurrence in HCC patients who underwent living donor liver transplantation (LDLT). This study aimed to validate the predictability of MoRAL model on solitary treatment-naïve HCC patients who underwent LR.

Methods: This study included 443 patients with intrahepatic HCC recurrence after LR in two large-volume hospitals in Korea from January 2005 to December 2011. Patients were divided into the early recurrence group, who developed recurrence within 2 years after hepatectomy (n=312), and the late recurrence group (n=131). Various clinicopathological factors and the MoRAL score were retrospectively analysed.

Results: Median AFP, PIVKA-II, and MoRAL score in the early recurrence group were significantly higher than in the late recurrence group. In pathologic characteristics, median tumor

size, the presence of grade 3 or 4, tumor necrosis, microvascular invasion, and macrovascular invasion in the early recurrence group were also higher than in the late recurrence group. Multivariate analysis showed that high ICG-R15, MoRAL score > 314.8, and tumor grade 3 or 4 were predisposing factors for HCC recurrence after curative LR.

Conclusions: MoRAL score could be used as the factor to predict the early recurrence in the patients who underwent curative LR. Using this model, we can find the early recurrence-risk group, follow up this group more thoroughly, and improve the survival rate by implementing appropriate treatments at more suitable timing.

Keywords: Tumor markers, Outcomes, Hepatocellular carcinoma, Surgery

FP-059

Liver Transplantation for Combined Hepatocellular Carcinoma and Cholangiocarcinoma in Korea

Jong Man KIM[1], Dong Jin JOO[2], Shin HWANG[3], Nam-Joon YI[4], Je Ho RYU[5], Yang Won NA[6], Dong-Sik KIM[7], Doo Jin KIM[8], Young Kyoung YOO[9], Hee Chul YU[10], Myoung Soo KIM[2]

[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea; [2]Department of Surgery, Yonsei University College of Medicine, Korea; [3]Department of Surgery, Asan Medical Center, College of Medicine University of Ulsan, Korea; [4]Department of Surgery, Seoul National University College of Medicine, Korea; [5]Department of Surgery, Pusan National University College of Medicine, Korea; [6]Department of Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Korea; [7]Department of Surgery, Korea University College of Medicine, Korea; [8]Department of Surgery, Gachon University Gil Medical Center, Gachon University College of Medicine, Korea; [9]Department of Surgery, College of Medicine, Catholic University of Korea, Korea; [10]Department of Surgery, Chonbuk National University School of Medicine, Korea

Aims: There is still no consensus about the actual role of liver transplantation (LT) in the therapeutic algorithm of combined hepatocellular-cholangiocarcinoma (cHCC-CC) because of low incidence and few clinical information.

Methods: We retrospectively identified 111 patients at nine centers from 2001 to 2019 in Korea.

Results: Of the 111 patients, 85.6% (n=95) was male and the median age was 54 years (range 31-66 years). HBV is 82% (n=91) and HCC is 96% (86.3%) preoperatively. Seventy-four patients (66.7%) received locoregional therapy (LRT) before LT. Median tumor size was 2.5cm (range, 0.5-7.2cm) and the ratio of beyond Milan criteria was 40.5% (n=45). The 1-year, 3-year, and 5-year disease-free survival rates and tumor-related patient survival rates were 77.6%, 56.3%, and 51.1% and 84.4%, 63.8%, and 56.7%, respectively. The extrahepatic site was 75.5% as an initial tumor recurrence site in recurrent tumor patients. Numbers of LRT before LT >3 and tumor size >3cm were closely associated tumor recurrence and early tumor recurrence within 1 year after LT. Tumor size >3cm was only predisposing factor for tumor-related death.

Conclusions: It is difficult to diagnose cHCC-CC before LT, but a good prognosis can be expected if the tumor size is less than 3 cm in pathology.

FP-060

Impact of Anatomical Liver Resection for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

SeongWook SHIN, Tae-Seok KIM*

Division of Hepatobiliary & Pancreatic Surgery, Department of Surgery, Dongsan Medical Center, Keimyung University School of Medicine, Korea

Aims: Although several retrospective studies comparing anatomical liver resection (AR) and non-anatomical liver resection (NAR) for hepatocellular carcinoma (HCC) have been published, the efficacy of anatomic liver resection for HCC remains unclear. This study aimed to compare the oncologic and surgical outcomes of AR and NAR for HCC by performing meta-analysis of published studies.

Methods: We systemically reviewed the MEDLINE, Embase, and Cochrane Library databases for propensity score matching (PSM) studies compared AR and NAR for HCC. The primary outcome was overall survival (OS) and recurrence free survival (RFS). Secondary outcomes were recurrence patterns and peri-operative outcomes.

Results: A total of 19 PSM studies were included. AR was superior to NAR in 3- and 5-year OS (3-year OS HR:0.79, 95% CI: 0.68~0.91, *P*=0.001; 5-year OS HR:0.83, 95% CI:0.71~0.95, *P*=0.009). AR showed a significantly better 1-, 3-, and 5-year RFS than NAR with low local recurrence rate, intra- and extra-hepatic recurrence (1-year RFS HR:0.79, 95% CI:0.69~0.90, *P*=0.0005; 3-year RFS HR:0.81, 95% CI: 0.75~0.87, *P*=0.00001; 5-year RFS HR:0.82, 95% CI:0.76~0.88, *P*<0.00001). In subgroup analyses about tumor with diameter less than 5cm and with microscopic cancer spread, RFS in AR group was significantly better than NAR. However, AR showed comparable 3- and 5-year RFS with NAR group in patients with cirrhotic liver. Also, post-operative overall complications including biliary leakage and hepatic failure were similar between two groups.

Conclusions: Our meta-analysis revealed that AR showed better OS and RFS with low local recurrence than NAR especially patients with tumor diameter less than 5cm and non-cirrhotic liver.

FP-061

Long-Term Surgical Outcomes of Liver Resection for Hepatocellular Carcinoma in Patients with HBV and HCV Co-Infection: A Multicenter Observational Study

Hang-Dong JIA[1,2], Lei LIANG[1,2], Chao LI[3], Han WU[3], Hong WANG[4], Ying-Jian LIANG[5], Ya-Hao ZHOU[6], Wei-Min GU[7], Xin-Ping FAN[8], Wan Yee LAU[9], Timothy M. PAWLIK[10], Yong-Kang DIAO[1,2], Qiu-Ran XU[1,2], Feng SHEN[3], Cheng-Wu ZHANG[1], Dong-Sheng HUANG[1,2], Tian YANG[1,2,3]

[1]Department of Hepatobiliary Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medical College), Hangzhou, Zhejiang, China; [2]School of Clinical Medicine, Hangzhou Medical College, Hangzhou, Zhejiang, China; [3]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [4]Department of General Surgery, Liuyang People's Hospital, Hunan, China; [5]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Harbin Medical University, Heilongjiang, China; [6]Department of Hepatobiliary Surgery, Pu'er People's Hospital, China; [7]The First Department of General Surgery, The Fourth Hospital of Harbin, Heilongjiang, China; [8]Department of General Surgery, Pingxiang Mining Group General Hospital, Jiangxi, China; [9]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China; [10]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, Ohio, USA

Aims: Hepatocellular carcinoma (HCC) is one of the most serious consequences of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. This study sought to investigate long-term outcomes after liver resection for HCC among patients with HBV/HCV co-infection (HBV/HCV-HCC) compared with patients with HBV infection (HBV-HCC).
Methods: Patients who underwent curative-intent liver resection for HCC were identified from a multicenter Chinese database. Using propensity score matching (PSM), patients with HBV/HCV-HCC were matched one-to-one to patients with HBV-HCC. Overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups before and after PSM.
Results: Among 2,467 patients identified, 93 (3.8%) and 2,374 (96.2%) patients had HBV/HCV-HCC and HBV-HCC, respectively. Compared with patients with HBV-HCC, patients with HBV/HCV-HCC were older, have poorer liver-related characteristics but better tumor-related characteristics. PSM created 88 pairs of patients with comparable liver- and tumor-related characteristics (all $P>0.2$). In the PSM cohort, the 3- and 5-year RFS rates in patients with HBV/HCV-HCC were 48.3% and 38.9%, which were significantly poorer than patients with HBV-HCC (61.8% and 49.2%, $P=0.037$). Meanwhile, the 3- and 5-year OS rates in patients with HBV/HCV-HCC were also poorer than patients with HBV-HCC (65.4% and 51.1% vs. 73.7% and 63.0%), with a difference close to be significant between them ($P=0.081$).
Conclusions: Comparing to patients with HBV-HCC, liver resection resulted in relatively poorer long-term surgical outcomes in patients with HBV/HCV-HCC.

FP-062

Prognostic Significance of the Microscopic Serosal Invasion in Hepatocellular Carcinoma

Incheon Kang[1], Dai Hoon Han[2]

[1]Department of Surgery, CHA Bundang medical center, CHA University, Seongnam, Korea; [2]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

Aims: The prognostic significance of microscopic serosal invasion (MiSI) was not clarified in patients with hepatocellular carcinoma (HCC). We investigated the impact of MiSI for the long-term outcome after curative surgical resection in patients with HCC.
Methods: In total, 783 consecutive patients with HCC who underwent curative surgical resection without any preoperative treatment were histologically evaluated for MiSI. Patients with MiSI were classified into two groups: positive for MiSI (pSI; n=333) and negative for MiSI (nSI; n=450). Clinicopathologic features, recurrence-free survival (DFS), and overall survival (OS) were compared between patients with pSI and nSI.
Results: The pSI group showed more aggressive tumor characteristics, such as higher tumor marker levels (alpha-fetoprotein, $P<.001$; protein induced by vitamin K absence-II, $P<.001$), larger tumor size ($P<.001$), higher prevalence of microvascular invasion ($P=.002$), and poorer differentiation ($P<.001$), than the nSI group. In survival analysis, 5-year DFS was 48.1%, 61.2% in the pSI, nSI, respectively ($P<.001$), while 5-year OS was 74.8%, 86.1%, respectively ($P=.002$). In multivariate analysis, MiSI was independent prognostic factors for DFS ($P=.043$) and OS ($P=.042$).
Conclusions: The MiSI was associated with more aggressive clinicopathologic characteristics and a higher risk of poor survival. Therefore, intensive careful follow-up is essential for patients with pSI after curative surgical resection in patients with HCC.
Keywords: Hepatocellular carcinoma, Prognosis, Serosal invasion

Saturday, May 15, 2021, 13:30-14:50

9. Surgery,Technical Issues

FP-063

Surgical Resection of Huge Hepatocellular Carcinoma: Prognostic Factors and Outcomes in a Mexican Cohort Study

Carlos FLOREZ-ZORRILLA[1,2,3], Karina MENDOZA-GALLO[1]

[1]HPB and Liver Transplant, Hospital Puerta de Hierro Andares Guadalajara, Mexico; [2]HPB and Liver Transplant, Hospital Ángeles Lomas Ciudad de México, Mexico; [3]HPB and LIver Transplant, Centro Médico ABC Ciudad de México, Mexico

Aims: Surgery is the best choice for curative treatment for hepatocellular carcinoma (HCC), that includes liver resection (LR) or liver transplantation (LT). Tumors larger than 10 cm are considered huge HCC. Huge HCC doesn´t fit any criteria for LT. Although surgical resection may be associated with higher morbidity it´s still the best chance of survival in this subgroup of patients. The purpose of our stydy is to analyze prognostic factors and outcomes in a mexican population.
Methods: We analyzed patients who underwent liver resection for huge HCC between january 2015 to january 2021. Prognostic factors included in the study were age, HCC size, serum

alphafetoprotein (AFP) and vascular invasion. Only patients with Child–Pugh grade A in absence of extrahepatic disease was offered major liver resection. The future liver remnant volume was calculated by CT scan volumetry. Morbidity, disease free-survival and overall survival was evaluated.
Results: 52 patients underwent major liver resection: male 30 (57.6%) and female 22 (42.3%). The median age was 65 years (range 25 to 76 years), median HCC size was 16 cm (range 14 to 45 cm), median AFP was 85 ng/ml (range 18 to 19500 ng/ml). Lymphovascular invasion was found in 58% of liver specimens. The overall morbidity was 12% and perioperative mortality was seen in 1 (1.95) due to heart failure. The overall 1-year and 3-year survival were 88.4% and 51.9% respectively,
Conclusions: Factors of adverse outcome after major liver resection in patients with huge HCC were the presence of lymphovascular invasion, AFP 》 1000, and age 》 65 years.

FP-064

Randomised Controlled Trial to Evaluate a New Sealant to Prevent Biliary Fistula in Liver Surgery: Should We Reconsider Bile Leak Classification?

Matteo Maria CIMINO, Fabio PROCOPIO, Simone FAMULARO, Jacopo GALVANIN, Simone GIUDICI, Valentina TAGLIAFERRI, Matteo DONADON, Luca VIGANO', Daniele DEL FABBRO, Guido TORZILLI

General and Hepatobiliary Surgery, Humanitas Clinical and Research Center - IRCCS, Rozzano Milan – Italy

Aims: Biliary fistula (BF) is the most common post hepatectomy complication. Different definitions have been proposed. The International Study Group of Liver Surgery (ISGLS) definition is the most used. The definition adopted in Humanitas Research Hospital (HRH) defines BF as bilirubin concentration in the drain fluid greater than 10 mg/dL on or after POD 3. Various topical haemostatic agents have been developed, their usefulness in preventing BF remains unclear and needs to be assessed.
Methods: First endpoint: assess the clinical benefit of using Hemopatch to prevent post-operative BF. Secondary endpoint: evaluate the clinical impact of the two definitions. we designed a randomized controlled study on 220 patients: 110 Hemopatch group (group-A) and 110 standard group (group-B), who underwent hepatic resection from 2018 to 2020. All patients were drained. Drains were removed with drain bilirubin concentration less than 10 mg/dL on POD 7.
Results: BF (ISGLS definition) occurred in 139(63.5%) patients, 67(60.9%) in group-B and 72(66.1%) in group-A (*P*=0,515). One-hundred- twenty fistulas (54.5%) were grade A, 18(9%) grade B, 1(0.5%) grade C. Considering HRH definition, BF occurred in 19(8.7%) patients, 6(5.5%) in group-B and 13(11.9%) in group-A(*P*=0.144). Sixteen (84.2%) were treated conservatively, 2(10.5%) performed ERCP, 1(5.3%) underwent relaparotomy. At multivariate analysis the only factor associated with BF increased risk was transection of the main portal branch (OR=54.35; *P*=0.026).
Conclusions: Hemopatch does not reduce the incidence of BF, considering both the ISGLS and HRH definition. The different rate of BF in the two classification may lead to reconsider its definition.

FP-065

Role of MHV Resection in Standard Right or Left Hepatectomy on Post Hepatectomy Outcomes

Anisa NUTU, Isaac JOHN, Bobby VM DASARI

Liver Unit, Queen Elizabeth Hospital Birmingham, United Kingdom

Aims: Middle hepatic vein (MHV) is preserved in standard right or left hepatectomy in order to maintain the venous outflow of the remnant liver. Resection of MHV can cause venous parenchymal congestion, reflux of blood flow into portal vein, avoiding the regeneration of liver. The aim of this study was to evaluate if preservation or not of the MHV will influence post-surgical outcomes including post hepatectomy liver failure (PHLF) in standard right or left hepatectomy.
Methods: A retrospective analysis was carried out using a prospectively maintained database. A total of 144 patients underwent standard right or left hepatectomy (Brisbane 2000 nomenclature) between January 2015 and March 2019 were included. Anatomical remnant liver volumes were measured retrospectively using Hermes software.
Results: A right hepatectomy was performed in the 79% of the cases and a left one in the 21%. MHV was resected in 13 patients (10%) in addition to standard right or left hepatectomy. Median remnant liver volume in the MHV resected group was significantly more (*P*=0.006). In the multivariable analysis, resection of the MHV did not influence in the occurrence of PHLF (*P*=0.518). Similarly, there was no significant difference in the serum bilirubin, INR, ALT, creatinine levels on post op days 1,3,5,10, and no significant difference in Grade IIIa or more complications, and 90-day mortality rates.
Conclusions: Resection of the MHV as a part of standard right or left hepatectomy in liver resection surgery did not have a negative impact on the post-operative outcomes in patients with adequate remnant liver volume.

FP-066

Laparoscopic and Robotic Volume Preserving Major Hepatectomy

Jin Hong LIM, Dong Sup YOON*

Division of Hepatobiliary Pancreatic Surgery, Department of Surgery, Gangnam severance hospital, Yonsei University College of Medicine, Korea

Aims: Transection along the right anterior fissure was proposed as a mechanism by which to open the third door of the liver for anatomical hepatectomy. Nowadays, laparoscopic anatomical liver resection is gaining momentum with less blood loss and

shorter postoperative hospital stay. In this study, we sought to evaluate the feasibility, safety and potential benefits of laparoscopic assisted volume preserving major hepatectomy.

Methods: Between October 2016 and december 2020, 76 patients underwent volume preserving major hepatectomy at the authors' institution. except 3 patients underwent combined CBD resection, 45 patients underwent laparoscopic(42 patients) or robotic(3 patients) volume preserving major hepatectomy and 31 patients underwent open volume preserving major hepatectomy. Patient demographics and perioperative outcomes were analyzed and compared.

Results: There was no open conversion during laparoscopic procedure. There were no differences in operation time and length of hospital stay between laparoscopic assisted and open ventral segment preserving right hepatectomy. Patients who underwent laparoscopic procedure had less bleeding amount than those who underwent open procedure.

Conclusions: Laparoscopic and robot volume preserving major hepatectomy is a feasible and safe procedure. However, more experience is essential to reveal the long term oncological results of volume preserving major hepatectomy.

FP-067

A Novel Online Calculator for Estimating Survival Benefit of Adjuvant TACE in Patients Undergoing Surgery for HCC

Lei LIANG[1], Chao LI[2], Ming-Da WANG[2], Hao XING[2], Yong-Kang DIAO[1], Wan Yee LAU[2,3], Cheng-Wu ZHANG[1], Timothy M. PAWLIK[4], Feng SHEN[2], Dong-Sheng HUANG[1], Tian YANG[1,2]

[1]Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, China; [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), China; [3]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China; [4]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, USA

Aims: Although adjuvant transcatheter arterial chemoembolization (TACE) for resected hepatocellular carcinoma (HCC) may improve survival for some patients, identifying which patients can benefit remains challenging. The present study aimed to construct a survival prediction calculator for individualized estimating the net survival benefit of adjuvant TACE for patients with resected HCC.

Methods: From a multicenter database, consecutive patients undergoing curative resection for HCC were enrolled and divided into the developing and validation cohorts. Using the independent survival predictors in the developing cohort, two nomogram models were constructed for patients with and without adjuvant TACE, respectively, which predictive performance was validated internally and externally by measuring concordance index (C-index) and calibration. The difference between two estimates of the prediction models was the expected survival benefit of adjuvant TACE.

Results: A total of 2,514 patients met the inclusion criteria for the study. The nomogram prediction models for patients with and without adjuvant TACE were respectively built by incorporating the same eight independent survival predictors, including portal hypertension, Child-Pugh score, alpha-fetoprotein level, tumor size and number, macrovascular and microvascular invasion, and resection margin. These two prediction models demonstrated good calibration and discrimination, with all the C-indexes of greater than 0.75 in the developing and validation cohorts. A browser-based calculator was generated for individualized estimating the net survival benefit of adjuvant TACE.

Conclusions: Based on large-scale real-world data, an easy-to-use online calculator can be adopted as a decision aid to predict which patients with resected HCC can benefit from adjuvant TACE.

FP-068

A Scoring System to Predict the Risk of Postoperative Complications after Laparoscopic Liver Resection in Elderly Hepatocellular Carcinoma Patients

Boram LEE, Jai Young CHO*, Ho-Seong HAN, Yoo-Seok YOON, Hae Won LEE, Jun Suh LEE, Munhwan KIM

Department of Surgery, Seoul National University Bundang Hospital, Korea

Aims: The safety of laparoscopic liver resection (LLR) in elderly patients is a matter of concern because reduced physiologic reserve increased the risk of morbidity. However, few studies have been designed to develop scoring system to predict complications after LLR in elderly patients. This study aimed to investigate the clinical value of the geriatric nutritional risk index (GNRI) and propose a new simplified scoring system for predicting the risk of postoperative major complications after LLR in elderly hepatocellular carcinoma (HCC) patients.

Methods: We retrospectively reviewed 257 consecutive patients aged ≥ 65 years who underwent LLR for HCC from January 2004 to December 2019. The GNRI formula was calculated as follows: 1.489 x serum albumin (g/L) + 41.7 x present weight/ideal weight (kg).

Results: Major complication following LLR was noted in 24 patients (10.9%). On multivariate analysis, the GNRI (Hazard ratio (HR) 3.396, 95% confidence interval (CI) 1.242-9.288, *P*=0.017), Child-Pugh score (HR 2.191, 95% CI 1.400-8.999, *P*=0.036), major liver resection (HR 2.683, 95% CI 1.082-7.328) and intraoperative transfusion (HR 1.802, 95% CI 1.428-7.591, *P*=0.022) independently predicted postoperative major complications. Four significant predictors were identified and assigned points based on hazard ratio. The 10-point model showed good discrimination (Area under the curve 0.756, 95% CI 0.649-0.836, *P*=0.001).

Conclusions: The GNRI is an important predictor of postoperative major complications and the proposed risk score can help to predict the risk of planned surgery in elderly HCC patients.

FP-069

Institutional Experience and Clinical Outcomes of Robotic Major Hepatectomy for Liver Tumors

Iswanto SUCANDY, Sharona ROSS, Valerie PRZETOCKI, Cameron SYBLIS, Kaitlyn CRESPO, Timothy BOURDEAU, Alexander ROSEMURGY

Digestive Health Institute, AdventHealth Tampa, USA

Aims: The majority of published literature has only reported outcomes of robotic minor non-anatomical hepatectomy. We aim to examine our clinical outcomes, safety, and feasibly with robotic major hepatectomy.

Methods: We prospectively followed 235 patients who underwent robotic hepatectomy since 2016. Major hepatectomy is defined as a resection of ≥3 segments. Data are presented as median(mean+SD).

Results: Of the 235 patients, 142 of the patients underwent a major hepatectomy. Median age was 63(61±14.0) years, 51% were women, BMI was 28(29±6.1) kg/m² and ASA Class was 3(3±0.5). 25% of operations were for metastatic colorectal cancer, 23% for hepatocellular carcinoma, 11% cholangiocarcinoma, and 6% for gallbladder adenocarcinoma. Regarding the type of resection, 15 patients (11%) had central hepatectomy, 30 (21%) had formal right, 41 (29%) had formal left, 31 (22%) had non-anatomical right, 11 (8%) had non-anatomical left, 7 (5%) had extended right, and 7 (5%) had extended left. Prep time (in the room until incision) 64(74±67.3) minutes, Extraction time (incision until specimen extraction) 138(159±99.3) minutes, Console time 198(213±119.8) minutes, Closure time (extraction until dressing placement) 106(214±271.3) minutes, Operative duration was 288(305±119.0) minutes and time under anesthesia 359(369±115.6) minutes. Estimated blood loss was 200(258±252.1) mL and length of stay was 4(5±2.7) days. 9 patients experienced postoperative complications (4 ileus, 1 pneumonia, 1 bile leak, 1 gram-negative bacteremia, 1 jaundice, 1 pneumothorax). 22 patients were readmitted within 30 days with one death after readmission, due to aspiration.

Conclusions: Application of the robotic platform to major hepatectomy is safe and feasible with excellent perioperative outcomes.

FP-070

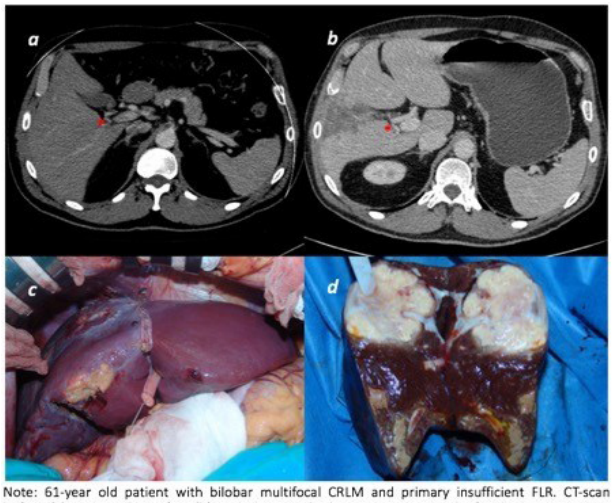
Simultaneous Ipsilateral Dual (DSM-TACE and PVE) Embolization (SIDE technique) for Preoperative Augmentation of Future Liver Remnant (FLR) in Patients with Solid Liver Malignancies

Oleksandr KORSHAK[1], Denis FEDOROV[2], Nellya ABLAEVA, Andrii ZHYLENKO, Oleksandr HRINENKO, Oleksandr OSTAPYSHEN, Maria STASSIUK, Vadim KONDRATIUK, Andriy HUSIEV, Tetyana TERZOVA, Ivan MAZANOVYCH, Vlad KROPELNYTSKYI, Mykhailo KOSTYLEV

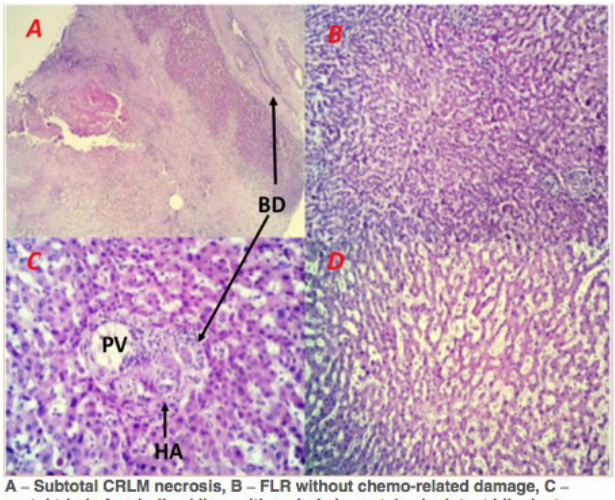
Department of liver surgery and transplantation, National Institute of surgery and transplantology, Kyiv, Ukraine

Aims: Portal Vein Embolization(PVE) is gold standard strategy to increase FLR at level of Kinetic Growth Rate (KGR) about 2.3 cc/day and prevent posthepatectomy liver failure (PHLF). Up to 30% of patient with liver malignance still couldn't underwent surgery after PVE due to tumor progression and/or insufficient FLR regeneration during waiting period. Currently there are no methods that resolves both mentioned issues.

Methods: 9 initially unresectable, due to small FLR, patients with colorectal liver metastases (CRLM) having more than three criteria of Fong Clinical Risk Score for CRLM, in close proximity to FLR critical structures were approved for Simultaneous PVE and Transarterial Chemoembolization with Degradable Starch Microspheres (DSM-TACE). Simultaneously, immediately after standard PVE, was performed oxaliplatin based DSM-TACE with short-term embolic material of the whole tumor bearing liver to be resected that allowed to achieve a)tumor control and b)postembolic infarction c)pharmacologically induced hepatic Veno-Occlusive Disease(VOD(Fig 2d)) in liver to be removed, as a trigger of increased FLR regeneration(Fig.1), without biliary tree damage(Fig. 2 a,c).



Note: 61-year old patient with bilobar multifocal CRLM and primary insufficient FLR. CT-scan before (a) and 21-days after (b) embolization, both scans are at level of right hepatic artery bifurcation (asterisk), note the atrophy of right liver lobe with unprecedented regeneration of left liver lobe that was not visualized on the same level scan before. Intraoperative photo showing significant increase of FLR w/out any signs of chemo-related lesion/damage of FLR (c). Operative specimen after right trisectenectomy is showing atrophy of liver lobe with infarction of liver parenchyma without biliary tree damage (d).



A – Subtotal CRLM necrosis, B – FLR without chemo-related damage, C – portal triad of embolized liver with embols in portal vein, intact bile duct, hepatic artery with restored arterial flow, D – VOD- oxaliplatin-related damage of embolized liver. Note intact bile duct (BD) in A and C.

Results: Unprecedented FLR regeneration with KGR 23.5 cc/day(range from 17.6 to 57.25 cc/day) was observed. The latter allow us to achieve safe FLR volume to perform extended hepatectomies within recommended 2-3 weeks period to avoid chemotherapy related neutropenic window in all 9 patients even so there were no myelosuppression observed. This allows us safely shortening time to resection to 15 days in 5 last consecutive patients. In all CRLM about 60% (range from 40% to 90%) necrosis was achieved(Fig. 2 a). All patients have successfully underwent major liver resection with 0% dropout. There was no severe morbidity and mortality.

Conclusions: We propose method of preoperative FLR adaptation which is not only second to none in the achieving liver regeneration rate but also is the only one that allows local tumor control and/or downsize borderline resectable tumors.

Keywords: DSM-TACE, PVE, SIDE, VOD

Saturday, May 15, 2021, 15:00-16:20

10. Liver Cancer,Clinical

FP-071

A Comparative Study of Microwave and Radiofrequency Ablation Therapy for Hepatocellular Carcinoma

Soon Kyu Lee[1], Se Hyun Cho[1*], Joon-Yeol Han[1], Dong Jin Chung[2]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [2]Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Recently, microwave ablation (MWA) has been introduced in the treatment of hepatocellular carcinoma (HCC). In this study, we evaluated and compared the treatment outcomes of MWA and RFA for HCC in treatment-naïve and experienced patients.

Methods: A total of 144 HCC patients (100 in the RFA group and 44 in the MWA group) were consecutively enrolled in our study. The primary outcome was disease free survival (DFS) at 1 and 2 years. Secondary outcomes were complete response rate (CRR), local recurrence rate, survival rate at 2 years, risk factors for DFS and complication rate. Treatment outcomes were also assessed by propensity-score matching (PSM).

Results: Of 144 enrolled patients, 103 patients (71.5%) were male with the mean age of 65.9 years. The MWA group has more treatment-naïve patients, perivascular tumor and larger tumor than the RFA group. The MWA group had significantly better DFS at 1 and 2 years than the RFA group in the entire cohort (1 year, P=0.018; 2 years, P=0.012) and PSM cohort (1 year, P=0.005; 2 years, P=.008). CRR was also higher in the MWA group than the RFA group (97.7% vs. 84.0%, P<0.05, respectively). However, local recurrence rate and survival rate at 2 years were not different between the two groups. Complication rate was similar between the two groups with less major complications in the MWA group (P=0.048). In multivariate analysis, treatment-naïve, MWA and smaller tumor size were favorable factors for DFS at 1 and 2 years. Finally, multiple subgroup analyses demonstrated that patients with perivascular tumor, single with small tumor size (≤2cm) were more favorable to MWA than RFA.

Conclusions: Our study suggests that MWA provide better treatment outcomes than RFA especially in patients with perivascular or a small single HCC.

Keywords: Hepatocellular carcinom, Ablation, Microwave, Radiofrequency, Progression, Recurrence, Response

FP-072

Comparison of Dexamethasone and Celecoxib for Prophylaxis for Transarterial Chemoembolization

Min-Woo Chung, Ji-Yun Hong, Jae Hyun Yoon, Dae Seong Myung, Sung Bum Cho, Wan Sik Lee, Young-Eun Joo, Sung Kyu Choi

Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

Aims: Transarterial Chemoembolization(TACE) is one of the most frequently used treatment method for hepatocellular carcinoma(HCC). The prevalence of Post-embolization syndrome(PES) has been reported till 90%, but its significance has been ignored. The mechanism of PES has not been elucidated yet, but it is thought to be an inflammatory reaction due to ischemic and necrotic changes of the tumor and normal tissue according to the procedure. Recently, studies using steroids and non-steroidal anti-inflammatory drugs have been published to prevent PES. However, its stability and practical application are not yet known. In this study, we compared the effect of COX-2 inhibitor on the low-dose dexamethasone pretreatment and the effect of high-dose dexamethasone on the prevention of PES and its stabilities.

Methods: This prospective, randomized trial was conducted in a single center from May 2019 to December 2020. A total of 236 patients with HCC were enrolled. After randomization, 118 patients were assigned to the COX-2 inhibitor group and the other 118 to the dexamethasone group. The dexamethasone group received intravenous dexamethasone 15 mg and ramosetron 0.3 mg on the first day, and intravenous injection of dexamethasone 5 mg and oral ramosetron 0.1 mg on the second, and third day. In the COX-2 inhibitor group, Celecoxib 200 mg was administered the night before the procedure, and the dose was administered for 3 days after the procedure at 12-hour intervals (total 6 times). In addition, 5 mg of dexamethasone and 0.3 mg of ramosetron were administered intravenously before procedure, and on the second, third day oral ramosetron 0.1 mg.

Results: The incidences of PES were 61.9% in the COX-2 inhib-

itor group and 48.3% in the dexamethasone group (*P*=0.049). Mean hospitalization times after TACE were 3.63 days in the COX-2 inhibitor group and 3.58 days in the dexamethasone group. Underlying stage of HCC, baseline characteristics, re-admission rate and treatment response showed no statistical differences between two groups.

Conclusions: This study demonstrates that the prophylactic administration of high-dose dexamethasone before TACE is better to prevent PES than COX-2 inhibitor without significant complication.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Post-embolization syndrome, dexamethasone

FP-073

Transarterial Chemoembolization Plus Radiotherapy as a First-Line Treatment for Liver-Confined Hepatocellular Carcinoma with Macroscopic Vascular Invasion: Significance of Early Response

Jinhong Jung[1], So Yeon Kim[2], Jonggi Choi[3], Ju Hyun Shim[3], Young-Suk Lim[3], Han Chu Lee[3], Jin-hong Park[1], Sang Min Yoon[1]

[1]Department of Radiation Oncology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Radiology and the Research Institute of Radiology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

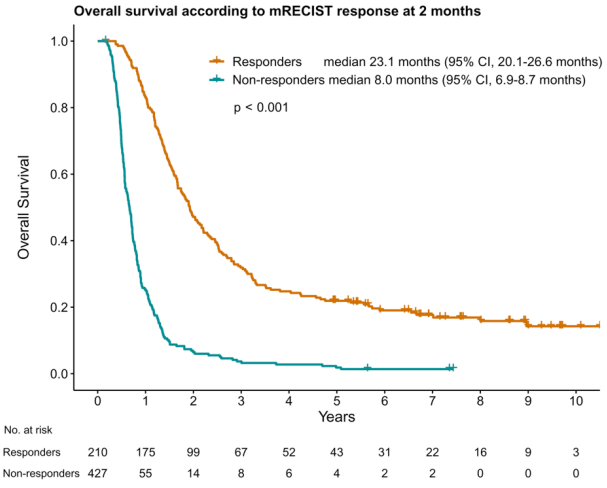
Aims: We evaluated the radiologic response rate of combined transarterial chemoembolization (TACE) plus radiotherapy in treatment-naïve patients with liver-confined hepatocellular carcinoma (HCC) with macroscopic vascular invasion (MVI), and analyzed its clinical importance in the overall survival (OS) of patients with advanced-stage HCC.

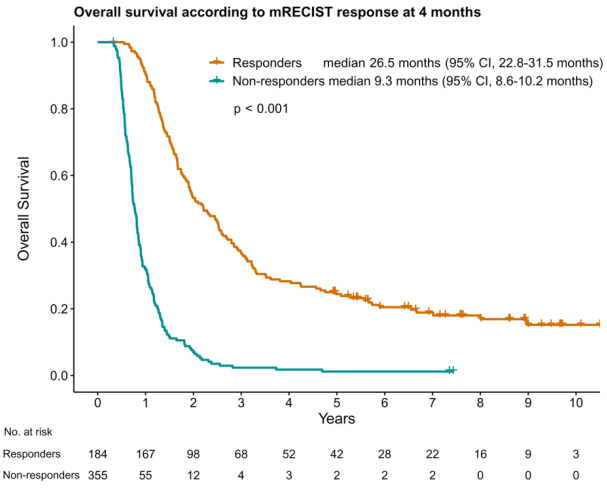
Methods: We retrospectively reviewed the medical records of patients who were treated with combined TACE and respiratory-gated 3-dimensional conformal radiotherapy as a first-line treatment for HCC with MVI between January 2010 and December 2015. Radiologic response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) at two fixed time points (2 months and 4 months) after the initiation of treatment. Landmark analysis at 2- and 4-months and time-dependent Cox regression analysis with treatment response as a time-dependent covariate to avoid guarantee-time bias were performed for univariable and multivariable analyses.

Results: A total of 427 patients were included in the 2-month landmark analysis. After excluding patients without imaging studies for response evaluation at 4 months, 355 patients were included in the 4-month landmark analysis. Radiologic responses were observed in 210 (49.2%) patients in the 2-month analysis and 181 (51.8%) patients in the 4-month analysis. In multivariable analysis, radiologic response at 2 months (hazard ratio [HR]: 3.194; 95% confidence interval [CI]: 2.455–4.156, *P*<0.001) and at 4 months (HR: 4.534; 95% CI: 3.391–6.062, *P*<0.001) were identified as independent prognosticators for OS.

Conclusions: Radiologic response assessed by mRECIST was a significant prognostic factor for OS in patients with advanced-stage HCC with MVI treated with combined TACE plus radiotherapy. Radiologic response can be used as a reliable surrogate for predicting OS at a relatively early timing and aid the decision-making process in the treatment of patients with advanced-stage HCC.

Keywords: Hepatocellular carcinoma, Vascular invasion, Radiotherapy, Transarterial chemoembolization, Response





FP-074

Benefits of Local Treatment including External Radiotherapy for Hepatocellular Carcinoma with Portal Invasion

Han Ah Lee[1,3], Sunmin Park[2], Yeon Seok Seo[3], Won Sup Yoon[2], Chai Hong Rim[2]

[1]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea; [2]Department of Radiation Oncology, Korea University Ansan Hospital, Korea University Medical College, Gyeonggido, Korea; [3]Department of Internal Medicine, Korea University Anam Hospital, Korea University Medical College, Seoul, Korea

On behalf of the Korean Liver Cancer Study Group

Aims: Background/Aim: Local treatment including radiotherapy (LRT) has been applied as one of palliative treatment for hepatocellular carcinoma (HCC) patients with portal invasion, although the survival benefit of LRT has not been established. We aimed to identify the oncologic benefit of LRT and its differences according to the categorized hepatic reserve in patients with HCC invading portal vein.

Methods: Methods: We included patients who were diagnosed with HCC invading portal vein and extracted using Korean Central Cancer Registration between 2008 to 2014. Patients were classified into LRT and best supportive care (BSC) groups. We used 1:1 propensity score matching to reduce selection bias and the effect confounders.

Results: Results: A total of 1,163 patients were analyzed. The LRT group was younger than the BSC group (P<0.001). The mean Child-Pugh score of the LRT group was 6.1, which was lower than that of the BSC group (7.7) (P<0.001). The PS-matched analysis generated 222 pairs. The median survival of all patients, LRT, and BSC groups were 5.0, 8.0, and 2.0 months, respectively. The overall survival (OS) rates in the LRT and BSC groups were 34.2% and 16.2% at 1 year, and 12.6% and 6.8% at 2 years, respectively (P<0.001). Multivariate analysis showed that LRT (HR 0.41, 95% CI 0.32–0.52), age >60 years, presence of extrahepatic metastases, tumor size of ≥10 cm, and Child-Pugh class (CPC) B or C were independent predictors for higher mortality (all P<0.05) (Table). Similar results were observed for cancer-specific survival. In subgroup analysis, the statistical differences in survival were maintained in all CPC-Albumin-Bilirubin (ALBI) classes (CPC-ALBI A1 and A2, and CPC B; all P<0.05).

Conclusions: Conclusions: LRT demonstrated significant survival benefits compared to BSC in HCC patients with portal invasion. The benefit was valid for both CPC A and B patients. LRT could be effective palliative option in these patients.

Table. Predictors for mortality

		Overall survival				Cancer-specific survival			
		Univariate		Multivariate		Univariate		Multivariate	
Covariates	Rating	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p-value	HR (95% CI)	p value
LRT		0.46 (0.38–0.55)	<0.001	0.41 (0.32–0.52)	<0.001	0.47 (0.39–0.58)	<0.001	0.43 (0.34–0.54)	<0.001
Age	>60 years	1.78 (1.42–2.22)	<0.001	1.83 (1.40–2.39)	<0.001	1.78 (1.42–2.24)	<0.001	1.82 (1.40–2.38)	<0.001
Male		0.96 (0.71–1.28)	0.759			0.92 (0.68–1.25)	0.609		
Hepatitis B virus		1.11 (0.89–1.38)	0.376			1.12 (0.89–1.40)	0.331		
Extrahepatic metastases		1.87 (1.50–2.34)	<0.001	1.90 (1.42–2.53)	<0.001	1.90 (1.51–2.38)	<0.001	1.90 (1.42–2.54)	<0.001
Main tumor size	≥10 cm	1.51 (1.24–1.84)	<0.001	1.60 (1.26–2.05)	<0.001	1.51 (1.24–1.85)	<0.001	1.56 (1.22–2.00)	<0.001
Multiple tumors		1.23 (1.01–1.48)	0.038	1.00 (0.79–1.27)	0.980	1.27 (1.04–1.54)	0.018	0.98 (0.78–1.24)	0.882
Alpha-fetoprotein	μg/mL	1.17 (1.05–1.31)	0.006	1.22 (0.94–1.59)	0.073	1.17 (1.04–1.30)	0.008	1.24 (0.95–1.62)	0.072
Child-Pugh Class	A vs. B	1.47 (1.19–1.81)	<0.001	1.87 (1.40–2.50)	<0.001	1.43 (1.15–1.77)	0.001	1.78 (1.32–2.39)	<0.001
Performance status	≥2	1.89 (1.28–2.80)	0.001	1.01 (0.64–1.57)	0.981	1.87 (1.26–2.78)	0.002	1.00 (0.64–1.58)	0.992

HR, hazard ratio; CI, confidence interval; LRT, local treatment including radiotherapy; CPC, Child-Pugh class; ALBI, albumin-bilirubin

Keywords: Radiotherapy, Portal vein thrombosis, BCLC C, ALBI grade

FP-075

Comparison of Lenvatinib and Hepatic Arterial Infusion Chemotherapy on the Efficacy and Safety in Unresectable HCC : A Multi-Center, Propensity Score Analysis

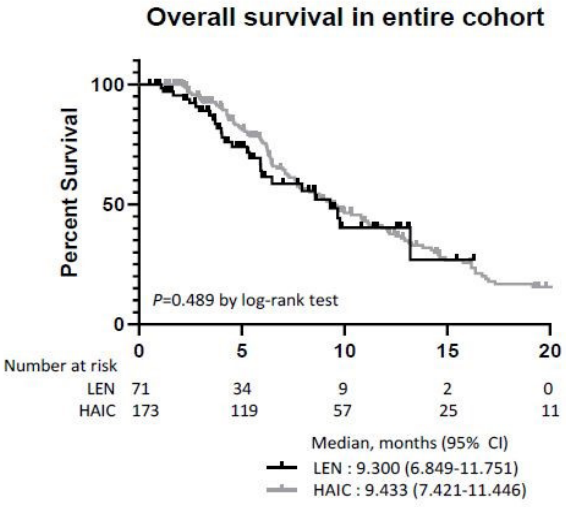
Jaejun Lee[1,2], Ji Won Han[1,3], Hyun Yang[1,2], Soon Kyu Lee[1,3], Hee Chul Nam[1,2], Sun Hong Yoo[1,4], Hae Lim Lee[1,5], Hee Yeon Kim[1,6], Sung Won Lee[1,5], Jung-Hyun Kwon[1,4], Jeong Won Jang[1,3], Chang Wook Kim[1,6], Soon Woo Nam[1,4], Si Hyun Bae[1,2], Jong Young Choi[1,3], Seung Kew Yoon[1,3], Pil Soo Sung[1,3,*]

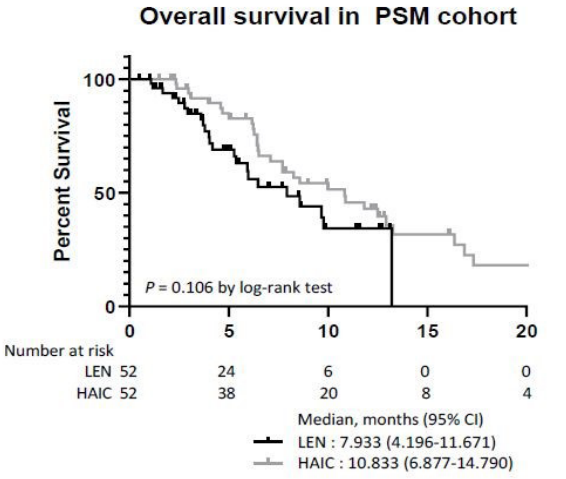
[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul 03382, Republic of Korea; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul 06591, Republic of Korea; [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Incheon St. Mary's Hospital, The Catholic University of Korea, Seoul 22711, Republic of Korea; [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Seoul 14647, Republic of Korea; [6]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Seoul 11765, Republic of Korea

Aims: After REFLECT trial, Lenvatinib has been approved as a first-line multikinase inhibitor in advanced HCC. Since there has been a lot of retrospective studies comparing between sorafenib and HAIC, we focused on comparing efficacy of HAIC to that of lenvatinib in unresectable hepatocellular carcinoma.

Methods: A total of 244 patients with unresectable HCC whose been treated with HAIC (n = 173) or lenvatinib (n= 71) were enrolled between November, 2012 and November, 2020. To reduce confounding, we used PSMA regarding on several variables, resulting in selection of 52 patients for each group.

Results: Comparing baseline characteristics between two groups, hepatic reserve, extent of HCC and history of previous treatment were significantly different. In whole cohort, median follow up duration was 6.900 and 4.767 months for HAIC and lenvatinib group, respectively. Before PSMA, median PFS was 4.300 months for lenvatinib group and 3.733 months for HAIC group (P=0.422). Median OS also had no significant differences in two groups with 9.300 months for lenvatinib group and 9.433 months for HAIC group (P=0.489). After PSMA, there were still no statistical differences in PFS and OS between two groups (PFS 3.600 vs 4.000 months, P=0.706; OS 10.833 vs 7.933 months, HAIC and LEN, respectively, P=0.106). However, in patients with tumor burden beyond 'REFLECT criteria', HAIC showed superior outcomes over lenvatinib in terms of survival rate in both before and after PSMA.





Conclusions: Our multicenter real-world, propensity-matched data demonstrate that lenvatinib is comparable to HAIC in terms of anti-cancer efficacy and survival rate in unresectable HCC.

Keywords: Hepatocellular carcinoma, Lenvatinib, HAIC, Overall survival

FP-076

Comparison of the Effects between Sorafenib and Lenvatinib as The First-Line Systemic Chemotherapy in Hbv Associated Hepatocellular Carcinoma with Real-World Data

Na Ryung Choi, Hee Jin Cho, Min Kyung Park, Jihye Kim, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea

Aims: In REFLECT trial, lenvatinib has shown to be non-inferior to sorafenib in overall survival and had positive effects in progression-free survival and the objective response rate in patients with unresectable hepatocellular carcinoma (uHCC). This study was aimed to compare the effects between sorafenib and lenvatinib as the first-line systemic therapy for HBV-related uHCC with real-world data.

Methods: We reviewed data from single center retrospectively. The study was based on 138 patients with HBV-related uHCC. Propensity score matching was used to adjust confounding. Adjusted factors were age, sex, AFP, Child-Pugh class, BCLC stage, tumor size.

Results: With propensity score matching, the analysis included 46 patients who had treated with lenvatinib, and 92 patients who had treated with sorafenib. Compared with sorafenib treatment group, lenvatinib showed significant higher objective response rate [17.4% vs. 4.3%, p=0.021] and disease control rate [76.1% vs. 50.0%, p=0.003] according to the modified Response Evaluation Criteria in Solid Tumors. However, median time to progression was comparable statistically [138 days vs. 88 days, *P*=0.076]. In multivariate analysis as well as univariate analysis showed that AFP>200 [HR = 1.772, 95% CI 1.176-2.668, *P*=0.007] and ECOG performance status 1 or 2 [HR = 1.974, 95% CI 1.198-3.215, *P*=0.007] were significant predictors of tumor progression, but lenvatinib treatment did not reduce the risk of tumor progression significantly.

Conclusions: In real-world prospensity score-matched analysis, lenvatinib had an advantage over sorafenib on disease control rate and showed a comparable effect on time to progression in HBV-associated hepatocellular carcinoma.

Keywords: HBV-associated HCC, Lenvatinib, Sorafenib

FP-077

Effectiveness of Lenvatinib versus Sorafenib for Unresectable Hepatocellular Carcinoma in Patients with Hepatic Decompensation

Min Kyung Park[1], Yun Bin Lee[1], Hyemi Moon[2], Na Ryung Choi[1], Minseok Albert Kim[1], Heejoon Jang[1], Joon Yeul Nam[1], Eun Ju Cho[1], Jeong-Hoon Lee,[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Biostatistics, College of Medicine, Korea University, Seoul, Korea

Aims: Lenvatinib and sorafenib are currently available to treat patients with advanced hepatocellular carcinoma (HCC). However, since the clinical trials evaluating the efficacy of lenvatinib and sorafenib included only patients with Child-Pugh class A, little is known about the effectiveness of the treatments in patients with hepatic decompensation. We compared the effectiveness of lenvatinib and sorafenib in decompensated patients with unresectable HCC.

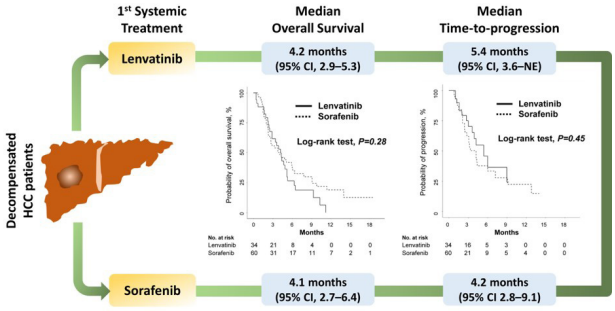
Methods: Consecutive patients who were classified as Child-Pugh class B or C and received lenvatinib or sorafenib as first-

line systemic therapy for unresectable HCC between November 2018 and April 2020 at the Seoul National University Hospital were included in this retrospective study. The primary outcome was overall survival (OS), and the secondary outcomes were time-to-progression (TTP) and best overall tumor response.

Results: Among 94 patients, 34 received lenvatinib and 60 received sorafenib. The median OS was 4.1 months (95% confidence interval [CI], 2.9–5.2): 4.2 months (95% CI, 2.9–5.3) for lenvatinib and 4.1 months (95% CI, 2.7–6.4) for sorafenib. The treatment regimen was not associated with significant improvement in OS after adjusting for baseline characteristics (adjusted hazard ratio [aHR], 0.92; 95% CI, 0.54–1.54; *P*=0.74). The treatment regimen was not an independent predictor for TTP (lenvatinib vs. sorafenib; aHR, 0.77; 95% CI, 0.41–1.48; *P*=0.44). HRs were maintained even after balancing with the inverse probability treatment weighting method. Objective response rates were 11.8% and 6.7% in patients treated with lenvatinib and sorafenib, respectively (*P*=0.45).

Conclusions: The effectiveness of lenvatinib and sorafenib was comparable for the treatment of unresectable HCC in decompensated patients.

Keywords: Liver cancer, Chemotherapy, Targeted therapy, Survival, Child-Pugh classification



FP-078

Real-World Experience of Atezolizumab/Bevacizumab in Hepatocellular Carcinoma

Yeonjung Ha[1], Jaekyung Cheon[2], Beo Deul Kang[2], Young Eun Chon[1], Mi Na Kim[1], Joo Ho Lee[1], Seong Gyu Hwang[1], Hong Jae Chon[2]

[1]Department of Gastroenterology; [2]Department of Oncology, CHA Bundang Medical Center, CHA University

Aims: Atezolizumab/bevacizumab became the standard of care for advanced hepatocellular carcinoma (HCC) patients; however, data on efficacy and safety are limited in a real-world clinical setting.

Methods: We retrospectively reviewed consecutive advanced HCC patients who received atezolizumab/bevacizumab between Jun 2020 and Jan 2021 at CHA Bundang Medical Center. Baseline variables, treatment patterns, response rates, toxicities, and clinical outcomes including overall survival (OS) and progression-free survival (PFS) were described. Predictive factors for the outcomes were determined by Cox proportional hazards models.

Results: A total of 50 patients were analyzed. The mean age was 63 years and 42 (84.0%) patients were male. Thirty-five (70.0%) patients received various anti-cancer therapies before atezolizumab/bevacizumab. Atezolizumab/bevacizumab was used as the first-line systemic therapy for 47 (94.0%) patients. In the Child–Pugh A group (n=45), 28 (62.2%) patients showed non-progression as of Feb 2021. The mean OS and PFS were 7.4 (95% confidence interval [CI], 6.7–8.2) and 5.6 (95% CI, 4.5–6.6) months, respectively. The average OS and PFS were 4.9 (2.9–7.0) and 7.7 (95% CI, 1.5–13.9) months in 5 patients with Child–Pugh B liver function. Grade 3 treatment-related hypertension occurred in 5 (10.0%) patients and 2 (4.0%) patients experienced duodenal perforation. Patients with high neutrophil-to-lymphocyte ratio (NLR), low lymphocyte-to-monocyte ratio, high platelet counts, high aspartate aminotransferase (AST) levels, and high Child–Pugh score showed shorter OS (hazard ratio [HR], 1.52; 95% CI, 1.24–1.86; *P*<0.001 for NLR and HR, 0.20; 95% CI, 0.07–0.58; *P*=0.003 for LMR). Similarly, NLR (HR, 1.29; 95% CI, 1.08–1.54; *P*=0.005), platelet counts, and AST levels were associated with PFS.

Conclusions: Atezolizumab/bevacizumab was well tolerated and effective in heavily treated advanced HCC patients in real-world clinical practice. Pretreatment NLR predicted OS and PFS.

Keywords: Atezolizumab, Bevacizumab, Hepatocellular carcinoma

Saturday, May 15, 2021, 15:00-16:20

11. Biliary and Pancreatic Disease

FP-079

5-Year Study Results of Simultaneous Pancreas Resection during Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Murat KALIN[1], Hanife Şeyda ÜLGÜR[1], Özgül DÜZGÜN[*2], Ömer Faruk ÖZKAN[1]

[1]Department of General Surgery, Health Sciences University Ümraniye Research and Training Hospital İstanbul, Turkey; [2]Department of Surgical Oncology, Health Sciences University Ümraniye Research and Training Hospital İstanbul, Turkey

Aims: Aim is to present the results of application of simultaneous pancreas resection in cytoreductive surgery (CRS) and HIPEC(hyperthermic intraperitoneal chemotherapy) in patients with peritoneal carcinomatosis (PC) due to intraabdominal tumor without distant metastases.

Methods: CRS+ HIPEC was performed in 264 patients with PC due to different etiologies between years 2016-2020 in Umraniye Research and Training Hospital. Among these 264 patients, simultaneous pancreas resection was performed in 43 patients.

Long term mortality and morbidity of these 43 patients were evaluated on the basis of their age, sex, diagnosis,duration of operation, bleeding amount applied during HIPEC and simultaneous pancreas resection.

Results: Among these 43 patients, 20 were male, 23 were female. Average age was 59.3 (range 18-77). Of 43 patients with simultaneous pancreas resection 14 patients had ovarian cancer, 10 patients had colorectal cancer, 6 patients had gastric cancer, 5 patients had mesothelioma, 4 patients had sarcomatosis and 4patients had PC due to other etiologies. Average operation time was 7 hours (3-12), average bloodloss was 500 cc(150-2200). Among these 43 patients total pancreatectomy was performed in 3, whipple was performed in 2, subtotal pancreatectomy was performed in 24 and distal pancretectomy was performed in 14 patients. 2 patients had pancreas fistule, 1 patient had hepaticojejunostomy anastomose leakage and 3 patients died within 30 days postoperatively. Mortality rate was 6.9%.

Conclusions: CRS+HIPEC can be succesfully performed in patients with PC due to intrabdominal tumor without distant metastases. Pancreas resection can also be performed simultaneously with multiple organ resection in selected patients by experienced surgical teams.

FP-080

MCT4 as a Potential Therapeutic Target to Augment Gemcitabine Chemosensitivity in Resected Pancreatic Cancer

Sung Hwan LEE[1,2], Ho Kyoung HWANG[3,4], Woo Jung LEE[3,4], Chang Moo KANG[*3,4]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Korea; [2]Laboratory of HBP Integrative Precision Oncology, CHA Bio Complex, CHA Health System, Korea; [3]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, Korea; [4]Pancreatobiliary Cancer Center, Yonsei Cancer Center, Severance Hospital, Korea

Aims: Pancreatic cancer is a devastating disease with a high relapse rate, even in resectable pancreatic cancer. This study aimed to identify the prognostic significance and therapeutic chance of the metabolic subtypes for resectable pancreatic cancer.

Methods: We obtained transcriptomic data from the TCGA-PAAD cohort via the The Cancer Genome Atlas (TCGA) data portal (n=182). After integrative analysis of transcriptomic data in the discovery cohort, immunohistochemical (IHC) staining was performed in the independent cohort to validate the molecule of interest. Experimental testing for the molecule of interest was performed using pancreatic cancer cell lines, including AsPC1, BxPC3, MIA PaCa-2, and PANC-1 *in vitro*.

Results: Two subtypes showing distinct gene expression patterns in the TCGA-PAAD dataset were identified. The active glucose metabolism subtype showed significantly lower survival regarding cancer relapse after surgical resection. The genes SLC2A1 (GLUT1) and SLC16A3 (MCT4) were highly enriched in the active metabolism subtype. The validation cohort showed high IHC staining intensity for MCT4 and a significantly high relapse rate (P=0.01). Several molecular pathways associated with aggressive tumor biology regarding cell cycle, Myc, and mTOR downstream signaling were highly enriched in the high glucose uptake subtype as well as distinct response for immunotherapy. MCT4 inhibition suppressed pancreatic cancer cell lines *in vitro* and showed a synergetic effect with gemcitabine treatment.

Conclusions: MCT4 was identified from integrative analysis as a potential therapeutic target in resectable pancreatic cancer. The precision strategy for resectable pancreatic cancer should be validated in a clinical setting with a prospective study design.

FP-081

"Anatomic" Liver Resection Performed by Approaching the Umbilical Plate for Perihilar Cholangiocarcinoma

Ji Su KIM[1,2], Dai Hoon HAN[1,2], Kyung Sik KIM[1,2], Jin Sub CHOI[1,2], Gi Hong CHOI[*1,2]

[1]Division of Hepatobiliary and Pancreatic Surgery, Dpartment of Surgery, Yonsei University College of Medicine, Seoul, Korea; [2]Liver Cancer Center, Yonsei Cancer Center, Severance Hospital, Seoul, Korea

Aims: The Anatomic right hepatic trisectionectomy with caudate lobectomy for hilar cholangiocarinoma was reported in 2006. This technique need the umblical plate access. With extension of this technique, anatomic central bisectionectomy can be also performed for the Bismuth type 4 of perihilar cholaniocarcinoma (CCA).

Methods: From 2010 to 2020, anatomic right trisectionectomy (N=9) and anatomic central bisectionectomy (N=7) was performed for the patients with the Bismuth type 4 of perihilar CCA. All anatomic liver resection was performed by approaching the umblical plate, in which the bile ducts of the left lateral section were divided at the left side of the umblical fissure following complete dissection of the umblical plate.

Results: Liver resection was successfully performed, and there was no postoperative mortality. All patients were histologically diagnosed as having CCA. Among the patients who underwent anatomic right trisectionectomy, 4 patients received portal vein embolization and 5 patients did not. R0 resection rate was 60%. 3 patients performed portal vein wedge resection. 7 patients died of cancer progression and 2 patients died of biliary sepsis. One patients survived without recurrence for 8 years. 5 patients are under follow-up without recurrence. The remaining one patient recurred after 28 months and is undergoing radiation therapy. There were only four patients had biliary leakage.

Conclusions: Anatomic liver resection that is performed by approaching the umblical plate can be safely and effectively performed even in perihilar CCA.

FP-082

Precision Strategy Based on Cancer-Specific Molecular Subtypes of Bile Duct Cancer from Comprehensive Analysis Using Multi-Omics Dataset

Hye Jung CHO[1], Incheon KANG[1], Sung Hoon CHOI[1], Sunyoung LEE[2], Ju-Seog LEE[3], Sung Hwan LEE[*1]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Korea; [2]Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, USA; [3]Department of Systems Biology, Division of Basic Sciences, University of Texas MD Anderson Cancer Center, USA

Aims: Bile duct cancer is a heterogeneous tumor entity harboring distinct tumor biology and clinical phenotype according to their unique tumor microenvironment (TME), especially anatomic location in terms of intrahepatic, peri-hilar, and distal extrahepatic portion. Therefore, there is a clear unmet need for the precision strategy based on cancer-specific genomic features rather than previous molecular subtypes from bulk RNA sequencing.

Methods: Comprehensive analyses were performed using the dataset from the cancer dependency map (DepMap) project, including cancer-specific molecular characterization with multi-omics data, genome-wide loss-of-function screening with CRISPR-Cas9 system, and drug sensitivity with compound screening to uncover cancer-specific molecular subtypes showing clinical relevance. The cancer-specific molecular signatures were validated in independent translational cohorts (TCGA-CHOL; n=45, ICGC-BTC; n=181, GSE132305; n=220).

Results: Out of 8 patients, 6 were females. Median age was 54 years. 6 patients underwent left hepatectomy, and 1 each underwent right hepatectomy and right trisectionectomy. Trisectionectomy was done after liver volumetry showed a future liver remnant volume of 48% with right posterior section atrophy. Mean intra-operative blood loss was 226mL, median hospital stay was 11.2 days. 1 patient had Clavien-Dindo grade 3 complication in the form of intra-abdominal collection requiring percutaneous drain placement. 6 patients had significant elevation of transaminases that resolved by a median duration of 8 days. No patient had post-hepatectomy liver failure. None of the patients developed recurrent hepaticolithiasis or biliary stricture, with follow up duration of 11-64 months.

Conclusions: Comprehensive analysis using a multi-omics dataset revealed precision strategies based on cancer-specific molecular subtypes of bile duct cancer in terms of tumor classification and discriminative therapeutic chances. Prospective translational studies companion with clinical trials based on cancer-specific molecular subtypes is mandatory to establish the precision strategy for managing bile duct.

FP-083

The Comparison of Short-Term Postoperative Outcomes between Upfront Surgery and Surgery Following Neoadjuvant Treatment in Pancreatic Ductal Adenocarcinoma

Ji Hye JUNG, So Kyung YOON, So Jeong YOON, Sang Hyun SHIN, In Woong HAN, Jin Seok HEO[*]

Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Aims: In cases that neoadjuvant treatment (NAT) was performed before surgery, research on short-term postoperative outcomes seems to have been insufficient. We aimed to compare short-term outcomes between patients who received upfront surgery and those who received surgery following NAT for pancreatic ductal adenocarcinoma (PDAC).

Methods: We retrospectively reviewed 1244 cases of PDAC that had pancreatectomy at Samsung Medical Center from January 2010 to March 2020. The resectability status was evaluated according to NCCN guidelines 2017, and cases with distant metastasis were excluded. All cases were classified into two groups of resectable group (R group) and borderline resectable group (BR group). In each group, factors were compared between the cases that upfront surgery was performed (UpS cases) and the cases that surgery was performed after NAT (NAT cases).

Results: In R group (n= 981), the clinical, operative, pathologic features did not show distinct differences between UpS cases (n= 973) and NAT cases (n= 8). In BR group (n= 248), patients were younger, preoperative/ pre-NAT tumor size was larger, and less cases were accompanied by vascular resection in NAT cases (n= 85) compared with UpS cases (n= 163). There were many oncologic benefits in BR group compared with R group. The short-term postoperative outcomes had no significant differences between UpS cases and NAT cases in both R group and BR group.

Conclusions: In cases of NAT, there were no significant differences from upfront surgery in terms of short-term outcomes including postoperative complication. Therefore, we think it is reasonable to perform aggressive surgery for NAT patients.

FP-084

Does Timing of Completion Radical Cholecystectomy Determine the Survival Outcome in Incidental Carcinoma Gallbladder – A Single Center Retrospective Analysis

Rahul R.[1], Kulbhushan HALDENIYA[1], Ashish SINGH[1], Prabhakar MISHRA[2], Rajneesh Kumar SINGH[1], Anu BEHARI[1], Vinay Kumar KAPOOR[1], Rajan SAXENA[*1]

[1]Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, India; [2]Biostatistics and Health Informatics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, India

Aims: Incidental discovery of gallbladder cancer (GBC) on post-operative histopathology or intra-operative suspicion has become a usual phenomenon. Incidental GBC (IGBC) portends a better survival than primarily detected GBC. Various factors affect the outcome of re-resection with timing of re-intervention an important determinant of survival.
Methods: All patients of IGBC who underwent curative resection from Jan 2009 to Dec 2018 were considered for analysis. Details of demographic profile, index surgery, primary histopathology, operative findings on re-resection, final histopathology and follow up data were retrieved from the prospectively maintained database. Patients were evaluated in three groups based on the interval between index cholecystectomy and re-intervention {Early (<4weeks), Intermediate (4-12weeks) and Late (>12weeks)} using appropriate statistical tests.
Results: Forty eight patients underwent re-resection with curative intent. Median age of presentation was 55 years. Mean and median follow-up was 51.6 and 40.6 months respectively (Range: 1.2-130.6). The overall survival and disease free survival among the three groups was the best in 'E' group (104&102 months) as compared to the 'I' (84&83) and 'L' groups (75&73 months), though the difference was not statistically significant (*P*=0.588 and 0.581). On Multivariate analysis, poor differentiation was the only independent factor affecting survival. Other attributes which were associated with poor outcome, but could not reach statistical significance were node metastasis, delay in re-resection, residual tumor, need for CBD excision and lymphovascular invasion.
Conclusions: Grade of tumor is the most important determinant of survival in IGBC. Early surgery, preferably within 4 weeks possibly entails better survival.

FP-085

Organ Preserving Pancreatic Resections Offers Better Long-Term Conservation of Pancreatic Function at the Expense of Significantly High Perioperative Major Morbidity- A Fair Trade-Off for Benign or Low Malignant Potential Pancreatic Neoplasms

Vikas GUPTA, Manish BHANDARE, Vikram CHAUDHARI, Shailesh SHRIKHANDE

Surgical oncology, TATA memorial hospital, India

Aims: Standard pancreatic resections often remove excess pancreatic parenchyma than required for tumors of low malignant potential (LMP) or benign neoplasms. We aimed to compare short and long-term outcomes following organ-ppreserving pancreatic resections (OPPAR) and standard pancreatic resections (SPR).
Methods: Data was collected from a prospectively maintained database of patients who underwent OPPAR or SPR for benign or LMP pancreatic tumors from January 2011 to January 2020 at Tata Memorial Hospital.
Results: 40 and 110 patients were identified in OPPAR and SPR groups respectively. The mean surgery duration (277 vs 339 mins, *P*-0.006) and mean blood loss (602 vs 937 ml, p-0.01) were significantly lower in patients who underwent OPPAR. Although the overall morbidity (57.5% vs 43.6%, *P*-0.13) was comparable, the major morbidity (42.5% vs 20.9%, p-0.008), post-operative pancreatic fistula (POPF) (65% vs 33.6%, *P*-0.001) and clinically relevant POPF (42.5% vs 19.1%, *P*-0.004) were significantly higher in OPPAR. After a median follow up of 29 months the post operative endocrine insufficiency (10% vs 15.5 %, *P*- 0.39), exocrine insufficiency (20 % vs 0%, *P*- 0.002) and requirement of long-term pancreatic enzyme replacement (18.2% vs 0%, p-0.004) were higher in SPRs. Left sided SPRs had higher endocrine insufficiency (17.1% vs 11.2%, *P*-29) and right sided SPRs had higher exocrine insufficiency (20% vs 8.6%, p-0.04)
Conclusions: OPPAR should be considered for treatment of benign tumors and tumors of LMP with favorable features. Although the incidence of post-operative major morbidity and POPF is higher with OPPAR than standard resections, there appears to be long term functional benefit.

FP-086

Impact of Neoadjuvant Chemoradiotherapy on Post-Operative Clinically Significant Pancreatic Fistula – A Systemic Review and Updated Meta-Analysis

BHAVIN VASAVADA, Hardik PATEL

Hepatobiliary and liver transplant, Consultant hepatobiliary and liver transplant, India

Aims and objectives: The primary aim of our analysis was to do a systemic review and updated meta-analysis of literature published in the last 10 years and look for the association of neoadjuvant chemoradiation and risk of subsequent clinically significant pancreatic fistula.
Methods: EMBASE, MEDLINE, and the Cochrane Database were searched for Studies comparing outcomes in patients receiving neoadjuvant chemoradiotherapy first with those patients who received surgery first in case of pancreatic cancer. A systemic review and Metanalysis were done according to MOOSE and PRISMA guidelines. Heterogeneity was measured using Q tests and I2, and *P*<0.10 was determined as significant.
Results: Twenty-six studies including 17021 patients finally included in the analysis. 339 patients out of a total of 3386 developed clinically significant pancreatic fistula in the neoadjuvant first group. 2342 patients out of 13335 patients developed clinically significant pancreatic fistula in the surgery first group. Neoadjuvant treatment significantly reduced the risk of subsequent clinically significant pancreatic fistula (*P*=<0.0001). The number of patients with soft pancreas was significantly higher in the surgery first group (*P*<0.0001). Pancreatic duct

diameter mentioned in only two studies but there was no significant difference between both groups [*P*=1]. Blood loss was significantly more in the surgery first group [*P*<0.0001]. There was no difference in pancreaticoduodenectomy or distal pancreatectomy performed between both groups (*P*=0.82). There was no There was no difference in the number of borderline resectable pancreatic tumors between both groups (*P*=0.34). There was no difference in overall grade 3/grade 4 complications rate between both groups (*P*=0.39).

Conclusions: Neoadjuvant treatments may be responsible for the lower rates of clinically significant pancreatic fistula after subsequent surgery.

The Liver Week 2021

May 13-15, 2021 | Virtual Conference

The Liver Week 2021

Free Paper VOD Presentation

FV-001	Basic
FV-002~FV-025	Hepatitis B Virus
FV-026~FV-038	Hepatitis C Virus
FV-039~FV-042	Alcoholic Liver Disease
FV-043~FV-052	Cirrhosis/Liver Fibrosis
FV-053~FV-059	Drug Induced Liver Injury
FV-060~FV-089	Nonalcoholic Fatty Liver Disease
FV-090~FV-100	Liver Cancer_Basic
FV-101~FV-121	Liver Cancer_Clinical
FV-122~FV-141	Liver Transplantation
FV-142~FV-158	Biliary and Pancreatic Disease
FV-159~FV-170	Surgery, Technical Issues
FV-171~FV-184	Others

1. Basic

FV-001

Protective of 17β-Estradiol on Oxidative Stress and Hepatic Metabolism in Aged Female Rats

Pardeep Kumar, Sagar Lavenia

Department of Biochemistry, F H M College, India

Aims: The objective of this study was to observe the changes in activity of antioxidant enzymes, hepatic glucose homeostasis, lipogenic enzymes and lipid metabolism, serum lipid profile and liver function occurring in livers of female rats of 3, 12 and 24 months age groups, and to see whether these changes are restored to 3 months control levels rats after exogenous administration of steroid hormone estrogens (17-β-estradiol, E2).

Methods: The aged rats (12 and 24 months old) (n= 8 for each group) were given subcutaneous injection of 17beta estradiol (0.1 ug/g body weight) daily for one month. After 30 days of hormone treatment, experimental animals of all the groups were sacrificed and livers were isolated for further study. A detailed study was carried on non-enzymatic glutathione (GSH) and enzymatic antioxidants [superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT)], hepatic glucose homeostasis, lipogenic enzymes, lipid metabolism, serum aspartate aminotransferase (GOT), alanine aminotransferase (GPT),alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), phosphatase alkalin (PAL) as well as bilirubin level.

Results: The results obtained in the present work revealed that normal aging was associated with significant decrease in the activities of antioxidant enzymes, serum expression and an increase in hepatic glucose homeostasis, lipogenic enzymes and lipid profile and GGT, PAL, GOT, GPT, ALP as well as bilirubin level increased significantly in livers of aging female rats. Our data showed that exogenous administration of E2 brought these changes to near normalcy in aging female rats.

Conclusions: The present study showed that E2 treatment reversed the changes to normal levels. E2 treatment may be beneficial in preventing some of the age related changes in the liver by increasing antioxidant defences and decrease oxidative stress. E2 plays important role in the progression of chronic hepatic diseases.

Keywords: Estradiol, Aging rat liver, Lipogenic enzymes, Enzymatic antioxidants

2. Hepatitis B Virus

FV-002

The Release of Viral Particle from Hepatitis B Virus Infected Hepatocytes Is Inhibited by Recombinant Hepatitis B Virus Immunoglobulin (Lenvervimab)

Kyung Chul YOON, Kwang-Woong LEE*, SooIn SEO, Seung Cheol OH, Min-Young PARK, Suk Kyun HONG, Jeong-Moo LEE, Nam-Joon YI, Kyung-Suk SUH

Department of Surgery, Seoul National University College of Medicine, Korea

Aims: Potent and relatively low cost HBIG could be good alternatives by overcoming the drawbacks of recent regimen and recombinant monoclonal HBIG (lenvervimab) has been reported the consistent avidity of variety to cloned S antigens including the immune escape mutant G145R and it did not interfere with the antibody binding in HBV with mutations of the S gene sequence which makes drug resistance to NA. We investigated the action of intracellularly located lenvervimab in HBV infected cells which is incompletely understood yet.

Methods: We used five human hepatoma cell lines; Huh7, HepG2 as HBV negative and PLC/PRF/5, HepG2.2.15, and Hep3B expressing HBsAg. and various intracellular orgarnells markers; endosome(Rab5), autophagy marker(LC3), anti-calnexin(ER), giantin(golgi), multivesicular body (Rab7). Immunofluorescence images were used to investigate the intracellular locations of lenvervimab and HBsAg. Western blot and PEG down, ELISA were used for protein analysis.

Results: Lenvervimab was co-localized with Rab5(early endosome marker) and and induces autophagosome but not autolysis. HBsAg and Lenvervimab were co-localized with making precipitations in cytoplasm and these precipitations were not co-localized with ER and golgi marker. Rab7 (multivesicular body marker) and lenvervimab, HBsAg were co-localized in PLC/PRF/5.

Conclusions: The release of viral particle is suppressed by lenvervimab with antigen-antibody reaction in multivesicular body.

FV-003

Relationship between HBV-DNA Viral Load and Transaminase Enzymes in Hepatitis B Patients in a Low Setting Area

Arum Tri WAHYUNINGSIH, Osman SIANIPAR, Adika Zhulhi ARJANA*, Rhaina KHAIRANI, Budi MULYONO

Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia

Aims: Chronic hepatitis B is still an infectious disease that is a major problem in Asia. The success of antiviral therapy against hepatitis B infection has been widely supported by very sensitive

laboratory tests to monitor HBV-DNA. However, in developing countries like Indonesia, the measurement of HBV DNA level is still a challenge. Apart from limited access, a limited health insurance system contributes to this obstacle. Potential markers are transaminase enzymes (ALT and AST) although not all studies show a strong association. This study aims to analyze the relationship between HBV-DNA viral load and transaminase enzymes (ALT and AST) in hepatitis B patients in a low setting area

Methods: This study was funded by Deputi Bidang Penguatan Riset dan Pengembangan, Kemenristek/BRIN. This study using observational research with secondary data from January to November 2020 in hepatitis B patients at Dr. Sardjito Hospital. This study has been approved by the Committee of Ethics Committee of the Faculty of Medicine, Public Health and Nursing (FK-KMK) Universitas Gadjah Mada.

Results: The subjects of this study were 139 hepatitis B patients. The median of HBV-DNA level was 4.56 log IU/mL (0.84-8.20). The median ALT and AST levels were 41.0 (6.0-1041.0) U/L and 43.0 (13.0-1058.0) U/L, respectively. Correlation analysis showed that there was a weak but statistically significant relationship between HBV-DNA and both ALT and AST levels (r=0.383; *P*<0.01; r=0.334; *P*<0.01).

Conclusions: This study demonstrates the possibility of using transaminase enzymes to monitor hepatitis B patients in a low setting area.

FV-004

Association of Physical Activity with the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

Ho Soo Chun[1,2], Sojeong Park[3], Minjong Lee[1,2], Ha Sung Kim[3], A Reum Choe[1,2], Hwi Young Kim[1,2], Kwon Yoo[1,2], Tae Hun Kim[1,2]

[1]Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, Korea; [2]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea; [3]Data Science Team, Hanmi Pharmaceutical Co., Ltd, Seoul, Korea

Aims: In the general population, previous studies reported that physical activity was associated with risk of hepatocellular carcinoma (HCC) development and mortality. However, it is unclear whether physical activity is associated with risk of HCC development in patients with chronic hepatitis B (CHB). We aimed to elucidate the association between physical activity and risk of HCC development and mortality in CHB patients.

Methods: This nationwide cohort study involved treatment-naive patients with CHB (n=9,727) who started treatment with entecavir or tenofovir and answered self-reported questionnaires between January 2012, and December 2017, using data from the Korean National Health Insurance Service database. Primary endpoint was development of HCC. Multivariable Cox regression and competing risk analyses were used.

Results: During a median follow-up of 3.1 years, cumulative HCC incidence rates were 8.3% and all-cause mortality rates were 1.8%. There was an inverse association between physical activity and the risk of HCC (*P*<0.001). Patients with 1,000–1,500 metabolic equivalent task (MET)-min/week, compared to those without physical activity, showed a significantly lowest risk of HCC in both patients without cirrhosis (adjusted hazard ratio [aHR] 0.66, *P*=0.02) and patients with cirrhosis (aHR 0.61, *P*=0.02). In patients who were younger age (<60), male, without diabetes, and with high BMI, amounts of physical activity of 1,000–1,500 MET-min/week showed an inverse association with the risk of HCC (aHR 0.65, 0.63, 0.65. and 0.64, respectively, all *P*<0.05).

Conclusions: Physical activity was significantly associated with a low risk of HCC in CHB patients treated with entecavir or tenofovir.

Keywords: Chronic hepatitis B, Physical activity, Hepatocellular carcinoma, Mortality

FV-005

Hepatitis B e Antigen Seroconversion during Antiviral therapy Is Not Related to the Development of Hepatocellular Carcinoma

Han Ah Lee[1,2], Jihwan Lim[1], Young-Sun Lee[1], Young Kul Jung[1], Ji Hoon Kim[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Kwan Soo Byun[1], Yeon Seok Seo[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Aims: Delayed or absence of hepatitis B e antigen (HBeAg) seroconversion have been known to increase the risk of hepatocellular carcinoma (HCC). We investigated the association of HBeAg seroconversion and HCC development in HBeAg-positive patients treated with high genetic barrier antiviral agents.

Methods: Treatment-naive, HBeAg-positive patients who received entecavir (ETV) or tenofovir disoproxil fumarate (TDF) as a first-line antiviral agent in Korea University Medical Center from 2007 to 2016 were included. Patients with decompensated cirrhosis or HCC at enrollment were excluded.

Results: In total, 734 patients were included. During a median follow-up period of 90.3 months, 200 patients (27.2%) achieved HBeAg seroconversion. The HBeAg seroconversion rates after 1-year and 2-years of antiviral treatment were 6.1% and 10.9%, respectively. Among all patients, HCC developed in 56 patients (7.6%). Patients who achieved HBeAg seroconversion were significantly younger than those who had not (43.1 vs. 45.4 years, *P*=0.018). 28.0% of patients who achieved HBeAg seroconversion and 42.7% of patients who had not were treated with TDF (*P*<0.001). Significantly lower HBV DNA levels were observed in patients who achieved HBeAg seroconversion than those who had not (all *P*<0.05). Cumulative incidences of HCC were not statistically different between patients who had and had not achieved HBeAg seroconversion after 1-year and 2-years of antiviral therapy, respectively (log-rank test, all *P*>0.05). In cox-regression analyses for HCC, neither

HBeAg seroconversion after 1-year (*P*=0.958) nor 2-years of antiviral therapy were significantly related to the development of HCC (*P*=0.852). On multivariate analyses, older age, presence of cirrhosis, higher alanine aminotransferase level, and treated with TDF were significant predictors for HCC (all *P*<0.05). After propensity score-matching, treated with TDF was not significantly associated with HCC development (*P*=0.207) (Table).

Table. Predictor for hepatocellular carcinoma in propensity score matched cohort

Variables	Rating	Univariate	Multivariate		
		P value	Hazard ratio	95% confidence interval	*P* value
Age	years	<0.001	1.066	1.024-1.110	0.002
Male sex		0.282			
Body mass index	kg/m^2	0.637			
Diabetes	0=no; 1=yes	0.234			
Hypertension	0=no; 1=yes	0.332			
Liver cirrhosis	0=no; 1=yes	<0.001	3.241	1.370-7.669	0.008
Platelet count	× 10^3/L	0.663			
Prothrombin time, INR		0.327			
Alanine aminotransferase	IU/L	0.001	0.991	0.982-0.999	0.030
Total bilirubin	mg/dL	0.999			
Serum albumin	g/dL	0.948			
HBV DNA	log IU/mL	0.078			
HBeAg seroconversion in 1 year	0=no; 1=yes	0.997			
HBeAg seroconversion in 2 year	0=no; 1=yes	0.340			
Alpha-fetoprotein	ng/mL	0.911			
Antiviral agent	0=ETV; 1=TDF	0.133			

HBeAg, Hepatitis B e antigen; HBsAg

Conclusions: The achievement of HBeAg seroconversion during the treatment with potent antiviral agents is not significantly associated with the risk of HCC.

Keywords: Hepatitis B e Antigen, Seroconversion, Antiviral, Hepatocellular carcinoma

FV-006

Pre and Post M2BPGi Level Can Predict Hepatocellular Carcinoma in Chronic Hepatitis B Patients Treated with Antiviral agents

Young Youn Cho[1], Hyun Woong Lee[2], Hyung Jun Kim[1]*

[1]Department of Internal Medicine, Chung-Ang University Hospital; [2]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine

Aims: Mac-2 binding protein glycosylation isomer (M2BPGi) is a non-invasive marker which can evaluate liver fibrosis. The aim of this study is to compare the change of M2BPGi before and after high potent antiviral treatment, and evaluate whether M2BPGi could predict hepatocellular carcinoma (HCC) development.

Methods: This retrospective study included chronic hepatitis B (CHB) patients who underwent high potent antiviral treatment and had stored serum samples at the baseline and 1–2 years after treatment initiation. Primary endpoint was HCC development evaluated by the Cox proportional hazard model.

Results: Among 268 patients, 187 (69.8%) were treated with entecavir, 81 (30.2%) were treated with tenofovir, 95 (35.4%) had initial radiologic liver cirrhosis. After follow-up, 24 (8.9%) developed HCC. The mean M2BPGi levels did not change in the liver cirrhosis group after antiviral treatment; 1.50 cut-off index (COI) at baseline and 1.55 COI after 1–2 years. However, in the chronic hepatitis group the mean M2BPGi decreased after antiviral treatment; 0.63 COI at baseline and 0.42 COI after 1–2 years. Multivariate analysis showed that the pre-M2BPGi level (adjusted hazard ratio [aHR]=1.215, 95% confidence interval [CI]=1.047–1.411, *P*=0.010) and the post-M2BPGi level (aHR=1.442, 95% CI=1.126–1.710), *P*<0.001) both predicted HCC development.

Conclusions: Both pre and post treatment M2BPGi levels can predict HCC development in chronic hepatitis B patients.

Keywords: Liver fibrosis, Hepatocellular carcinoma, Non-invasive marker

FV-007

Efficacy and Safety of Tenofovir Disoproxil Orotate in Chronic Hepatitis B Patients Previously Treated with Tenofovir Disoproxil Fumarate: Multi-Center, Open Label, Prospective Study

Young Chang[1], Soung Won Jeong[1*], Jae Young Jang[1], Jeong-Ju Yoo[3], Sae Hwan Lee[2], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2], Hyung Woong Lee[4], Suyeon Park[5]

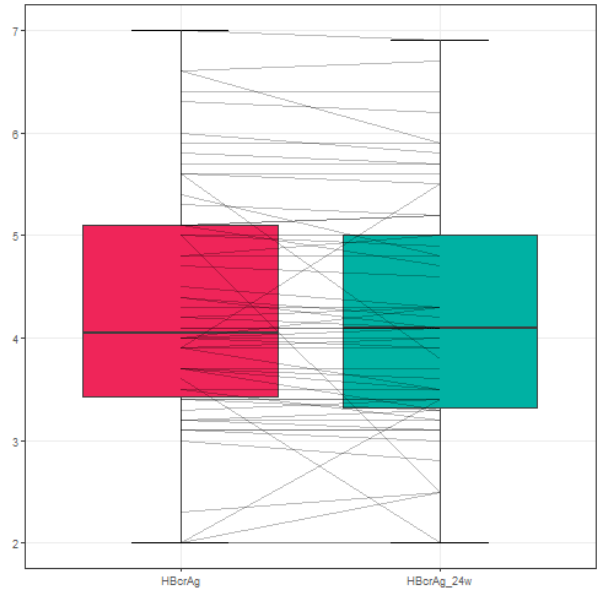
[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea, [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea, [4]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, and [5]Department of Data Innovation, Soonchunhyang University Hospital, Seoul, Korea

Aims: We compared the efficacy and safety of the two drugs (tenofovir disoproxil fumarate,Viread® versus tenofovir disoproxil orotate, Vireal®) in patients with chronic hepatitis B by a non-inferiority study.

Methods: This study is a multicenter, open-labeled, prospective clinical trial (KCT0004185) that evaluates the efficacy of 24 weeks treatment after switching from tenofovir disoproxil fumarate to tenofovir disoproxil orotate among chronic hepatitis B patients who have taken tenofovir disoproxil fumarate with HBV DNA less than IU/mL 20 for at least 48 weeks. A total of 64 patients were replaced with tenofovir disoproxil orotate, and visited every 12 weeks to complete 24 weeks of treatment unless there is a reason for discontinuation of medical examination and drug prescription. The primary efficacy endpoint is the maintained virologic response (HBV DNA < 20 IU/mL) rate after 24 weeks of replacement dosing. The secondary efficacy endpoints are normalization of serum alanine aminotransferase (ALT) level, HBeAg loss rate, and changes in HBcrAg titer. Safety is assessed by evaluating major adverse events, changes in renal function, and occurrence of hepatocellular carcinoma (HCC). Paired nominal variables were compared using McNemar's test, and paired continuous variables were compared using the paired sample t-test or Wilcoxon signed rank test.

Results: Among a total of 64 patients, one patient dropped out during the study period. At 24 weeks of tenofovir disoproxil orotate administration, 61 out of 63 patients maintained virologic response, and 2 patients showed the increase of HBV

DNA over 20 IU/ml, indicating no statistical difference in the proportion of patients with viral suppression compared to baseline (100% vs. 96.83%; *P*=0.5). The proportion of patients with normalized ALT levels was 82.26% at 12 weeks and 87.3% at 24 weeks, which were not significantly different from that of baseline (*P*=0.44 and *P*=1.00, respectively). There were no cases of HBeAg loss or seroconversion during the study period. Interestingly, HBcrAg titer significantly decreased at 24 weeks of tenofovir disoproxil orotate treatment with mean titer of 3.91 logU/mL from 4.15 logU/mL at baseline (*P*=0.01; Figure 1). In safety assessment, there were no cases of grade 3 or higher adverse events and HCC during the study period. Renal function, assessed by glomerular filtration rate (GFR) and serum phosphorus level, showed improving trend during the study period. Mean GFR, 91.09 mL/min at baseline, was increased to 93.34 mL/min at 24 weeks (*P*=0.056), mean serum level of phosphorus was increased from 3.33 mg/dL to 3.44 mg/dL at 24 weeks (*P*=0.044).



Conclusions: In patients with chronic hepatitis B, the efficacy of tenofovir disoproxil orotate was non-inferior to that of tenofovir disoproxil fumarate, and HBcrAg titer significantly decreased at 24 weeks of tenofovir disoproxil orotate treatment.

Keywords: Tenofovir disoproxil orotate, Non-inferiority, HBcrAg

FV-008

Laboratory Healthcare Gap of Hepatitis B Care in Yogyakarta, Indonesia

Arum Tri WAHYUNINGSIH[*1], Osman SIANIPAR[1], Adika Zhulhi ARJANA[1], Rhaina KHAIRANI[1], Romi Ade SELSATA[2], Fadhilah Khairuna LARASATI[2], Alfin Herjuno DWIPUTRO[2], Intan Susmita RAFSANJANI[3], Budi MULYONO[1]

[1]Clinical Pathology and Laboratory Medicine, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia; [2]Medical Doctor Programme, Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Indonesia; [3]Medical Doctor Programme, Faculty of Medicine, Universitas Islam Indonesia, Indonesia

Aims: Serological markers of hepatitis B virus infection (HBsAg, anti-HBs, hepatitis B envelope antigen (HBeAg), anti-HBe, and anti-HBc (hepatitis B core) IgM / IgG) was used as the basis for diagnosis and differences in the chronicity of hepatitis B infection. This study aims to explore the laboratory healthcare gap of the patient with hepatitis B infection in our setting and whether laboratory data completeness affects the results.

Methods: This study used retrospective data taken from the Medical Records of hepatitis B patients at Dr. Sardjito Hospital in 2020. The subjects in this study were hepatitis B patients with positive HBsAg. The exclusion criteria were individuals who had co-infection with the hepatotropic virus or HIV. This study was funded by Deputi Bidang Penguatan Riset dan Pengembangan, Kementerian Riset dan Teknologi/Badan Inovasi Nasional

Results: A total of 232 patients were included in the study. All patients underwent HBsAg examination and tested positive, with 65.09% of subjects had HBV DNA examination. HBeAg examination result was only found in 18% of patients. Anti HBc examinations were only found in 2 patients. No subjects were examined for anti-HBs in this study. The proportion of subjects examined for the liver function was still low (<50%), with the most widely checked parameters are AST and ALT while other parameters are very rare.

Conclusions: The utilization of serological tests and hepatic function in hepatitis B patients in Yogyakarta, Indonesia is still low. Intervention and financial support are needed to improve the quality of life of patients with hepatitis B who were treated

FV-009

HBcrAg; Useful Biomarker to Predict HBeAg Seroconversion in Chronic Hepatitis B Patients Treated with Antivirals

Sunghwan Yoo[1], Sora Kim1, Young Youn Cho[2], Hyung Joon Kim[2], Hyun Woong Lee[1]

[1]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine; [2]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Aims: HBeAg seroconversion is an important treatment endpoint for HBeAg-positive patients and is a pre-requisite for HBsAg loss or functional cure. We aimed to identify predictors of seroconversion using serum ultrasensitive HBsAg and HBcrAg, in HBeAg-positive patients treated with nucleos(t)ide analogues (NA).

Methods: Data and samples from 37 HBeAg-positive patients started on entecavir between Jan 2007 and Dec. 2017 were retrospectively analysed. The mean follow-up duration was 11 years. The predictive power of on-treatment levels of HBsAg and HBcrAg was determined using receiver operating curve (ROC) analysis and cut-off values determined by maximized Youden's index.

Results: Thirteen patients (35.1%) achieved HBeAg serocon-

version at a mean of 28 months (12-84 months) after antiviral treatment. On treatment kinetics of HBV DNA, HBsAg and HBcrAg differed between HBeAg seroconversion and non-seroconversion. The decline of HBcrAg level had the greatest predictive value for HBeAg seroconversion at 2 years. The decline of HBcrAg level ≥ 1.25 $\log_{10}$ U/mL at 2 years after antiviral therapy had a sensitivity of 76.9%, specificity of 75.0%, positive predictive value of 75.5% and negative predictive value of 76.5%, with AUROC of 0.837 (0.706, 0.967; 95%CI) to predict HBeAg seroconversion.

Conclusions: In chronic hepatitis B patients achieved entecavir induced HBeAg seroconversion, HBcrAg level declined at a relatively better rate. The decline of HBcrAg level ≥ 1.25 $\log_{10}$ IU/ml at 2 years after antiviral therapy might be used to predict HBeAg seroconversion.

Keywords: HBcrAg, Ultrasensitive HBsAg, Entecavir, HBeAg seroconversion

FV-010

Association of Aspirin and Statin Use with Hepatocellular Carcinoma Risk in Chronic Hepatitis B: a Nationwide Population-Based Study

Won-Mook Choi[1], Hyo Jeong Kim[2], Ae Jeong Jo[2], So Hyun Choi[2,3], Seungbong Han[4], Min Jung Ko[2], Young-Suk Lim[1]

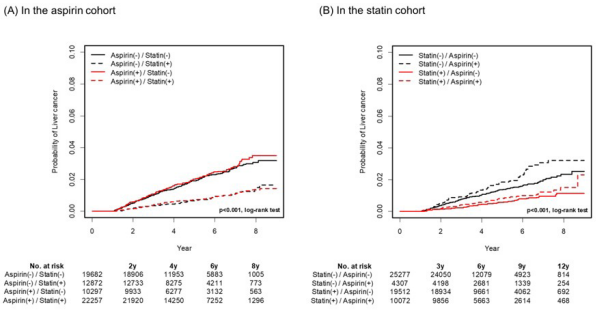
[1]Liver Center, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Division for Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul, Republic of Korea; [3]Department of Statistics, Kyungpook National University, Daegu, Republic of Korea; [4]Department of Applied Statistics, Gachon University, Seongnam-si, Gyeonggi-do, Republic of Korea

Aims: Aspirin and statins have been suggested to prevent hepatocellular carcinoma (HCC). However, the combined effects of aspirin and statins on HCC risk is not clear. Here, we investigated the individual and combined effects of aspirin and statins on the risk of HCC in patients with chronic hepatitis B (CHB).

Methods: A nationwide nested case-control study was performed with data from the National Health Insurance Service gathered between 2005 and 2015 in Korea. In a cohort of 538,135 treatment-naïve, non-cirrhotic patients with CHB, 6,539 HCC cases were matched to 26,156 controls and were analyzed by conditional logistic regression. Separate historical cohort studies for each drug were analyzed by time-dependent Cox regression as a sensitivity analysis.

Results: In the nested case-control study, statins (OR 0.34; 95% CI 0.32–0.37) were associated with a greater HCC risk reduction than aspirin (OR 0.92; 95% CI 0.85–0.99). Dose-dependent HCC risk reduction was observed only with statins. By sensitivity analysis in the historical cohorts, statin users (n = 244,455; HR 0.67; 95% CI 0.66–0.68) were associated with a greater HCC risk reduction than aspirin users (n = 288,777; HR 0.81; 95% CI 0.80–0.82). In the drug-stratified analyses, statins were associated with significantly reduced risk of HCC regardless of aspirin, whereas aspirin did not show such associations.

FIGURE. Stratified analysis for the cumulative incidence of hepatocellular carcinoma in the propensity score-matched historical cohorts for aspirin and statins.



Conclusions: In this nationwide population-based study of patients with CHB, statins were independently associated with a significant HCC risk reduction. However, the association between aspirin and HCC risk reduction was not consistent and suggested to be confounded by statins.

Keywords: Anti-platelet, Hepatitis B virus, Lipid-lowering agent, Liver cancer

FV-011

No Influence Of Hepatic Steatosis on the 3-Year Outcomes Of Patients With Quiescent Chronic Hepatitis B

Jin Won Chang[1], Jae Seung Lee[1-3], Hye Won Lee[1-3], Beom Kyung Kim[1-3], Jun Yong Park[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Seung Up Kim[1-3]

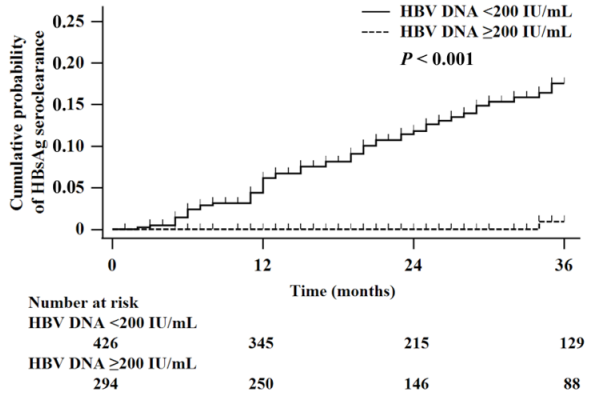
[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

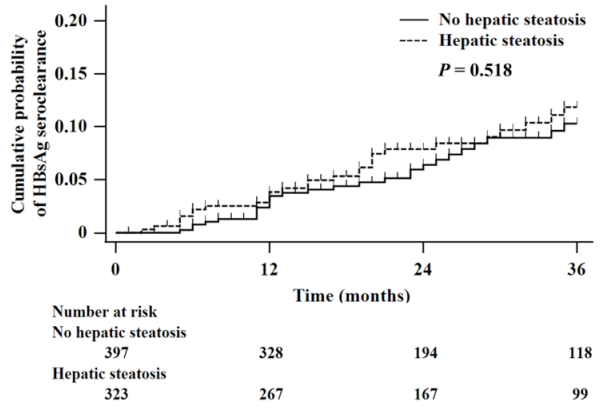
Aims: The influence of hepatic steatosis (HS) on the natural history of chronic hepatitis B (CHB) virus is unclear. Therefore, we investigated whether concurrent HS in patients with CHB influenced the probability of hepatitis B surface antigen (HBsAg) loss, fibrosis progression, and hepatocellular carcinoma (HCC) development.

Methods: This study enrolled treatment-naïve patients with virologically (HBV DNA <2,000 IU/mL) and biochemically (alanine aminotransferase level <40 IU/L) quiescent CHB who underwent transient elastography between January 2004 and December 2015 and completed a 3-year follow-up.

Results: Mean age of the study population (n=720) was 52.0 years, and there were more men than women (n=419, 58.2%). Mean HBV DNA level was 321.6 IU/m. During the 3-year period, 74 (10.3%) patients achieved HBsAg seroclearance. Lower HBV DNA levels (hazard ratio=0.995, P<0.05) were independently associated with HBsAg seroclearance, while HS was not (P>0.05). Fibrosis progressed in 89 (12.4%) patients. Male gender [odds ratio (OR)=1.720] and higher body mass index (OR=1.083) were

independently associated with increased probability of fibrosis progression (all *P*<0.05), while higher total cholesterol levels (OR=0.991) and higher liver stiffness values (OR=0.862) were independently associated with decreased probability of fibrosis progression (all *P*<0.05). HCC developed in 46 (6.4%) patients. Male gender (OR=3.917) and higher AST levels (OR=1.036) were independently associated with an increased probability of HCC development (*P*<0.05).





Conclusions: HS was not associated with the probability of HBsAg seroclearance, fibrosis progression, and HCC development in patients quiescent CHB in our study. Further studies with longer follow-up periods are required to validate our findings.

Keywords: Hepatitis B surface antigen, Liver fibrosis, Hepatocellular carcinoma

FV-012

Study on Fibrosis Change with Transient Elastography in Chronic Hepatitis B Virus Treatment with Tenofovir

HA PHUONG LINH, HOANG VAN TIEP, DINH CONG DANG

Department of Internal Medicine, 103 Cam Khe Clinic, Phu Tho, Vietnam

Aims: Background: Tenofovir disoproxil fumarate (TDF) is one of the first optimal choices to be used in the treatment of chronic hepatitis B. FibroScan is non-invasive methods to assess liver fibrosis.Aims: to evaluate the therapeutic effect of TDF on fibrosis via FibroScan after treatment.

Methods: This study was conducted in 63 chronic hepatitis B patients who had the indication of antiviral therapy at 103 Cam Khe Clinic from March 2019 to March 2020. All patients with chronic hepatitis B treated with TDF during 6 months. Liver fibrosis stages was appreciated using transient hepatic elastography by Fibroscan before and after 6 months treatment.

Results: The average age of patients was 46 years, with men accounted for 69% of the total. After treatment, normalization of ALT 71.26%, viral response of 90.23%, HBV DNA below the detection level was 66.3%. Liver fibrosis evaluated by FibroScan before and after 6 months treatment were 7.15 ± 1.56 kPa, and 3.58 ± 1.19 kPa eveluated by FibroScan.

Conclusions: TDF was effective for patients after treatment on liver fibrosis assessed by FibroScan in chronic hepatitis B patients.

FV-013

Proportion, Characteristics, and Outcome of Chronic hepatitis B Who are 'Linked to Care' in Korea: A Nationwide Retrospective Longitudinal Study

Young Cheol Ju[1], Dae Won Jun[1,2*], Eileen L. Yoon[2*], Sang Bong Ahn[3], Yun Jin Kim[4], Mindie H. Nguyen[5]

[1]Department of Translational Medicine, Graduate school of Biomedical Science and Engineering, Hanyang University, [2]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, [3]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University College of Medicine, Seoul, Republic of Korea; [4]Biostatistical Consulting and Research Laboratory, Medical Research Collaborating Center, Hanyang University, [5]Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA

Aims: Apart from the prevalence of chronic hepatitis B (CHB), 'linkage to care' rate is less well characterized. We aimed to characterize the proportion of CHB patients who have been linked to care, their characteristic and long-term outcomes.

Methods: This was a retrospective longitudinal cohort study using the Korean National Health Insurance Service (NHIS) database data from 2002 to 2018. Our operational definition of 'in-care' CHB patients includes those who had at least two clinic or hospital visits that were associated with a CHB diagnostic code during a 5-year study period (2002-2006). The period from 2007 to 2018 was used for long-term follow-up of this selected population.

Results: Of the estimated 1,545,377 CHB patients during the study period, 553,085 patients (35.8%) were found to be "linked to care", with lower rate in men (35.7% in men vs. 36.0% in women) (*P*=0.006). The "linkage to care" rate was highest in the 40-49 year age group (48.5%), and lowest in the 20-29 year age group (29.4%). Interestingly, "Linkage to care" rate was higher in the rural than metropolitan area (39.1% vs. 35.7%, *P*<0.0001). The 15-year cumulative incidence of hepatocellular carcinoma and overall survival rates among "linked to

care" CHB patients were 18.2% and 93.8%, respectively.
Conclusions: Two thirds (64.2%) of CHB Koreans are under inadequate care. Those who are male, dwelling in metropolitan, not in life transitioning period need to be focused for improvement of 'linkage to care' rate in Korean CHB population.
Keywords: Chronic hepatitis B, Linkage to care, Hepatocellular carcinoma, Survival

FV-014

Prediction of Hepatocellular Carcinoma by On-Therapy Response of Non-Invasive Fibrosis Markers In Chronic Hepatitis B

Heechul Nam[1,2] Sung Won Lee[1,2] Jung Hyun Kwon[1,2], Hae Lim Lee[1,2] Sun Hong Yoo[1,2], Hee Yeon Kim[1,2], Do Seon Song[1,2], Pil Soo Sung[1,2], U Im Chang[1,2], Chang Wook Kim[1,2], Soon Woo Nam[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jin Mo Yang[1,2], Nam Ik Han[1,2], Jeong Won Jang[1,2]*

[1]Devision of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic University Liver Research Center, Seoul, Republic of Korea

Aims: Antiviral therapy improves hepatic fibrosis and reduces hepatocellular carcinoma (HCC) incidence. This study aimed to evaluate whether on-therapy changes in scores for fibrosis index based on four factors and aspartate aminotransferase-to-platelet ratio index are associated with HCC development and establish an HCC risk score model incorporating non-invasive fibrosis marker (NFM) response.
Methods: This multi-center study recruited 5147 chronic hepatitis B patients (4028 for derivation cohort, 1119 for validation cohort) who were given entecavir/tenofovir for >12 months between 2007 and 2018. A risk prediction model for HCC was developed using predictors based on multivariable Cox models and bootstrapping was performed for validation.
Results: The 10-year cumulative HCC incidence rates were 12.6% and 13.7% in the derivation and validation cohorts, respectively. The risk of HCC significantly differed with early NFM response, with a marked reduction in HCC risk in patients achieving a significant decrease in NFM by 12 months (P<0.001). NFM response, sex, age and cirrhosis were independently predictive of HCC. We developed the Fibrosis marker response, Sex, Age, and Cirrhosis (FSAC) score based on regression coefficients of each variable. For the 10-year prediction of HCC, FSAC showed higher C-index values than PAGE-B, modified PAGE-B, CU-HCC, and REACH-B (0.84 vs. 0.77, 0.80, 0.77, and 0.67, respectively; all P<0.005). The predictive performance of FSAC was corroborated in the validation cohort, with higher C-index than other models (all P<0.050).
Conclusions: On-therapy changes in NFM are an independent indicator of HCC risk. FSAC incorporating NFM response is a reliable risk score for risk estimation for HCC with better performance than other models.
Keywords: CHB, Fibrosis, HCC, On-therapy response, Prediction model

FV-015

Association between Chronic Hepatitis B Infection and COVID-19: A Nationwide Case-Control Study

Seong Hee Kang[1¶], Seul Ki Han[1], Jimi Choi[2], Soon Koo Baik[1], Moon Young Kim[1*]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea, [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea

Aims: Few studies have reported the impact of coronavirus disease 2019 (COVID-19) in patients with chronic hepatitis B (CHB). We measured the association between underlying CHB and antiviral use with infection rates among patients who underwent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing.
Methods: In total, 204,418 patients > 20 years old who were tested for SARS-CoV-2 between January and June 2020 were included. For each case-patient with a positive SARS-CoV-2 test, random controls were selected from the target population who had been exposed to someone with COVID-19 but had a negative SARS-CoV-2 test result. We merged claim-based data from the Korean National Health Insurance Service database collected January 1, 2015, and August 18, 2020. Endpoints examined were SARS-CoV-2 infection rate and severe clinical outcomes of COVID-19.
Results: The proportion of underlying CHB was lower in COVID-19 positive patients (n = 267, 3.5%) than in COVID-19 negative controls (n = 2482, 5.4%). Underlying CHB was significantly associated with a lower SARS-CoV-2 positivity rate, after adjusting for comorbidities (adjusted odds ratio [aOR] 0.65; P<0.001). Among patients with confirmed COVID-19, underlying CHB tended to confer a 66% greater risk of severe clinical outcomes of COVID-19, although this value was statistically insignificant. Antiviral agent treatment including tenofovir and entecavir was associated with a reduced SARS-CoV-2 positivity rate (aOR 0.49; P<0.001), while treatment was not associated with severe clinical outcomes of COVID-19.
Conclusions: Patients with CHB who received antiviral agents had a reduced risk of SARS-CoV-2 infection, and no statistically significant indication that they experienced enhanced risk of severe clinical outcomes of COVID-19 was observed.
Keywords: COVID-19, Chronic hepatitis B, Epidemiology

FV-016

Entecavir Is Associated with Higher Risk of Kidney Function Decline than Tenofovir Alafenamide in Patients with Chronic Hepatitis B

Chan-Young Jung[1], Hyung Woo Kim[1], Sang Hoon Ahn[1,2,3] Seung Up Kim[1,2,3], Beom Seok Kim[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine,

Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Entecavir (ETV) and tenofovir alafenamide (TAF) are the preferred agents in patients with predisposing factors to nephrotoxicity. We compared the risk of kidney function decline among patients with treatment-naïve chronic hepatitis B (CHB) treated with ETV or TAF.

Methods: This study included 1,991 patients with CHB who were treated with ETV (n=1,842) or TAF (n=149) between 2007 and 2020. The primary outcome was chronic kidney disease (CKD) progression, which was defined as an increase in CKD stage for at least one stage for at least three consecutive months. Secondary outcomes included annual estimated glomerular filtration rate (eGFR) decline, with moderate and rapid progression defined as decline rate >3 and >5 mL/min/1.73m^2, respectively.

Results: In the 5:1 propensity score matched cohort, 226 vs. 15 patients in the ETV and TAF group developed progression in CKD stage ≥1, respectively (19.9 vs. 5.5 per 100 person-years; *P*<0.001; adjusted HR 4.05 [*P*<0.001] by multivariate analysis). The adjusted annual eGFR decline was significantly higher in the ETV group (mean -2.17 vs. -1.33 mL/min/1.73m^2 in the ETV and TAF group, respectively; *P*<0.001). A total of 217 (32.9%) patients in the ETV group and 47 (31.8%) patients in the TAF group developed moderate progression, and 151 (22.9%) patients in the ETV group and 24 (16.2%) patients in the TAF group developed rapid progression, but without statistical significance (*P*>0.05).

Conclusions: ETV was associated with a higher risk of kidney function decline than TAF in patients with treatment-naive CHB.

Keywords: Hepatitis B virus, Kidney function, Entecavir, Tenofovir alafenamide

FV-017

An Episode of Detectable Serum Hepatitis B Virus-DNA Level Does Not Affect Risk of Hepatic Decompensation Among Untreated Compensated Cirrhosis Patient with Viral Load of < 2,000 IU/mL

Hye Won Lee[1-3*], Soo Young Park[4*], Yu Rim Lee[4], Jae Seung Lee[1-3], Seung Up Kim[1-3], Jun Yong Park[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Beom Kyung Kim[1-3]

[1]Department of Internal medicine, Yonsei University College of medicine, Seoul, Republic of Korea; [2]Institute of Gastroenterology, Yonsei University College of medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [4]Department of Internal medicine, School of Medicine, Kyungpook National University, Daege, Republic of Korea

Aims: Whether antiviral therapy (AVT) is necessary for hepatitis B virus (HBV)-infected compensated cirrhosis patients with low-level viremia (LLV) is still controversial. Herein, we evaluated their natural history.

Methods: From three academic teaching hospitals, we enrolled untreated compensated cirrhosis patients having persistently serum HBV-DNA < 2,000 IU/mL; LLV group was defined as patients having detectable serum HBV-DNA (20~2,000 IU/mL) episode at least one time, whereas maintained virological response (MVR) group as remaining patients having persistently undetectable serum HBV-DNA (< 20 IU/mL) during the whole follow-up. In case of serum HBV-DNA ≥ 2,000 IU/mL, AVT was commenced. The study end-point was development of cirrhotic complication event (CCE) such as ascites, spontaneous bacterial peritonitis, hepato-renal syndrome, variceal hemorrhage, hepatic encephalopathy, deterioration of liver function into Child-Pugh class B, and liver transplantation.

Results: Among 567 patients finally analyzed, all belonged to Child-Pugh class A. Cumulative CCE risks at 1, 3, 5, and 7 years were also comparable between LLV (n=391) and MVR (n=176) groups; 2.2%, 7.5%, 12.8%, and 13.7% vs. 2.4%, 7.8%, 12,3%, and 14.6%, respectively (*P*=0.880). After adjusting for other key variables, LLV (vs. MVR) group was not associated with CCE risk with adjusted hazard ratio (HR) of 1.290 (95% confidence interval [CI] 0.712~2.338; *P*=0.402). Through inverse probability of treatment weighting analysis, similar outcome was also re-produced with *P*=0.767; those of LLV vs. MVR groups at 1, 3, 5, and 7 years were 3.2%, 8.1%, 10.9%, and 10.9% vs. 3.1%, 7.2%, 12.8%, and 13.9%, respectively (HR 1.097, 95% CI 0.534~2.254; *P*=0.801).

Conclusions: An instantaneous LLV episode among untreated patients with compensated cirrhosis does not increase the risk of hepatic decompensation, compared to MVR status. Thus, the benefit from prompt AVT for such a LLV group should be re-evaluated.

Keywords: Compensated cirrhosis, Hepatitis B virus, Low-level viremia, Decompensation

FV-018

Establishment of a Prospective and Longitudinal Korean Chronic Hepatitis B Cohort: A Pilot Study

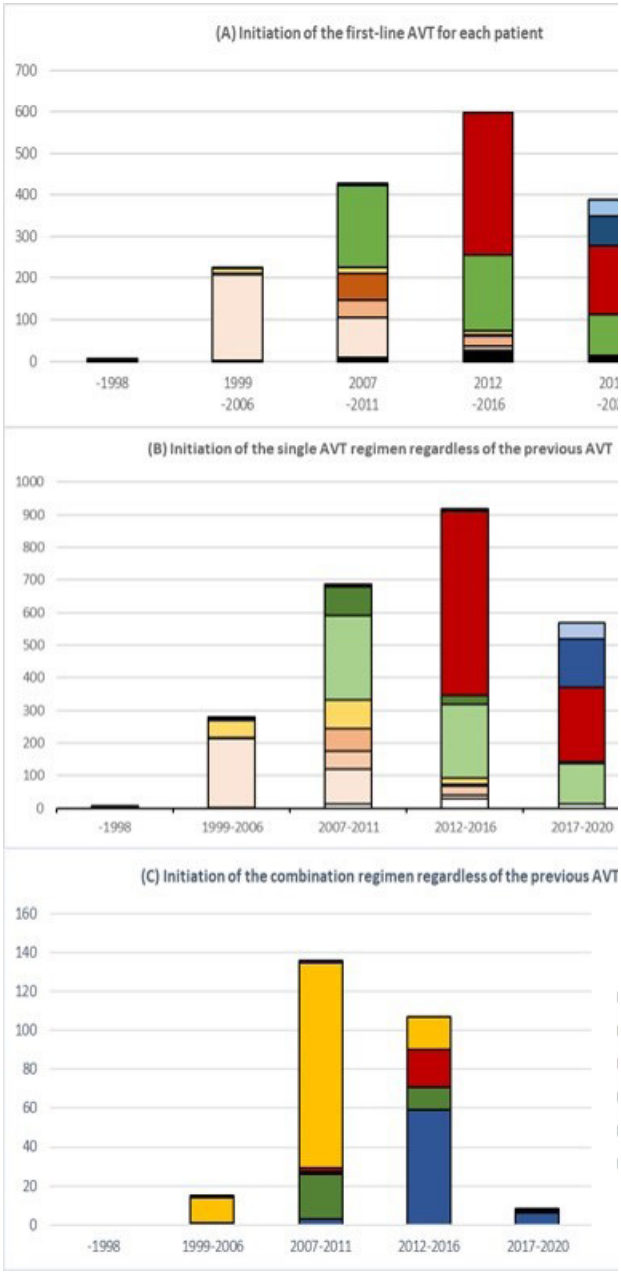
Jae Seung Lee[1*], Beom Kyung Kim[1*], Hye Won Lee[1], Seung Up Kim[1], Jun Yong Park[1], Do Young Kim[1], Sang Gyune Kim[2], Eun Young Cho[3], Young Mi Hong[4], Ki Tae Yoon[4], Han Ah Lee[5], Yeon Seok Seo[5], Soo Min Kim[6], Yunsu Choi[6], Bo Youl Choi[6], Sang Hoon Ahn[1]**

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea; [3]Department of Internal Medicine, Wonkwang University College of Medicine, Iksan, Republic of Korea; [4]Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [5]Department of Internal Medicine, Korea University Anam Hospital, Korea University Medical College, Seoul, Republic of Korea; [6]Institute for Health and Society, Hanyang University, Seoul, Republic of Korea

Aims: Although the Republic of Korea is still an endemic area of chronic hepatitis B (CHB), there were only a few longitudinal

and prospective cohorts covering the population, guiding the establishment of health policy. We aimed to report the longitudinal clinical outcome of Korean CHB patients from a prospective cohort.

Methods: This prospective cohort funded by the Korea Centers for Disease Control and Prevention was established in 2015, where CHB patients are planned to be registered from five tertiary hospital during the 10 years' follow-up.



Results: From 2015 to 2020, a total of 2052 patients (1287 male) with the mean age of 52.5 years participated in this study. Male patients have more amount of smoking and hazardous alcohol intake (P<0.001). Ninety-seven (11.0%), 607 (68.9%) and 804 (39.2%) patients were in state of immune tolerant phase, HBeAg(+) and HBeAg(-) chronic hepatitis, respectively. HBeAg(+) and HBeAg(-) liver cirrhosis were revealed in 177 (8.6%) and 367 (17.9%) patients, respectively. Most patients received entecavir (n=515, 25.1%), tenofovir disoproxyl fumarate (n=802, 39.1%), tenofovir alafenamide (n=121, 5.9%) and besifovir (n=58, 2.8%) at enrollment. Among 245 patients who initiated antiviral agents after study enrollment, the $\log_{10}$ hepatitis B virus DNA was effectively within one year (5.80 to 1.27 $\log_{10}$ IU/mL, P<0.001). Hepatocellular carcinoma occurred in 23 (1.1%) patients, all meeting Milan criteria.

Conclusions: This cohort study will evaluate long-term liver-related outcomes among Korean CHB patients. Future researches using this cohort could reveal the unmet needs to manage CHB.

Keywords: Antiviral therapy, Cohort, Chronic hepatitis B, Korea

FV-019

Reactivation of Resolved Hepatitis B after Daratumumab for Multiple Myeloma

Soon Kyu Lee[1,2], Pil Soo Sung[1,2*], Sung-Soo Park[3], Chang-Ki Min[3], Heechul Nam[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [3]Division of hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Daratumumab, a monoclonal antibody targeting CD38, has shown promise in the treatment of multiple myeloma (MM). In this study, we aimed to evaluate the risk of reactivation of resolved HBV infection in HBsAg-negative patients after daratumumab treatment.

Methods: Ninety-three HBsAg-negative MM patients treated with daratumumab were consecutively enrolled. Reactivation of resolved HBV infection was defined as HBsAg seroreversion or detection of HBV DNA (≥ 10 IU/mL) in initially HBsAg-negative patients. When the reactivation of resolved HBV infection was diagnosed, patients with reactivation were treated with potent antiviral treatment including tenofovir disoproxil fumarate (TDF) and entecavir.

Results: Among 93 HBsAg-negative patients treated with daratumumab, reactivation of resolved HBV infection occurred in six patients (6.5%) at the median time of 8.5 months (1-26 months) and the number of treatment cycles of 2.5 (1-18). Among these six patients, two (2.2%) had severe hepatitis (alanine aminotransferase > 200 mg/dL). All the patients with reactivation were treated with potent antiviral drugs (TDF, n = 2; entecavir, n = 4). During the follow-up, five patients achieved maintained virological response with undetectable HBV DNA levels, one of whom achieved HBsAg seroclearance. One pa-

tient with HBV reactivation and severe hepatitis expired due to hepatic failure.

Conclusions: Overall, our observations suggest that daratumumab, alike with rituximab, may cause significant viral reactivation in patients with resolved HBV infection, which might have stemmed from impairment of HBV-specific humoral responses. This prompts the prophylactic antivirals during daratumumab in MM patients.

Keywords: Daratumumab, Hepatitis B virus, Reactivation, Multiple myeloma, Resolved hepatitis B

FV-020

Temporal Trends of Liver Disease among Young Men in Korea

Byeong Geun Song[1], Dong Hyun Sinn[2], Wonseok Kang[2], Geum-Youn Gwak[2], Yong-Han Paik[2], Moon Seok Choi[2], Joon Hyeok Lee[2], Kwang Cheol Koh[2], Seung Woon Paik[2]

[1]Department of Medicine, Armed Forces Seoul Hospital, Seoul, South Korea; [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

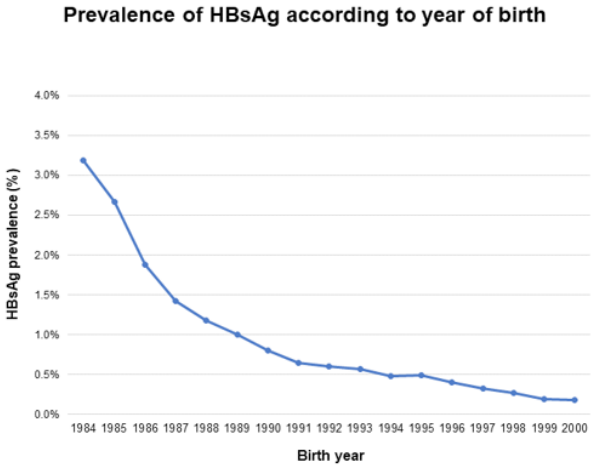
Aims: Temporal trends of liver disease in the region can provide valuable information on public health perspectives. Korea has a draft system that every male must undergo a medical examination for conscription that include serum hepatitis B surface antigen (HBsAg) and alanine aminotransferase (ALT) level measurement. This provide a unique opportunity to see temporal trends of liver disease at a population level among young men in Korea.

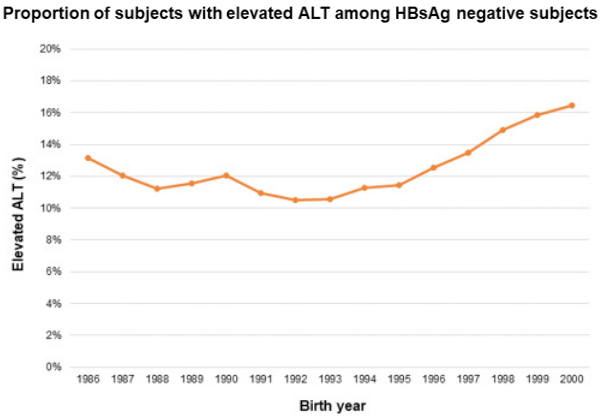
Methods: We used data from Korea Military Manpower Administration medical examination for conscription between 2003 and 2019 (n = 5,355,941), which was performed for young men at age of 19 years. Trends in prevalence of HBsAg, elevated ALT levels, fibrosis-4 index, obesity and hypertension were assessed. Elevated ALT was defined as >34 IU/L.

Results: Prevalence of HBsAg has been steadily decreased from 3.19% for men born in year 1984 to 0.18% for men born in year 2000. Among HBsAg negative subjects, prevalence of elevated ALT levels increased from 13.15% for men born in year 1986 to 16.48% for men born in year 2000. Proportion with obesity, hypertension, those with high FIB-4 score (≥ 1.45) increased among men born in later periods.

Conclusions: This population based nationwide figure showed decreasing trend of HBsAg, while increasing trend of young men with elevated ALT levels, along with increase in obesity. The epidemiologic change is evident in Korea which calls for proactive and strategic response from a national perspective.

Keywords: Chronic hepatitis B, Prevalences, Non alcoholic fatty liver disease





FV-021

Tenofovir Is Associated with Higher Risk of Kidney Function Decline than Entecavir in Patients with Chronic Hepatitis B

Chan-Young Jung[1], Hyung Woo Kim[1], Sang Hoon Ahn[1,2,3] Seung Up Kim[1,2,3], Beom Seok Kim[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Nephrotoxicity of antiviral agents used to treat patients with chronic hepatitis B (CHB) is still an issue under debate. We investigated the differences in the risk of kidney function decline in CHB patients who were treated with entecavir (ETV) or tenofovir disoproxil fumarate (TDF).

Methods: This study included 3,426 treatment-naïve patients with CHB who were treated with either ETV (n=1,917) or TDF (n=1,509) between 2007 and 2019. The primary outcome was development of incident chronic kidney disease (CKD), defined as the occurrence of estimated glomerular filtration rate (eGFR)

≤60 mL/min/1.73m^2 on two consecutive measurements. The secondary outcome was a 25% decline in eGFR on two consecutive measurements.

Results: During 19,471 person-years of follow-up, 50 patients developed incident CKD: 27 in the ETV, and 23 in the TDF group, with corresponding incidence rates of 2.2 and 3.2 per 1,000 person-years (*P*=0.376), respectively. Propensity score (PS) matching revealed a significantly higher risk of incident CKD in the TDF group (1.1 vs. 3.6 per 1,000 person-years [*P*=0.002], respectively; adjusted HR 4.18 [*P*=0.001] by multivariate analysis). During 16,944 person-years of follow-up, 104 patients developed a 25% decline in eGFR: 48 in the ETV, and 56 in the TDF group, with corresponding incidence rates of 4.7 vs. 8.5 per 1,000 person-years (*P*=0.003), respectively. PS matching revealed similar findings: 3.1 vs. 8.4 per 1,000 person-years (*P*<0.001), respectively; adjusted HR 2.97 (*P*<0.001) by multivariate analysis.

Conclusions: TDF was associated with a higher risk of kidney function decline than ETV in treatment-naïve CHB patients.

Keywords: Hepatitis B virus, Kidney function, Entecavir, Tenofovir

FV-022

Fibrotic Burden in Patients with HBV-Related Cirrhosis Is Independently Associated with Adverse Kidney Outcomes

Chan-Young Jung[1], Hyung Woo Kim[1], Geun Woo Ryu[1], Sang Hoon Ahn[1,2,3], Seung Up Kim[1,2,3], Beom Seok Kim[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Liver cirrhosis and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated whether differences in remaining fibrotic burdens, assessed using transient elastography (TE), were independently associated with adverse kidney outcomes in patients with hepatitis B virus (HBV)-related cirrhosis.

Methods: A total of 1,204 patients with HBV-related cirrhosis but without baseline CKD who underwent TE between March 2012 and August 2018 were selected. The study outcome was the composite of development of incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 or proteinuria (≥ 1+ on dipstick test) on two consecutive measurements during follow-up, 50% decline in eGFR or onset of end-stage kidney disease (initiation of chronic dialysis), or all-cause mortality.

Results: The mean age was 53.3 years and 711 (59.1%) patients were male. During 6,312 person-years of follow-up (median follow-up of 5.5 years), 32 patients (2.7%) developed adverse kidney outcomes. When stratified into TE-defined remaining fibrotic burden, multivariable Cox models revealed that risk of adverse kidney events was 4.58-fold (95% CI, 1.51-13.96, *P*<0.001) higher in patients with cirrhosis (≥11.7 kPa), compared to patients with minimal liver fibrosis (<7.9 kPa). These associations remained significant even after adjustment for potential confounding factors, including comorbidities of hypertension and diabetes, history of acute kidney injury, and use of potentially nephrotoxic antiviral agents.

Conclusions: Higher remaining fibrotic burden assessed using TE was independently associated with unfavorable long-term kidney outcomes in patients with HBV-related cirrhosis.

Keywords: Liver fibrosis, Hepatitis B virus, Cirrhosis, Transient elastography, Kidney outcome

FV-023

Toxicological Assessment of the Potential Extrahepatic Carcinogenicity of Oral Nucleos(t)ide Analogues in Chronic Hepatitis B Carriers: A 35,000-Patient Outcome Study

Jihye Lim[1*], Jung Bok Lee[2*], Jihyun An[3], Gi-won Song[4], Kang Mo Kim[1,5], Han Chu Lee[1,5], Ju Hyun Shim[1,5]

[1] Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; [3]Gastroenterology, Hanyang University College of Medicine, Guri, Gyeonggi-do, Republic of Korea; [4]Hepatobiliary Surgery and Liver Transplantation, Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Evidence on the carcinogenicity of oral nucleos(t)ide analogues (NAs) is inconclusive and lacks data on the effects by chemical structure of the NAs in patients with chronic hepatitis B (CHB). We aimed to provide definitive results on this issue using a large set of CHB patients, and data on all major NA drugs.

Methods: The study population consisted of 10,331 patients with CHB receiving primary NA treatment for more than 6 months, and 24,836 untreated controls followed for at least as long as the treated patients, based on International Council of Harmonization guidelines. Using the inverse-probability-of-treatment-weighted (IPTW) method, the cumulative incidence of extrahepatic cancers was compared in the treated and untreated patients and across the cyclopentane (entecavir), L-nucleoside (clevudine, lamivudine, and telvibudine), and acyclic phosphonate categories of NAs (adefovir, besifovir, and tenofovir). Analyses of individual cancers as sub-endpoints were also performed.

Results: During averages of 4.1 and 6.8 years in the respective pairs, extrahepatic cancers occurred in 208 treated and 1,014 untreated patients. The cumulative incidence of overall extrahepatic malignancies did not differ between the two groups in the IPTW cohort (hazard ratio [HR] 1.002; 95% confidence interval [CI] [0.859-1.169]). Similar statistical trends were observed in

analyses across the three NA chemical subsets and controls. Per-cancer analyses indicated that NA treatment was significantly associated with increased risks of colorectal/anal cancers and lymphoma (IPTW-adjusted HRs [95% CI], 1.538 [1.175-2.013]; and 1.784 [1.196-2.662], respectively). Conversely, breast cancer and prostate cancer were less prevalent in the NA-treated group (IPTW-adjusted HRs [95% CI], 0.669 [0.462-0.967]; and 0.521 [0.329-0.825], respectively).

Conclusions: Prolonged NA treatment presents carcinogenic risks for colorectal/anal and lymphoid tissues in CHB patients, although it does not affect most extrahepatic organs. The protective effect of NAs on breast and prostate cancers should be confirmed.

Keywords: Hepatitis B, Chronic, Antiviral agents, Carcinogens, Adverse effects

FV-024

Risk of Hepatitis B Virus Reactivation in Patients Treated with Immunotherapy for Anti-Cancer Treatment

Sun Yoo[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Changhoon Yoo[2], Baek-Yeol Ryoo[2], Jonggi Choi[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Oncology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Hepatitis B virus (HBV) reactivation is a well-known complication in chronic hepatitis B (CHB) patients treated with cytotoxic chemotherapy. However, the risk of HBV reactivation by using immune checkpoint inhibitors (ICIs) is not well understood so far. Therefore, we aimed to evaluate the risk of HBV reactivation and hepatic adverse events in cancer patients receiving ICIs according to their cancer types and virologic serology.

Methods: This historical cohort study included 3,465 cancer patients treated with ICIs between January 2015 and September 2020. The primary outcome was the occurrence of HBV reactivation and the secondary outcome was hepatic adverse events during ICI treatment.

Results: The mean patient age was 62.2 years and 68.8% of the patients were men. Of the 3,465 eligible patients, 511 (14.7%) showed HBsAg positivity. The incidence rates of HBV reactivation of the total patients, HBsAg-positive patients, and HBsAg-negative patients were 0.14% (5/3,465), 1.0% (5/511), and 0.0% (0/2,954), respectively. Among HBsAg-positive patients, HBV reactivation occurred in a rate of 0.5% (2/409) and 2.9% (3/102) in patients with HCC and non-HCC, respectively. The HBV reactivation rates were 0.4% (2/464) and 6.4% (3/47) in patients with and without antiviral prophylaxis, respectively. Grade 3-4 hepatitis occurred in 23 (4.5%) in HBsAg-positive, and 218 (7.4%) in HBsAg-negative patients. Only 3 patients (0.6%) experienced immune-related hepatitis among patients with HBsAg-positivity. No HBV related fatal outcome occurred in total patients.

Conclusions: HBV reactivation rarely occurred in cancer patients treated with ICIs. No reactivation occurred in HBsAg-positive patients with antiviral prophylaxis and HBsAg-negative patients.

Keywords: Hepatitis B virus reactivation, Immunotherapy, Immune checkpoint inhibitors

FV-025

Continuing Besifovir Dipivoxil Maleate versus Switching from Tenofovir Disoproxil Fumarate for Treatment of Chronic Hepatitis B : 288 Weeks Results of Phase 3 Trial

Jae Young Jang[1], Won Kim[2], Sang Hoon Ahn[3], Kwang-Hyub Han[3], Hyung Joon Yim[4], Yong Oh Kweon[5], Yong Kyun Cho[6], Yoon Jun Kim[7], Gun Young Hong[8], Dong Joon Kim[9], Young Kul Jung[4], Soon Ho Um[4], Joo Hyun Sohn[10], Jin Woo Lee[11], Sung Jae Park[12], Byung Seok Lee[13], Ju Hyun Kim[14], Hong Soo Kim[15], Seung Kew Yoon[16], Moon Young Kim[17], Kwan Sik Lee[3], Young Suk Lim[18], Wan Sik Lee[19], Jin Mo Yang[20]

[1]Department of Internal Medicine, College of Medicine, Soonchunhyang University, Seoul, Korea, [2]Department of Internal Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea,[5]Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, Korea, [6]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Korea, [7]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [8]Department of Internal Medicine, Kwangju Christian Hospital, Gwangju, Korea, [9]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea, [10]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [11]Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea, [12]Department of Internal Medicine, Paik Hospital, Inje University, Busan, Korea, [13]Department of Gastroenterology and Hepatology, Chungnam National University School of Medicine, Daejeon, Korea, [14]Department of Internal Medicine, Gacheon University College of Medicine, Incheon, Korea, [15]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea, [16]Department of Internal Medicine, Catholic University of Korea, Seoul, Korea, [17]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea, [18]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, [19]Department of Internal Medicine, Chonnam University Medical School, Gwangju, Korea, [20]Department of Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, Seoul, Korea

Aims: Besifovir dipivoxil maleate (BSV) is an acyclic nucleotide phosphonate with a potent antiviral activity against hepatitis B virus (HBV). An antiviral efficacy of BSV for forty-eight week was shown to be comparable to tenofovir disoproxil fumarate (TDF) with improved renal and bone safety. We evaluated the efficacy and safety of BSV in treatment-naïve chronic hepatitis B patients in 288 weeks follow-up study.

Methods: After 48 weeks of double-blind comparison of BSV to TDF, patients continued to participate in the open-label BSV longterm follow-up. We evaluated antiviral efficacy and drug safety for both BSV group (BSV-BSV) and the group switched from TDF to BSV (TDF-BSV) up to 288 weeks. At week 288, patients were assessed for virological suppression, alanine aminotransferase normalization, serological response, safety including renal parameter and BMD (Bone Mineral Density).
Results: Among 197 patients who received randomized treatments, 170 (86.29%) patients entered the open-label phase, and 147 (74.61%) completed 288 weeks of the study. The virological response rate of those who have taken BSV over 288 weeks is 94.94% while 97.06% of patients who switched the treatment from TDF (TDF-BSV) were respondent (*P*=0.69). HBeAg seroconversion and ALT normalization rates were similar between the groups. There were no drug resistant mutations to BSV and no adverse events related to BMD or renal function.
Conclusions: BSV maintained efficacy in both suppression of HBV DNA and ALT normalization over 288 weeks without any evidence of resistance to BSV. Also, BSV is safe, well tolerated, and effective for those who have switched to BSV from TDF.
Keywords: Antiviral therapy, Hepatitis B, Drug resistance, Bone mineral density, Nephrotoxicity

3. Hepatitis C Virus

FV-026

Successful or Failure? How Treatment of Hepatitis C Virus Infection Using Direct-Acting Antiviral Agents (DAAs) in Indonesia: Analysis Literature Review

Zulfa Saumia[1], Ade Kartika Sari Sebba[2]

[1]Alumnus Universitas Gadjah Mada, [2]Epidemiology, Universitas Hasanuddin Makassar

Aims: In Indonesia, more than 1,9 million people are chronically infected with the hepatitis C virus (HCV), but a national strategic plan for elimination has not yet been developed. According to World Health Organisation, the global public health response to the hepatitis C virus (HCV) and introduction of direct-acting antiviral (DAA) medicines in 2014 with high cures rates, shorter treatment durations, fewer side-effects and simplified delivery as compared to previous medicines, accessible. This medicine is successful among selected low-and middle-income countries such as Brazil, China, Egypt, Georgia, India, Malaysia, Mongolia, Morocco, Pakistan, Russian Federation, Rwanda, and Ukraine (WHO survey 2019), but there is no other reported about Indonesia research treatment of Hepatitis C Virus successful or not. How about Indonesia in clinical practice with this medicine? It will be the main aim.
Methods: This abstract uses data from WHO Global progress report 2020, International Journal of Nephrology and Renovacular Disease,The Indonesian Journal of Gastroenterology Hepatology and Digestive Endoscopy, Hepat Oncol, and Liver International-Wiley.
Results: Firstly, HCV infection, the anti-HCV prevalence in Indonesia was 1,0% with a peak incidence in subjects aged 60 years and older. In 2014, an estimated 9% of the viremic population develop cirrhosis and HCC, and it is projected to increase to 15% by 2030 (Muljono 2017:55-9). In Indonesia, the availability of pangenotypic DAA regiment in Indonesia for right now is only a combination Sofobuvir/Declatasvir regiment for chronic HCV infection (Kurniawan 2019:2). Secondly, successful treatment using the DAAss sofosbuvir/daclatasvir regimen as an interferon-free therapy is a safe, effective option for HCV infection in pediatric kidney transplant recipients for males 13 years old and females 14 years old (Ambarsari et.all, 2020). Thirdly, there is a crucial need to develop a shared approach in biomarker discovery and validation studies that accelerates the diffusion of newly discovered biomarkers into clinical practice (Pasut et all 2020).
Conclusions: This study shows that there has been success using DAAs as a treatment for HCV in Indonesia but further research is needed to prove the efficacy.
Keywords: Hepatitis C virus infection, DAAs, Treatment

FV-027

Sphingolipids as Potential Biomarkers to Direct Acting Antiviral Therapy in Chronic Hepatitis C Virus Infection

Ankit Jain, DK Singh, AR Rao

Pharmaceutical Sciences, Institute of Pharmaceutical Sciences and Research, India

Aims: Elimination strategies of chronic hepatitis C virus (HCV) infection aim to optimize the high antiviral potency of direct acting antivirals (DAA's). Our group has already shown that serum sphingolipid levels associate with fibrosis progression in patients with HCV infection and also with responsiveness to interferon treatment. Aim of the current study is to decipher the role of sphingolipids as biomarkers of response to antiviral therapy with DAA's in patients with chronic HCV infection.
Methods: In the present study we used liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) in order to retrospectively quantify various sphingolipid metabolites in baseline serum samples of 100 HCV Indian patients with DAA-failure compared to an age- and sex-matched cohort of 120 HCVpatients with sustained viral response (SVR).
Results: Sphingosine and sphinganine serum concentrations were significantly upregulated at baseline ($P< 0.001$) in patients who experienced a relapse compared to patients with SVR . Also their phosphate derivatives, sphingosine-1-phosphate (S1P) and sphinganine-1-phosphate (SA1P), showed higher baseline concentrations in relapse patients ($P< 0.05$ and $P< 0.05$ respectively). In multivariate analysis sphinganine (OR 0.9830, CI 0.05347 – 0.6908, *P*=0.03128), SA1P (OR 0.8790, CI 0.8970 –

0.9089, *P*=0.02467) and the glycosylated ceramides GluCerC18 (OR 1.0135, CI 1.08769 – 1.4009, *P*=0.000657) and GluCer24:1 (OR 0.8768, CI 0.989 – 0.998, *P*=0.000394) constituted independent predictors of treatment response.

Conclusions: Serum sphingolipid concentrations, in particular sphingosine and sphinganine and their phosphate derivatives S1P and SA1P as well as glucosylceramides, are able to identify at baseline the minority of HCV

Keywords: Chronic HCV infection, Sphingolipids, Liquid chromatography, Phosphate derivatives

FV-028

NLRP3 Inflammasome Activation Correlate with Oxidative Stress, Serum Inflammatory Markers, and Hepatic Inflammation, Fibrosis and Steatosis in Patients with Chronic Hepatitis C Virus Infection

Hoda El Aggan[1], Sabah Mahmoud[2], Nevine El Deeb[3], Assem El-Shendidi[1], Islam Eleishi[1]

[1]Department of Internal Medicine (Hepatobiliary Unit), [2]Department of Medical Biochemistry, and [3]Department of Pathology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Aims: Hepatitis C virus (HCV) evolves a chronic inflammatory response and oxidative stress contributing to liver damage. Inflammasomes are multi-protein complexes that are assembled and become activated in response to pathogens and danger signals such as oxidative stress resulting in caspase-1 (CASP1) activation and initiation of inflammation. The present study was conducted to investigate Nod-like receptor pyrin domain containing 3 (NLRP3) inflammasome activation in patients with chronic HCV infection and its correlation with oxidative stress, serum inflammatory markers and hepatic inflammation, fibrosis and steatosis.

Methods: 70 patients with chronic HCV infection [46 patients with chronic hepatitis C (CHC) and 24 patients with cirrhosis] and 30 healthy controls were enrolled in the study. Liver specimens were examined for METAVIR histological activity grade and fibrosis stage and steatosis grade and the expression of NLRP3 and CASP1 was scored by immunohistochemistry. Serum NLRP3 and high-sensitivity C-reactive protein (hsCRP) levels were quantified using ELISA. Oxidative stress was assessed by measuring serum malondialdehyde level and total antioxidant capacity.

Results: NLRP3 and CASP1 expression in the liver was significantly higher in cirrhotic patients than in CHC patients in parallel with a progressive increase in serum NLRP3 level (*P*<0.001). Hepatic NLRP3 and CASP1 expression and serum NLRP3 level showed positive correlations with serum levels of aminotransferases, HCV RNA, and hsCRP, oxidative stress, histological activity grade, fibrosis stage and steatosis grade (*P*<0.05). Receiver operating characteristic curve showed a high diagnostic performance of serum NLRP3 in determining the severity of hepatic necroinflammation, fibrosis and steatosis (AUC = 0.964, 0.979, and 0.941 respectively, *P*<0.001).

Conclusions: The NLRP3 inflammasome is activated in the liver during chronic HCV infection, possibly related to oxidative stress, and may act as a link between inflammation and hepatic fibrosis and steatosis. Serum NLRP3 reflects inflammasome activation in the liver and could be a potential biomarker for HCV-related liver damage.

Keywords: Hepatitis C virus, NLRP3 inflammasome, Caspase-1, Liver fibrosis, Hepatic steatosis

FV-029

Progress and Prognosis of Treatment Options of Antivirals in Patients with Hepatitis C Infection in Single Center

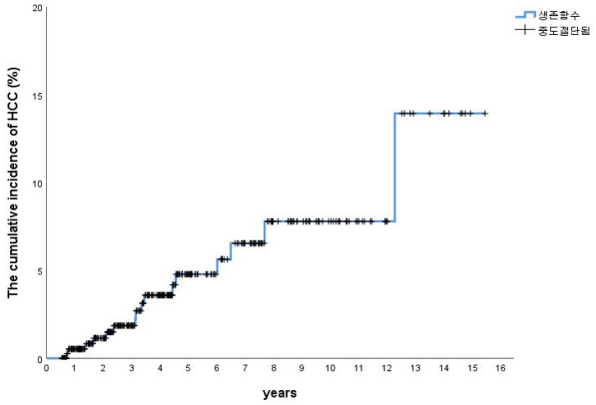
Myung Kim, Sunghwan Yoo, Sora Kim, Da-sol Kim, Jung Il Lee, Kwan Sik Lee, Hyun Woong Lee

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine

Aims: Hepatitis C infection can lead to liver cirrhosis and hepatocellular carcinoma (HCC) if treatment is delayed. We report on the progress and prognosis of antiviral treatment in patients with hepatitis C infection.

Methods: We evaluated 3,325 patients with anti-HCV positive in a single center from 2005 to 2020. The primary endpoint was the Gangnam Severance hepatitis C elimination care cascade. The secondary endpoints were the rate of sustained virological response (SVR) and the incidence of HCC.

Results: From 2005 to 2020, of the 3,325 patients with positive anti-HCV test results, 1,182 (35.5%) received HCV RNA testing; of those, 861 (72.8%) tested positive. Of the 321 patients with negative anti-HCV test results, 38 (11.8%) received recombinant immunoblot assay (RIBA) testing; 21 (55.3%) tested positive, 9 (23.7%) tested negative and 8 (21.1%) tested undetermined. 497 (57.7%) of 861 patients received 1st line antiviral treatment; of those, 212 (42.7%) underwent pegylated interferon plus ribavirin, 184 (86.8%) experienced SVR. 92 (18.5%) patients who underwent daclatasvir/asunaprevir, 84 (91.3%) patients experienced SVR. Among 49 (9.9%) patients treated with sofosbuvir/ledipasvir, 45 (91.8%) experienced SVR. Among 62 (12.5%) patients who were treated with sofosbuvir and ribavirin, 54 (87.1%) experienced SVR. Among 39 (7.8%) patients treated with elbasvir/grazoprevir, 36 (92.3%) experienced SVR. Among 3 (0.6%) patients treated with ombitasvir/paritaprevir/ritonavir, 3 (100%) experienced SVR. Among 40 (8.0%) patients treated with glecaprevir/pibrentasvir, 37(92.5%) experienced SVR. In 16 (4.1%) of 393 patients without HCC at baseline, HCC occurred after antiviral therapy. The cumulative incidence of HCC was 14% at 15 years after the end-of-treatment (Figure). Of the 16 patients, 9 patients (56.3%) had liver cirrhosis at baseline.



Conclusions: Only one-third of patients with anti-HCV positive are tested for HCV RNA. High SVR rates were achieved overall(89.1%). Patients with cirrhosis require long-term regular follow-up for surveillance of HCC.

Keywords: Hepatitis C infection, HCC, SVR, RIBA

FV-030

Study on Correlation between Serum Ferritin Levels and Liver Stiffness Assessed by Fibroscan in Patients with Chronic Hepatitis C

HA PHUONG LINH, DINH CONG DANG, HOANG VAN TIEP

Department of Internal Medicine, 103 Cam Khe Clinic, Phu Tho, Vietnam;

Aims: Background: Chronic hepatitis C is a major infectious disease which is mainly cause of morbidity worldwide in patients with liver disease, and liver transplantation. Raised ferritin levels play an important role of intervening the process which is associated with hepatic injury. Screening with non-invasive strategies can detect the disease at early stage and intervention could be initiated.Aims: To determine correlation between serum ferritin levels and liver stiffness values in patients of chronic hepatitis C.

Methods: A cross-sectional study was conducted at 103 Cam Khe Clinic from May 2019 to April 2020. 93 patients with chronic hepatitis C fulfilling inclusion criteria were included in this study. Liver fibrosis stages was appreciated using transient hepatic elastography by Fibroscan, the activities of serum liver function biomarker enzymes and serum ferritin levels were determined by automated analyser.

Results: The average age of patients was 48 years, with men accounted for 78% of the total. The mean serum ferritin value was 148.19 ng/ml, liver stiffness measurements range from 12.5 to 75.5 kPa, with a median value of 17.39 ± 15.98 kPa. Significantly elevated levels of serum ferritin (P<0.001), were detected in patients with severe fibrosis compared to mild fibrosis. Concentration of serum ferritin was increased with the evolution of fibrosis in all stages from F0 to F4 and this increase was significant (P<0.01) in cirrhotic patients (F4). There was a positive correlation between serum level of ferritin and progression of fibrosis (0.979391) (r = 0.976).

Conclusions: There is significant correlation between serum ferritin and liver stiffness. Serum ferritin concentration may be used as liver fibrosis biomarkers.

Keywords: Liver stiffness, Chronic hepatitis C, Fibroscan, Ferritin

FV-031

The Effectiveness and Safety of Glecaprevir/pibrentasvir for the Treatment of Patients with Chronic HCV Infection: A Real-World Multicenter Study

Hae Lim Lee[1,2], Sung Won Lee[1,2], Hee Yeon Kim[1,2], Chang Wook Kim[1,2], Do Seon Song[1,2], U Im Chang[1,2], Jin Mo Yang[1,2], Sun Hong Yoo[1,2], Jung Hyun Kwon[1,2], Soon Woo Nam[1,2], Seok-Hwan Kim[1,2], Myeong Jun Song[1,2], Jaejun Lee[1,2], Hyun Yang[1,2], Si Hyun Bae[1,2], Ji Won Han[1,2], Soon Kyu Lee[1,2], Hee Chul Nam[1,2], Pil Soo Sung[1,2], Jeong Won Jang[1,2*], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[2]The Catholic University Liver Research Center

Aims: Glecaprevir/pibrentasvir is approved for the treatment of patients with chronic HCV genotypes (GT) 1-6. This study aimed to evaluate the efficacy and safety of glecaprevir/pibrentasvir in real-world settings.

Methods: Consecutive patients treated with glecaprevir/pibrentasvir for chronic HCV infection between July 2019 and November 2020 were enrolled at the liver unit of Catholic university in South Korea. Glecaprevir/pibrentasvir was given for 8 weeks in most patients, but for 12 weeks in some patients with liver cirrhosis (LC). The primary outcome was the sustained virological response at post-treatment week 12 (SVR12). Safety was also assessed.

Results: In total, 356 patients were treated and mean age was 58 ± 12. Of the patients, 144 (40.4%) were male, 57 (16.0%) were diagnosed as LC, and 11 (3.1%) had been treated for hepatocellular carcinoma. GT 2 (58.4%) was the most common type, followed by GT 1b (38.5%), GT 1a and 3 (1.4% for both), and GT 6 (0.3%). Twelve patients (3.4%) were on dialysis for end-stage renal disease. Twenty-eight patients (7.9%) were treatment-experienced for HCV, 13 (3.7%) patients with interferon-based therapy and 15 (4.2%) patients with direct-acting antivirals. The SVR12 rate was 98.6% for evaluable patients with post-treatment week 12 data. All 4 patients who failed to achieve SVR12 were GT 2, treatment naïve, and had no cirrhosis. In 3 of them, HCV RNA was not detected at the end of treatment. Adverse events (AEs) including nausea, dizziness, pruritis, ALT elevation and rash were reported in 12 patients (3.4%). Four patients had grade 2 ALT or AST elevations during the treatment period. AEs-related treatment discontinuation was reported in 7 patients (2.0%).

Conclusions: In real-world practice, treatment with glecaprevir/pibrentasvir for 8 or 12 weeks was well-tolerated and achieved

extremely high SVR in patients with chronic HCV infection across all genotypes.

Keywords: Hepatitis C virus, Glecaprevir/pibrentasvir, Sustained virologic response

FV-032

Clinical Features and Outcomes of Hepatitis C Patients Co-Infected with Hepatitis B Virus in South Korea: A Prospective, Multicenter study

Gwang Hyeon Choi[1]*, Eun Sun Jang[1], Young Seok Kim[2], Youn Jae Lee[3], In Hee Kim[4], Sung Bum Cho[5], Byung Seok Lee[6], Kyung-Ah Kim[7], Woo Jin Chung[8], Han Chu Lee[9], Jang Jeong Won[10], Moran Ki[11], Hwa Young Choi[11], Dahye Baik[11], Sook-Hyang Jeong[1]

[1]Departments of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea; [2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [3]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea; [4]Department of Internal Medicine, Jeonbuk National University Hospital, Jeonju, Republic of Korea; [5]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [6]Departments of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea; [7]Departments of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang Republic of Korea; [8]Departments of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea; [9]Department of Internal Medicine, Asan Medical Center, Seoul, Korea; [10]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [11]National Cancer Center, Goyang, Republic of Korea

Aims: Studies related to co-infected patients with hepatitis C virus (HCV) and hepatitis B virus (HBV) are scares. This study aimed to investigate the epidemiology, clinical characteristics, and outcomes of HCV-HBV co-infected patients compared to HCV mono-infected patients.

Methods: A total 2,702 patients with HCV RNA positivity (mean age 57.5 years, 51.5% male, 20.5% cirrhosis and 11.4% HCC) were prospectively enrolled in 9 university hospitals in South Korea from May 2007 to June 2020. The patients were classified into HBV+HCV group (n=73, 2.70%) and HCV group (n=2,629, 97.3%). Kaplan-Meier curve analysis and propensity score (PS) matching were performed to evaluate development of HCC and overall mortality.

Results: At enrollment, the HBV+HCV group showed significantly higher proportion of male sex (64.4% vs 51.2%, *P*=0.026), multiple sex partner (57.6% vs 44.0%, *P*=0.038), and family members with HBV infection (17.8% vs 2.7%, *P*<0.001) than the HCV group. Serum HCV RNA level and distribution of HCV genotype were similar between the 2 groups. The coinfected group showed a significantly lower albumin level and platelet count, and higher prothrombin time. The HBV+HCV group showed similar anti-HCV treatment uptake rate (72.6% vs 67.4%, *P*=0.353), and sustained virologic response (SVR) rate to the HCV group. At enrollment, the HBV+HCV group had higher rate of past or currently active hepatocellular carcinoma (HCC) (26.0%) than the HCV group (10.9%) (*P*=0.002). Among those without HCC at enrollment, PS matching analysis (48 in HBV+HCV group, 96 in HCV group) showed that a higher trend for HCC development (HR 1.80, 95% CI 0.57-5.09, *P*=0.347) in the HBV+HCV group than the HCV group, thought statistically not significant.

Conclusions: The prevalence of HBV coinfection in chronic HCV patients was 2.7% in South Korea. The HBV coinfected patients had different epidemiological features, similar treatment status and SVR, higher prevalence of HCC than the HCV group, and higher trend for HCC development and mortality, which warrants further study.

Keywords: Hepatitis B, Hepatitis C, Epidemiology, Outcome

FV-033

Prevalence and Incidence of Anti-HAV and Anti-HEV Antibodies in Patients with Chronic Hepatitis C Virus Infection

Eun Sun Jang[1], Gwang Hyeon Choi[1], Young Seok Kim[2], In Hee Kim[3], Youn Jae Lee[4], Sung Beom Cho[5], Sook-Hyang Jeong[1]*

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi; [2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Gyeonggi; [3]Department of Internal Medicine, Chonbuk National University Hopital, Chonbuk National University College of Medicine, Chonju, Republic of Korea; [4]Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [5]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Chonnam

Aims: In patients with chronic hepatitis C virus (HCV) infection, superimposed acute infection with hepatitis A (HAV) or E viruses (HEV) can result in life-threatening outcomes. In this study, we evaluated anti-HAV and HEV immunoglobulin G (IgG) antibody prevalence in Korean HCV-infected population.

Methods: A total of 300 subjects with serial blood samples collected at intervals of ≥ 12 months were selected from Korea HCV cohort including patients who were positive HCV RNA for >6 months and consecutively enrolled at 5 tertiary hospitals prospectively from Jul 2013 ~ Dec 2018. Anti-HAV and HEV IgG status analyzed using commercial kit by central laboratory.

Results: The mean age of subjects was 57.0 ± 11.0 years old and 134 (44.7%) were males. The prevalence of positive anti-HAV IgG was 50% in 20's, 60% in 30's, 92% in 40's, 96.7% in 50's, 98.8% in 60's and 100% after 70's. One 24-year-old male subject showed anti-HAV IgG seroconversion (4.3%/year incidence rate in 20's). The positive anti-HEV IgG prevalence increased according to subjects' age: 0% under 30's, 10.7% in 40's, 23.5% in 50's, 53.4% in 60's, and 68.5% after 70's. Males (*P*=0.01), current alcohol drinkers (*P*=0.002) and smokers (*P*=0.007), liver cirrhosis patients (*P*=0.049) showed significantly higher an-

ti-HEV IgG positive rate. The incidence rate of anti-HEV seroconversion was 0.63%/year with 6 incident cases whose age were 40's-60's. Nine subjects had died during the follow-up period of 4.9 ± 1.5 years, but it was not independently correlated with anti-HEV IgG status (*P*=0.970).

Conclusions: About 15% of adult patients with chronic HCV infection are subjects for HAV vaccination in Korea. Subclinical or clinical HEV infection developed at an incidence rate of 0.63%/year in middle-aged HCV patients over 40 years. Therefore, clinicians should be aware of HAV and HEV infection in those patients.

* This study was supported by a grant for the Chronic Infectious Disease Cohort Study (Korea HCV Cohort Study, 4800-4859-304) from the Korea Disease Control and Prevention Agency.

Keywords: Hepatitis C virus, Hepatitis A, Hepatitis E, Antibody, Prevalence, Incidence

FV-034

Clinical and Epidemiological Characteristics of Hepatitis C Virus Infection According to Genotype in South Korea from 2007 to 2020: A Prospective Multicenter Cohort Study

Sangmi Jang[1]*, Gwang Hyeon Choi[1]*, Eun Sun Jang[1], Young Seok Kim[2], Youn Jae Lee[3], In Hee Kim[4], Sung Bum Cho[5], Kyung-Ah Kim[6], Byung Seok Lee[7], Han Chu Lee[8], Si Hyun Bae[9], Moran Ki[10], Da hye Paik[10], Sook-Hyang Jeong[1]

(*Both authors contributed equally to this study.)

[1]Departments of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, [2]Soonchunhyang University Bucheon Hospital, [3]Inje University Busan Paik Hospital, [4]Chonbuk National University Hospital, [5]Chonnam National University Hwasun Hospital, [6]Inje University Ilsan Paik Hospital, Goyang, [7]Chungnam National University Hospital, Daejeon, [8]Asan Medical Center, [9]The Catholic University of Korea, [10]National Cancer Center, Republic of Korea

Aims: The aim of this study is to investigate the clinical and epidemiological characteristics of chronic hepatitis C virus (HCV) infected patients according to genotype in South Korea from 2007 to 2020, with emphasis on the uncommon genotype 3, 4 and 6 in South Korea.

Methods: We analyzed data from the prospective multicenter Korea HCV cohort including 2,817 patients with genotype testing result at 9 tertiary centers. Baseline clinical information prior to antiviral treatment was collected with questionnaire survey results on the lifetime risk factors for HCV infection, and baseline laboratory data.

Results: Among the 2,817 HCV RNA-positive patients, the proportions of each genotype of 1, 2, 3, 4 and 6 were 51.2% (n=1441), 47.6% (n=1342), 0.6% (n=18), 0.1% (n=3) and 0.5% (n=13), respectively. Therefore, genotype 1 and 2 were attributable to 98.8%, and the others to only 1.2%. The mean age of genotype 1, 2, 3, 4 and 6 were 56, 59, 50, 61, and 45 years, respectively (*P*<0.001). The male proportion of the above 5 genotype were 55%, 41%, 67%, 100% and 54%, respectively (*P*<0.001). Among the risk factors, tattooing (69%) and intravenous drug use (23%) were more frequently found in the patients with genotype 6 than the other genotypes. The overall treatment rate with either of interferon-based therapy and direct acting antivirals was 71.9%, which was not different according to HCV genotype. The overall sustained virological response (SVR) rate was 60.1%, showing lower SVR rate in genotype 3 (33%) and 4 (33%), but higher SVR rate of genotype 6 (77%) compared to genotype 1 and 2 (60%). During the follow-up period, clinical outcomes according to the genotype will be presented.

Conclusions: About 99% of HCV infection in Korea were attributed to genotype 1 and 2, and only 1% consisted of genotype 3, 4, and 6. Compared to the other genotypes, genotype 6 patients showed younger age and more frequent history of tattooing and intravenous drug use, and genotype 3 patients showed lower SVR rate.

Keywords: Hepatitis C virus, Chronic hepatitis C, HCV genotype, Uncommon HCV genotype

FV-035

Real-Life Experience of Ledipasvir and Sofosbuvir for HCV Infected Korean Patients: A Multicenter Cohort Study

Sung Won Lee[1,2], Hae Lim Lee[1,2], Hee Yeon Kim[1,2], Chang Wook Kim[1,2], Do Seon Song[1,2], U Im Chang[1,2], Jin Mo Yang[1,2], Sun Hong Yoo[1,2], Jung Hyun Kwon[1,2], Soon Woo Nam[1,2], Seok-Hwan Kim[1,2], Myeong Jun Song[1,2], Jaejun Lee[1,2], Hyun Yang[1,2], Si Hyun Bae[1,2], Ji Won Han[1,2], Soon Kyu Lee[1,2], Hee Chul Nam[1,2], Pil Soo Sung[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic University Liver Research Center

Aims: We have evaluated the efficacy and safety of ledipasvir (LDV) and sofosbuvir (SOF) therapy in hepatitis C virus (HCV) infected Korean patients in real clinical settings.

Methods: A total of 273 patients who received LDV/SOF between May 2016 and February 2021 were consecutively enrolled and analyzed. Weight-based ribavirin was added for the treatment of decompensated cirrhosis and treatment-experienced compensated cirrhosis patients. Per protocol analysis was done for the evaluation of virologic response.

Results: Eighty-nine percent of the patients were treatment-naïve. Seventy-five percent were infected with genotype 1 and 25% with genotype 2 HCV, respectively. One hundred and seventy-nine (65.6%) patients had chronic hepatitis, 66 (24.2%) compensated cirrhosis, and 8 (2.9%) decompensated cirrhosis, respectively. Ten patients (3.7%) had a history of hepatocellular carcinoma and 10 (3.7%) had received liver transplantation prior to HCV treatment. Undetectable HCV RNA at week 4 was achieved in 91% (230/253) of the patients, 99.2% (245/247) achieved end of treatment response and 97.9%

(187/191) achieved sustained virologic response at 12 weeks post-treatment (SVR12). According to underlying liver function, SVR12 rates were 99.2% (124/125) in chronic hepatitis, 96.1% (49/51) in compensated cirrhosis and 100% (6/6) in patients with decompensated cirrhosis. SVR12 rates according to genotypes were 98.2% (161/164) in genotype 1, and 96.3% (26/27) in genotype 2, respectively. Eight weeks LDV/SOF treatment in treatment-naïve, chronic hepatitis patients who had less than 6,000,000 IU/mL HCV RNA at baseline resulted in 100% (21/21) SVR12 rates. Overall, LDV/SOF was well-tolerated with 0.7% (2/273) treatment discontinuation rate due to adverse events. Both events were unrelated to LDV/SOF.

Conclusions: LDV/SOF for the treatment of HCV infected Korean patients was effective and safe with high SVR rates.

Keywords: Hepatitis C, Ledipasvir, Sofosbuvir, Sustained virologic response

FV-036

The Current Status of Comorbidities and Comedications of Patients with Chronic Hepatitis C in Korea

Kyung min Kwon[1], Gi-Ae Kim[2], Hyun Jung Ahn[3], Helin Han[3], Jae-Jun Shim[2]

[1]Gilead Science Korea; [2]Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, Korea; [3]Kantar Korea

Aims: Chronic hepatitis C (CHC) is the second leading cause of liver-related mortality and is more prevalent in the elderly population in Korea. Decisions to initiate treatment and selection of proper antiviral agents may be challenging among elderly patients due to relevant comorbidities, co-medications. It may be helpful to understand current demographic status and comorbidities of CHC patients in the country. Therefore we investigated the latest demographic trend of CHC patients including age, cirrhosis status, comorbidities and comedications in Korea.

Methods: The Health Insurance Review & Assessment Service (HIRA) database was retrospectively examined. The information of patients above 18 years old, who were diagnosed with B18.2 (ICD-10) "Chronic viral hepatitis C" were collected. To identify comorbidities and comedications, all the disease codes and prescribed medications during one year (2018) were analyzed.

Results: A total of 50,476 patients with CHC were identified. Median age was 60 and 37.2% of patients were greater than 65 years of age. Male patients accounted for 46.7% of the total study population. The proportion of patients with cirrhosis, hepatocellular carcinoma, and those with liver transplantation was 6%, 4%, and 0.3%, respectively. Almost all patients (97.5%) had at least one comorbidity. The mean number of total comorbid diseases was 7.6. The prevalence of patients with a comorbidity and mean number of concurrent diseases increased with age. The three most common comorbidities were diseases of the digestive system (83.7%), diseases of the respiratory system (58.2%), and diseases of the musculoskeletal system and connective tissue (57.6%). Hypertension, dyslipidemia, and diabetes were identified in 34%, 21%, and 20% of patients. The three most common co-medications were analgesics (91.6%), gastrointestinal agents (85%), and antibacterials (80.3%). Lipid lowering agents and anticonvulsants were prescribed in 28.5% and 14.8% of patients.

Table 1. Demographic characteristics and other clinical characteristics according to liver diseases groups

	Total n=50,476
Age, mean (SD)	60.30 (12.65)
Age group, n (%)	
18-34 yrs	1,405 (2.8%)
35-44 yrs	3,474 (6.9%)
45-54 yrs	11,312 (22.4%)
55-64 yrs	15,536 (30.8%)
65-74 yrs	11,402 (22.6%)
75- yrs	7,347 (14.6%)
Gender, n (%)	
Male	23,592 (46.7%)
Female	26,884 (53.3%)
Comorbidities, n (%)	
No. of pts on ≥ 1 comorbidity**	49,235 (97.5%)
Comedication, n (%)	
No. of pts on ≥ 1 comedication	49,846 (98.8%)

Table 2. Comorbidity and comedication of Chronic hepatitis C (CHC) patients

	Total	Age group of total CHC patients					
		18-34	35-44	45-54	55-64	65-74	75-
CHC patients	50,476	1,405	3,474	11,312	15,536	11,402	7,347
Patient with ≥1 comorbidities, n(%)	49235 (97.5%)	1213 (86.3%)	3227 (92.9%)	10862 (96.0%)	15269 (98.3%)	11340 (99.5%)	7324 (99.7%)
Patient with ≥1 comedications, n(%)	49846 (98.8%)	1315 (93.6%)	3360 (96.7%)	11092 (98.1%)	15380 (99.0%)	11363 (99.7%)	7336 (99.9%)

Conclusions: Compared to previous study[1], this study shows that the proportion of elderly patients with CHC is increasing in Korea, and comorbidities and comedications are also increasing. With many patients having multiple comorbidities and comedications, through history taking and review of comedications should be taken into consideration when treating HCV patients.

Reference

1. Chung, J.W., et al., Comorbidities and Prescribed Medications in Korean Patients with Chronic Hepatitis C: A Nationwide, Population-Based Study. Gut Liver, 2020.

Keywords: HCV epidemiology, Cormorbidity, Comedication

FV-037

Screening, Confirmation and Treatment Rates of Hepatitis C Virus Infection in a Tertiary Academic Medical Center in South Korea

Jae Seung Lee[1-3], Hong Jun Choi[1,3], Hye Won Lee[1-3], Beom Kyung Kim[1-3], Jun Yong Park[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Seung Up Kim[1-3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; [3]Yonsei Liver Center, Severance

Hospital, Seoul, Korea

Aims: Several barriers prevent the proper screening, diagnosis, and treatment of hepatitis C virus (HCV) infection. We aimed to evaluate the status of HCV screening, confirmation, and treatment rates in a tertiary academic medical center in Korea.
Methods: Patients who visited Severance Hospital between 2015 and 2019 were eligible in this retrospective study. The testing and positivity rates for anti-HCV antibodies and HCV RNA were sequentially analyzed.
Results: Between 2015 and 2019, 252,057 patients (117,131 males, 46.5%) who underwent anti-HCV antibody testing were retrospectively reviewed. The median age of the study population was 51.0 years. Patients with positive anti-HCV antibody test results (n=2,623, 1.0%) showed a higher proportion of liver cirrhosis (17.6% vs. 2.0%) and unfavorable laboratory test results (all P<0.05). The positivity rates were 1.3% and 0.8% in the medical and surgical departments, respectively. HCV RNA was tested in 1,628 (62.1%) patients, with a 57.4% (n=928) positivity rate. The medical department had a higher HCV RNA testing rate than the surgical department (75.4% vs. 40.8%). Among the 928 patients who showed positivity for HCV RNA, 847 (90.7%) underwent genotype testing (mostly 1 and 2 [95.4%]). The treatment rate was 66.9% (n=567); it was higher in the gastroenterology department (70.8%) than in the non-gastroenterology departments (62.3%).
Conclusions: A considerable proportion of patients testing positive for anti-HCV antibodies were not referred for proper management. Systematic and automated screening and referral systems, which may help identify patients requiring treatment for HCV infection, are necessary even in tertiary academic medical centers.
Keywords: Hepatitis C, Mass screening, Diagnostic screening programs, Disease notification

FV-038

Prognosis of Daclatasvir/Asunaprevir treated Genotype 1b Chronic Hepatitis C Patients after Sustained Virologic Response: Interim Analysis of Multicenter Prospective Observational Study

Jeong Han Kim[1], Jae Hyun Yoon[2], Jae-Jun Shim[3], Gi-Ae Kim[3], Sung Eun Kim[4], Eileen L. Yoon[5], Young-Sun Lee[6]

[1]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Chonnam National University Hospital School of Medicine, Gwangju, Korea; [3]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea; [4]Department of Internal Medicine, Hallym University College of Medicine, Anyang, Korea; [5]Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea; [6]Department of Internal Medicine, Korea Unviersity Medical Center, Seoul, Korea

Aims: Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC) and daclatasvir (DCV)/asunaprevir (ASV) is the first introduced interferon free DAA in Korea. Good prognosis is expected in patients achieved sustained virologic response (SVR) after DAA treatment. However, information about prognosis after SVR with DCV/ASV combination is still limited. We aimed to investigate prognosis of these patients.
Methods: This is a multicenter prospective observational study. The CHC patients achieved SVR after DCV/ASV treatment were enrolled and final follow up date was December 2020. Primary end-point was hepatocellular carcinoma (HCC) occurrence and secondary end-points was recurrence or reinfection. At last one time in year, we checked about this end-point.
Results: Total 306 patients were included in this analysis and mean follow up duration was 29.4 months. Mean age was 58.5 years and male was 145 patients (48.6%). Cirrhosis was 115 patients (34.3%) and mean Child-Pugh score was 5.1. HCC occurrence cases were 13 patients (4.2%) up to 4 years. HCC patients were older (74 years vs. 57 years, P=0.001), had more cirrhosis prevalence (76.9% vs. 32.4%, P=0.002), higher AFP (7.3 ng/ml vs. 3.7 ng/ml, P=0.006) and higher MELD score (8 vs. 7, P=0.035). On cox-proportional analysis, age over 72 years (P<0.001) and MELD over 7.19 (P=0.043) were significant variables. Recurrence or reinfection was occur in 3 patients (1.0%) and all occurred within 1 year after SVR.
Conclusions: Although prognosis of SVR achieved patients was generally good, HCC risk was not completely removed especially older patients. Recurrence or reinfection is also possible. Therefore, regular follow up surveillance is still warranted and early treatment is important.
Keywords: Hepatitis C, Direct-acting antiviral, Sustained virologic response, Hepatocellular carcinoma, Daclatasvir, Asunaprevir

4. Alcoholic Liver Disease

FV-039

Serum Milk Fat Globule-EGF Factor 8 Protein Is Useful in Prognosis Prediction of Patients with Alcoholic Hepatitis

Han Ah Lee[1,2], Seong Hee Kang[3], Young-Sun Lee[1], Ki Tae Suk[4], Young Kul Jung[1], Moon Young Kim[3], Ji Hoon Kim[1], Hyung Joon Yim[1], Sang Gyune Kim[5], Jong Eun Yeon[1], Kwan Soo Byun[1], Yeon Seok Seo[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea; [4]Institute for Liver and Digestive Diseases, Hallym University College of Medicine, Chuncheon, Korea; [5]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea

Aims: Although various prediction models have been developed in alcoholic hepatitis (AH) patients, those were insufficient in se-

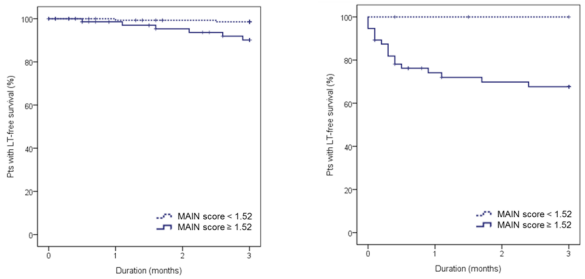
vere AH. We investigated the predictive accuracy of serum milk fat globule-EGF factor-8 (MFG-E8), the key mediator of inflammatory pathway, in assessment of prognosis in AH.

Methods: Patients with known alcoholic liver disease or heavy alcohol use for >6 months who present jaundice were prospectively enrolled from 4 academic teaching hospitals. Patients with viral, or other causes of liver diseases, or hepatocellular carcinoma were excluded. Serum MFG-E8 level were measured at baseline.

Results: Among total of 256 patients, 25 patients (8.9%) died in 3 months. The mean MFG-E8 level was significantly higher in patients died in 3 months than in those who had not (9.18 vs. 5.99 ng/mL, *P*=0.032). MFG-E8 level was significantly correlated with total bilirubin (TB), MELD and DF score (all *P*<0.05). Because of a strong correlation of TB and MFG-E8 (r=0.388, *P*<0.001), variables significantly correlated with MFG-E8 were investigated in patients with TB level <1.2 mg/dL, and used as follows: Expected MFG-E8 = -0.093′age (years)-3.038′sex (men=1, women= 0)+11.720. In multivariate analyses, higher measured/expected MFG-E8 ratio (m/e ratio) and INR and lower albumin level were significant predictors for 3-months mortality. A new prediction model, "MFG-E8, Albumin, and INR" (MAIN) score was developed: MAIN score= 0.141′m/e ratio+7.817′$\log_e$ (INR)-3.263′$\log_e$ (albumin, g/dL). The AUROC of MAIN score for 3-month mortality was 0.845 (sensitivity 87.9%, specificity 80.4%, optimal cut-off value 1.52), similar with that of MELD score (AUROC 0.841). In subgroup analyses according to MELD score, patients with MAIN score ≥1.52 had significantly higher 3-months survival rate than those with <1.52 in both groups (98.5% vs. 90.8%, *P*=0.001 in MELD score <21; 69.6% vs. 100%, *P*=0.007 in MELD score≥21) (Figure).

Conclusions: Serum MFG-E8 could be a potent predictive marker in AH patients with various disease severity.

Figure. Kaplan-meier analysis for 3-months survival according to the MAIN score in (A) patients with MELD score <21 and (B) MELD score ≥ 21



Keywords: MFG-E8, Inflammation, Alcoholic hepatitis, MELD score

FV-040

New Prognostic Model in Hospitalized Patients with Non-Severe Alcoholic Liver Disease

Tae Hyung Kim[1], Hyung Joon Yim[1], Eileen L. Yoon[2], Seong Hee Kang[3], Hee Yeon Kim[4], Young Chang[5], Sung Won Lee[5], Jeong-Ju Yoo[5], Baek Gyu Jun[6], Jung Gil Park[7], Tae Yeob Kim[8], Do Seon Song[4], Soung Won Jeong[5], Ki Tae Suk[9], Young Kul Jung[1], Moon Young Kim[3], Sang Gyune Kim[5], Jae Young Jang[5], Won Kim[10], Jin Mo Yang[4], Dong Joon Kim[9], on behalf of the Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Wonju Severance Christian Hospital, Wonju, Korea; [4]Department of Internal medicine, The Catholic University College of Medicine, Seoul, Korea; [5]Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea; [6]Department of Internal Medicine, Gangneung Asan Hospital, Gangneung, Korea; [7]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea; [8]Department of Internal Medicine, New Hope Internal Medicine Clinic Seoul, Korea; [9]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea; [10]Department of Internal Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul, Korea

Aims: Several prognostic models have been developed for patients with severe alcoholic liver disease, but few studies have yet investigated prognosis of patients with non-severe alcoholic liver disease (NSALD). In this study, we aim to develop a new prognostic model for patients with NSALD.

Methods: We extracted 364 patients with NSALD, defined as lower than 32 of Maddrey's discriminant function score from the retrospective KACLiF cohort for the derivation of a new prognostic model (training set), and validated it in 526 patients from the prospective KACLiF cohort (validation set); These cohorts consist of patients who had chronic liver disease and were hospitalized due to acute decompensations. Independent prognostic factors for death and liver transplantation were analyzed using Cox proportional hazard model.

Results: Twenty-five and 36 patients died or received transplantation within 6 months in training and validation sets. The highest area under the curve (AUC) of conventional prognostic models (e.g. MELD-Na score) was 0.744, 0.741, 0.688 for 28-, 90-, 180-days mortality. Neutrophil proportion, large ascites, overt hepatic encephalopathy and use of vasopressor were significantly associated with the mortality of patient with NSALD. The new model consisting of four factors showed high predictivity for mortality in the training set as well as in the validation set (0.837 and 0.807, 0.822 and 0.771, and 0.782 and 0.733 for 28-, 90-, 180-days mortality in training and validation sets, respectively). In addition, the 6-month transplantation free survivals were 96.6%, 91.8%, and 45.5% of patients with new model score 0, 1-3, and 4-6 in the training set (*P*<0.001); 97.6%, 88.7%, and 39.0% in the validation set (*P*<0.001).

Conclusions: There is the high-risk group even in patients with NSALD, and a new model will help identify them. For these patients, steroid administration can be considered with close monitoring for the need for liver transplantation. Thus, our findings warrant further studies of new treatment strategies for them.

Keywords: Alcoholic liver disease, Prognosis, Maddrey's discriminant function

FV-041

The Values of Acoustic Radiation Force Impulse Elastography of Liver in Evaluating the Degree of Liver Fibrosis in Alcoholic Liver Disease

LE THI THU HIEN[3], HA PHUONG LINH[1], TRAN HUU NGOC[2]

[1]Department of Internal Medicine, 103 Cam Khe Clinic, Phu Tho, Vietnam; [2]Department of Internal Medicine, Hung Vuong Hospital, Phu Tho, Vietnam; [3]Department of Internal Medicine, Thai Nguyen University of Medicine and Pharmacy, Thai Nguyen, Vietnam

Aims: Background: Prevalence of alcoholic liver disease (ALD) is increasingly elevated all over the world. The degree of liver fibrosis (LF) is an important factor that affects the treatment and prognosis. Acoustic radiation force impulse (ARFI) elastography is a noninvasive and a new way of assessing LF.Aims: to evaluate the diagnostic performance of ARFI elastography for assessing LF in ALD.

Methods: This prospective study included 40 patients with ALD at Thai Nguyen National Hospital from June 2019 to February 2020. These patients had been diagnosed with ALD according to the guideline of the AASL 2010. Collecting samples for laboratory testing. Liver stiffness measurement was done using ARFI elastography. Liver biopsy was graded using Metavir classification.

Results: Majority were in age group of 41-50 years (63%). The mean ARFI elastometry showed 2.71 ± 0.59 m/s (range 0.86-4.53) in 40 male patients. Shear wave velocity (SWV) significantly correlated with the fibrosis stage. The area under the ROC curves (AUROCs) for diagnosis of ≥ F2 and ≥ F3 were 0.87 (95% CI: 0.78-0.95) and 0.89 (95% CI: 0.81-0.97), respectively. The cut-off values of SWV for ≥ F2 and ≥ F3 were 1.98 m/s (Se 78.25%, Sp 88.37%, PPV 85.6% and NPV 82.4%) and ≥ 2.31 m/s (Se 95.68%, Sp 85.58%, PPV 71.6%, NPV 97.8%), respectively. APRI significantly correlated with the fibrosis stage. AUROCs for diagnosis of ≥ F2 and ≥ F3 were 0.8 (95% CI: 0.58-0.76) and 0.78 (95% CI: 0.84-0.82), respectively. The cut-off values of APRI for diagnosis of ≥ F2 and ≥ F3 were ≥ 0.62 (Se 51.1%, Sp 87.13%, PPV 72.3% and NPV 68.1%) and ≥ 1.171 (Se 42%, Sp 95.52%, PPV 81%, NPV 83.1%), respectively.

Conclusions: Increasing SWV correlates with higher degree of LF. ARFI elastography is a noninvasive, reliable, and repeatable diagnostic test in evaluating the degree of LF.

Keywords: Acoustic radiation force impulse elastography, Liver fibrosis, Alcoholic liver disease, Evaluating the degree

FV-042

Hepatoprotective and Antioxidant Capacity of Madhuca Longifolia Leaves Extracts against Early Alcohol-Induced Liver Injury in Rat

Ranbir Singh[1,2], VK Sharma[2]

[1]Department of Applied Sciences, IARI-ICAR, Campus, New Delhi, India; [2]Department of Applied Sciences, Shri Maha maya Vaishnav Devi Mandir Research Institute, New Delhi, India

Aims: Madhuca longifolia leaves has been used as a traditional medicine for a long history in developing countries and showed significant free radical-scavenging activities, antioxidant activities and anti-leukemia effects in experimental rats. Free radicals and oxidants have been shown to be involved in alcohol-induced liver injury. This study was designed to determine whether aqueous extract of Madhuca longifolia leaves (AMLE), composed mostly of flavonol glycosides and terpene lactones, protects against early alcohol-induced liver injury in rats.

Methods: Total sixty four female Wistar rats (n=8) were fed high-fat liquid diets with or without ethanol (10-14 g/kg per day) and AMLE extract (100 and 250 mg/kg per day) continuously for 4 weeks using an enteral feeding protocol. Biochemical and molecular parameters were evaluated in experiments rat livers.

Results: Result shown that, mean body weight gains were not significantly different between treatment groups. After 4 weeks, serum alanine amino transferase levels of the ethanol group were increased nearly fourfold compared to control values; this effect of ethanol was blocked by AMLE extract (250 mg/kg). Additionally, enteral ethanol caused severe fat accumulation, mild inflammation, and necrosis in the liver; AMLE extract significantly blunted these changes. Increases in liver TNF alpha protein levels caused by ethanol were completely blocked by AMLE extract. Further, ethanol significantly increased the accumulation of protein adducts of 4-hydroxynonenal, a product of lipid peroxidation serving as an index of oxidative stress; again this was counteracted by the addition of AMLE extract.

Conclusions: The result indicates that the AMLE extract exhibit the antioxidant activity through correction of oxidative stress and validates the traditional use Madhuca longifolia leaves in prevent early alcohol-induced liver injury.

Keywords: Madhuca longifolia leaves, Alcohol-Induced liver injury, Antioxidant, Female rats

5. Cirrhosis/Liver Fibrosis

FV-043

Clinical Impact of Exosomal microRNA in Liver Fibrosis: Based on Next-Generation Sequencing Analysis

Young Chang[1], Jae-A Han[5], Suk Min Kang[1], Soung Won Jeong[1], Tom Ryu[1], Han Seul Park[1], Jeong-Ju Yoo[3], Sae Hwan Lee[2], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2], So Young Jin[4], Seongho Ryu[5], Jae Young Jang[1]

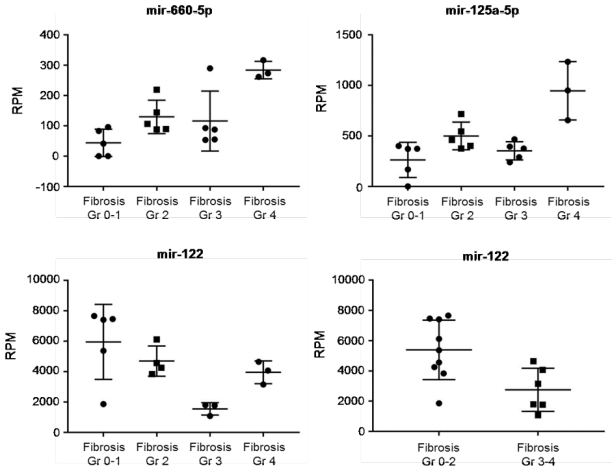
[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea; [3]Department

of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea; [4]Department of Pathology, Soonchunhyang University College of Medicine, Seoul, Korea; [5]Soonchunhyang Institute of Medi-bio Science (SIMS), Soonchunhyang University, Cheonan, Korea

Aims: We investigated alterations in the expression of serum exosomal miRNAs with the progression of liver fibrosis and evaluated their clinical applicability as biomarkers

Methods: This study prospectively enrolled 71 patients who underwent liver biopsy at an academic hospital in Korea. Exosomes were extracted from serum samples, followed by next-generation sequencing (NGS) of miRNAs and targeted real-time quantitative polymerase chain reaction. A model was derived to discriminate advanced fibrosis based on miRNA levels and the performance of this model was evaluated. Validation of the effect of miRNA on liver fibrosis *in vitro* was followed.

Results: NGS data revealed that exosomal miR-660-5p, miR-125a-5p, and miR-122 expression were changed significantly with the progression of liver fibrosis, of which miR-122 exhibited high read counts enough to be used as a biomarker (Figure 1). The level of exosomal miR-122 decreased as the pathologic fibrosis grade progressed and patients with biopsy-proven advanced fibrosis had significantly lower levels of exosomal miR-122 (P<0.001) than those without advanced fibrosis. Exosomal miR-122 exhibited a fair performance in discriminating advanced fibrosis especially in combination with fibrosis-4 score and transient elastography. In a subgroup of patients with a non-viral etiology of liver disease, the performance of exosomal miR-122 as a biomarker was greatly improved. Inhibition of miR-122 expression increased the proliferation of the human hepatic stellate cell line, LX-2, and upregulated the expression of various fibrosis related proteins.



Conclusions: Exosomal miR-122 may serve as a useful non-invasive biomarker for liver fibrosis, especially in patients with non-viral etiologies of chronic liver disease.

Keywords: Exosome, microRNA, Liver fibrosis, Next-generation sequencing

FV-044

Unveiling the Association of MICA Variant rs2596542 and Hepatocellular Carcinoma: A Meta-Analysis

Md Abdullah Al Maruf[1], Farhana Sultana Mitu[2]

[1]Department of Health Technology & Informatics, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR, China; [2]Department of Biotechnology & Genetic Engineering, Faculty of Biological Sciences, Islamic University, Kushtia, Bangladesh

Aims: Background/Aims: A tumor antigen, MICA (Major histocompatibility complex class I-related chain A) playing crucial role in liver function while its expression has been affected by its germline polymorphisms. Though the relationship between rs2596542 single nucleotide polymorphism (SNP) in MICA promoter region and hepatocellular carcinoma (HCC) was found in several studies but yet not fully discovered so far. The aim of this study is making a summary of the relationship between rs2596542 and the risk of HCC development through a comprehensive meta-analysis.

Methods: Methods: Four electronic scientific databases including PubMed, Web of Science, Google Scholar and EMBASE were systematically searched to extract relevant studies. A meta-analysis was conducted to investigate the association between MICA rs2596542 polymorphism and susceptibility to HCC. Moreover, Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results: Results: Seventeen case-control studies involving 6,325 HCC cases and 20,427 controls were included. Five genetic models revealed the significant association between MICA rs2596542 and HCC with increasing risk. Homozygous model showed the highest risk of HCC (OR = 1.34, 95% CI = 1.22-1.48, P<.001). In addition, other genetic models showed similar findings; recessive genetic model (OR = 1.25, 95% CI = 1.15—1.37, P<.001), dominant genetic model (OR= 1.20, 95 % CI = 1.12-1.27, P<.001), allelic genetic model (OR = 1.17, 95% CI = 1.11-1.22, P<.001), and, heterozygous genetic model (OR= 1.17, 95% CI = 1.06-1.28, P<.001).

Conclusions: Conclusions: The T allele in MICA rs2596542 is a risk factor for hepato-carcinogenesis. To validate the findings till to date, further large and well-designed case-control studies along with functional analysis are needed.

Keywords: HCC, rs2596542, Genetic Models, Meta-analysis

FV-045

Using Novel Nanosensor-Based Microrna Detection and Amplification Technique, Whole Blood Circulating Microrna Levels Can Predict Liver Cirrhosis

Hyun Yang[1,2], Jung Hoon Cha[1], Ahlim Lee[1,2], Jae Jun Lee[1,2], Pil Soo Sung[1,3], Seong Wook Yang[4*], Si Hyun Bae[1,2*]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, 03312, Republic of Korea;

[2]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [3]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [4]Department of Systems Biology, College of Life Science and Biotechnology, Yonsei University, Seoul, Korea, 03722

Aims: Accurate prediction of liver cirrhosis is important for clinical decision making and disease management. This study aimed to evaluation the value of whole blood circulating levels of microRNA (miRNA)-A* and miRNA-B* as novel noninvasive biomarkers in prediction of cirrhosis in patient with liver disease. *We cannot provide exact name of microRNAs before patent application.

Methods: Total 38 patient with clinically diagnosed liver disease were analyzed. Among them, 7 patients of cirrhosis included. The whole blood circulating levels of miRNA-A and miRNA-B were quantified using nanosensor-based miRNA detection and amplification method. Receiver operating characteristic curve analysis was performed to evaluate the sensitivity and specificity of the miRNAs for prediction of cirrhosis.

Results: Compare to various qPCR-based miRNA analyses that are currently available, which generally require cDNA synthesis, the nanosensor-based miRNA detection method used in the study directly recognizes target miRNAs before amplification. By applying this method, we found that circulating miRNA-A levels were significantly downregulated in cirrhosis patients compared to those without fibrosis (Metavir stage F0) (P=0.009). Likewise, circulating miRNA-B levels showed downregulated tendency in cirrhosis patients compared to those without fibrosis (P=0.076). Receiver operating characteristic curve analysis revealed that both serum miRNA-A and miRNA-B levels were associated with high diagnostic accuracy for patients with cirrhosis (0.852, P=0.025 and 0.815, P=0.045, respectively)

Conclusions: Our results indicate that whole blood circulating levels of miRNA-A and miRNA-B by using nanosensor-based miRNA detection and amplification method might be useful non-invasive biomarker for prediction of cirrhosis in patient of liver disease.

Keywords: MicroRNA, Cirrhosis

FV-046

Compositional Shift of Gut Microbiome According to the Complications In Patients With Liver Cirrhosis

Satya Priya Sharma, Raja Ganesan, Haripriya Gupta, Ye Rin Choi, Hyeong Seop Kim, Sang Jun Yoon, Yoseph Asmelash Gebru, Dong Joon Kim, Ki Tae Suk*

Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Republic of Korea

Aims: Change in gut microbiome is closely associated with liver cirrhosis diseases initiation, progression, establishment, and severity. Nevertheless, compositional alterations in gut microbiome during cirrhosis development still not been evaluated, comprehensively. Here, we compared the gut microbial composition in cirrhosis patients to encompassing the gut microbial role in whole spectrum of disease.

Methods: Stool samples was collected prospectively from 142 cirrhosis patients. 16S rRNA sequencing were performed using the MiSeq sequencer on the illumine platform and based on the phylogenetic relationship, 16S-based Microbiome Taxonomic Profiling was performed to discovery gut microbial compositional shift along with cirrhosis severity progression.

Results: Out of total 142 cirrhosis patients, 33% were females (n= 47, aged between 36-81) and 67% were males (n=95, aged between 36-79). Mortality rate was 24% (n= 34, aged between 47-81), whereas higher mortality rate was found in male (74%) in comparison to female (26%) cirrhosis patients. All 142 patients were classified in five groups: only cirrhosis (n= 10, aged between 43-79), cirrhosis with hepatocellular carcinoma (HCC) (n= 26, aged between 43-77), cirrhosis with varices (n= 7, aged between 36-79), cirrhosis with ascites (n= 26, aged between 41-78), and cirrhosis with 3 or more complication (n=71, aged between 36-81). In gut microbial composition, relative abundance of Bacteroidetes was decreased and Firmicutes was increased in patients having cirrhosis with other complication compared with patients only having cirrhosis. Moreover, 3 species are only observed in cirrhosis patients whereas Veillonella dispar species found in all other 4 groups but not only cirrhosis patients.

Conclusions: This comparative analysis presented a gut microbial compositional alteration as severity of liver cirrhosis progresses. This compositional shift in gut microbiome possibly contribute to the disease severeness therefore, further studies are required for the identification of the diseases related species.

Keywords: Cirrhosis, HCC, Gut microbiome, Compositional change

FV-047

Circulating Neutrophil Phagocytic Dysfunction Is Associated with Systemic Inflammation, Hyponatremia, and Renal Impairment in Patients with Cirrhosis

Hayam El Aggan,[1] Myriam Helmy[2]

[1]Department of Internal Medicine (Nephrology and Transplantation Unit) and [2]Department of Clinical Pathology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt

Aims: Liver cirrhosis is characterized by innate immune dysfunction and systemic inflammation predisposing to the development of complications. The present study was designed to assess the phagocytic function of circulating neutrophils and monocytes in patients with cirrhosis and its relation to systemic inflammation, hyponatremia, and renal impairment.

Methods: Thirty patients with cirrhosis were prospectively studied and compared with 15 healthy subjects. The severity of liver

disease was assessed by Child-Pugh classification and the Model for End Stage Liver Disease Sodium (MELDNa) score. Systemic inflammation was estimated by measuring serum high-sensitivity C-reactive protein (hsCRP) level and calculating neutrophil-lymphocyte ratio (NLR). Renal function was evaluated by serum creatinine and estimated glomerular filtration rate (eGFR). Phagocytosis of fluorescein-labelled opsonized Escherichia coli by circulating neutrophils and monocytes was determined using a flow cytometry kit. The phagocytic activity (PA) was expressed as the percentage of phagocytizing cells and the phagocytic capacity was quantified as the total number of bacteria phagocytized per cell by measuring the mean fluorescence intensity (MFI).
Results: The neutrophil PA and MFI and monocyte MFI [but not monocyte PA] showed significant decreases and serum hsCRP level and NLR showed significant increases in patients with cirrhosis compared with healthy controls (P<0.001). The neutrophil PA and MFI were inversely correlated with serum levels of aminotransferases, creatinine, and hsCRP, NLR, and Child-Pugh and MELDNa scores and were positively correlated with serum sodium level and eGFR (P<0.05). The monocyte PA and MFI showed significant inverse correlations with serum hsCRP level, NLR and Child-Pugh and MELDNa scores (P<0.05).
Conclusions: Patients with cirrhosis are characterized by neutrophil and monocyte dysfunction particularly with advanced liver disease that may be related to systemic inflammation. Further impairment of neutrophil function was associated with hyponatremia and renal impairment. Neutrophils could be a target for future anti-inflammatory therapeutic strategies in cirrhosis.
Keywords: Liver cirrhosis, Phagocytic function, Hyponatremia, Renal impairment

FV-048

Characteristics of Red Cell Distribution Width (RDW) in Cirrhotic Patients in Thai Nguyen Nation Hospital

HA PHUONG LINH[2], LÊ QUỐC TUẤN[2], ĐỒNG ĐỨC HOÀNG[1]

[1]Department of Internal Medicine, Thai Nguyen University of Medicine and Pharmacy, Thai nguyen, Vietnam; [2]103 Cam Khe Clinic, Phu Tho, Vietnam

Aims: To determination of red blood cell distribution (RDW) and association with some blood tests in cirrhotic patients.
Methods: A descriptive cross-sectional study. Subjects include 68 cirrhotic patients who were treated at the Department of Gastroenterology of Thai Nguyen Central Hospital from January 2020 to September 2020.
Results: There are 68 male patients and no female patients. The mean age of 52.0 ± 19.0 years. RDW in HBV-related cirrhosis group (16.2 ± 3.6%) and alcoholic cirrhosis group (16.6 ± 4.3%) were both higher than control group (12.02 ± 1.01%), there is a statistically significant difference, P<0.01. RDW was positively correlated with bilirubin and creatinine in plasma. RDW was negatively correlated with PT, platelet count and albumin in plasma.
Conclusions: RDW is a potential prognostic index for cirrhosis.
Keywords: Red cell distribution width (RDW), Prognosis, Cirrhosis

FV-049

Prevalence and Risk Factors of Erectile Dysfunction in Patients with Liver Cirrhosis: A Systematic Review and Meta-Analysis

Hye Jin Yoo, Jeong Ju Yoo, Sang Gyune Kim, Young Seok Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine,Soonchunhyang University School of Medicine Bucheon Hospital, Bucheon, Korea

Aims: Liver cirrhosis is associated with an increased risk of developing erectile dysfunction (ED) of men. The aim of this systematic review and meta-analysis was to evaluate the prevalence ED and its risk factors in male patient with liver cirrhosis.
Methods: A systematic search of PubMed (Medline), EMBASE, OVID Medline, the Cochrane Library and other databases was performed for this review. The abstracts obtained from the search were reviewed by two investigators who choose manuscripts for full-text review. The event rates were calculated with a random-effects model and quality effects model.
Results: Fourteen studies evaluating ED with International Index of Erectile Function (IIEF) scores were finally selected. A total of 770 patients with liver cirrhosis were analyzed. The prevalence of ED in cirrhotic patients were 79%, respectively [decompensated:88.4%,$I^2$85%, confidence interval (CI) 35.95-70.84, Compensated: 53.6%, $I^2$80%,CI 77.64-96.32]. Through a meta-regression analysis, we found that presence of decompensation, use of beta-blocker and diuretics were related with ED. In addition, risk factors for ED were high body mass index [odds ratio (OR) 1.13, 95% CI1.01-1.26], advanced child-pugh class (OR 2.29, 95% CI1.12-4.72), MELD score (OR 1.19, 95% CI 1.05-1.35), diabetes (OR 3.44, 95% CI 1.38-8.57), and hypertension (OR 8.24, 95% CI 1.62-41.99).
Conclusions: ED is relatively common in male patients with cirrhosis, and the prevalence increases, especially in the presence of risk factors.
Keywords: Liver cirrhosis, Erectile dysfunction, Risk factor, Prevalence

FV-050

Prognostic Impacts of the Change in Muscle Mass on Patients with Cirrhosis

Tae Hyung Kim, Young Kul Jung, Sun Young Yim, Young-Sun Lee, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um

Department of Internal Medicine, Korea University College of Medicine

Aims: Sarcopenia has a negative impact on the prognosis of patients with cirrhosis. Although muscle mass changes are also

expected to be an important factor, available data are limited yet.

Methods: Adults with cirrhosis were included from the prospective cohort who received the abdomen CT annually for HCC surveillance. L3 skeletal muscle index (SMI) was adopted as a proxy of skeletal muscle mass, and we calculated a change of SMI between baseline and one-year (ΔSMI/yr).

Results: Among a total of 155 patients, 113 and 21 had sarcopenia and Child-Pugh class B/C decompensation, respectively. During a median follow-up of 36 months, five patients died and 19 had undergone complications of cirrhosis. Multivariate Cox regression analyses showed 1% decrease in ΔSMI/yr was associated with a 1.15-1.19-fold increased risk of complication occurrence even adjusted for Child-Pugh or MELD score. In addition, ΔSMI/yr showed good prediction of aggravation of liver function (Child-Pugh score at 2 years after baseline), especially in female patients (n=46), with a cut-off of -2.5% (sensitivity 57.1%, specificity 94.9%).

Conclusions: ΔSMI/yr was significantly associated with prognosis of patients with cirrhosis independent of baseline Child-Pugh and MELD scores.

Keywords: Muscle, Cirrhosis, Prognosis

FV-051

Thermoneutrality Induces Interleukin-10 to Attenuate Liver Fibrosis

Ha Thi Nga[1,2,3], Ji Sun Moon[1,2,3], Jingwen Tian[1,2,3], Ho Yeop Lee[1,2,3], Seok-Hwan Kim[4], Young-Sun Lee[5], Jae-Han Jeon[6], Hyon-Seung Yi[1,2,3*]

[1]Laboratory of Endocrinology and Immune System, Chungnam National University School of Medicine, Daejeon, Republic of Korea; [2]Department of Medical Science, Chungnam National University School of Medicine, Daejeon, Republic of Korea [3]Research Center for Endocrine and Metabolic Diseases, Chungnam National University School of Medicine, Daejeon, Republic of Korea; [4]Department of Surgery, Chungnam National University School of Medicine, Daejeon, Republic of Korea; [5]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea; [6]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea

Aims: Crosstalk between brown adipose tissue (BAT) and the liver is receiving increasing attention. This study investigated the effect of BAT dysfunction by thermoneutral (TN) housing on liver fibrosis in mice and examined the effect of secreted factors from brown adipocytes on the activation of hepatic stellate cells (HSCs).

Methods: The carbon tetrachloride (CCl_4)-induced liver fibrosis mouse model was used to evaluate fibrotic changes in the livers of mice housed under standard and TN conditions. The effect of BAT on the activation of HSCs was examined using cultured cells treated with conditioned media from brown adipocytes.

Results: Under TN conditions, mice with CCl_4-induced liver fibrosis exhibited increased liver injury, collagen deposition, and alpha smooth muscle actin (α-SMA) expression in the liver compared with mice maintained at room temperature. The numbers of liver-infiltrating immune cells and T cells producing IL-17A and IFN-γ were also significantly increased in the livers of mice housed under TN conditions. Treatment of HSCs with conditioned media from brown adipocytes markedly attenuated HSC activation, as shown by down-regulated α-SMA expression. At thermoneutrality, IL-10-deficient mice exhibited more severe liver fibrosis than wild-type mice. Interestingly, conditioned media from IL-10-deficient brown adipocytes could up-regulate the expression of α-SMA and induce HSCs activation.

Conclusions: BAT inactivation by thermoneutrality contributes to the activation of pro-inflammatory and pro-fibrotic pathways in mice with CCl_4-induced liver fibrosis. Normal brown adipocytes secreted factors that impair the activation of HSCs, while this protective effect was lost in IL-10-deficient brown adipocytes. Thus, the BAT–liver axis may serve as a potential therapeutic target for liver fibrosis, and IL-10 may be a key factor regulating the activation of HSCs by BAT.

Keywords: Liver fibrosis, Hepatic stellate cells, Thermoneutrality, Brown adipose tissue, IL-10, Conditioned media

FV-052

Improvement in Nutritional Status of Liver Cirrhosis Through A Nutritional Regimen at Sultan Daeng Radja Hospital

Sahnaz Vivinda PUTRI, Evy ELFIANY, Sitti MAESYAROH

Health Management, International University Semen Indonesia, Indonesia

Aims: Nutrition is needed in patients with hepatic cirrhosis to increase liver tissue regeneration and prevent further damage and improve the function of remaining liver tissue, prevent weight loss/malnutrition or increase body weight if it is less, prevent further complications (portal hypertension, ascites, esophageal varices, and hepatic encephalopathy. This study aims to determine the improvement of the nutritional status of patients with cirrhosis of the liver through a nutritional regimen at Sultan Daeng Radja Hospital, Bulukumba.

Methods: This type of research uses a quasi-experimental with a control group approach pre-posttest design with a sample size of 20 respondents in the control group and 20 respondents in the intervention group. Collecting data in this study using a nutritional status assessment sheet, namely Form Full The Mini Nutritional Assessment of 18 questions with a ratio scale and BMI (Body Mass Index) measurement. Data were analyzed using a dependent t-test which aims to compare the average nutritional status before and after treatment in each group while analyzing the comparison of the average nutritional status in the intervention and control groups.

Results: The results showed that the average nutritional status in the intervention group was 24.40, while the average nutritional status in the control group was 20.85. The statistical test results

obtained a p-value of 0.000 (P<0.05), there is a significant difference in the mean nutritional status between the intervention group and the control group.

Conclusions: There was a significant difference in the mean nutritional status between the intervention group and the control group.

6. Drug induced liver injury

FV-053

Comparative Therapeutic Efficacy of Aloe vera and Moringa oleifera with Curcumin in Prevention of Beryllium Induced Liver Injury

Narottam Das Agrawal

Rajkiya Medical College Jalaun (Orai), U.P. India

Aims: Beryllium is poisonous to all the life forms, induces oxidative stress and play important role in the development of many life threatening diseases in humans including cancer. Therapeutic efficacy of Moringa oleifera root extract with curcumin and Aloe vera with curcumin were compared in prevention of beryllium induced oxidative stress, liver dysfunction, histopathological alterations and beryllium body burden in rats.

Methods: $Be(NO_3)_2$ at doses of 1.0 mg/kg, i.p. once a day, daily for 5 weeks were administered in female Wistar albino rats followed by oral administration of Moringa oleifera (150 mg/kg, p.o) with curcumin (5.0 mg/kg, p.o.) and Aloe vera (150 mg/kg, p.o) with curcumin (5.0 mg/kg, p.o.) once a day, daily for 5 weeks. Markers of oxidative stress, blood sugar, hepatic glycogen, G6Pase, SDH, G6PDH, markers of liver function, beryllium body burden and histopathogical alterations were monitored.

Results: Beryllium enhanced lipid peroxidation with decrease in cellular reduced glutathione, SOD and catalase activities. Beryllium decreased blood sugar, glycogen, G-6-Pase, Succinate dehydrogenase (SDH) and increase in G6PDH activity. Beryllium altered liver function by significantly increase in total bilirubin, AST and ALT activities, and significantly decrease in albumin and SALP activity. Liver deposited maximum amount of administered beryllium. Beryllium disturbed histoarchitecture of liver and altered normal function. Co-administration of Moringa oleifera with curcumin and Aloe vera with curcumin were effective in prevention of beryllium toxicity, however, combination therapy of Moringa oleifera with curcumin showed better therapeutic effect in prevention of beryllium toxicity, which were shown by prevention of oxidative stress, restoration of liver biochemical markers with normal sugar level, prevention in deposition of beryllium in liver with almost normal histoarchitecture of liver.

Conclusions: Combination therapy of Moringa oleifera root extract with curcumin was found to be better in prevention of beryllium induced oxidative stress and liver injury in rats.

Keywords: Beryllium toxicity, Liver dysfunction, Beryllium body burden, Histopathology

FV-054

Comparative Study on the Ameliorating Effects of Pyrroloquinoline Quinone, S. Cumini and Vitamin C in Liver of STZ-Induced Diabetic Mice: Biochemical and Histopathological Study

Narendra Kumar, Anand Kar

School of Life Sciences, Devi Ahilya University, Takshashila Campus, Indore, M. P., 452017, India

Aims: Pyrroloquinoline quinone (PQQ) is known to a strong antioxidant and has high free radical scavenging activities. It protects cells from oxidative stress-induced damage, effectively improves the activities of free radical scavenging enzymes and decreases the level of lipid peroxidation. Vitamin C and S. cumini seed extracts are also known to possess high anti-oxidative properties and can protect against several types of oxidative damages in diabetes mellitus. With respect to PQQ, nothing was known on its relative efficacy as compared to vitamins and plant extracts that possess antioxidant activity in any diseased condition. However, to its comparative effects in regulating diabetes associated hepatotoxicity, practically nothing has been studied so far. In the present investigation we evaluate and compare the ameliorating effects of PQQ with vitamin C and S.cumini seed extracts in STZ-induced diabetes mellitus with an emphasis on the oxidative stress in liver of mice.

Methods: Mice were randomly divided into five groups. Group I receiving only citrate buffer served as the normal control. Animals of groups II–V were rendered diabetic by single dose of streptozotocin (STZ, 150 mg/kg body weight), following which PQQ at a dose of 20 mg/kg, was injected to the animals of group III, while in group IV 50 mg/kg of vitamin C was injected and in group V animals S.cumini seed extract was injected 100 mg/kg for 15 days. At the end, alterations in different serum indices including glucose, lipid profile, α-amylase, urea, SGPT and SGOT; liver tissue peroxidation and antioxidants alterations; histopathological alterations in liver were evaluated.

Results: STZ-treated animals developed oxidative stress as indicated by a significant increase in lipid peroxidation, serum glucose, total cholesterol, triglyceride and urea, with a parallel decrease in the levels of liver tissue antioxidants. When diabetic animals received dose of PQQ, vitamin C and S. cumini in animals of group III, IV and V respectively, these adverse effects were ameliorated. However, 20 mg/kg of PQQ appeared to be more effective than vitamin C and S.cumini seed extracts.

Conclusions: These findings revealed for the first time that PQQ has the better potential than vitamin C and S.cumini seed extracts to mitigate diabetes associated oxidative damages in liver of mice.

Keywords: Diabetes mellitus, Liver, Lipid peroxidation, PQQ

FV-055

Hepatoprotective Effects of Cinnamomum Zeylanicum Bark and Vitamin E Against Hepatic Damage Induced by Acetaminophen in Rats

Saroj, Ekta Kumari, BH Prakash

Pharmaceutical Sciences, U T University, India

Aims: Acetaminophen is a common over-the-counter drug with antipyretic-analgesic action. When APAP is used in large doses, it causes hepatotoxicity and nephrotoxicity but safe at therapeutic doses. Cinnamon (Cinnamomum zeylanicum) is extensively used in folk medicine due to its high content of natural antioxidants. This study investigated efficacy of aqueous extract of Cinnamomum zeylanicum (CZ) pretreatment in alleviating acetaminophen-induced acute hepatotoxicity in rats.

Methods: Male Wistar rats were divided into six groups; negative control, acetaminophen (APAP) (600 mg/kg single intraperitoneal injection); vitamin E (75 mg/kg), CZ (200 mg/kg), vitamin E + APAP, and CZ+ APAP.

Results: Administration of APAP elicited significant liver injury that was manifested by remarkable increase in plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), arginase activities, and total bilirubin concentration. Meanwhile, APAP significantly decreased plasma total proteins and albumin levels. APAP administration resulted in substantial increase in each of plasma triacylglycerols (TAGs), malondialdhyde (MDA) levels, and total antioxidant capacity (TAC). However, CZ extract or vitamin E treatment prior to APAP showed significant hepatoprotective effect by lowering the hepatic marker enzymes (AST, ALT, ALP, and arginase) and total bilirubin in plasma. In addition, they remarkably ameliorated the APAP-induced oxidative stress by inhibiting lipid peroxidation (MDA). Pretreatment by CZ extract or vitamin E significantly restored TAGs, and total protein levels. Histopathological examination of APAP treated rats showed alterations in normal hepatic histoarchitecture, with necrosis and vacuolization of cells. These alterations were substantially decreased by CZ extract or vitamin E.

Conclusions: Our results demonstrated that CZ extract can prevent hepatic injuries, alleviating oxidative stress in a manner comparable to that of vitamin E. Combination therapy of CZ extract and APAP is recommended especially in cases with hepatic disorders or when high doses of APAP are required. However, pre-treatment with cinnamon ameliorated the APAP-induced cellular alterations and apoptosis, possibly through its high content of antioxidants.

Keywords: Madhuca longifolia, Hepatic fibrosis, Carbon tetrachloride, Rats

FV-056

Protective and Antioxidant Activities of Vitamin E in Carbofuran-Induced Hepatic Damage in Rats

Ankush Kumar, P Mishra

Department of Basic Sciences,, DAV, A State university, India

Aims: Vitamin E is a potent antioxidant, anti-inflammatory that has been shown to reduce oxidative stress in diabetic patients. The aim of the present investigation was to evaluate the hepatoprotective and antioxidant effects of the vitamin E against carbofuran (CF)-intoxicated liver injuries in Wistar male rats.

Methods: For this purpose, levels of serum diagnostic markers, hepatic antioxidant enzymes, and liver histo-architecture were employed to justify the protective efficacy of vitamin E. And antioxidant activity was investigated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide, hydrogen peroxide, and hydroxyl free radical scavenging assays.

Results: Results revealed that the vitamin E caused a significant decrease of the level of hepatic enzymes, triglycerides, and bilirubin and an increase of the total protein. Vitamin E has also significantly lowered the level of malonylaldehyde. Carbofuran markedly suppressed hepatic antioxidant enzymes, however, the vitamin E significantly augmented these enzymes. The hepatoprotective effect was demonstrated by the improvement in the histo-architectural features of liver sections of CF-intoxicated rats treated with vitamin E at 50 mg/kg dose. In addition, vitamin E showed moderate total phenolic and total flavonoid content, whereas the IC50 values of DPPH, nitric oxide, hydrogen peroxide, and hydroxyl free radical scavenging assays were 71.31 ± 0.42, 134.82 ± 0.14, 47.69 ± 0.38, and 118.44 ± 0.30 μg/mL, respectively.

Conclusions: In conclusion, the present study suggests the protective role of vitamin E against hepatic injury induced by CF, which may be attributed to its higher antioxidant properties and thereby scientifically justifies its traditional use.

Keywords: Carbofuran-induced hepatic damage, Antioxidant, Vitamin E, Rats

FV-057

Effects of Syzygium Cumini Seeds on Biochemical and Molecular Parameters in Isoniazid-Induced Hepatotoxic Rat Model

Rahul Kumar, Anjali Kanojia

Department of Zoology, J K College, Bihar, India

Aims: Syzygium cumini (S. cumini) (L.) (jambolan) is one of the widely used medicinal plants in the treatment of various diseases in particular diabetes in India. Here, we assessed the beneficial metabolic effects of the aqueous extract of S. cumini seeds (AESC) in isoniazid-induced hepatotoxic rat model. Dietary anthocyanins have been shown to reduce inflammation in animal models and may ameliorate hepatic-related complications.

S. cumini is one of the richest sources of anthocyanins.This study aimed at investigating the hepatoprotective role of AESC against isoniazid-induced hepatotoxicity in female albino rats.

Methods: Wistar rats (n = 8 per group) were divided into four groups: saline-treated control, saline-treated control with AESC extract (200 mg/kg), isoniazid treatment alone (100 mg/kg, intraperitoneal [i.p.]), and isoniazid-AESC extract (200mg/kg) administered orally as cotreatment. Animals were treated for 28 days and euthanized 1 h after the last drug administration. Evaluated body weight, serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, g-glutamyl transferase, total protein, albumin, hepatic malondialdehyde content, superoxide dismutase, catalase, cytochrome P450 2E1 (CYP2E1)activity and glutathione (GSH).

Results: AESC prevented isoniazid-induced hepatotoxicity, indicated by both diagnostic indicators of liver damage, liver functional profile, significantly inhibited CYP2E1 activity, markedly attenuated oxidative stress by improved enzymatic, non-enzymatic antioxidants levels and mitigate malondialdehyde, lipid hydroperoxide significantly.

Conclusions: These results suggest that AESC extract exerts its hepatoprotective activity by inhibiting the production of free radicals and acts as a scavenger, reducing the free radical generation via inhibition of hepatic CYP2E1 activity, increasing the removal of free radicals through the induction of antioxidant enzymes and improving

Keywords: Isoniazid-Induced Hepatotoxic, Syzygium cumini, Superoxide dismutase, Rat

FV-058

Hepatoprotective Evaluation of The Effects of The Hydroalcoholic Extract of Zingiber Officinale on Paracetamol Induced Liver Toxicity In Male Rats

Minakshi Sarswati, A K Gaur

Department of Alternative Medicine, Ayush diabetes research foundation, India

Aims: Oxidative stress induced by toxicants is known to cause various complications in the liver. Paracetamol causes oxidative stress and dysfunction of the liver. The pathogenesis and progression of paracetamol hepatic toxicity are associated with free radical injury and oxidative stress, which could be partially attenuated by antioxidants and free radical scavengers. Red ginger (Zingiber officinale) has been prescribed as an analgesic for antidiabetic and anti-inflammatory in Indian traditional medicine. This study was undertaken to evaluate the effects of the hydroalcoholic extract from dried red ginger (red ginger extract [RGE]) on some biochemical and histopathological parameters of liver tissue in against paracetamol induced hepatic damage in rats.

Methods: Wistar male rats were orally administered with 2g/kg body weight Paracetamol. Vehicle (distilled water) and silymarin (50 mg/kg body weight) were used as the negative and positive control groups, respectively. Paracetamol -administered groups were treated with RGE (100, 200, and 500 mg/kg). After 15 days of treatment, the blood specimens and liver samples were examined. Alteration in the levels of biochemical markers of hepatic damage like AST, ALT, ALP and lipid peroxides were tested, and phytochemical tests were also performed.

Results: In Paracetamol -treated group, the levels of serum urea, high density lipoprotein (HDL), and liver superoxide dismutase (SOD), catalase (CAT), and vitamin C significantly decreased (P<0.05) compared to control. Also, in this group, serum triglyceride (TG), total cholesterol (TC), very low density lipoprotein cholesterol (VLDL), protein carbonyl (PC), malondialdehyde, tumor necrosis factor-α (TNFα), and TNF-α gene expression significantly increased (P<0.05) as compared to the control (vehicle-treated rats). Treatment with RGE i(500mg/kg) n a significant increase (P<0.05) in CAT, SOD, vitamin C, HDL and a significant decrease (P<0.05) in the level of urea, MDA, PC, TG, TC, VLDL, TNF-α protein, and the gene expression of TNF-α compared with test without treatment group. Histopathological evidence demonstrated that treatment with RGE dose dependent could decrease liver lymphocyte infiltration.

Conclusions: It can be conclude that higher dose of RGE has protective effect against paracetamol induced liver toxicity in rats. The present study suggests that RGE possesses hepatoprotective activity. It could be an effective and promising preventive agent against Paracetamo-induced hepatotoxicity.

Keywords: Paracetamol induced hepatic damage, Red ginger (Zingiber officinale), Rats, Hepatoprotective

FV-059

Study of Ethanolic Extract of Sesuvium Portulacastrum Stem Against Hepatic Fibrosis Induced by Carbon Tetrachloride In Rats

Pardeep Kumar, Sagar Lavenia

Department of Biochemistry, F H M College, India

Aims: Sesuvium portulacastrum (S. portulacastrum), Aizoaceae is commonly known as Sea Purslane. It is used for medicinal purposes due to its choleretic, diuretic, antitumor, antioxidant, antiinflammatory, and hepatoprotective properties. Aim of present study was to investigate the ethanolic extract of Sesuvium portulacastrum stem (EES) as hepaptoprotective agent verse hepatic damages caused by carbon tetrachloride (CCl4).

Methods: Male Wistar albino rats were divided into two equal groups (n=8) and treated as follows: Group 1, kept as control group and orally given saline; Group 2, kept as control positive and were administered daily oral doses of EES extract (200 mg/kg) daily for 21 days and subsequently injected i.p. with CCl4 (50% v/v in olive oil; 1 ml/kg) on the 22nd day. CCl4-induced damages were assessed through liver function markers viz.; alkaline phosphatase, alanine transaminase, aspartate transaminase, and lactate dehydrogenase . Changes in lipid profile were checked by measuring on hepatic glucose homeostasis, lipo-

genic enzymes and lipid metabolism in liver tissues. Antioxidant status was checked by the activities of antioxidant enzymes (superoxide dismutase, glutathione peroxidise),malondialdehyde (MDA)content. The histopathological changes were observed with Masson staining.

Results: Administration CCl4 induced an elevation of serum amino- and glutamyl transferases activities and an increased peroxidation, as well as a decrease of superoxide dismutase and glutathione peroxidise activities in liver. Administration of CCl4 in rats caused significant increase in liver function and lipid profile indicating hepatic damages which were restored by co-administration of EES extract. Cellular and DNA damages in hepatic tissues were caused by CCl4 which shown clear hepatic fibrosis in addition to disturb antioxidant enzyme level. Co-treatment with EES extract regulated these markers of oxidative dysfunctions. EES extracts enhances hepatic glutathione and may contribute to the antioxidant defense of the liver.

Conclusions: It may be conclude that EES extracts have the ability to reverse CCl4 induced hepatic damages. Sesuvium portulacastrum stem has been used to treat alcoholic liver disease, acute and chronic viral hepatitis and toxin-induced liver diseases.

Keywords: Extract of sesuvium portulacastrum, Carbon tetrachloride, Hepatic fibrosis, Rats

7. Nonalcoholic Fatty Liver Disease

FV-060

Effects of Aqueous Extract of Amorphophallus Paeoniifolius Tuber in Treatment of Experimental Steatohepatitis

Seema Devi, Aarti Kashyap

Department of Biochemistry, Raja Mahendra Pratap Post Graduate College, India

Aims: Amorphophallus paeoniifolius known as "Elephant foot yam" is a highly potential tropical tuber crop of Araceae family. The tubers are used as antihaemorrhoidal, haemostatic, expectorant, appetizer, anthelmintic, aphrodisiac and rejuvenating agent. In this study, we were aimed to evaluate the probable effect of the aqueous extract of Amorphophallus paeoniifolius tuber (APT), on experimental nonalcoholic steatohepatitis (NASH).

Methods: To induce NASH, a methionine and choline deficient (MCD) diet was given to Wistar male rats for 8 weeks. After NASH development, MCD-fed rats were divided into two groups: MCD groups received MCD diet and MCD diet plus aqueous extract of APT (250 and 500 mg/kg, each) orally for 4 weeks. Control group was fed a normal diet for 11 weeks. Finally, all rats were sacrificed. Plasma alanine amino transferase (ALT) and aspartate amino transferase (AST) levels were evaluated. In addition, the following hepatic factors were also evaluated: liver histology, malondialdehyde (MDA) and reduced glutathione (GSH) contents and gene expressions of TNF-α and TGF-β.

Results: Histopathological evaluations of the liver samples revealed that treatment with the APT aqueous extract has abated the severity of NASH among the MCD-fed rats. Also, a significant reduction was observed in the sera ALT and AST activities. In addition, the aqueous extract of APT caused dose dependent dramatic reduction in the elevated hepatic TNF-α and TGF-β mRNA and MDA levels along with an increase in the GSH content.

Conclusions: These results suggest that the aqueous extract of APT, beneficial effects on NASH are mainly due to its antioxidant and anti-inflammatory activities.

Keywords: Experimental nonalcoholic steatohepatitis, Amorphophallus paeoniifolius

FV-061

Role of Inulin-Type Fructans on Serum and Hepatic Levels of Triglycerides and Cholesterol in Female Diabetic Rats

Saroj, Ekta Kumari, BH Prakash

Pharmaceutical Sciences, U T University, India

Aims: Liver disease as a major cause of mortality in patients with diabetes mellitus. Inulin-type fructans (ITFs) are a type of fermentable dietary fiber that can confer beneficial health effects through changes in the gut microbiota. Inulin-type fructans based formulations have major significance in insulin delivery system due to their ability to protect the insulin from enzymatic degradation and its efficient inter-epithelial transport. This study was designed to investigate the role of ITFs administration on serum and hepatic levels of triglycerides and cholesterol, in female diabetic rats.

Methods: The Wistar female rats were divided into three groups: Control (C), Diabetic (DM); Diabetic ITFs (DITFs), treated with diet containing 50mg/kg of ITFs. After 5 weeks of experiment, glucose, insulin, gonadal fat and liver mass were evaluated. Serum and liver concentrations of triglycerides and cholesterol concentrations were quantified. Total liver thiols were determined.

Results: After the 5 weeks, experimental groups shower ($P<0.05$): Lower body mass; lower serum insulin; higher food intake and higher blood glucose concentration. DITFs (vs. DM) group showed ($P<0.001$): Lower blood glucose; higher gonadal fat mass; lower serum and hepatic triglycerides; higher hepatic cholesterol and thiols concentrations. DITFs (vs. C) group showed: Similar serum and hepatic triglycerides and hepatic thiols.

Conclusions: Inulin-type fructans alleviated the consequences of the experimental diabetic disease,suggesting protection to hypertriglyceridemia and lipid peroxidation.

Keywords: Inulin-type fructans, Hepatic levels, Diabetes mellitus, Serum

FV-062

The Relationship between Serum Low-Density Lipoprotein (LDL) and Lipid Fraction Area in The Dyslipidemic Rat's Liver after Intervention of Probiotic Beverage from Date Palm and Kefir Milk

Hilmi Ardian Sudiarto, Rafik Prabowo, Miranti Dewi Pramaningtyas

Department of Physiology, Faculty of Medicine, Universitas Islam Indonesia

Aims: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. The metabolic syndrome includes dyslipidemia, has been implicated for the recent increase in hepatocellular carcinoma. Progressed non-alcoholic fatty liver disease (NAFLD) due to dyslipidemia is said to be the primary cause of HCC. The purpose of this research is to know the correlation between LDL and lipid fraction area in the dyslipidemic rat's liver after the intervention of probiotic beverage from date palm and kefir milk.

Methods: This study used a quasi-experimental method with post-test only control group design. This research was conducted in the laboratory of physiology, Universitas Islam Indonesia (UII) for 2 months. This research used male Wistar strain rats (Rattus norvegicus) aged 1-2 months with BW of 100-150 grams. Rats were divided into three groups. All groups were given fed ad libitum for 2 months. In the first month, the first group and third group were given 5 ml/200 gram BW/day quail egg yolks (G1 and G3), while the second group was not given the quail egg yolks (G2). In the second month, the third group was given 5 ml/200 gram BW/day probiotic beverage from date palm and kefir milk. At the end of the research, the rats were terminated.

Results: The mean of LDL (mg/dL) in G1, G2, and G3 consecutively were 29.24 ± 1.50, 70.03 ± 2.04, and 45.92 ± 3.33. The mean of lipid fraction area (%) in G1, G2, and G3 consecutively were 1.00 ± 0.14, 3.03 ± 2.04, and 1.83 ± 0.69. The result showed there is a strong correlation between LDL and lipid fraction area with r 0.721 (strong correlation) and $P<0.05$ ($P=0.012$).

Conclusions: Serum LDL and lipid fraction area in dyslipidemic rat's liver after the intervention of probiotic beverage from date palm and kefir milk have a strong correlation.

Keywords: Probiotic beverage, Date palm, Kefir milk, Low-density lipoprotein, Fatty liver

FV-063

Exploration of the Target Population and Biomarker for Optimizing Red Ginseng Treatment Using Umbrella Trial Design in Non-Alcoholic Fatty Liver Disease Animal Models

Eileen L. Yoon[1], Dae Won Jun[1,2], Hye Young Kim[2], Ju Hee Oh[2], Seong Ji Choi[1], Ji Hyun An[1], Jai Hoon Yoon[1], Kang Nyeong Lee[1], Hang Lak Lee[1], Joo Hyun Sohn[1], Oh Young Lee[1], Byung Chul Yoon[1], Ho Soon Choi[1]

[1]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine; [2]Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science and Engineering, Seoul, Korea

Aims: There are currently no approved drugs for non-alcoholic fatty liver disease (NAFLD) so far. Response rates of drugs under clinical trials are less than 50%. Exploration of the biomarkers assessing treatment response and the target population who may most benefit from the candidate drugs is the urgent unmet need to maximize the efficacy of NAFLD treatment. We aimed to figure out the saponin responding NAFLD models and related biomarkers.

Methods: For the umbrella NAFLD trial design, NAFLD animal models were induced by High Fat (HF), Western Diet (WD), and Methionine/Choline Deficient Diet (MCD) for 20 weeks (4 weeks for MCD). Pre- and post- study liver biopsy was performed. Saponin was treated in these NAFLD animal models. NAFLD activity score (NAS) was evaluated and mRNA sequencing analysis was performed to discover biomarkers for predicting treatment response.

Results: NAS was significantly increased in all the NAFLD models compared to that of normal control mice. Saponin treatment decreased NAS in WD model, but not in the HF and MCD models. NAS was not decreased in saponin untreated groups in all NAFLD models. In the responder group to saponin treatment on WD model, lipid/triglyceride/fatty acid metabolic processes were significantly changed. HAMP1 expression was significantly lower in the responder from pre-study biopsy, and higher in responder from post-study biopsy.

Conclusions: Among various NAFLD phenotypes, saponin treatment was effective in the WD induced NAFLD model. Hepatic HAMP1 expression might be used as biomarker for saponin treatment in NAFLD.

Keywords: Non alcoholic fatty liver disease, Biomarker, Saponin, Hepcidin

FV-064

Protective and Therapeutic Effects of Trigonella Foenum Graecum Seed Extract in Non-Alcoholic Fatty Liver Disease in Rat

Shivani Verma, NK Tiwari

Department of Biological Sciences, A Central University, India

Aims: Trigonella foenum-graecum (Fenugreek) is found to have many active bio molecules. It has a long history of use in folk medicine where, in India and South Asia use the plant to treat diabetes, various infections and kidney problems. We designed this study to investigate protective and therapeutic effect of ethanolic extract of Trigonella foenum graecum seed (TSP) on non-alcoholic fatty liver (NAFLD) induced by high fat diet in rat models.

Methods: NAFLD was induced by High Fat Diet+fructose (HFD), 64 Wistar rats were divided to 8 groups including control,

HFD, HFD+diet change, HFD+diet change+TSP 200 mg/kg, co treatment of HFD+TSP 100, 200 and 400 mg/kg, and normal diet+TSP 400 mg. TSP was administered orally. Samples were then taken to observe pathological changes of the liver tissue (HE staining); changes in the fat metabolism pathway, alterations in liver function, i.e. serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity; and differences in tumor necrosis factor alpha expression in the liver tissue.

Results: The diet change from high fat to low fat ameliorated liver damage. However, consumption of TSP (100 & 200 mg/kg) caused significant reduction in the level of all examined liver biomarkers, that showed TSP can restore the hepatocyte damage due to HFD. TSP treatment showed a protective effect which was more prominent in the animals treated with the 200 mg/kg TSP. The administration of TSP caused increased antioxidant status and decreased lipid peroxidation in treated animals.

Conclusions: Accordingly, TSP have both therapeutic and protective effect for NAFLD and may be a potential candidate for further assessments in clinical studies.

Keywords: Non-alcoholic fatty liver, Rat models., Trigonella foenum-graecum seed, High fat diet

FV-065

Pharma-Biotics, Strain X, Inhibits Inflammation of Non-Alcoholic Fatty Liver Disease

Ye Rin Choi, Hyeong Seop Kim, Hee Jin Park, Ji Ye Hyun, Jung A Eom, Min Kyo Jeong, Byeong Hyun Min, Sang Jun Yoon, Satya Priya Sharma, Haripriya Gupta, Yoseph Asmelash, Raja Ganesan, Sung Min Won, Eun Ju Park, Mi Ran Choi, Dong Joon Kim, Ki Tae Suk

Institute for Liver and Digestive Disease, Hallym University College of Medicine, Chuncheon, Korea

Aims: The interaction between liver and microbiota, gut-liver axis, is involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Considering strain X is increased in patients with hepatitis patients or diabetes, it can be postulated that it rises as a compensatory for suppression of the disease. We evaluate the effects of strain X in the prevention of NAFLD in mice.

Methods: 6 weeks male C57BL/6J mice were divided into 6 groups (n=8/group; Normal, Western diet [60% kcal fat diet], and 4 Western diet with strains [strain X, Lactobacillus lactis, and L. rhamnosus GG $2*10^9$ CFU/g] or ursodeoxycholic acid (UCDA) groups for 12 weeks. We measured liver/body weight ratio, liver pathology, serum level, cytokine level, and metagenomics by 16s rRNA-sequencing. To examine the effect of strain X, we used LPS-induced RAW 264.7 cells, treated strain X culture supernatant.

Results: Strain X, L. lactis, L. rhamnosus GG, and UDCA (3.4±0.9) supplementation significantly ameliorate Western diet-induced increase in liver/body weight ratio, NAFLD activity score, and serum liver enzymes. Strain X supplementation improved the elevated level of pro-imflammatory cytokines and chemokines (tumor necrosis factor-α, interferon-γ, chemokine ligand [CXCL]3, CXCL4, and CXCL10). Mice stool metagenomics analysis showed increased gut microbial diversity at species level in strain X supplementation group compared to other groups. Moreover, 4 bacterial species are exclusively found in strain X supplemented group only. The expression of cytokine and chemokine levels in LPS-stimulated RAW 264.7 cells was significantly reduced in strain X group.

Conclusions: Strain X effectively improved the inflammation of NAFLD and it can be a promising target in the therapeutical approach to NAFLD.

Keywords: Non-alcoholic fatty liver disease, Gut-microbiome, Probiotics, Metabolite

FV-066

The Therapeutic Effect of Lactobacillus Plantarum on Metabolic Phenotypes in Non-Alcoholic Fatty Liver Disease Mice Model

Dong Yun Kim[1,2], Jae Seung Lee[3,4], Heon Yung Gee[1,2], JunYong Park[3,4]

[1]Department of Medicine, Physician-Scientist Program, Yonsei University Graduate School of Medicine, Seoul, Korea; [2]Department of Pharmacology, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul 03722, Republic of Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Lactobacillus is considered a potential probiotic and has shown therapeutic potential for several liver diseases including NAFLD. However, it is not known how dietary supplementation of L. plantarum has favoring effect on liver. Therefore, we investigated the therapeutic potential of L. plantarum supplementation on NAFLD in a mouse model and aimed to elucidate its mechanism.

Methods: We used the choline-deficient high fat diet (CD-HFD)-induced murine model of NAFLD that recapitulate key features of human metabolic syndrome. To induce NASH status, C57BL/6N mice were fed a CD-HFD for 30 weeks. Then these mice were divided into three groups: vehicle, L. plantarum (10^9 CFU/day), and empagliflozin, selective SGLT2 inhibitor (10 mg/kg/day). After 12 weeks of treatment, mice were sacrificed and subjected to blood measurements, and liver tissue for RNA isolation, lipid measurements, histology, and stool for microbiome analysis.

Results: L. plantarum and empagliflozin treatment significantly improved several metabolic phenotypes such as body weight gain, insulin tolerance, and hepatic lipid contents compared to vehicle group, respectively. However, the histological NAFLD activity score (NAS) was more improved in the L. plantarum group (3.0, P=0.0286) than in the empagliflozin group (4.0, P=0.0591) compared to vehicle group (5.5). RNA-sequencing analysis revealed that administration of L. plantarum downregulated genes related to inflammation such as T cell differentiation and

leukocyte activation in liver. In the microbial analysis of stool samples, the elevated Firmicutes-to-Bacteroidetes ratio in the vehicle group (21.97) was decreased in the L. plantarum group (0.86). Furthermore, disrupted intestinal epithelial barrier function was restored in L. plantarum group and elevated serum endotoxin level was significantly reduced in L. plantarum group compared to vehicle group.

Conclusions: Our data demonstrated that administration of L. plantarum can improve NAFLD associated phenotypes by altering gut microbiome composition and decreasing serum endotoxin levels.

Keywords: NAFLD, Lactobacillus, Probiotic, NASH

FV-067

Protective Effects of Resveratrol on Liver Fibrosis an a Non-Alcoholic Steatohepatitis (NASH) Rodent Model

Gireesh Dayma, Tejpal Singh

Applied Sciences, Manipal University, India

Aims: Nonalcoholic steatohepatitis (NASH) is a major form of chronic liver disease and is becoming the leading indication for liver transplantation. Resveratrol, a natural polyphenol, possesses antioxidant, anti-inflammatory, and anti-apoptotic properties. As a natural food ingredient, numerous studies have demonstrated that resveratrol possesses a very high antioxidant potential. We investigated the effects of resveratrol in preventing liver fibrosis in a rodent model of NASH.

Methods: Adult Sprague-Dawley rats were fed a choline-deficient high-fat diet and exposed to diethylnitrosamine for 6 weeks. The NASH group (n=10) received vehicle and the resveratrol group (n=10) received 10 IU/kg/day by gavage. A control group (n=4) received only standard diet and vehicle. Following treatment, animals were sacrificed and liver tissue was collected for histologic examination, mRNA isolation, lipoperoxidation analysis and analysis of mitochondrial function. Genes related to fibrosis (MMP9, TIMP1, TIMP2), oxidative stress (HSP60, HSP90, GST), and mitochondrial biogenesis (PGC1α) were evaluated by real-time quantitative polymerase chain reaction (RT-qPCR). Liver mitochondrial oxidation activity was measured by a polarographic method, and cytokines by enzyme linked immunosorbent assay (ELISA).

Results: Resveratrol treatment restored mitochondrial function and reduced lipoperoxidation levels, collagen deposition by nearly 76% compared to the NASH group. Resveratrol upregulated PGC1α and MMP9 and reduced TIMP1 and TIMP2 mRNA and IL-6 and IL-10 protein expression. There were no significant differences in HSP60, HSP90 and GST expression.

Conclusions: Resveratrol modulated PGC1α expression, improved mitochondrial respiration and prevented collagen deposition. It may, therefore, be useful in the treatment of liver fibrosis in NASH.

Keywords: Nonalcoholic steatohepatitis, Resveratrol, Rodent model, Lipoperoxidation

FV-068

The Effect of Synbiotic Drink From Kefir Milk And Jicama Concentrate (Pachyrhizus erosus) on Malondialdehyde Level and Superoxide Dismutase Activity In The Liver Tissue of The Hyperlipidemic Rats (Rattus norvegicus)

Rafik Prabowo[1], Saosanti Mariana[2]

[1]Clinical Program of Medicine, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia; [2]Chemical Engineering, Faculty of Industrial Technology, Universitas Islam Indonesia, Yogyakarta, Indonesia

Aims: Hyperlipidemia condition can makes liver cell damage and can be marked by an increase of malondialdehyde (MDA) levels and a decrease of superoxide dismutase (SOD) activity. Synbiotics is a product that contains prebiotics and probiotics. One source of prebiotic is jicama and probiotic is kefir milk. The aim of this research is to know the effect of synbiotic drink from kefir milk and jicama concentrate on MDA level and SOD activity in the liver tissue of the hyperlipidemic rats.

Methods: This research used 25 rats divided into 5 groups (K+, K-, P1, P2, and P3). Group of K+, P1, P2, P3 were given quail egg yolk for the first 4 weeks. For the next 4 weeks, K+ and K- group were only given fed ad libitum. Group of P1, P2, and P3 were given synbiotic with the formulation of P1: 85% kefir milk (K) and 15% jicama Concentrate (J), P2: 75% K, 25% J, and P3: 65% K, 35% J. The dose of quail egg yolks and synbiotic was 5 ml/200 grBW. In the end, the animal model was terminated to get liver organs to measure the MDA level and SOD activity.

Results: Mean of MDA level (nmol/gr) were 11.8±0.17 (K+), 2.5±0.12 (K-), 7.7±0.18 (P1) 5.7±0.10 (P2), 4.1±0.09 (P3). The result showed significant differences between all groups (P<0,001). Mean of SOD activity (%) were 21.43±2.52 (K+), 71.43±3.91 (K-), 30.71±1.53 (P1) 50.35±2.84 (P2), 63.93±1.53 (P3). The result showed significant differences between all groups (P<0,001) except between K+ with P1 and K- with P3 (P>0.05).

Conclusions: The intervention of synbiotic drink from kefir milk and jicama concentrate significantly decrease MDA level in all groups and increase SOD activity in the P2 and P3 groups, with the P3 group clinically significant.

Keywords: Synbiotic, Kefir, Jicama, Hyperlipidemia

FV-069

Bifidobacterium Breve and Bifidobacterium longum Attenuate Western Diet Induced Nonalcoholic Fatty Liver Disease in Mice

Sang Jun Yoon, Yoseph Asmelash, Raja Ganesan, Haripriya Gupta, Sung Min Won, Eun Ju Park, SatyaPriya Sharma, Hyeong Seop Kim, Ye Rin Choi, Byeong Hyun Min, Min Kyo Jeong, Ji Ye Hyun, Jung A Eom, Hee Jin Park, Dong Joon Kim, Ki Tae Suk

Institute for Liver and Digestive Disease, Hallym University College of Medicine, Chuncheon, Korea

Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of liver disease worldwide. However, definitive medical treatments have not been established apart from lifestyle modifications. Probiotics can be a lucrative choice due to its availability, cost, and absence of severe side effects. Our previous study demonstrated that treatment with probiotics ameliorates western diet-induced NAFLD in mice. This study aimed at elucidating the underlying mechanisms by which western diet-induced NAFLD is associated with gut microbiome and exploring the effects of probiotics from the gut metagenomic and metabolomic profiles perspective.
Methods: Six weeks old C57BL/6J mice were fed the western diet with or without probiotics for 8 weeks. Two probiotic strains, Bifidobacterium breve, and B. longum were administered at 10^9 CFU/day. We compared liver/body weight ratios, hepatitis score, NAFLD activity score (NAS) and performed liver function tests. We also conducted histopathological examination (H&E staining) of liver tissue, fecal metagenomics and metabolomics analysis, quantitative PCR analysis of mRNA levels of markers for inflammation, lipogenesis, and β-oxidation in the liver.
Results: Western diet-induced full spectrum NAFLD. Metagenomic analysis revealed noticeable alterations of gut microbiota where a decrease in Bacteriodetes and an increase in Proteobacteria and Firmicutes phyla were observed. Treatment with both probiotic strains resulted in significant reduction in liver enzymes, liver/body weight ratio and improved liver histological parameters compared with untreated group. It effectively modulated gut microbiota mainly by enhancing relative abundance of Bacteriodetes thereby resulting in visible changes in cecal short-chain fatty acid and indole metabolites levels. Moreover, probiotic Bifidobacterium downregulated expression of hepatic steatosis and inflammation biomarkers while upregulating the β-oxidation inducing molecule peroxisome proliferator-activated receptor-alpha (PPARα).
Conclusions: Western diet induces NAFLD through dysbiosis caused by reduction in Bacteriodetes and an increase in Proteobacteria and Firmicutes phyla. Probiotic Bifidobacterium ameliorates NAFLD through modulation of gut microbiota resulting in reduced hepatic inflammation and steatosis.
Keywords: Nonalcoholic fatty liver disease, Western diet, Gut microbiota, Probiotics, Metagenomics

FV-070

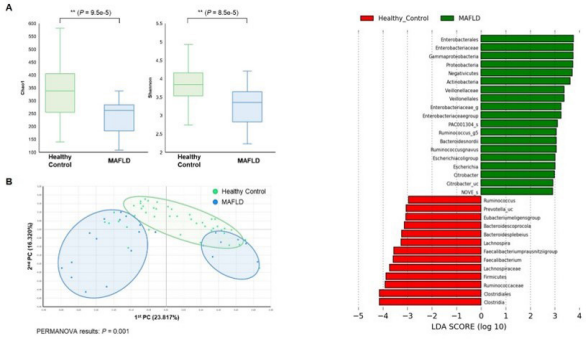
Characterization of Gut Microbiome in Korean Patients with Metabolic Associated Fatty Liver Disease

Joo Hyun Oh[1†*], Je Hee Lee[2*], Jongsik Chun[2], Min Seok Cho[2], Wonseok Kang[1,3], Joon Hyeok Lee[1], Yeup Yoon[3]

[1]Department of Medicine, Nowon Eulji Medical Center, Eulji University School of Medicine; [2]ChunLab, Inc., Seoul, Korea; [3]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[†]Current affiliation: Department of Medicine, Eulji General Hospital, Eulji University School of Medicine, Seoul, Republic of Korea

Aims: Metabolic associated fatty liver disease (MAFLD) is a new concept that the presence of both fatty liver and metabolic abnormality are necessary for diagnosis. Several studies have reported that altered gut microbiome is closely associated with metabolic diseases and non-alcoholic fatty liver disease. However, the studies on MAFLD population are scarce. This prospective study aimed to identify differences in gut microbiome between patients with MAFLD and healthy controls in Korean population.
Methods: In this study, patients with MAFLD and age, sex-matched healthy controls were included, and their stool samples were collected. Taxonomic composition of gut microbiota was analyzed using 16S ribosomal ribonucleic acid pyrosequencing.
Results: Twenty-two MAFLD patients and 44 healthy controls were included. Taxonomic diversity was lower in patients with MAFLD in the aspect of alpha and beta diversity. The differences were also found at phylum, class, family, and genus levels between the two groups. Phylum Proteobacteria, family Enterobactereriaceae, genus Citrobacter abundance was significantly increased and genus Faecalibacterium was significantly decreased in patients with MAFLD. In addition, butyrate- producing bacteria were decreased and ethanol-producing bacteria were increased in patients with MAFLD.



Conclusions: The composition of gut microbiome was different between MAFLD and healthy controls in Korean population. This could offer potential targets for therapeutic intervention in MAFLD.
Keywords: Gut microbiome, Metabolic associated fatty liver disease, Non-alcoholic fatty liver disease, Short-chain fatty acids

FV-071

The Role of the Biliary Microbiota in Hepatic Steatosis

Min-Su Park, Bum Soo Kim, Sang Mok Lee

Department of Surgery, Kyunghee University

Aims: Hepatic steatosis is a multifactorial condition that is often observed in obese patients and is a prelude to non-alcoholic fatty liver disease. The current changes in biliary flora are thought to be involved in the formation of many liver diseases. There-

fore, we want to investigate whether the hepatic steatosis has a certain correlation with biliary microecology, and to detect specific strains.

Methods: All participants underwent three-phase CT examinations to identify the hepatic steatosis. Hepatic steatosis were determined using the unenhanced CT examination: a liver-spleen attenuation difference of greater than 10 HU and the absolute attenuation of the liver less than 40 HU. A total of 52 adults were enrolled in this study, including 10 hepatic steatosis subjects and 42 controls. Bile samples were collected and analyzed with metagenomics. We used Shannon index to reflect the alpha diversities of microbiota. Wilcoxon rank sum test and Kruskal-Wallis test were performed to evaluate alpha diversities between groups. At last, the differences of microbiota composition between hepatic steatosis subjects and healthy controls were assessed by Kruskal-Wallis test.

Results: Significant differences in microbiota composition between two groups have been observed. Deep sequencing of microbiota revealed high abundance of streptococcus in hepatic steatosis group, comparing with the control group. Compared to the control group, in hepatic steatosis group, the abundance of Veillonella, Barnesiella, Megasphaera, Parabacteroides were significantly reduced. There was no significant difference in terms of alpha diversity between two groups.

Conclusions: Significantly differences were observed in biliary microbiota composition of hepatic steatosis group in comparison to the control group.

Keywords: Hepatic steatosis, Biliary, Microbiota, Metagenomics

FV-072

Association with Physical Activity with the Risk of Sarcopenia in Patients with Nonalcoholic Fatty Liver Disease: A Nationwide Cohort Study

Ho Soo Chun[1,2], Minjong Lee[1,2], Tae Hun Kim[1,2], Seung Up Kim[3,4]

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Previous studies reported that reduced physical activity was a significant predictor of liver-related mortality in general population. We investigated the association between physical activity and the risk of sarcopenia in patients with nonalcoholic fatty liver disease (NAFLD).

Methods: We enrolled patients with NAFLD from the Korean National Health and Nutrition Examination Surveys database from 2008 and 2011 with cross-sectional study design. The level of physical activity based on self-reported questionnaire about weekly leisure-time physical activity (metabolic equivalent task [MET]-min) was categorized into 0 (totally sedentary), <500, 500–1,000, and ≥1,000 METs-min/week. Sarcopenia index (total appendicular skeletal muscle mass [kg]/body mass index (kg/m^2]) was calculated using dual-energy X-ray absorptiometry. Sarcopenia was defined as sarcopenia index <0.789 in men and <0.521 in women.

Results: A total of 3,099 patients with NAFLD were recruited. Of these, 365 (11.8%) patients with NAFLD had sarcopenia. The prevalence of sarcopenia significantly decreased as the amount of physical activity increased (all P trend<0.05). When the study population was stratified according to metabolic factors, physical activity was significantly associated with a decreased risk of sarcopenia among all of subgroups with obesity, central obesity, metabolic syndrome, insulin resistance and diabetes (all P trend<0.05). In multivariable logistic regression analyses, physical activity was an independent negative risk factor for sarcopenia (<500 MET-min/week, odds ratio [OR]=0.87, 95% CI=0.60–1.27, *P*=0.48; 500–1,000 MET-min/week, OR=0.66, 95% CI=0.44–0.99, *P*=0.047; 1,000–1,500 MET-min/week, OR=0.59, 95% CI=0.42–0.82, *P*=0.002; compared with totally sedentary). In subgroup of patients with obesity, central obesity, metabolic syndrome, insulin resistance and diabetes, physical activity more than 1,000 MET-min/week was significantly associated with a lower risk of sarcopenia (OR 0.67, 0.60, 0.56, 0.57, and 0.37, respectively, all *P*<0.05).

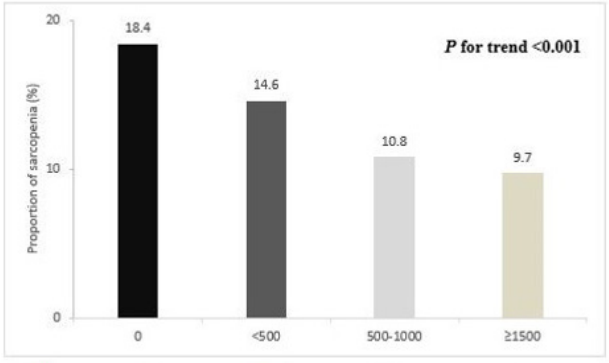


Figure. Prevalence and relative risk of sarcopenia according to physical activity-related energy expenditure.

Table. The odds ratio of sarcopenia according to physical activity-related energy expenditure

Variables	Unadjusted			Model 1			Model 2		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Stratification by MET									
0	1.000 (reference)			1.000 (reference)			1.000 (reference)		
<500	0.757	0.532-1.076	0.121	0.887	0.617-1.276	0.518	0.873	0.602-1.267	0.476
500-1000	0.534	0.361-0.789	0.002	0.653	0.437-0.977	0.038	0.660	0.438-0.995	0.047
≥1000	0.473	0.346-0.647	<0.001	0.583	0.421-0.806	0.001	0.586	0.421-0.817	0.002

Model 1 = age, and gender (age was applied as a categorical variable with a median cut-off value of 56).

Model 2 = model 1 + obesity, central obesity, hypertension, diabetes, total cholesterol, triglyceride, AST, ALT, gamma-GTP, smoking, alcohol, CKD, and malignancy.

MET, metabolic equivalent task; AST, aspartate aminotransferase; ALT, alanine aminotransferase; gamma-GTP, gamma-glutamyl transpeptidase; CKD, chronic kidney disease.

Conclusions: The increased physical activity was significantly associated with a lower risk of sarcopenia in patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, Physical activity, Sarcopenia, Metabolic factors

FV-073

The Genetic Variation in PNPLA3 and Sodium Intake are Associated with the Risk of Non-Alcoholic Fatty Liver Disease in the Korean Genome and Epidemiology Study

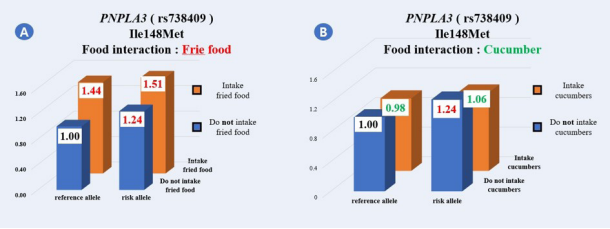
Sooyeon Oh[1], Jooho Lee[2*], Da-Hyun Park[3], Su-Kyung Chun[1], Sang Woon Choi[1], Kyung-Won Hong[3]

[1]Department of Gastroenterology, Chaum Life Center, CHA University School of Medicine, Seoul, Korea; [2]Department of Gastroenterology and Hepatology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea; [3]Theragen Bio Co. Ltd., Suwon, Korea

Aims: Many genetic studies of non-alcoholic fatty liver disease (NAFLD) suggested the patatin-like phospholipase domain-containing 3 (PNPLA3) gene as the major candidate gene. NAFLD is affected by genetic and environmental factors interaction, therefore, we tested the interaction between the PNPLA3 rs738409 and food frequency habits using a large Korean cohort (KoGES: Korean Genome and Epidemiology Study cohort) dataset obtained from Korea Biobank database.

Methods: We obtained a large genome and epidemiology cohort (KoGES, n =72,299) from Korea BioBank. NAFLD can be diagnosed when the individuals have a historical medical record of fatty liver disease without alcohol overdrinking. The criteria of alcohol overdrinking were > 210 g/week for male, and > 140 g/week for female. For dietary assessment, a semi-quantitative food frequency questionnaire was developed for the KoGES. The PNPLA3 rs738409 SNP was assessed for NAFLD risk by x^2 tests.

Results: From the subjects with available SNP data (n = 61,623), total 2,950 NAFLD cases were confirmed after excluding cases with alcohol overdrinking. Finally, 2,950 NAFLD and 12,907 control cases without other medical diseases were enrolled in our study. In the univariate analysis of x^2 test, the presence of PNPLA3 rs738409 G allele showed a significant association with the occurrence of NAFLD (Adjusted OR = 1.24; P=4.05×10^{-7}). Moreover, in multivariate logistic regression analyses with adjusting for age, sex and smoking, PNPLA3 rs738409 G allele still remained as an independent risk factor for NAFLD (OR = 1.223; P=1.75×E^{-10}). Interestingly, for the nutritional impact on a genetic susceptibility of NAFLD, high sodium (more than 2 g/day) and kimchi intake decreased the risk of NAFLD (HR = 0.77 and 0.68, respectively) especially among the high risk allele (PNPLA3 rs738409 G) group (P<0.0001).



Conclusions: Using the KoGES database, we can find significant association between PNPLA3 rs738409 G allele and NAFLD occurrence among Korean population. Further we can find the concurrent impact of sodium (or Kimchi) intake on a genetic susceptibility of NAFLD. Future basic studies will be needed to reveal the exact interaction between genetic and nutritional factors on the development of NAFLD.

Keywords: Single nucleotide polymorphism, Korean, PNPLA3, Non-alcoholic fatty liver disease, Sodium

FV-074

Liver Biomarker and Body Mass Index Level in Adults with Non-Alcoholic Steatohepatitis after Probiotics Intervention: A Meta-Analysis of Randomized Controlled Trial

Mochamad Afifudin

Department of Internal Medicine, Universitas Islam Indonesia

Aims: Non-Alcoholic Steatohepatitis (NASH) is a chronic liver disease characterized by macrovesicular hepatic fat accumulation in a total of more than 5% of the hepatocyte. Untreatable NASH may develop cirrhosis and hepatocellular carcinoma. The non-pharmacological approach such as probiotic has developed as the adjuvant therapy of NASH. It can reduce the number of lipid fraction area and has antioxidant properties. The aim of this study was to perform a meta-analysis about the effect of the probiotic intervention on liver biomarker and body mass index of non-alcoholic steatohepatitis patients.

Methods: The Meta-analysis was performed by using Review Manager 5.4 software. The article searched by using the PubMed database. The inclusion criteria were the article written in English, published in the last 10 years, and the article with randomized controlled trial study design. The exclusion criteria were abstract with no full-text article, book or review article, and incomplete trial. Several data which extracted and analyse are including body mass index (BMI), alanine transferase (ALT), and aspartate transferase (AST).

Results: Four randomized clinical controlled trials with 219 total number of participants were included. Lactobacillus sp. are the most common use as probiotic intervention followed by Bifidobacterium sp. and Streptococcus sp. The statistical analysis showed that probiotic intervention has significantly decreased BMI (random effect, MD -3.63; 95% CI -7.04- -0.02, P<0.00001). The level of ALT was significantly lower in the probiotic group than the control group (random effect, MD -29.46; 95% CI -46.65 - -12.27, P<0.00001). The probiotic group has also a lower AST level than the control group (random effect, MD -9.11; 95% CI -15.26 - -2.95, P=0.07).

Conclusions: Probiotic intervention can reduce body mass index and liver biomarker including alanine transferase and aspartate transferase in adults patient with non-alcoholic steatohepatitis.

Keywords: Non-alcoholic steatohepatitis, Probiotic, Body mass index, Alanine transferase, Aspartate transferase

FV-075

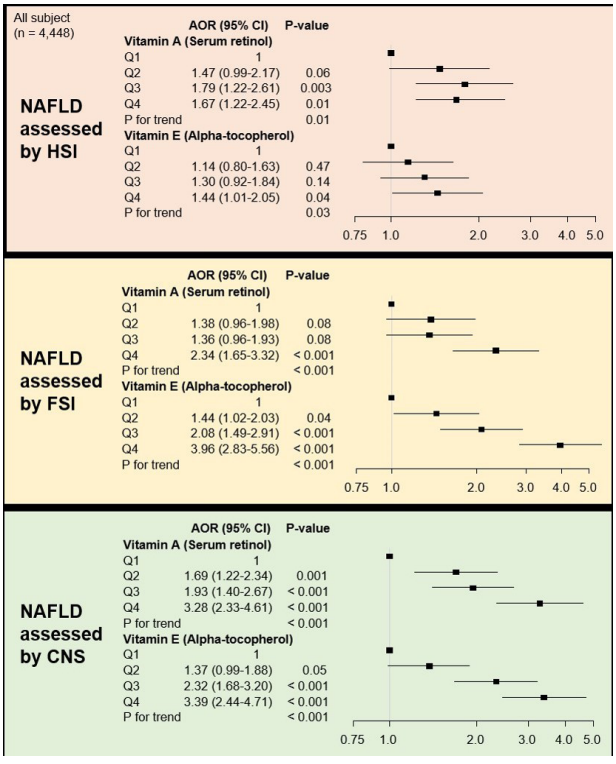
Dynamics of Serum Retinol and Alpha-Tocopherol Levels in Accordance with Non-Alcoholic Fatty Liver Disease Status

Dongsub Jeon[1], Minkook Son[2], Ju Hyun Shim[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, Republic of Korea

Aims: There are little data on the association between micronutrients in the blood and non-alcoholic fatty liver disease (NAFLD). To investigate clinical implications of such relationship, we sought to identify the difference in serum levels of vitamins A and E according to NAFLD and its status in a large public dataset of Korean populations

Methods: This study is a cross-sectional study using data of 4,488 subjects older than 20 years from the seventh Korea National Health and Nutrition Examination Survey. No participants had chronic hepatitis, liver cirrhosis, cancer, and alcohol abuse. They were equally divided into quartiles based on serum retinol and alpha-tocopherol levels. Presence of NAFLD was defined as the use of three indexes: Hepatic Steatosis Index, HSI; Framingham Steatosis Index, FSI; and Comprehensive NAFLD Score, CNS. NAFLD fibrosis was assessed using FIB-4 or BARD calculation. Statistical comparisons were based on chi-squared test and multivariable-adjusted logistic regression.



Results: Serum levels of retinol and alpha-tocopherol were positively associated with increased risks of NAFLD defined by HSI, FSI, and CNS: adjusted odds ratios and 95% confidence intervals for the associations between the quartiles of serum retinol and alpha-tocopherol levels and presence of NAFLD are presented in Figure 1. A subset analysis of NAFLD subjects showed that serum retinol deficiency was significantly correlated with advanced fibrosis assessed by FIB-4 and BARD. In contrast, serum alpha-tocopherol levels did not differ between individuals with and without advanced fibrosis by either criterion.

Conclusions: We found that while circulating concentrations of both retinol and alpha-tocopherol had positive relationships with the existence of NAFLD, fibrotic sequelae was affected only by serum retinol levels. Our findings could provide a micro-nutritional insight into the NAFLD patient care.

Keywords: NAFLD, Micronutrient, Vitamin A, Vitamin E

FV-076

FIB-4-Based Algorithm for Screen Significant Hepatic Fibrosis in Diabetes with or without Fatty Liver in Primary Care Setting

Eileen L. Yoon[1], Dae Won Jun[1,2], Su Hyun Park[2], Seong Ji Choi[1], Jai Hoon Yoon[1], Kang Nyeong Lee[1], Hang Lak Lee[1], Oh Young Lee[1], Byung Chul Yoon[1], Ho Soon Choi[1]

[1]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine; [2]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine

Aims: Apart from the NAFLD patients, the effectiveness of FIB-4 or NFS based screening in all diabetic patients regardless of fatty liver status is unknown. We investigated cost-effectiveness of screening algorithm in diabetes in primary care clinic.

Methods: A total of 1,288 who visited the health examination center and underwent the magnetic resonance elastography (MRE) were enrolled. The performance of FIB-4 and NFS was compared in diabetes patients. And diagnostic performance and cost-effectiveness according to screening algorithm were evaluated in three kinds of target population (diabetes, sonographic fatty liver, and elevated liver enzyme group). If FIB-4 value (≥1.3) falls into intermediate or high-risk group, FIB-4 was followed by transient elastography. Lifestyle modification and monitoring prescribed to suspected significant hepatic fibrosis if hepatic fibrosis suspected in transient elastography.

Results: The prevalence of significant fibrosis (≥F2) was 3.9% in total cohort, 5.9% in patients with sonographic NAFLD patents, and 14.2% in diabetes. Prevalence of significant fibrosis was considerable in patient with diabetes without fatty liver (6.7%). Area under the curve of the receiver operating characteristic (AUROC) of FIB-4 and NFS for significant fibrosis was similar in sonographic NAFLD subjects. But AUROC was of FIB-4 was slightly higher than NFS in diabetes without statistical significance (0.688 vs. 0.582, *P*=0.05). Application of FIB-4 based algorithm for detecting significant fibrosis in diabetes showed comparable positive predictive value (31.4% vs. 7.6%)

and sensitivity (22.0% vs. 18.0%) compared to sonographic NAFLD without decreasing NPV (96.9% vs. 96.5%). FIB-4 based algorithm in diabetic patients reduced unnecessary referral rate by 23.8% compared to NAFLD subjects. One-time FIB-4 based screening and lifestyle modification showed cost-effectiveness ratios (ICER) of 21,849 $USD per quality-adjusted life year.
Conclusions: FIB-4 based transient elastography screening algorithm for significant hepatic fibrosis in patients with diabetes was cost effective.
Keywords: Non-alcoholic fatty liver, Algorithm, Sgnificant fibrosis, FIB-4, Referral pathway

FV-077

Gamma-Glutamyl Transpeptidase Dynamics as a Biomarker for Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

Yeonjung Ha (YH), Young Eun Chon (YEC), Mi Na Kim (MNK), Joo Ho Lee (JHL), Seong Gyu Hwang (SGH)

Department of Gastroenterology, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do 13496, South Korea

Aims: Abnormal lipid profiles and liver biochemistry are common in non-alcoholic fatty liver disease (NAFLD). However, it is unclear whether changes in blood tests are associated with advanced fibrosis.
Methods: Patients diagnosed with NAFLD between 2009 and 2017 at a health check-up were included. The changes in blood tests were calculated using the following formula: [(value at 6-month–value at baseline)/value at baseline]×100. The endpoint was advanced fibrosis determined by the NAFLD fibrosis score, calculated every year from the index date until 2019. Cox proportional hazards models were used to identify factors predicting advanced fibrosis.
Results: After a median follow-up of 31.7 (19.4–50.8) months, advanced fibrosis occurred in 64 (6.3%) of 1021 patients. The advanced fibrosis group was older and had a higher prevalence of obesity, hypertension, or diabetes (Ps<0.05). Gamma-glutamyl transpeptidase (GGT) levels (72.9 vs. 51.1 IU/L; *P*=0.23) and ΔGGT (+6.0% vs. -6.9%; *P*=0.06) were higher in the advanced fibrosis group. After multivariate adjustment, ΔGGT (hazard ratio [HR] 1.03; *P*<0.001), age, and platelet counts were significantly associated with advanced fibrosis. The positive ΔGGT group showed a higher incidence of advanced fibrosis than the negative group (*P*=0.01). The 1-standard deviation increment in ΔGGT showed a significant association with advanced fibrosis both in statin users (HR, 1.35) and in non-users (HR, 1.31; Ps<0.001). The restricted cubic spline model identified a positive correlation between ΔGGT and the NAFLD fibrosis scores (*P*<0.001). The sensitivity analysis showed consistent results.
Conclusions: ΔGGT calculated at 6 months following NAFLD diagnosis is associated with advanced fibrosis.
Keywords: Gamma-glutamyl transpeptidase, Non-alcoholic fatty liver disease, Advanced fibrosis, Apolipoprotein

FP-078

Liver Fibrosis in Patients with Metabolic Dysfunction-Associated Fatty Liver Disease

Won Sohn[1], Heon-Ju Kwon[2], Hong Joo Kim[1], Byung Ik Kim[1], Yong Kyun Cho[1]

[1]Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: The new concept of fatty liver disease introduced recently is based on metabolic dysfunction. This study aimed to evaluate liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD).
Methods: A cross-sectional study of 967 Korean patients with MAFLD involved a cohort from a health screening program during the years 2015-2018. The patients were classified into four MAFLD subgroups: Group 1 (overweight); Group 2 (obese); Group 3 (lean/normal weight with metabolic abnormalities); and Group 4 (diabetes). Liver fibrosis was assessed based on liver stiffness measurement (LSM) value using 2-dimensional real-time magnetic resonance elasstography (MRE). Significant fibrosis was defined as LSM ≥2.97 kPa. We investigated differences in liver fibrosis according to MAFLD subgroup classification and determined the risk factors for significant fibrosis in MAFLD.
Results: The mean age was 50.8 years and 869 patients (90%) were male. The mean value of LSM in MRE was 2.48 ± 0.47 kPa. Significant fibrosis was observed in 66 out of 967 patients (6.8%). The proportion of significant fibrosis in MAFLD group 1, group 2, group 3, and group 4 was 1.3%, 5.5%, 6.4%, and 18.9%, respectively (*P*<0.001). Multivariable analysis indicated that the risk factors for significant fibrosis were serum ferritin ≥300 ng/mL (odds ratio [OR], 1.96; 95% CI=1.10–3.49; *P*=0.023), FIB-4 ≥1.3 (OR, 2.97; 95% CI=1.68–5.24; *P*<0.001), homeostatic model assessment of insulin resistance (HOMA-IR) ≥2.0 (OR, 2.53; 95% CI=1.31–4.88; *P*=0.011), metabolic syndrome (OR, 2.42; 95% CI=1.26–4.65; *P*=0.006), and MAFLD group 4 (OR, 6.93; 95% CI=1.96–24.51; *P*=0.003).
Conclusions: Liver fibrosis differed according to MAFLD subgroup classification. Metabolic dysfunction is an independent risk factor for significant fibrosis in patients with fatty liver. Liver fibrosis in MAFLD depends on metabolic abnormalities rather than the etiology of liver disease.
Keywords: Fatty liver, Metabolic dysfunction, Liver fibrosis

FP-079

The FIB-4 Index Is an Useful Predictor for the Development of Hepatocellular Carcinoma in Patients with Coexisting Nonalcoholic Fatty Liver Disease and Chronic Hepatitis B

Minah Kim[1], Yeonju Lee[2], Jun Sik Yoon[3], Minjong Lee[4], So Shin Kye[1], Sun Woong Kim[2*], Yuri Cho[5*]

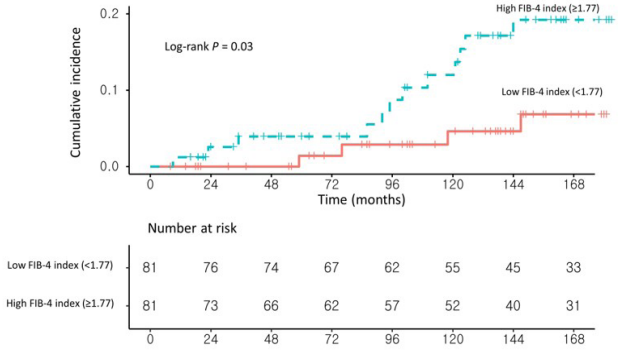
*Authors share co-corresponding authorship.

[1]Department of Family Medicine, National Police Hospital, Seoul, Republic of Korea; [2]Department of Internal Medicine, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea; [3]Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [4]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea; [5]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea

Aims: The FIB-4 index, a noninvasive tool [FIB-4 index=age × aspartate transaminase (AST)/(platelet count×√alanine aminotransferase (ALT))], is a useful assessment of liver fibrosis. Patients with a high FIB-4 index were reported to have a high risk of developing hepatocellular carcinoma (HCC). This study analyzed the clinical association of the FIB-4 index with HCC development in patients with coexisting nonalcoholic fatty liver disease and chronic hepatitis B (NAFLD-CHB).

Methods: This retrospective study analyzed 237 consecutive NAFLD-CHB patients between January 2006 and December 2010 at National Police Hospital in Korea. Patients with HCC at baseline and those diagnosed HCC within 6 months from baseline were excluded. Propensity score matching analysis was adopted to balance the baseline characteristics between patients with low and high FIB-4 index values. The cumulative rates of HCC development were compared between the two groups using the Kaplan-Meier method.

Results: The median follow-up duration was 13.0 years (interquartile range, 8.2–15.7). The optimal cutoff for the FIB-4 index of 1.77 was calculated based on the maximum Youden index value, with an AUC of 0.70. Among a total of 237 patients with NAFLD-CHB, HCC developed in 20 patients (8.4%) (14 of the 90 patients with a high FIB-4 index score vs. 6 of the 147 patients with a low FIB-4 index; *P*=0.004). Patients with a high FIB-4 index score had a significantly higher risk of HCC than those with a low FIB-4 index score (adjusted hazard ratio, 3.23; 95% confidence interval, 1.04–10.01; *P*=0.04).



Conclusions: A high FIB-4 index score (≥1.77) might be a useful marker for predicting the development of HCC in patients with NAFLD-CHB.

Keywords: Nonalcoholic fatty liver disease, Chronic hepatitis B, Hepatocellular carcinoma, FIB-4

FV-080

Predictors of The Development of Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease

Jae Seung Lee[1*], Dong Hyun Sinn[2*], Hye Won Lee[1], Jun Yong Park[1], Do Young Kim[1], Sang Hoon Ahn[1], Jung Il Lee[3], Seung Up Kim[1**]**

[1]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Medicine, Samsung Medical Center, Seoul, Korea; [3]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Aims: Non-alcoholic fatty liver disease (NAFLD) is associated with the increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC). We aimed to reveal independent predictors of the development of HCC in patients with NAFLD.

Methods: Between 2012 to 2017, 2,666 patients with NAFLD from three Korean high volume medical centers were retrospectively analyzed. The presence of hepatic fat infiltration was clinically defined based on abdominal ultrasonography or controlled attenuated parameter (CAP) >238 dB/m using transient elastography (TE).

Results: The median age of the study population (1,524 [57.2%] male and 1,142 [42.8%] female) was 52.3 years. The median body mass index was 26.2 kg/m^2 and under 23.0 kg/m^2 in 345 (12.9%) patients. Diabetes mellitus, hypertension, and liver cirrhosis were identified in 1,029 (38.6%), 1,080 (40.5%), and 171 (6.4%) patients, respectively. The median value of platelet count, aspartate aminotransferase (AST) and alanine aminotransferase levels were 236 (IQR 200–279) /mm^3, 33 (IQR 24–49) IU/L, and 41 (IQR 24–68) IU/L, respectively. The median liver stiffness (LS) and CAP was 5.9 (IQR 4.6–7.9) kPa and 303 (IQR 273–331) dB/m, respectively. During the median follow-up period of 64.6 (IQR 46.5–79.5) months after NAFLD diagnosis, 22 (0.8%) patients developed HCC. In multivariate analysis, older age (> 60 years) (hazard ratio [HR]=10.4), higher LS value (> 11 kPa) (HR=14.1), higher AST level (HR=1.015), and lower platelet count (<150 n/mm^3) (HR=4.3) were independently associated with the increased risk of HCC development (all *P*<0.05).

Conclusions: Older age, higher LS, higher AST level, and lower platelet count independently predicted the risk of HCC development in patients with NAFLD.

Keywords: Non-alcoholic fatty liver disease, Risk stratification, Hepatocellular carcinoma

FV-081

Metabolic Dysfunction-Associated Fatty Liver Disease Criteria Might Be Better in Identifying Subjects with High-Risk Fatty Liver Disease: A Nationwide Cohort Study

Ho Soo Chun[1], Eugene Han[2], Yong-ho Lee[3,4], Jae Seung Lee[3,5], Hye Won Lee[3,5], Beom Kyung Kim[3,5], Jun Yong Park[3,5], Do Young Kim[3,5], Sang Hoon Ahn[3,5], Byung-Wan Lee[3,5], Eun Seok Kang[3,5], Bong-Soo Cha[3,5], Seung Up Kim[3,5]

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea; [5]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: The clinical features of nonalcoholic fatty liver disease (NAFLD) who do not meet the diagnostic criteria of metabolic dysfunction-associated fatty liver disease (MAFLD) remain unclear. We investigated the risk of sarcopenia and cardiovascular disease (CVD) in subjects with MAFLD and those with NAFLD, but without MAFLD.

Methods: Subjects from the Korean National Health and Nutrition Examination Surveys 2008–2011 were selected. Significant liver fibrosis was defined as a fibrosis-4 (FIB-4) index categorized by age cutoffs. Sarcopenia was defined as the lowest quintile sarcopenia index. High probability of atherosclerotic CVD (ASCVD) was defined as ASCVD risk score >10%.

Results: A total of 7,248 subjects with NAFLD or MAFLD were recruited. Of these, 7,111 (98.1%) had MAFLD and 137 (1.9%) had NAFLD, but without MAFLD. In NAFLD, but without MAFLD group, 28 (20.4%) had significant liver fibrosis. Metabolic risk components were not different between subjects with and without significant liver fibrosis in NAFLD, but without MAFLD group (P>0.05), whereas those were significantly higher in subjects with MAFLD compared to those with NAFLD, but without MAFLD (P<0.05). After adjusting for confounders, the risk of sarcopenia and high probability of ASCVD were not statistically different according to the presence of significant liver fibrosis in subjects with NAFLD, but without MAFLD (all P>0.05), whereas those significantly increased in subjects with MAFLD, compared to those with NAFLD, but without MAFLD nor significant liver fibrosis (odds ratio [OR]=3.38-7.23 for sarcopenia, OR=3.73-6.64 for high probability of ASCVD; all P<0.05).

Table 1. Odds ratio and 95% confidential intervals of sarcopenia according to NAFLD with and without significant liver fibrosis and MAFLD

Adjustment	NAFLD, but without MAFLD		MAFLD
	Without significant liver fibrosis	With significant liver fibrosis	
Model 1	1.00 (ref.)	3.84 (0.85-17.20) P=0.079	7.23 (2.67-20.63) P<0.001
Model 2	1.00 (ref.)	4.20 (0.90-19.67) P=0.069	3.56 (1.25-10.12) P=0.018
Model 3	1.00 (ref.)	4.51 (0.97-21.04) P=0.055	3.38 (1.18-9.65) P=0.023

Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, body mass index, and waist circumference.
Model 3: adjusted for sex, age, body mass index, waist circumference, HOMA-IR*, HDL-cholesterol*, triglycerides*, systolic blood pressure, fasting blood glucose, aspartate aminotransferase*, alanine aminotransferase*, gamma glutamyltransferase*, and fatty burden by fatty liver index.
*Log-transformed.

Table 2. Odds ratio and 95% confidential intervals of high probability of ASCVD according to NAFLD with and without significant liver fibrosis and MAFLD

Adjustment	NAFLD, but without MAFLD		MAFLD
	Without significant liver fibrosis	With significant liver fibrosis	
Model 1	1.00 (ref.)	1.52 (0.34-6.78) P=0.581	6.64 (2.87-15.36) P<0.001
Model 2	1.00 (ref.)	1.59 (0.36-6.98) P=0.539	5.47 (2.39-12.73) P<0.001
Model 3	1.00 (ref.)	3.01 (0.60-15.13) P=0.180	3.73 (1.52-9.13) P=0.004

Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, body mass index, and waist circumference.
Model 3: adjusted for sex, age, body mass index, waist circumference, HOMA-IR*, HDL-cholesterol*, triglycerides*, systolic blood pressure, fasting blood glucose, aspartate aminotransferase*, alanine aminotransferase*, gamma glutamyltransferase*, and fatty burden by fatty liver index.
*Log-transformed.

Conclusions: The risks of sarcopenia and CVD significantly increased in subjects with MAFLD, whereas they did not differ according to fibrotic burden in subjects with NAFLD, but without MAFLD. Thus, MAFLD criteria might be better in identifying subjects with high-risk fatty liver disease.

Keywords: Metabolic dysfunction-associated fatty liver disease, Nonalcoholic fatty liver disease, Liver fibrosis, Sarcopenia, Cardiovascular disease

FV-082

Risk Stratification Using Sarcopenia Status Among Subjects with Metabolic Dysfunction-Associated Fatty Liver Disease: A Nationwide Cohort Study

Ho Soo Chun[1,2], Mi Na Kim[3,4], Jae Seung Lee[5,6], Hye Won Lee[5,6], Beom Kyung Kim[5,6], Jun Yong Park[5,6], Do Young Kim[5,6], Sang Hoon Ahn[5,6], Seung Up Kim[5,6]

[1]Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, Republic of Korea; [2]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea; [3]Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; [4]Clinical and Translational Hepatology Laboratory, Seongnam, Republic of Korea; [5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Sarcopenia is a significant indicator of the severity of nonalcoholic fatty liver disease (NAFLD). We investigated whether sarcopenia could identify subgroups with different risk of liver fibrosis and cardiovascular disease (CVD) among subjects with metabolic dysfunction-associated fatty liver disease (MAFLD).

Methods: Subjects from the Korean National Health and Nutrition Examination Surveys 2008–2011 were selected (n=8,361). Sarcopenia was defined using the sarcopenia index. Hepatic steatosis was defined as a fatty liver index ≥30. Significant liver fibrosis was defined as a fibrosis-4 (FIB-4) index ≥1.30, or the highest quartile of NAFLD fibrosis score (NFS). High probability of atherosclerotic CVD (ASCVD) was defined as ASCVD risk score >10%.

Figure 1. Prevalence and relative risk of significant liver fibrosis according to the status of MAFLD/sarcopenia. The prevalence and relative risk of significant liver fibrosis (A by FIB-4, B by NFS) significantly increased from non-sarcopenic subjects with MAFLD to sarcopenic subjects with MAFLD, compared with those without MAFLD (all P<0.001).

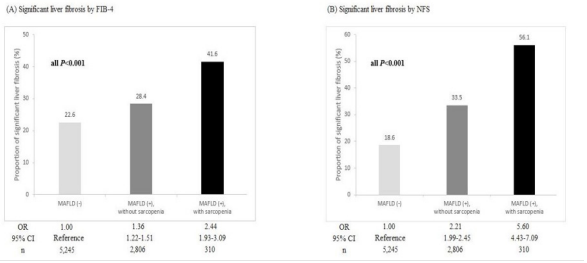
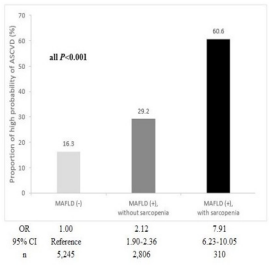


Figure 2. Prevalence and relative risk of high probability of ASCVD risk according to the status of MAFLD/sarcopenia. The prevalence and relative risk of high probability of ASCVD significantly increased from non-sarcopenic subjects with MAFLD to sarcopenic subjects with MAFLD, compared with those without MAFLD (P<0.001).



Results: The prevalence of MAFLD was 37.3% (n=3,116 of 8,361), and the proportion of sarcopenic subjects was 9.9% among those with MAFLD. After adjusting for confounders, the risk of significant liver fibrosis significantly increased from non-sarcopenic subjects with MAFLD (odds ratio [OR]=1.22 by FIB-4 and 2.13 by NFS) to sarcopenic subjects with MAFLD (OR=2.19 by FIB-4 and 5.72 by NFS), compared with subjects without MAFLD (all *P*<0.001). In addition, the risk for high probability of ASCVD significantly increased from non-sarcopenic subjects with MAFLD (OR=1.47) to sarcopenic subjects with MAFLD (OR=4.08), compared with subjects without MAFLD (all *P*<0.001).
Conclusions: The risks of significant liver fibrosis and CVD differed significantly according to sarcopenic status among subjects with MAFLD. An assessment of sarcopenia might be helpful in risk stratification among subjects with MAFLD.
Keywords: Metabolic dysfunction-associated fatty liver disease, Sarcopenia, Liver fibrosis, Cardiovascular disease, Risk stratification

FV-083

Methods for Analyzes and Monitor of Hepatology Data in Relation to Non-Alcoholic Fatty Liver Disease via Wearable Technology

Vikas Sharma, S Lavenia

Departement of Internal Medicine, SNM College and Research Center, India

Aims: Non-alcoholic fatty liver disease (NAFLD) is a burdensome and increasingly prevalent disease throughout the world. It is the most common cause of chronic liver disease among children and adolescents and represents the leading cause of chronic liver disease worldwide. New wearable sensor networks together with smartphone applications are being examined and tested for their potential to monitor and manage NAFLD in type 2 diabetic patients. To develop methods for analyzes and monitor of map the intersection(s) of hepatology data in relation to NAFLD via wearable technology (MI band) in type 2 diabetic patients in Jaipur city, India.
Methods: Total of 86 NAFLD with type 2 diabetes patients were taken as subject with an equal ratio of male and female. Wearable monitoring devices (MI band) were put on the wrist of NAFLD patients for 30 days and a questionnaire was filled out by each patient. Both diabetes and cardiovascular disease in turn are known as important factors for developing NAFLD and aggravation toward once end-stage liver disease. In all subjects, blood glucose was measured on daily basis with day to day data of their monitoring of step count (deep sleep, light sleep, wake up time), blood pressure, calorie burnt, insulin dose, motion time i.e. every time when your body was in motion, sleep monitoring, monitoring heart rate, cardiac arrhythmias to know daily routines and recording them for health purpose.
Results: Present results shown that (MI band) wearable device reading showed there was a normal heart rate, more calorie burnt with better control of sugar control and average good sleep count in more physically workout, include walking in NAFLD patients compared to less physically workout NAFLD patients, identified by professional physiotherapists. Wearable device reading showed that after changing lifestyle routine among less physically active NAFLD patients, their post- NAFLD events normalize with less requirement of medicine and insulin injection dose. While monitoring, daily life routine activities on data by a wearable devices that can obtain real-time NAFLD data, help technologists understand medical aspects, and clinicians to understand technological processes them and provides assistance based on pre-determined specifications in NAFLD in type 2 diabetic patients
Conclusions: With this study we show that, by using, wearable device ensured online assistive feedback for NAFLD patients with type 2 diabetes is possible with their health awareness, exercising and motivate further studies. Lifestyle modification through increased physical activity is beneficial in patients with NAFLD.
Keywords: Non-alcoholic fatty liver disease, Wearable technology (MI band), Type 2 diabetic patients, Daily life

FV-084

Modulation of Physical Activity, Diet Composition and Non-Alcoholic Fatty Liver Diseases in Type 2 Diabetic Patients

Vikas Sharma, S Lavenia

Departement of Internal Medicine, SNM College and Research Center, India

Aims: This study aimed to investigate the impact of physical activity, body adiposity and diet composition on non-alcoholic fatty liver diseases (NAFLD) in patients with type 2 diabetes (T2D).
Methods: Sixty-five adolescents with T2D (age range: 45-75 years; M/F: 33/32) were enrolled. Physical (height, weight, waist circumference, bioelectrical impedance analysis) and biochemical (HbA1c, lipid profile) parameters were recorded. Subjects were instructed to wear an activity monitor (SenseWear Xiaomi band) for 3 consecutive days, including a weekend day and to fill out a weighed dietary record for the same days. Regression models, using Triglyceride-to-HDL cholesterol ratio [(a gross index of cardiovascular risk (CVR)] as the dependent variable and fat mass (FM) %, lipid-to-carbohydrate intake ratio and physical activity (h/day) as independent ones, were calculated.
Results: Triglyceride-to-HDL cholesterol ratio was significantly associated with adiposity (FM%; r = 0.273; *P*=0.028), lipid-to-carbohydrate intake ratio (r = 0.258; *P*=0.038), the amount (h/day;r = -0.285; *P*=0.022) and intensity [expressed as metabolic equivalent (METs), kcal/kg/h; r = -0.283; *P*=0.022] of physical activity. Triglyceride-to-HDL cholesterol ratio was not associated with HbA1c (mmol/mol) (r=0.030, *P*=0.81). Multiple regression analysis showed that diet composition (lipid-to-carbohydrate intake ratio) and physical activity duration contributed to explaining the inter-individual variability of Triglyceride-to-HDL

cholesterol ratio (R2 = 0.152; *P*<0.05), independently from gender and the level of adiposity.

Conclusions: Intervention to reduce NAFLD risk in patients with T2D could take advantage from regular physical activity and adequate diet composition.

Keywords: Non-alcoholic fatty liver diseases, Type 2 diabetes, Diet composition, Physical activity

FV-085

Advanced Liver Fibrosis Predicts Chronic Kidney Disease Development in Patients with Nonalcoholic Fatty Liver Disease

Chan-Young Jung[1], Geun Woo Ryu[1], Hyung Woo Kim[1], Sang Hoon Ahn[2,3], Seung Up Kim[2,3], Beom Seok Kim[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated the association between liver fibrosis and the risk of incident CKD in patients with NAFLD.

Methods: A total of 5,983 participants with NAFLD (defined as controlled attenuation parameter > 222 dB/m) but without CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The primary outcome was incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or proteinuria (≥ 1+ on dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Results: The mean age was 51.8 years and 3,756 (62.8%) participants were male. During 17,801 person-years of follow-up (mean follow-up of 3.0 years), 62 participants (1.0%) developed incident CKD. When stratified into TE-defined fibrosis stages, multivariable Cox models revealed that risk of incident CKD was 3.63-fold (95% CI, 1.64-8.06, *P*<0.001) higher in the F3-4 group (≥ 9.5 kPa), compared to the F0 group (< 5.5 kPa). During 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants (3.4%) experienced the secondary outcome, for which the F3-4 group had a 2.69-fold increased risk (95% CI, 1.70-4.27, *P*<0.001), compared to the F0 group.

Conclusions: In this large cohort of NAFLD patients without baseline CKD, advanced liver fibrosis was significantly associated with a higher risk of incident CKD.

Keywords: Liver fibrosis, Transient elastography, Chronic kidney disease, Nonalcoholic fatty liver disease

FV-086

MAFLD Predicts the Risk of Cardiovascular Disease better than NAFLD in Asymptomatic Subjects Undergoing Medical Health Check-Ups

Hyoeun Kim[1], Chan Joo Lee[2], Sang Hoon Ahn[3,4], Kwan Sik Lee[3,5], Byoung Kwon Lee[6], Su Jung Baik[7], Seung Up Kim[3,4], Jung Il Lee[3,5]

[1]Department of Health Promotion, Health Promotion Center, Severance Hospital, Yonsei University Health System, Seoul, Korea; [2]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Korea; [5]Division of Gastroenterology and Hepatology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [6]Division of Cardiology, Heart Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [7]Healthcare Research Team, Health Promotion Center, Gangnam Severance Hospital, Seoul, Korea

Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed to compensate for the conventional concept of nonalcoholic fatty liver disease (NAFLD). We investigated the superiority of MAFLD vs. NAFLD in predicting the risk of cardiovascular disease (CVD).

Methods: A total of 2,144 subjects without a history of CVD, who underwent a comprehensive medical health check-up, were selected for the study. The associations between fatty liver status and coronary risk surrogates, such as coronary artery calcium score (CACS), coronary artery disease, quantitative stenosis grade, and 10-year atherosclerotic cardiovascular disease (ASCVD) risk, were analyzed.

Results: MAFLD and NAFLD were identified in 995 (46.4%) and 891 (41.6%) subjects, respectively. Subjects with MAFLD or NAFLD were more likely to be male and had a significantly higher prevalence of central obesity, obesity, hypertension, diabetes, and dyslipidemia (all, *P*<0.05) than their counterparts. In terms of coronary risk surrogates, the MAFLD or NAFLD population had a significantly higher proportion of subjects with CACS > 100, coronary artery disease, higher grade of coronary artery stenosis, and higher 10-year ASCVD risk (all, *P*<0.05) than their counterparts. Multivariable logistic regression models showed an independent association between MAFLD/NAFLD and coronary risk surrogates (all, *P*<0.05). However, NAFLD only, defined as 'NAFLD, but not MAFLD', was not associated with an increased coronary risk, compared to MAFLD.

Conclusions: Although both MAFLD and NAFLD discriminated different CVD risks, MAFLD predicted the risk of CVD better than NAFLD in asymptomatic subjects who underwent medical health check-ups.

Keywords: Metabolic dysfunction associated fatty liver disease, Nonalcoholic fatty liver disease, Cardiovascular disease, Risk assessment

FV-087

Incidence and Risk Factors for the Development of Non-Alcoholic Fatty Liver Disease after Pancreaticoduodenectomy

Dongsub Jeon[1], Han Chu Lee[1], Yejong Park[2], Woohyung Lee[2], Jae Hoon Lee[2], Ki Byung Song[2], Dae Wook Hwang[2], Song Cheol Kim[2], Jonggi Choi[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Small-scale studies reported that approximately 23-37% of the patients developed non-alcoholic fatty liver diseases (NAFLD) after pancreaticoduodenectomy (PD). However, it remains elusive regarding risk factor for the development of NAFLD after PD. Therefore, this study aimed to investigate the incidence and risk factors for new-onset NAFLD after PD in a large cohort.

Methods: We retrospectively analyzed 2,117 patients who received PD between 2012 and 2015. Patients with viral hepatitis, diabetes, pre-operative BMI ≥25 kg/m^2, NAFLD history, or cirrhosis were excluded. New-onset NAFLD was defined as a liver attenuation value <40 Hounsfield units (HU) or at least 10 HU lower than the spleen attenuation value on non-enhanced CT scan at 2 years after PD. Risk factors associated with development of NAFLD after PD were determined by multivariable logistic regression analysis.

Results: A total of 457 patients were included in the present study. The mean patient age was 61.1 years at baseline, and 57.5% of the patients were men. Baseline BMI was 21.4 and the median ALT level was 33 IU/L. 350 (76.6%) patients received pylorus-preserving PD (PPPD) and 107 (23.4%) received Whipple's operation. After 2 years of surgery, 152 (33.3%) patients developed new-onset NAFLD. The mean ALT of patients with and without NAFLD at 2 years of surgery were 57.6 and 28.2, respectively. By multivariable logistic regression analysis, Whipple's operation, as reference to PPPD, was independently associated with a higher incidence of NAFLD (adjusted odds ratio [AOR]: 1.83, 95% confidence intervals [CIs]: 1.16-2.89) as well as pre-operative BMI (AOR: 1.15, 95% CIs: 1.01-1.31).

Conclusions: In a large-scale cohort study, 33.3% of the patients who received PD were found to have new-onset NAFLD after 2 years of surgery. Operation type (Whipple's operation) and a higher pre-operative BMI were significantly associated with a higher incidence of new-onset NAFLD after PD.

Keywords: New-onset NAFLD, Pancreaticoduodenectomy, Non-obese NAFLD

FV-088

Feasibility of Hounsfield Unit Values in Diagnosis of Fatty Liver

Ha Neul Kim[1,2], Hei Gwon Choi[3], In Sun Kwon[4], Woo Sun Ryu[6], Seok Hyun Kim[6], Byung Seok Lee[6], Hyuk Soo Eun[5,6*]

[1]Department of Medical Sciences, Chungnam National University, Daejeon, Korea; [2]Department of BK21 plus CNU Integrative Biomedical Education Initiative; [3]Research Institute of Medical Sciences, School of Medicine, Chungnam National University, 266 Munwha-ro, Jung-gu, Daejeon, Republic of Korea; [4]Statistical consultation of Clinical Trials Center, Chungnam National University Hospital, Jung-gu, Daejeon, South Korea; [5]Department of Internal Medicine, Chungnam National University School of Medicine, Jung-gu, Daejeon, South Korea; [6]Department of Internal Medicine, Chungnam National University Hospital, Jung-gu, Daejeon, South Korea

Aims: Because of fatty liver could progress to liver cirrhosis or hepatocellular carcinoma, early accurate diagnosis is necessary. Gold standard diagnostic tool is histological examination such as liver biopsy, however, it is invasive. Fatty liver disease could be evaluated using computerized tomography (CT), though need to verify with results of liver biopsy. Therefore, our study was analyzed whether the Hounsfield units (HU) of liver value could be used to evaluate the degree of fatty liver on CT scan, and the correlation between the HU value of liver and hepatic steatosis verified by histological examination. Therefore, relationship HU value and degree of steatosis of the patients with steatosis were analyzed.

Methods: The patient's clinical baseline characteristics, value of liver HU and Liver / Spleen HU ratio (L/S HU ratio) on CT pre-phase were collected and analyzed. The collected data was analyzed and processed to a correlation graph and ROC curve between HU value of the liver or L/S ratio and degree of steatosis.

Results: Liver HU and L/S ratio analysis results were lower in patients with hepatic steatosis than in patients without hepatic steatosis. The correlation was shown negative between the degree of hepatic steatosis and the liver HU, L/S HU ratio in with steatosis group. In addition, with steatosis group, the higher the BMI of the patients, the lower the HU value. Moreover, AUROC values between HU value and L/S HU value were 0.316 and 0.325, respectively. However, in multivariate analysis, liver HU and L/S HU ratio were not shown any correlation with the degree of hepatic steatosis. (P=0.43, P=0.11)

Conclusions: Based on our analysis, liver HU and L/S HU ratio could not be used to predict the degree of hepatic steatosis.

Keywords: Hounsfield units, Fatty liver, Steatosis, Computed tomography

FV-089

Accuracy of Noninvasive Scoring Systems in Assessing Liver fibrosis in Patients with Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, SoonChunHyaung University Bucheon Hospital

Aims: Several non-invasive scoring systems have been developed to determine risk of advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). We examined the diagnotic accurary of FIB-4 score and NAFLD fibrosis score (NFS) in patient with biopsy-proven NAFLD.
Methods: A systematic search of PubMed (Medline), EMBASE, OVID Medline, the Cochrane Library and other databases was performed for this review. The abstracts obtained from the search were reviewed by two investigators who choose manuscripts for full-text review. The event rates were calculated with a random-effects model and quality effects model.
Results: Twenty-five studies evaluating biopsy-proven NAFLD were finally selected. A total of 17,790 patients were analyzed. The lower cut-off sensitivity of the FIB-4 score predicting histological stage 3 or more fibrosis (≥ F3) was 71%, specificity 68%, positive predictive value (PPV) 37%, and the negative predictive value (NPV) was 90%. The low baseline sensitivity of the NFS score predicting ≥ F3 was 74%, specificity 66%, PPV 37%, and NPV 90%. The area under the receiver operating characteristic curve (AUC) of FIB-4 score that predicts ≥ F2 was 72%. The AUC of the NFS score predicting ≥ F2 is 61%.
Conclusions: FIB-4 or NFS test can be used to predict the degree of liver fibrosis in NAFLD, and diagnostic accuracy is relatively high at predicting F3 or higher.
Keywords: Nonalcoholic fatty liver disease, FIB4 socre, NFS

8. Liver Cancer, Basic

FV-090

Inhibition of Dickkopf-1 Enhances Antitumor Efficacy of Sorafenib in Hepatocellular Carcinoma

SangHyun Seo[1,2] Kyungjoo Cho[1,2], Hye Jung Park[2], Hye Won Lee[2,3], Beom Kyung Kim[2,3], Jun Yong Park[2,3], Do Young Kim[2,3], Sang Hoon Ahn[2,3], Seung Up Kim[2,3]

[1]Brain Korea 21 PLUS project for Medical Science College of medicine, [2]Yonsei Liver Center, Severance Hospital, [3]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Sorafenib-based anticancer therapy is often unsatisfactory in treating hepatocellular carcinoma (HCC), due to insufficient response and the development of drug resistance. Dickkopf-1 (DKK1), a negative regulator of the Wnt/β-catenin signaling pathway, is upregulated in HCC, representing it a promising target for HCC. In this study, we investigated whether the inhibition of DKK1 enhances antitumor efficacy of sorafenib and elucidate the possible molecular mechanism in HCC.
Methods: We evaluated the expression of DKK1 in HCC using online database and validated its expression of tumor tissue and serum by immunofluorescence staining and ELISA analysis. Two human HCC cell lines (Huh7 and Hep3B) were used to examine the anticancer efficacy of the combined use of sorafenib and DKK1 inhibitor. Cell viability assay was used to identify the optimal dosage of sorafenib, DKK1 inhibitor, and their combination. Huh7 and Hep3B stable cells and transgenic mouse models were used to elucidate the molecular mechanism.
Results: DKK1 was highly expressed in patients with HCC compared with controls. Co-treatment with DKK1 inhibitor enhanced the cytotoxicity of sorafenib and reduced the IC_{50} of sorafenib in Huh7 and Hep3B cells. In the molecular level, Hep3B cells with DKK1 knock-out result in specific decrease of the PI3K and Akt protein level and Huh7 cells with DKK1 overexpression increased expression of PI3K and Akt, compared to the controls. In addition, DKK1 overexpression with HRASG12V increased the expression of Akt, PI3K, and mTOR in transgenic mouse livers, compared to the controls. Subsequently, the combination of sorafenib and DKK1 inhibitor led to significant inhibition of the activation of Akt, PI3K and mTOR in Huh7 cells.
Conclusions: Inhibition of DKK1 enhanced antitumor efficacy of sorafenib in HCC treatment, which might be a novel therapeutic strategy in HCC treatment.
Keywords: Dickkopf-1, Sorafenib, PI3K, Akt

FV-091

Association between Genetic Features and Serum Biomarkers in Hepatocellular Carcinoma

Keun Soo AHN[1], Koo Jeong KANG[1], Tae-Seok KIM[1], Yong Hoon KIM[1], Joong-Won PARK[2], Sang-Jae PARK[3], Seoung Hoon KIM[3]

[1]Surgery, Keimyung University Dongsan Hospital, Korea; [2]Internal medicine, National Cancer Center, Korea; [3]Surgery, National Cancer Center, Korea

Aims: Serum alpha-fetoprotein (AFP), Lens culinaris agglutinin–reactive AFP (AFP-L3), and des-gamma-carboxyprothrombin (DCP) are useful biomarkers of hepatocellular carcinoma (HCC). However, associations among molecular characteristics and serum biomarkers are unclear.
Methods: We analyzed RNA expression and DNA variant data from The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) to examine their associations with serum biomarker levels and clinical data. From 371 TCGA-LIHC patients, we selected 91 seen at 3 institutions in Korea and the United States and measured AFP, AFP-L3, and DCP from preoperatively obtained serum. We conducted an integrative clinical and molecular analysis, focusing on biomarkers, and validated the findings with the remaining 280 patients in the TCGA-LIHC cohort.
Results: Patients were categorized into 4 subgroups: elevated AFP or AFP-L3 alone (↑AFP&L3), elevated DCP alone (↑DCP), elevation of all 3 biomarkers (↑All), and reference range values for all biomarkers (RR). CTNNB1 variants were frequently observed in ↑DCP patients (n=7 [53.8%]) and RR patients (n=10 [38.5%]),

but ↑DCP patients with a CTNNB1 variant had worse survival than RR patients. TP53 sequence variants were associated with ↑AFP (n=8 [30.8%]) and ↑DCP (n=4 [30.8%]). The Wnt–□-catenin signaling pathway was activated in the ↑AFP&L3, whereas liver-related Wnt signaling was activated in the RR. TGF-□ and VEGF signaling are activated in high AFP&L3, while dysregulated bile acid and fatty acid metabolism were dominant in ↑DCP. We validated these finding using the remainder of the TCGA-LIHC cohort and showed similar results to the test cohort.

Conclusions: Serum AFP, AFP-L3, and DCP levels can help predict variants in the genetic profile.

FV-092

Transcriptomic Analyses of Livers From Mice Exposed to 1,4-Dioxane For Assess Potential Mode(s) of Action Underlying Liver Tumor Development

Megawati Megawati[1], Zulfiah Mondir[2]

[1]Department of Agribusiness, Sebelas Maret University Surakarta, [2]Department of Public Health, Airlangga University Surabaya

Aims: 1,4-Dioxane is a volatile organic compound currently used in industrial processes as a solvent, in the manufacture of other chemicals, and as a laboratory reagent (ATSDR, 2012). However, questions remain as to whether there is sufficient information to understand early events in the development of hepatic tumors in mice exposed to 1,4-dioxane, and to support an initiating event of hepatotoxicity.

Methods: 1,4-Dioxane has been demonstrated to induce liver tumors in chronic rodent bioassays conducted at very high doses. The available evidence for 1,4-dioxane-induced liver tumors in rodents aligns with a threshold-dependent mode of action (MOA), with the underlying mechanism being less clear in the mouse than in rats. To gain a better understanding of the underlying molecular mechanisms related to liver tumor development in mice orally exposed to 1,4-dioxane, transcriptomics analysis was conducted on liver tissue collected from a 90-day drinking water study in female B6D2F1/Crl mice (Lafranconi et al., 2020). Using tissue samples from female mice exposed to 1,4-dioxane in the drinking water at concentrations of 0, 40, 200, 600, 2,000 or 6,000 ppm for 7, 28, and 90 days.

Results: Transcriptomic analyses demonstrate minimal treatment effects on global gene expression at concentrations below 600 ppm. At higher concentrations, genes involved in phase II metabolism and mitotic cell cycle checkpoints were significantly upregulated. There was an overall lack of enrichment of genes related to DNA damage response. The increase in mitotic signaling is most prevalent in the livers of mice exposed to 1,4-dioxane at the highest concentrations for 90 days.

Conclusions: This finding aligns with phenotypic changes reported by Lafranconi et al. (2020) after 90-days of exposure to 6,000 ppm 1,4-dioxane in the same tissues. The transcriptomics analysis further supports overarching study findings demonstrating a non- mutagenic, threshold-based, mitogenic MOA for 1,4-dioxane-induced liver tumors.

Keywords: Transcriptomic, Liver, Tumor, 1,4-dioxane

FV-093

Solid Lipid Nanoparticle of Hesperidine Exerts Diethylnitrosamine/Phenobarbital-Induced Hepatocellular Carcinoma via Alteration of PI3K/Akt Pathway

Prakash BHATT

Biotechnology, Fermentis, India

Aims: Hepatocellular carcinoma (HCC) is the most frequently known liver disease and the third most common cause of tumour death in the world. Researchers targeted the pathways of phosphatidylinositol-4, 5-bisphosphate 3-kinase/protein kinase B and mitogen activated protein kinase to inhibit the proliferation and development of cells. In this analysis, the solid lipid nanoparticle (SLN) of hesperidine (HP) was manufactured and scrutinized against HCC induced by diethylnitrosamine (DEN) by altering the PI3K/Akt pathway.

Methods: For the preparation of HP-SLN, the double emulsion solvent displacement method was used and DEN (200 mg/kg) and phenobarbital (8 mg/kg) was used for the induction of HCC. Estimates were given for hepatic, non-hepatic, antioxidant, pro-inflammatory and inflammatory cytokines. The genetic effects of HP-SLN on Pdk1, Akt1, Pik3r1, Map3k1, Erbb2, Plk3ca were assessed using semiquantitative RT-PCR analysis. Morphological and histopathological hepatic tissue components were estimated.

Results: Surface methodology suggests the 174.5 nm particle size and 0.340 polydispersity index for HP-SLN. HP-SLN significantly (P<0.001) reduced the hepatic nodules (72%) and enhanced the body weight (48.3%); reduced hepatic nodules (83.3%). HP-SLN significantly (P<0.001) modulated the hepatic parameter viz.,AFP (78.3%), AST (61.3%), ALP (60.3%), ALT (55.8%)CEA (58.3%), GGT (63.2%); non-hepatic parameter viz., albumin (52.5%), total protein (63.4%), BUN (54.6%), bilirubin (67.3%), direct bilirubin (52.3%); antioxidant

Conclusions: In conclusion, HP-SLN regulated the Akt and PI3K pathways involved in suppression of hepatic cancer growth and proliferation and suggest the chemoprotective effect.

FV-094

The Profile of micro-RNA-221 in Hepatocellular Carcinoma Patient and Its Relevance to Pathogenic Pathway, Drug Resistance, and Potential Candidate Targeting-Therapy

Mochamad Afifudin

Department of Internal Medicine, Universitas Islam Indonesia

Aims: Hepatocellular carcinoma (HCC) is the most common liver malignancy driven by a multilevel biomolecular agent. The biomarker and therapeutical strategy study of HCC have developed

on a molecular basis, including by using Aptamer, nanoparticle, and micro-RNA. The previous study has shown that micro-RNA-221 has increased in several types of malignancy. The aim of the study is to review the role of micro-RNA-221 in HCC pathogenesis and its implication as a therapeutic agent.

Methods: The original research from January 2011-January 2021 was selected. The literature-based study was performed using PubMed, ScienceDirect, and google scholar databases. The data was extracted in the descriptive approach.

Results: The meta-analysis study has shown that micro-RNA-221 has a higher expression on HCC patient significantly (Univariate Analysis, HR 1.71, 95% CI 1.00-2.90, *P*=0.05; Multivariate Analysis, HR 1.83, 95% CI 1.38-2.42, *P*=0.000). High expression of micro-RNA-221 indicates a poor prognostic of HCC patients indicates by related to shorter time to local recurrence significantly (*P*<0.001). The level of micro-RNA-221 was higher in HCC patient with stages III and IV than stage I-II. micro-RNA-221 has any molecular target, including bmf as apoptosis inhibitor, cyclin-dependent kinase (cdkn) inhibitor, JAK-STAT3 pathway, p27, p57, and nuclear factor kappa β (Nf-kβ). Those mechanisms may modulate the inhibition of Caspase-3 activity and its relevance to Sorafenib drug resistance. This finding implies that micro-RNA-221 can be a promising candidate for drug targeting. *In Vitro* study has shown that micro-RNA-221 inhibition by using micro RNA sponge and adeno-associated viral factor increases the apoptosis percentage and reduces 42-45% of micro-RNA-221 expression.

Conclusions: micro-RNA-221 is a promising biomarker candidate of hepatocellular carcinoma especially for the metastasis stage because it has a higher level in stage III-IV. Micro-RNA-221 has any molecular target which promotes proliferation, migration, invasion, and drug resistance. Micro-RNA-221 targeting has a promising therapeutical strategy to develop in further research.

Keywords: Hepatocelullar carcinoma, Micro-RNA-221, Biomarker, Therapy

FV-095

The Inhibitory Effect of Ginsenoside Rh2-Rg5 Complex on Liver Cancer in a Preclinical Study: a Mechanism Analysis Based on Next-Generation Sequencing

Young Chang[1], Jae Young Jang[1]*, Sukmin Kang[1], Soung Won Jeong[1], Jeong-Ju Yoo[3], Sae Hwan Lee[2], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2], So Young Jin[4]

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea; [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea; [4]Department of Pathology, Soonchunhyang University College of Medicine, Seoul, Korea

Aims: We had found that the anti-cancer effects of ginsenosides Rh2 and Rg5 were similar to that of sorafenib in a xenograft hepatoma animal model. We investigated whether Rh2-Rg5 complex effectively inhibits liver cancer while reducing cytotoxicity, and analyzed the mechanism of anticancer effect of Rh2-Rg5 complex.

Methods: The anticancer effects of Rh2, Rg5, and Rh2-Rg5 complex were evaluated and compared *in vitro* using an MTT assay with human hepatoma Hep3B cells. Hep3B cells were implanted on the flanks of BALB/C nude mice for *in vivo* experiments, and sorafenib, ginsenosides Rh2, Rg5, and Rh2-Rg5 complex were injected intraperitoneally twice a week for 4 weeks. Area of necrosis in tumor tissue was calculated and the protein expression level of cleaved PARP was measured. Next-generation sequencing (NGS) of each tumor tissue was conducted to analyze gene expression differences in each treatment group.

Results: Of the three treatments in an *in vitro* experiment, ginsenoside Rh2 treatment showed the lowest cell viability. In the combination treatment of ginsenosides Rh2 and Rg5, the higher the concentration of Rg5, the higher the cell viability. Considering both cytotoxicity and anticancer effects, the most optimal ratio of ginsenoside Rh2 and Rg5 was 2:3 by volume. In animal experiments, increased necrotic area and higher levels of cleaved PARP protein expression were observed in sorafenib, Rh2, Rg5 and Rh2-Rg5 complex-treated groups compared to control group, of which Rh2-Rg5 complex-treated group showed the highest level of cleaved PARP protein expression. In NGS analysis, Rh2-Rg5 complex-treated group had 324 up-regulated and 145 down-regulated genes compared to control group. The final three genes were selected using adjusted P value (Benjamini-Hochberg) to adjust the false discovery rate of NGS and considering the known mechanisms of action and functions of each gene: Alpha kinase 2 (ALPK2) and Dehydrogenase/reductase 2 (DHRS2), known as tumor suppressor genes, and cytokine receptor like factor 1 (CRLF1), known as a oncogene (Table 1).

Conclusions: Ginsenoside Rh2-Rg5 complex effectively inhibits liver cancer while reducing cytotoxicity, and ALPK2, DHRS2, and CRLF1 genes are involved in the anticancer mechanism.

Keywords: Ginsenoside Rh2-Rg5 complex, Next-generation sequencing, ALPK2, DHRS2, CRLF1

FV-096

GTPBP4 Copy Number Segments as a Predictor of Overall and Disease-Specific Survival of Hepatocellular Carcinoma

Khaled Mohy Ismaeil

Department of Clinical Pathology, University of Ain Shams Faculty of Medicine, Egypt

Aims: Recent studies reported that GTPBP4 gene expression plays a role in gastric cancer progression and colorectal carcinoma metastasis. Furthermore, high GTPBP4 gene expression was also found to significantly affect hepatocellular carcinoma survival. Nonetheless, the role of GTPBP4 copy number segments in

predicting hepatocellular carcinoma overall and disease-specific survival is not clearly understood. This study aimed to evaluate the role of GTPBP4 copy number segments as a predictor of overall and disease-specific survival of hepatocellular carcinoma.

Methods: The UCSC Xena browser (https://xenabrowser.net) was used to access the liver hepatocellular carcinoma (LIHC) cohort of The Cancer Genome Atlas (TCGA) and information regarding patients' age, sex, tumor stage and GTPBP4 copy number segments were retrieved. Patients with incomplete or discrepant data were excluded. Copy number segments greater than or equal to the median were classified as high while those less than the median were classified as low. A univariable and a multivariable cox regression models were used to evaluate the role of GTBPB4 copy number segments in hepatocellular carcinoma overall and disease-specific survival. Multivariable models were adjusted for age, sex and stage. Rstudio version 1.2.1335 was used for all statistical purposes. A p-value of <0.05 was considered statistically significant.

Results: A total of 337 patients were included. Of which, 105 were females while the remaining 232 were males. The mean (SD) age of all patients was 59.01 (13.1). Most patients had stage one hepatocellular carcinoma where 169 patients were stage one, 85 were stage two, 79 were stage three and only four patients were stage four. Median copy number segments was 0.0161 log2 tumor/normal with 169 patients having high copy number segments and 168 patients having low copy number segments. On univariable analysis, high GTPBP4 copy number segments was significantly associated with worse overall and disease-specific survival with the HR (95% CI) being 1.616 (1.095-2.384) and 1.911 (1.15-3.176) respectively. Similarly, on multivariable analysis, overall and disease-specific survival were significantly worse with high GTPBP4 copy number segments where the HR (95% CI) were 1.525 (1.028-2.26) and 1.779 (1.06-2.978) respectively.

Conclusions: GTPBP4 copy number segments can be a potential predictor of overall and disease-specific survival in hepatocellular carcinoma patients and therefore should be investigated in further studies.

Keywords: Hepatocellular carcinoma, Survival, GTPBP4, Copy number

FV-097

Detection of Low Frequency Variants with Customized Cell-Free DNA Panel in Blood Samples of Hepatocellular Carcinoma Patients Undergoing Sorafenib Treatment

Hyojin Chae[1,2,*], Pil Soo Sung[3,*], Yonggoo Kim[1,2], Myungshin Kim[1,2,*], Seung Kew Yoon[3,*]

[1]Department of Laboratory Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Catholic Genetic Laboratory Center, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
*These authors contributed equally to this work.

Aims: It is urgently needed to explore new non-invasive strategies for diagnosis and prediction of treatment response in hepatocellular carcinoma (HCC) patients. In this study, we assessed pathogenic variants of HCC driver genes in circulating cell-free DNA (cfDNA) from HCC patients before sorafenib treatment.

Methods: Circulating cfDNA was collected from 20 advanced HCC patients before sorafenib treatment and deep sequencing was performed. Using a customized cfDNA sequencing panel, we targeted three major HCC driver genes (TP53, CTNNB1, TERT) using the Ion AmpliSeq Designer (Thermo Fisher Scientific). Seraseq ctDNA Reference Material v.2 (SeraCare Life Sciences) was used to validate the limit of detection. Clinical courses of these patients were reviewed by the experienced hepatologist.

Results: The median concentration of circulation plasma cfDNA was 4.1 ng/mL (range: 0.8-15.3 ng/mL). Targeted NGS for TP53, CTNNB1, TERT identified at least one pathogenic variant in 13 patients (65%). including 16 variants of TP53 and nine variants of CTNNB1. The TP53 and CTNNB1 variants had very low-level allele frequencies with median values of 0.17% (range: 0.06%–6.99%) and 0.07% (range: 0.05%–0.96%), respectively. The molecular coverage of variants was sufficient, with median values of 5,543 (range: 2,317–9,088) for TP53 variants and 7,568 (range: 2,400–9,633) for CTNNB1 variants. However, we did not find any statistically significant associations between clinical characteristics (patient demographics or tumor biology) and the presence of TP53 and/or CTNNB1 variants. Moreover, prolonged follow-up of these patients did not find out any clinical associations between the presence of plasma variants of these genes and patient survials, either.

Conclusions: Our data support that cfDNA profiling may be used as a blood biomarker to define somatic variants in HCC. Our on-going prospective study will demonstrate the prognostic value of plasma cfDNA profiling in patients with HCC undergoing systemic treatments.

Keywords: Hepatocellular carcinoma, Cell-free DNA, Circulating tumor DNA, Sorafenib

FV-098

Lactate-Related Risk Score (The LaRi Score): A Robust Risk Scoring System of Hepatocarcinoma Patients' Prognosis Base on Lactate-Related Genes

Zijian ZHANG[1,2], Jian XU[2], Yuyuan CHEN[2], Qi ZHOU[3]

[1]Digestive Medicine Center, The Seventh Affiliated Hospital of Sun yat-Sen University, China; [2]Department of General Surgery, The Seventh Affiliated Hospital of Sun yat-Sen University, China; [3]Department of General Surgery, Huiya Hosiptal of The First Affiliated Hospital of Sun yat-Sen University, China

Aims: Hepatocarcinoma(HCC) is one of the most lethal cancers worldwide. Lactate has recently been proved as a novel role in both metabolism and epigenetic in cancers. Our study aims

to establish and validate a novel scoring system based on lactate-related genes to estimate the prognosis of HCC patients.
Methods: Our study established a robust model to predict HCC patients' prognosis. Data from TCGA, ICGC, and GEO were explored. A LASSO-SVM-RFE algorithm model, Consensus clustering, and GDSC drug prediction were used to choose prognostic genes/subtypes and potential drugs.
Results: We establish a 4-mRNA robust model that can distinguish high-risk patients from low-risk patients with different prognosis significantly. The AUC of the Kaplan-Meier curve in 1 year, 3 years, and 5 years are all indicating the good performance of the Lari Score. Moreover, GO Enrichment results showed that several epigenetic regulation pathways and targets' expressions are significantly associated with high LaRi score, which means lactate-related genes could participate in tumorigenesis not only in metabolic but also epigenetic regulation. And the potential drugs are shown by the mean of GDSC drug predictions.
Conclusions: In conclusion, the LaRi Score provides a novel method to evaluate the prognosis of HCC patients based on the lactate-related genes. According to the GO enrichment results and GDSC drug-sensitive predictions, new therapeutic targets or drugs focus on the lactate metabolism and epigenetic function will be discovered and developed for HCC patients.

FV-099

YAP/TAZ Expression in Hepatocellular Carcinoma (HCC) and Effects of YAP/TAZ Inhibition on HCC

Sojung Han[1], Do Young Kim[1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Yonsei Liver Center, Severance Hospital, Yonsei University Health System, Seoul, Korea

Aims: Hippo signaling is a tumor suppressive pathway and its inactivation leads to tissue overgrowth and tumorigenesis via YAP- and TAZ- mediated transcriptional activation. Here, we investigated the expression levels of YAP and TAZ in patient-derived HCC tissue and identified the effects of YAP/TAZ inhibition depending on the baseline YAP/TAZ expression when combined with sorafenib, the first-line systemic therapeutic agent for HCC.
Methods: HCC tissue was obtained from surgical resection of HCCs and YAP/TAZ expression was analyzed using western blot. Nuclear accumulation of YAP/TAZ was confirmed by immunohistochemistry in HCCs but not in para-tumor tissue. Patient-derived primary HCC cell lines were established from patient-derived tissue. We selected six patient-derived HCC cell lines and they were classified into three groups depending on the YAP/TAZ expression: high, medium, low. Then, we generated MCTS by mixing patient-derived HCC cells and stroma cells (LX2, WI38, and HUVECs) at a 3:1:1:1 ratio in ultra-low attachment plates. We assessed the YAP/TAZ expression from protein extracted from MCTS. TAZ expression is major in monolayer HCCs (2D culture) and YAP was expressed in all HCCs in MCTS and several MCTS showed shifted YAP/TAZ expression with predominant YAP expression and TAZ depletion. We analyzed the cell viability upon 48hours of following drug treatment: sorafenib, sorafenib with CA3 0.1μM, and CA3 (novel YAP1 inhibitor).
Results: We confirmed that out of six patient-derived HCC cell lines, cell lines with high YAP/TAZ expression at MCTS level responded more sensitive to the combination therapy (Sorafenib + CA3 0.1μM) despite potent cytotoxic effect of CA3 exhibiting in all of the patient-derived HCCs. MCTS with predominant YAP expression and TAZ depletion showed chemoresistance to sorafenib and did not respond to combination therapy adding CA3 0.1μM
Conclusions: In conclusion, targeting YAP/TAZ inhibition using novel YAP1 inhibitor CA3 could be a promising therapeutic strategy to enhance sensitivity to sorafenib especially in HCCs with high and balanced YAP/TAZ expression at MCTS.
Keywords: Hepatocellular carcinoma (HCC), Multicellular tumor spheroids (MCTS), YAP, TAZ

FV-100

Targeting Nidogen1 in Tumor Cell-Derived Extracellular Vesicle Inhibits Growth, Motility and Metastasis of Hepatocellular Carcinoma

Cherlie Lot Sum Yeung, Xiaowen Mao, Sze Keong Tey, Judy Wai Ping Yam

Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Aims: Extracellular vesicles (EVs) are one of the important mediators within the complex tumor microenvironment. By delivering specific carcinogenic content, EVs regulate the formation of favorable pre-metastatic niche and facilitate dynamic intercellular communication. This study aims to identify and characterize key component of cancer-derived EVs to HCC progression.
Methods: EVs were first isolated from normal human hepatocyte MIHA and 2 metastatic HCC cell lines, MHCCLM3 and MHCC97L by ultracentrifugation. The quality of EVs were then assessed by western blot, electron microscopy and Zetaview Nanoparticle Tracking analysis. Proteomic content of EVs were profiled by mass spectrometry, which identified nidogen 1 (NID1) as our candidate target. Stable clones of NID1 knockdown, EV-targeting full-length and deletion mutants were then established for further *in vitro* and *in vivo* functional assays. Furthermore, custom-made monoclonal anti-NID1 antibody was developed.
Results: Nidogen 1 (NID1), an essential sulphated glycoprotein of the basement membrane, was found to be enriched in EVs derived from both metastatic HCC cell lines. Knockdown of NID1 significantly hampered the oncogenic effect of EVs in cell proliferation, motility and metastasis. Opposingly, overexpression of NID1 elevated capacity of EVs in promoting HCC cell aggressiveness. Functional comparison of EVs isolated from stable clones

of EV-targeting full-length and deletion mutants showed that loss of C-terminus domain demoted their oncogenic capacity. Finally, administration of custom-made anti-NID1 antibody were able to neutralize the cancer promoting effect of EVs derived from metastatic MHCC97L cells, NID1 overexpressing stable clone and late-stage patient.

Conclusions: This study identified metastatic HCC cell-derived EV-NID1 as our target candidate, which can augment HCC's tumorigenic and metastatic capability. In which, C-terminus domain is found to be critical for EV-NID1's oncogenic effect. Custom-made monoclonal anti-NID1 antibody shows promising potential for alternative HCC treatment option.

Keywords: Nidogen 1, Extracellular vesicles, Hepatocellular carcinoma, Tumor microenvironment

9. Liver Cancer, Clinical

FV-101

Hepatocellular Carcinoma in Children: Liver Resection and Liver Transplantation Outcomes

Karina MENDOZA-GALLO[1,2], Carlos FLOREZ-ZORRILLA[2,3]

[1]Pediatrics/Transplantation, Hospital General Regional n°46-IMSS Guadlajara, Mexico; [2]HPB and Liver Transplantation, Hospital Puerta de Hierro Andares, Mexico; [3]HPB and Liver Transplantation, Centro Médico Nacional 20 de noviembre-ISSSTE, Mexico

Aims: Hepatocellular carcinoma (HCC) in childhood is a rare type of malignant tumor of the liver. Childhood HCC is usually found in older children (10-15 years), rarely in children younger than 5. HCC is the second most common pediatric primary liver tumor accounting to around 25% following hepatoblastoma (HB) that accounts almost 70%. In children the only curative treatment of HCC is complete resection of the tumor and/or liver transplantation (LT). Traditionally some groups use Milan criteria (single tumor 〈 5 cm, or no more than 3 each ≤3 cm in diameter).

Methods: We collect patients data from january 2018 to january 2021. Our general policy is to offer LT to those patients with unresectable HCC (estimated liver remnant 《20%) without extrahepatic involvement. Liver resection remains the best approach and first line treatment option.

Results: Seven patients mean age 13.6 (range 1 to 16 years). Liver resection in 5 (71.4% and liver transplantation in 2 (28.5%). Liver resection group underwent right extended hepatectomy in 3 (60%), right hepatectomý in 1(20%) and left hepatectomy (20%). Liver transplantation group exceeded Milan and Total Tumor Volume criteria. Liver resection group overall survival at 1 and 3-year were 100% and 60% respectively. Liver transplant group 1 and 3-year survival were 100%.

Conclusions: HCC is a rare malignancy in children, occurring mainly in normal liver, its clinical behavior is different from adult HCC. Children LT criteria for HCC should not be the same as in adults. Management of childhood HCC includes chemotherapy, ablative procedures, surgical resection and liver transplantation.

FV-102

Long-Term Survival of Elderly Patients Undergoing Curative Liver Resection for Early-Stage Hepatocellular Carcinoma An International Multicenter Competing Risk Analysis

Lei LIANG[1], Yong-Kang DIAO[1], Chao LI[2], Ming-Da WANG[2], Hao XING[2], Feng SHEN[2], Wan Yee LAU[2,3], Timothy M. PAWLIK[4], Tian YANG[1,2]

[1]Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, China; [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), China; [3]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China; [4]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, USA

Aims: The impact of non-cancer-specific death needs concern when elucidating survival benefits from curative liver resection among patients with hepatocellular carcinoma (HCC), especially for the elderly. This study aimed to evaluate long-term prognosis of elderly patients following curative liver resection for early-stage HCC.

Methods: Patients undergoing curative-intent liver resection for early-stage HCC, which was defined as HCC within Milan criteria, were identified using a multicenter database. Patients were divided into the young (aged <70 years) and elderly (aged ≥70 years) groups. Using Fine and Gray's competing-risk regression model, multivariate analyses were performed to identify the real impact of age on recurrence, CSD and NCSD, respectively.

Results: Among 1354 patients, 286 (21.3%) and 1068 (78.7%) were the elderly and the young, respectively. The 5-year cumulative incidence of NCSD of the elderly were higher than that of the young (12.6% vs. 3.7%, *P*<0.001), while the 5-year cumulative incidences of recurrence and CSD of the elderly were lower than those of the young, respectively (20.3% vs. 21.1%, *P*=0.041, and 14.3% vs. 15.5%, *P*=0.066). After adjustment for other confounding risks on multivariate competing-risk regression analyses, age was independently associated with NCSD [subdistribution hazard ratio (SHR) 3.003, 95%CI 2.082~4.330, *P*<0.001], but neither associated with recurrence (SHR 0.837, 95% CI 0.659~1.060, *P*=0.120) nor CSD (SHR 0.736, 95% CI 0.537~1.020, *P*=0.158).

Conclusions: or patients undergoing curative liver resection for early-stage HCC, older age was independently associated with non-cancer-specific survival, but not recurrence and cancer-specific survival.

FV-103

Association of Postoperative Biomarker Response with Recurrence and Survival in Patients with Hepatocellular Carcinoma and High Alpha-Fetoprotein Expressions (> 400 ng/ml)

Ming-Da WANG[1], Lei LIANG[2], Cheng-Wu ZHANG[2], Wan Yee LAU[1,3], Feng SHEN[1], Timothy M. PAWLIK[4], Dong-Sheng HUANG[2], Tian YANG[1,2]

[1]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), China; [2]Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, China; [3]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China; [4]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, USA

Aims: High alpha-fetoprotein (AFP) expressions (>400 ng/ml) are associated with poor oncological characteristics for hepatocellular carcinoma (HCC). However, prognosis after liver resection for high-AFP HCC is poorly studied. To investigate long-term recurrence and survival after hepatectomy for high-AFP HCC, and to identify the predictive value of postoperative incomplete biomarker response (IBR) on overall survival (OS) and recurrence-free survival (RFS).

Methods: Patients undergoing curative resection for high-AFP HCC were analyzed. According to the decline magnitude of serum AFP as measured at first follow-up (4~6 weeks after surgery), all patients were divided into the complete biomarker response (CBR) and IBR groups. Characteristics, recurrence, and survival rates were compared.

Results: Among 549 patients, the overall and early recurrence rates in patients with IBR were significantly higher than patients with CBR (97.8%vs.56.4%, and 92.5%vs.33.3%, both P<0.001). On multivariate analysis, postoperative IBR was the strongest risk factor with the highest hazard ratio in predicting poor OS (2.97; 2.49~3.45; P<0.001) and RFS (4.29; 3.31~5.55; P<0.001).

Conclusions: Postoperative biomarker response of serum AFP can be used in predicting recurrence and survival for high-AFP HCC patients. Once postoperative IBR was identified at first follow-up, subsequent enhanced recurrence surveillance and available treatments against recurrence should actively be considered.

FV-104

Development and Validation of An Individualized Prediction Calculator of Postoperative Mortality Within 6 Months after Surgical Resection for Hepatocellular Carcinoma: An International Multicenter Study

Lei LIANG[1], Bing QUAN[2], Yong-Kang DIAO[1], Chao LI[3], Ming-Da WANG[3], Wan Yee LAU[4], Cheng-Wu ZHANG[1], Timothy M. PAWLIK[5], Dong-Sheng HUANG[1], Feng SHEN[3], Tian YANG[3]

[1]Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, China; [2]Department of Clinical Medicine, Second Military Medical University (Navy Medical University), China; [3]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), China; [4]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, China; [5]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, USA

Aims: Evidence-based decision-making is critical to optimize the benefits and mitigate futility associated with surgery for patients with malignancies. Untreated hepatocellular carcinoma (HCC) has a median survival of only 6 months. The objective was to develop and validate an individualized patient-specific tool to predict preoperatively the benefit of surgery to provide a survival benefit of at least 6 months following resection.

Methods: Using an international multicenter database, patients who underwent curative-intent liver resection for HCC from 2008 to 2017 were identified. Using random assignment, two-thirds of patients were assigned to a training cohort with the remaining one-third assigned to the validation cohort. Independent predictors of postoperative death within 6 months after surgery for HCC were identified and used to construct a nomogram model with a corresponding online calculator. The predictive accuracy of the calculator was assessed using C-index and calibration curves.

Results: Using an international multicenter database, patients who underwent curative-intent liver resection for HCC from 2008 to 2017 were identified. Using random assignment, two-thirds of patients were assigned to a training cohort with the remaining one-third assigned to the validation cohort. Independent predictors of postoperative death within 6 months after surgery for HCC were identified and used to construct a nomogram model with a corresponding online calculator. The predictive accuracy of the calculator was assessed using C-index and calibration curves.

Conclusions: An easy-to-use online prediction calculator was able to identify patients at highest risk of death within 6 months of surgery for HCC. The proposed online calculator may help guide surgical decision-making to avoid futile surgery for patients with HCC.

FV-105

Surgical Outcomes of Left Side Hepatectomy compared with Right Side Hepatectomy in Type I, II or IV Hilar Cholangiocellular Carcinoma

Seung Soo HONG, Dai Hoon HAN, Kyung Sik KIM, Jin Sub CHOI, Gi Hong CHOI*

Division of Hepatopancreaticobiliary Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea, Korea

Aims: Right-side hepatectomy(RH) has been considered an oncological resection for hilar cholangiocarcinoma(HCCC), however

the decision for left-side hepatectomy(LH) or RH is still a controversial issue. We compared surgical and oncologic outcomes of LH and RH in HCCC type I, II or IV in which either side of hepatectomy was expected to have a negative margin.

Methods: From 2001 to 2020, 85 patients underwent major liver resection for type I, II or IV HCCC. Among them, 52 patients who had no vascular invasion, no unilateral tumor growth and no atrophy of unilateral liver were enrolled. Preoperative characteristics, perioperative outcomes and long-term outcomes were compared between RH(n=29) and LH(n=23) group.

Results: Clinical characteristics and disease severity did not differ between two groups. Portal vein embolization rate(RH: 48.3% vs LH: 0.0%, *P*<0.001) and duration of diagnosis to operation(RH: 31.0±16.2 vs LH: 18.8±13.4, *P*=0.006) were significantly higher in RH group. Postoperative hepatic failure(over grade B) was more frequent in RH group(RH: 55.2% vs LH: 21.7%, *P*=0.015). R0 resection rate(RH: 72.4% vs LH: 78.3%, *P*=0.629), median disease free(*P*=0.620) and overall survival(*P*=0.487) did not differ between two groups. R1 resection and number of lymph node metastasis were significant risk factor for DFS in multivariate analysis.

Conclusions: In type I, II or type IV HCCC in which either LH or RH was a feasible option, LH provided shorter period of preoperative preparation, lower postoperative hepatic failure rate, similar R0 rate and comparable long-term outcomes compared with RH. Therefore, LH should be considered reasonable option to type I, II or IV HCCC.

FV-106

Suggestion for Selecting the Surgical Method of the Recurrent HCC: between Open and Laparoscopy

Eun Sung JEONG, Jong Man KIM*, Jaehun YANG, Ji Eun KWON, Manuel LIM, Kyeong Deok KIM, Okjoo LEE, Sang Jin KIM, Jinsoo RHU, Gyu-Seong CHOI, Jae-Won JOH

Department of Surgery, Samsung Medical Center, Korea

Aims: Repeat liver resection is a good treatment for recurrent hepatocellular carcinoma (HCC). However, laparoscopic repeat liver resection (LRLR) was technically more difficult and was not attempted well. The purpose of our study is to compare the surgical outcomes of ORLR (open repeat liver resection) and LRLR, and to carefully present the LRLR guideline.

Methods: We performed repeat liver resection at single institution from January 2017 to November 2019. We divided the patients into ORLR group (n=27) and LRLR group (n=25). This study retrospectively compared the patient characteristics and surgical outcomes between the two groups.

Results: There was no difference between the two groups in patient characteristics and preoperative blood test except PIVKA (*P*=0.043). In the second operation, the LRLR group had more contralateral cases than the ORLR group in tumor location (44.4% vs. 72.0%, *P*=0.044). The LRLR group had shorter operative time (154 minutes vs. 109 minutes, *P*=0.010), less blood loss (200 mL vs. 100 mL, *P*=0.003), and shorter hospital stay (8 days vs. 5 days, *P*<0.001). However the ORLR group had significantly greater tumor size than the LRLR group (1.9cm vs. 1.4cm, *P*=0.012). And disease free survival was significantly higher in the LRLR group than in the ORLR group (*P*=0.035).

Conclusions: LRLR has better short term outcomes than ORLR. LRLR might be feasible and useful if the recurrent HCC was located contralateral to the previous tumor at a size of less than 3 cm.

FV-107

Liver Resection in Elderly HCC Patients (≥ 75 years) Is Safe

Sunghae PARK, Young Ju OH, Sang Oh YUN, Manuel LIM, Ji Eun JEONG, Eun Sung JEONG, Jaehun YANG, Jinsoo RHU, Gyu-Seong CHOI, Jong Man KIM*, Jae-Won JOH

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Aims: As the general population continues to age, elderly patients have dramatically increased for detecting HCC and required for surgical management. The aim of this study was to compare the postoperative and long-term outcomes of hepatectomy those patients according to the operation time.

Methods: This study included 130 elderly patients who underwent surgical resection for solitary, treatment-naïve HCC between November 1998 and March 2020. Group 1 was defined as patients undergoing LR before 2016 (n=68) and Group 2 was defined as those undergoing LR after 2016 (n=62).

Results: The proportion of major liver resection and laparoscopic liver resection in the Group 2 were significantly higher than in the Group 1. Median operation time and blood loss during operation in the Group 2 were smaller than in the Group 1. In addition, intraoperative RBC transfusion rate, complication rates, and median hospitalization in Group 2 were significantly lower than Group 1. The disease-free survival and patient survival in the Group 2 were better than in the Group 1 even though the presence of tumor grade 3 or 4 and the incidence of microvascular invasion in the Group 1 were higher than in the Group 2. Group 1, long hospitalization, presence of satellite nodule, and intraoperative RBC transfusion were predisposing factors for patient death.

Conclusions: Laparoscopic liver resection in elderly HCC patients, was performed more frequently than in the past, resulting in an increase in the number of liver surgeries and improved survival.

FV-108

Hepatectomy Outcomes in Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma with or without Cirrhosis

Young Ju OH, Sunghae PARK, Sang Oh YUN, Manuel LIM, Jaehun YANG, Eun Sung JEONG, Ji Eun KWON, Kyeong Deok KIM, Jinsoo RHU, Gyu-Seong CHOI, Jong Man KIM*, Jae-Won JOH

Department of Surgery, Samsung Medical Center, Sungkyunkwan

University School of Medicine, Korea

Aims: Although HCC is rare in HCV patients without cirrhosis, little is known about the postoperative results of these patients. We performed this study to compare the outcomes of cirrhotic and non-cirrhotic HCV patients with solitary treatment-naïve HCC and to assess ability of non-invasive markers to predict prognosis in these patients.
Methods: Two hundred seven adult hepatectomy patients with HCV-related HCC were prospectively identified at our institution between July 2005 and May 2019.
Results: One hundred sixteen (56%) hepatectomy patients had HCC in a non-cirrhotic liver. The non-cirrhotic group had better liver function than the cirrhotic group. Consistently, the FIB-4 grade, ALBI grade, and APRI were higher in the cirrhotic group than in the non-cirrhotic group. The cumulative disease-free survival rates and patient survival rates in the non-cirrhotic group were significantly better than in the cirrhotic group. HCC recurrence is related to major liver resection (LR) and alpha-fetoprotein (AFP) >40 ng/mL, death is related to long hospitalization, and AFP >40 in multivariate analysis. APRI was the only predisposing factor for HCC recurrence in non-cirrhotic patients in multivariate analysis. The FIB-4 grade, ALBI grade, and the presence of cirrhosis were not related to HCC recurrence or patient survival in multivariate analyses.
Conclusions: The non-cirrhotic group had a higher survival than the cirrhotic group after curative LR, although the difference was not significant in multivariate analysis. The factors influencing HCC recurrence and patient survival were different in the cirrhotic and non-cirrhotic groups.

FV-109

Sorafenib vs. Nivolumab Treatment after Lenvatinib Failure in Patients with Advanced Hepatocellular Carcinoma

Yuna Kim[1,2], Jae Seung Lee[1,2,3], Hye Won Lee[1,2,3], Beom Kyung Kim[1,2,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Myung Ji Goh[4], Wonseok Kang[4,5], Seung Up Kim[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine; [2]Institute of Gastroenterology, Yonsei University College of Medicine; [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea; [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine; [5]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea

Aims: Lenvatinib has been increasingly selected as the first-line treatment in the patients with advanced hepatocellular carcinoma (HCC). We investigated the treatment outcomes of sorafenib vs. nivolumab as the second-line treatment after lenvatinib failure in Korean patients with advanced HCC in a real-world setting.
Methods: This retrospective study included 60 patients with advanced HCC treated with sorafenib (n=52) or nivolumab (n=8) between November 2018 to June 2020 as the second-line treatment after progressive disease to lenvatinib treatment at two Korean tertiary institutes (Severance Hospital and Samsung Medical Center).
Results: The median age of study participants (49 men and 11 women) was 63.5 years. The baseline demographic variables (age, gender, etiology, and comorbidity), laboratory variables (platelet count, liver function), and tumour-related variables (tumour markers, number, size, vascular invasion, and extrahepatic spread) were similar between the two groups (all *P*>0.05). In addition, the median duration of lenvatinib treatment was comparable (3.9 months in the sorafenib vs. 2.5 months in the nivolumab group, *P*=0.237). The median duration of sorafenib treatment was 1.2 months, whereas that of nivolumab was 2.6 months (*P*=0.164). During the follow-up period (median 7.8 months), 24 (40.0%) patients died. In the entire study population, the median overall survival (OS) was 14.9 months. The median OS of patients in the sorafenib group was significantly longer than that of patients in the nivolumab group (15.3 months vs. 7.2 months, *P*=0.025 by log-rank test). Sorafenib treatment (vs. nivolumab) was independently associated with the lower risk of mortality (hazard ratio=0.114, 95% confidence interval 0.026-0.510; *P*=0.004), together with ECOG performance status, maximal tumour size, presence of portal vein tumour thrombosis and presence of lymph node metastases. (all *P*<0.05).

Table 1. Survival predictors by multivariate cox regression analysis

Variables	Univariate	Multivariate	
	P-value	*P*-value	Hazard ratio (95% CI)
Duration of lenvatinib treatment, months	0.047	0.069	0.833 (0.684-1.014)
ECOG performance status	0.038	0.017	3.136 (1.228-8.012)
Maximal tumor size, cm	0.001	0.029	1.120 (1.012-1.241)
Portal vein thrombosis	0.026	0.009	7.708 (1.660-35.786)
Lymph node metastasis	<0.001	<0.001	14.125 (3.558-56.071)
Alpha fetoprotein, ng/mL	<0.001	0.066	1.000 (1.000-1.000)
Sorafenib as the second-line treatment (vs. nivolumab)	0.131	0.004	0.114 (0.026-0.510)

Conclusions: Lenvatinib-sorafenib sequential therapy showed a significantly better survival than lenvatinib-nivolumab sequential therapy in patients with advanced HCC. Further randomized controlled trials comparing the two second-line strategies after lenvatinib failure are warranted.
Keywords: Second-line, Hepatocellular carcinoma, Treatment outcome, Safety

FV-110

Clinical Features of Extrahepatic Recurrence after Curative Hepatectomy for Hepatocellular Carcinoma: Simple Parameters Predicting Extrahepatic Recurrence

Jae Hyun Yoon[1], Won Jae Lee[1], Sun Min Kim[1], Kwang Tack Kim[1], Sung Bum Cho[2], Hee Joon Kim[3], Yang Seok Ko[4], Hyun Yi Kook[5], Chung Hwan Jun[6], Sung Kyu Choi[1]

[1]Department of Gastroenterology, Chonnam National University Hospital and Medical School, Gwangju, South Korea; [2]Department of Gastroenterology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea; [3]Department of Surgery,

Chonnam National University Hospital and Medical School, Gwangju, South Korea; [4]Department of Surgery, Chonnam National University Hospital and Medical School, Gwangju, South Korea; [5]Department of Nursing, Chonnam National University, Gwangju, South Korea; [6]Department of Internal Medicine, Mokpo Hankook Hospital, Mokpo, South Korea

Aims: Extrahepatic recurrence (EHR) after curative hepatectomy for hepatocellular carcinoma (HCC) is associated with a poor prognosis. We investigated the features of EHR and identified its predictive factors.

Methods: This retrospective study included 398 treatment-naive patients who underwent curative hepatectomy for HCC at two tertiary hospitals. Multivariate analysis via Cox-regression was performed to identify the variables associated with EHR.

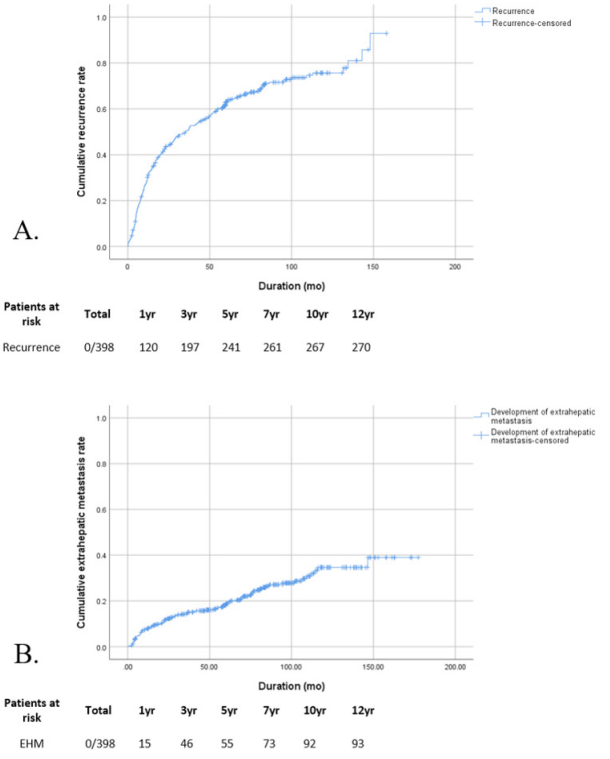


Figure 1. Recurrence curves of hepatocellular carcinoma after surgical resection (A): cumulative rates of HCC recurrence. (B): Cumulative rates of extrahepatic recurrence.

Results: EHR was diagnosed in 94 patients (23.6%) over a median follow-up period of 5.92 years, most commonly in the lungs (42.6%). The 5-/10-year cumulative rates of HCC recurrence and EHR were 63.0%/75.6% and 18.1%/35.0%, respectively. The median time to EHR was 2.06 years. Intrahepatic HCC recurrence was not observed in 38.3% of patients on EHR diagnosis. On multivariate analysis, Pathologic mUICC stage (III, IVa), surgical margin involvement, tumor necrosis, sum of tumor size >7cm, and macrovascular invasion were predictive of EHR. Four risk levels and their respective EHR were defined: very low risk, 1-/5-year, 3.1%/11.6%; low risk, 1-/5-year, 12.0%/27.7%; intermediate risk, 1-/5-year, 36.3%/60.9%; and high risk, 1-year, 100.0%.

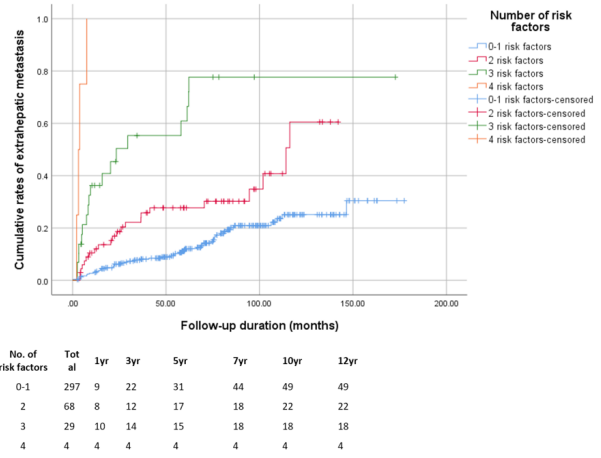


Figure 2. cumulative rate of extrahepatic recurrence after curative hepatectomy, stratified by the number of risk factors present.

Conclusions: Our predictive model clarifies the clinical course of EHR and could improve the follow-up strategy to improve outcomes.

Keywords: Hepatocellular carcinoma, Extrahepatic recurrence, Recurrence, Risk factor

FV-111

Efficacy and Safety of Atezolimumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma : A Real-World Data in Korea

Beom Kyung Kim[1], Jaekyung Cheon[2], Hyeyeong Kim[3], Beo Deul Kang[2], Yeonjung Ha[4], Do young Kim[1], Sung Kyu Hwang[4], Hong Jae Chon[2], Young Eun Chon[4]

[1]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Department of Medical oncology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [3]Department of Gastroenterology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [4]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea

Aims: The combination of atezolimumab and bevacizumab has been recently approved as a first-line treatment for patients with advance hepatocellular carcinoma (HCC) in Korea. We investigated the efficacy and safety of atezolimumab and bevacizumab therapy in a real-world clinical practice.

Methods: Patients with unresectable HCC who received atezolimumab plus bevacizumab therapy between June 2020 and February 2021 from 3 tertiary hospitals were retrospectively analyzed. The primary endpoints were overall survival (OS) and progression-free survival (PFS) assessed with Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.

Results: Efficacy analysis was conducted in 79 patients, who had a mean age of 64 years (male predominance, 81.1%). The median follow up duration was 5.2 (3.2-7.2) months. OS and PFS at 6 months was 80.7% and 49.6%, respectively. The objective

response rate was 36.8%, and disease control rate was 74.6%. Child-Pugh class A (versus B) was a favorable predictor for PFS. Safety analysis was conducted in 90 patients, adding 11 more patients who did not receive 1st tumor response assessment. The most common AEs were hypertension (41.1%), followed by alanine aminotransferase elevation (36.7%), and fatigue (34.4%). The most common grade 3 or 4 AE was hypertension, which occurred in 5.6% of patients.

Conclusions: In patients with unresectable HCC, atezolimumab plus bevacizumab therapy in a real-world demonstrated a favorable efficacy. AEs including hypertension were manageable and well-tolerated.

Keywords: Atezolimumab, Bevacizumab, Hepatocellular carcinoma, Efficacy

FV-112

Post-Resection Prognosis of Patients with Hepatic Epithelioid Hemangioendothelioma

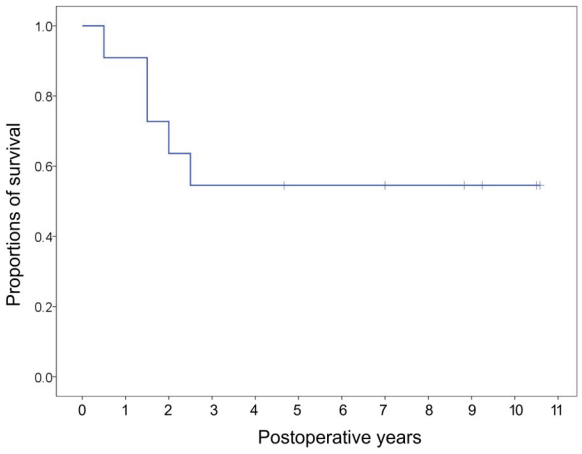
Shin Hwang[1], Byeong-Gon Na[1], Chul-Soo Ahn[1], Ki-Hun Kim[1], Deok-Bog Moon[1], Tae-Yong Ha[1], Gi-Won Song[1], Dong-Hwan Jung[1], Seung-Mo Hong[2], Sung-Gyu Lee[1]

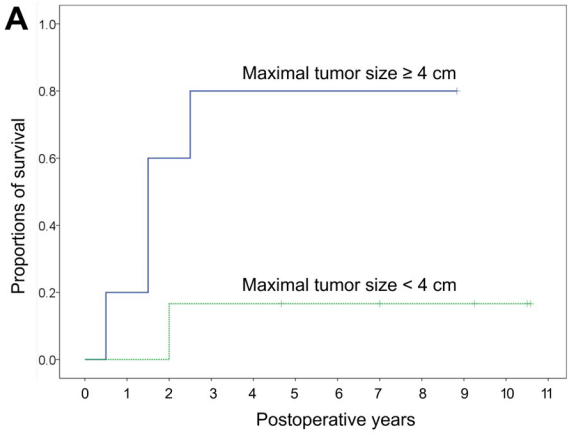
[1]Department of Surgery and [2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

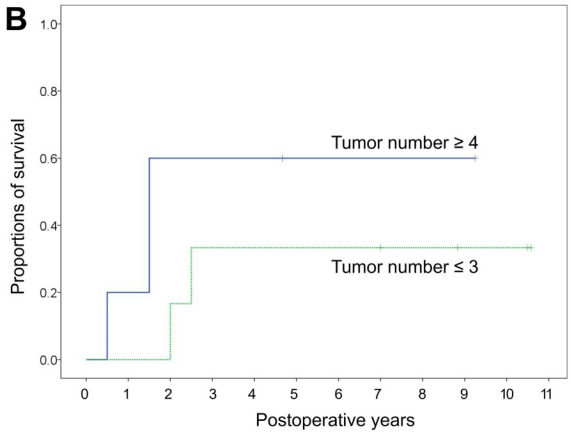
Aims: Epithelioid hemangioendothelioma (EHE) is a rare borderline vascular tumor. This retrospective, single-center study evaluated the outcomes of hepatic resection (HR) in patients with hepatic EHE.

Methods: Over the 10-year period from 2009 to 2018, 11 patients with hepatic EHE underwent HR, accounting for 0.1% of the 11,979 adults who underwent HR at our center. Diagnosis of hepatic EHE was confirmed by immunohistochemical staining for CD34, CD31 and factor VIII-related antigen.

Results: The 11 patients included nine (82%) women and two (18%) men, of mean age 43.5±13.6 years. Preoperative imaging resulted in a preliminary diagnosis of suspected liver metastasis or EHE, with nine patients (82%) undergoing liver biopsy. No patient presented with abnormally elevated concentrations of liver tumor markers. The extents of HR were determined by tumor size and location from trisectionectomy to partial hepatectomy. All patients recovered uneventfully from HR. Five patients showed tumor recurrence, with four receiving locoregional treatments for recurrent lesions. The 1-, 3- and 5-year disease-free survival rates were 90.9%, 54.5% and 54.5%, respectively. Currently, all patients remain alive and are doing well. Univariate analysis on tumor recurrence showed that tumor size ≥4 cm was significantly associated with tumor recurrence (P=0.032), but tumor number ≥4 was not related to tumor recurrence (P=0.24).







Conclusions: Hepatic EHE is a rare form of primary liver tumor often misdiagnosed as a metastatic tumor. Because of its malignant potential, HR is indicated if possible. HR plus, when necessary, treatment of recurrence yields favorable overall survival rates in patients with hepatic EHE.

Keywords: Hemangioendothelioma, Vascular tissue neoplasm, Hemangioma

FV-113

Post-Resection Prognosis of Combined Hepatocellular Carcinoma-Cholangiocarcinoma According to the 2019 WHO Classification

Shin Hwang[1], Minjae Kim[1], Chul-Soo Ahn[1], Ki-Hun Kim[1], Deok-Bog Moon[1], Gi-Won Song[1], Dong-Hwan Jung[1], Seung-Mo Hong[2]

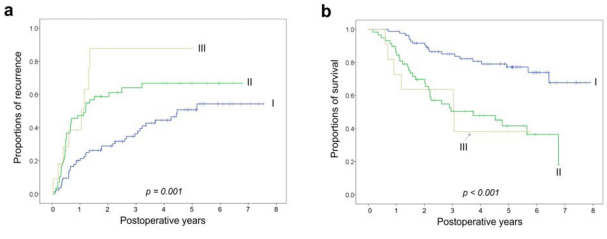
[1]Department of Surgery and [2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

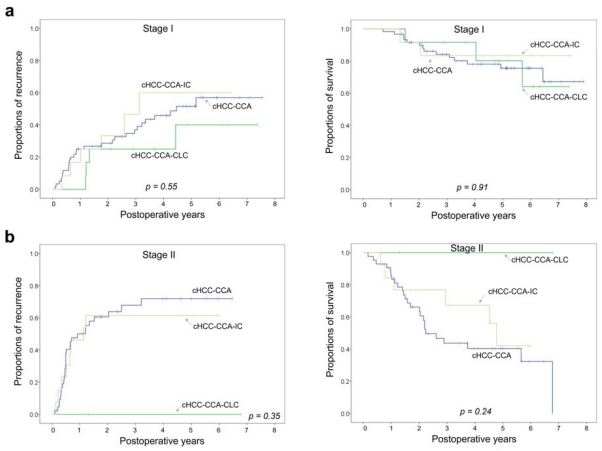
Aims: Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CCA) has wide histologic diversity. This study investigated the prognostic impacts of cHCC-CCA histology according to the 2019 World Health Organization (WHO) classification.

Methods: This retrospective observational study included 153 patients who underwent surgical resection for cHCC-CCA at Asan Medical Center between August 2012 and July 2019.

Results: During the study period, 153 patients, 112 (73.2%) men and 41 (26.8%) women with a mean age of 56.4±10.8 years, underwent R0 resection for cHCC-CCA. Mean tumor diameter was 4.2±2.6 cm, and 147 (96.1%) patients had solitary tumors. According to 2019 WHO classification, 111 (72.5%) patients had cHCC-CCA alone, and 29 of them (26.1%) showed stem cell features. cHCC-CCA-intermediate cell carcinoma and cHCC-CCA-cholangiolocellular carcinoma were identified in 27 (17.6%) and 15 (9.8%), respectively. The 1-, 3-, and 5-year tumor recurrence and patient survival rates were 31.8% and 92.1%, 49.8% and 70.9%, and 59.0% and 61.7%, respectively. Univariate analyses revealed that significant prognostic factors were tumor size >5 cm, microscopic and macroscopic vascular invasion, lymph node metastasis, 8th American Joint Committee on Cancer (AJCC) tumor stage, and status of stem cell feature. Multivariate analysis revealed 8th AJCC tumor stage and status of stem cell features as independent prognostic factors. The 2019 WHO classification was not associated with post-resection prognosis.

Conclusions: The 2019 WHO classification was not associated with post-resection prognosis, thus was considered as a simple histologic classification. We suggest that stem cell features should be included as an essential component of the pathology report for cHCC-CCA.





Keywords: Mixed tumor, Stem cell feature, Hepatic progenitor cell, Combined tumor

FV-114

Prediction of Post-Resection Prognosis with ADV Score for Huge Hepatocellular Carcinoma ≥13 cm

Shin Hwang, Ki-Hun Kim, Deok-Bog Moon, Chul-Soo Ahn, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park

Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

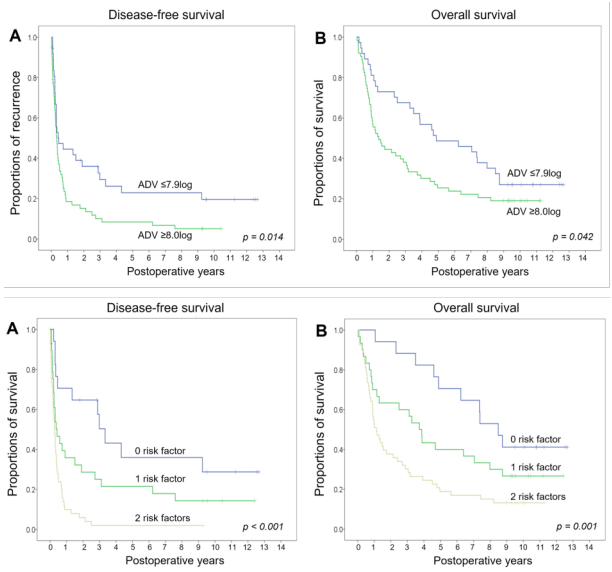
Aims: Multiplication of α-fetoprotein, des-γ-carboxy prothrombin and tumor volume (ADV score) is a surrogate marker for post-resection prognosis of hepatocellular carcinoma (HCC). The objective of this study was to validate the predictive power of ADV score-based prognostic prediction model for patients with solitary huge HCC.

Methods: Of 3,018 patients, 100 patients who underwent hepatic resection for solitary HCC ≥13 cm between 2008 and 2012 were selected.

Results: Median tumor diameter and tumor volume were 15.0 cm and 886 mL, respectively. Tumor recurrence and overall survival (OS) rates were 70.7% and 66.0% at 1 year, and 84.9% and 34.0% at 5 years, respectively. Microvascular invasion was the only independent risk factor for disease-free survival (DFS) and OS. DFS and OS stratified by ADV score with 1log intervals showed significant prognostic contrasts (P=0.007 and P=0.017, respectively). DFS and OS stratified by ADV score with a cutoff of 8log showed significant prognostic contrasts (P=0.014 and P=0.042, respectively). Combination of MVI and ADV score with cutoff of 8log also showed significant prognostic contrasts in DFS (P<0.001) and OS (P=0.001) according to the number of risk factors. Prognostic contrast was enhanced after combination of MVI and ADV score than each alone.

Conclusions: The prognostic prediction model with ADV score could reliably predict the risk of tumor recurrence and long-term patient survival outcomes in patients with solitary huge HCCs ≥13 cm. Results of this study suggest that our prognostic

prediction models can be used to guide surgical treatment and post-resection follow-up for patients with huge HCCs.



Keywords: Hepatocellular carcinoma, Resection, Recurrence, Microvascular invasion

FV-115

Improved Oncologic Outcomes by Ablative Radiotherapy in Patients with Bone Metastasis from Hepatocellular Carcinoma

Tae Hyung Kim, Sangjoon Park, Chai Hong Rim, Chiwhan Choi, Jinsil Seong

Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Aims: For bone metastasis from hepatocellular carcinoma (HCC), radiotherapy (RT) has been used a palliative treatment with little impact on survival. Currently, ablative RT is popularly used, and a more than palliative effect is expected. Herein, we investigated the clinical efficacy of ablative RT in patients with bone metastasis from HCC.

Methods: In total, 530 patients with 887 lesions treated in 1992–2019 were reviewed. Oligometastasis was defined as the presence of <5 lesions. Total doses were normalized to obtain biologically effective doses (BEDs). The cut-off threshold of the BED was determined via receiver operating characteristics curve analysis. The Kaplan-Meier method was used to calculate overall survival (OS); propensity score matching (PSM) was performed to balance the heterogeneity in cases while comparing BEDs of ≥60 and <60 Gy.

Results: The most common site of metastasis was the spine (59%); 59 patients (11%) presented with oligometastasis, and 76.2% of patients showed objective pain palliation after RT. Median OS was 5.1 months for all patients; patients with oligometastasis showed longer OS than those without (9.8 vs. 4.7 months). A Cox proportional hazards model showed that performance status, Child-Pugh class, extraosseous metastasis, primary HCC status, α-fetoprotein level, and radiation dose (BED) were significant prognostic factors. Post-PSM, BED was the only treatment-related prognostic factor that remained significant; the median OS durations were 8.1 and 4.4 months when the BEDs were ≥60 and <60 Gy, respectively.

Conclusions: Ablative RT improved OS and pain palliation in patients with bone metastasis from HCC.

Keywords: Bone metastasis, Radiotherapy, Overall survival, Oligometastasis, Ablative dose

FV-116

Laparoscopic Right Posterior Sectionectomy (LRPS) in Semi Prone Position: Surgical Aspects and Results

Nikolay BELEV, Panche KRASTEV*, Radoslav PENKOV, Mihail SLAVCHEV

Surgical department, Medical Training and Simulation Center, MU-Plovdiv, Bulgaria

Aims: Laparoscopic hepatectomy has been accepted widely due to its advantages as a minimally invasive surgery, but laparoscopic right posterior sectionectomy (LRPS) has rarely been reported. Tumors located over the right posterior section are considered to be difficult for laparoscopic resection. The Glissonean approach is our technique of choice. The aim of this work is to present our experience in LRPS in semi prone position and to show surgical technical aspects.

Methods: For six years period we were performed 12 LRPS procedures. Patient's data were prospectively collected. Demographics data, tumor characteristics, operative data, and postoperative outcome were collected and analyzed. There were 8 patients with colorectal liver metastasis, 2 patients HCC, one melanoma metastasis and one breast cancer liver metastasis.

Results: During the period of 2014–2020, we performed 12 LRPS. There were 8 patients with colorectal liver metastasis, 2 HCC patients, one melanoma metastasis and one breast cancer liver metastasis.Median operative time was 200 minutes, and median blood loss was 300 ml. Significant bleeding occurred in 1 cirrhotic liver patients. The median size of the tumor resected was 3.5 cm, and the median resection margin was 7 mm. Nine patients show single tumor nodule, 2 patients had two metastases and 1 with 3 metastases. There was no postoperative mortality. Median hospital stay was 6 days.

Conclusions: LRPS is a technically demanding procedure. LRPS in semi prone position is feasible and safe. Semi prone position offers a maximum amount of working space. A proper inflow and outflow control is mandatory for proper anatomical resection. The Glissonean approach allows

FV-117

Angiomyolipoma Mimicking Hepatocellular Carcinoma on Preoperative Magnetic Resonance Image: The way to Prevent Unnecessary Surgery for HAML

Hyeo Seong HWANG[1], Young Nyun PARK[2], Dai Hoon HAN[*1], Gi Hong CHOI[1], Kyung Sik KIM[1], Jin sub CHOI[1]

[1]Department of Surgery, Yonsei University College of Medicine, Korea; [2]Department of Pathology, Yonsei University College of Medicine, Korea

Aims: The Image of magnetic resonance (MR) of hepatic angiomyolipoma (AML) is often mistaken for hepatocellular carcinoma (HCC). In this study, clinicopathological, and imaging features of hepatic AML misdiagnosed with a malignant tumor before surgery were reviewed.

Methods: A total of 34 patients diagnosed with hepatic AML by surgery (n=20) or biopsy (n=14) were included (2008-2020). Twenty female and 14 male patients with a mean age of 52.9 years (range 28-78) were followed up for about 68.23 months.

Results: Only one patient was positive for HBsAg among 34 cases, and preoperative levels of serum alpha-fetoprotein and protein induced by vitamin K absence-II were not increased for all patients. Two patients showed non-alcoholic fatty liver disease. Twenty-nine patients have solitary liver tumor and the remainder has multiple ones. In two cases, renal AML was simultaneously diagnosed. In preoperative MRI, AML was misdiagnosed as HCC(n=14, 41.2%), adenoma(n=1, 2.9%), cholangiocellular carcinoma(n=1, 2.9%), intrahepatic metastasis of malignant tumor (n=2, 5.8%), or inconclusive opinions (n=6, 17.6%). In subgroup analysis, overall survival was not different (*P*=0.496), on the contrary, biopsy group showed significantly short length of hospitalization (*P*=0.001), small tumor size (23.5mm versus 45.8mm, *P*=0.017), better diagnostic accuracy (50% versus 15.0%, *P*=0.011). In immunohistochemical analysis, several antibodies were detected including HMB45 (in 32 cases), SMA (n=19), CD 34 (n=7), Melanin A (n=5).

Conclusions: Since AML is a benign tumor, for the suspicious HCC suddenly discovered in a patient without clinical risk factors, it is better to perform biopsy first to prevent unnecessary surgery.

FV-118

The Role of R0/R1vasc Resection in the Treatment of Patients Affected by Marginal Resectable Colorectal Liver Metastases: A Pairwise Propensity Score Match Analysis

Matteo Maria CIMINO, Fabio PROCOPIO, Simone FAMULARO, Daniele DEL FABBRO, Matteo DONADON, Luca VIGANO', Guido TORZILLI

General and Hepatobiliary Surgery, Humanitas Clinical and Research Center - IRCCS, Rozzano Milan - Italy, Italy

Aims: Increasingly, patients with multiple colorectal liver metastases (CRLM) are surgically treated. R1par surgery remains one of the negative prognostic factors for overall survival(OS). According to our data on R1 in main intrahepatic vascular contact (MVC), we investigate the oncological outcome of patients with multiple bilobar disease with bilateral MVC (BC), compared to patients with unilateral MVC (UC) and patients with disease and no MVC (NC).

Methods: This single-institution study included patients who underwent hepatectomy for multiple (≥4) bilobar CRLM lesions from 2004-2019. Three-hundred-fifty-five patients meet the inclusion criteria. One-hundred-thirty-two patients with R1par resection were excluded. Three groups were defined: NC, UC, BC. After pairwise propensity score match 145 patients were analyzed.

Results: No differences between groups were observed in the preoperative variables. Increased surgical time, hilar clamping, and blood loss were reported in the BC group. Postoperative minor morbidity, liver failure rate, overall and local recurrences were higher in the BC group. BC patients were more likely to be re-resected. Cumulative OS 3-5 years survival in NC, UC, BC were 54%- 40%, 49% - 35%, 57%-24% (*P*<0.91). At multivariate analysis, factors influencing OS, were N status of the primitive lesions, RAS status, and repeated hepatectomy.

Conclusions: Patients with BC and lesions ≥ 4 are generally considered unresectable or suitable for staged hepatectomy. This retrospective study shows that these patients can be submitted to the so called enhanced-one-staged hepatectomy with the same oncological results, however surgical complexity, postoperative minor morbidity and postoperative liver failure are increased.

FV-119

Prognostic Significance of Cachexia Index in Patients with Advanced Hepatocellular Carcinoma Treated with Lenvatinib Therapy

Myung Ji Goh[1], Wonseok Kang[1,2*], Joo Hyun Oh[1], Ye-wan Park[1], Jihye Kim[1], Dong Hyun Sinn[1], Woo Kyoung Jeong[3], Geum-Youn Gwak[1], Yong-Han Paik[1,2], Moon Seok Choi[1], Joon Hyeok Lee[1], Kwang Cheol Koh[1], Seung Woon Paik[1]

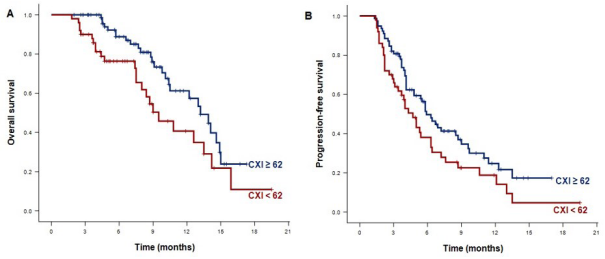
[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Radiology and Center for Imaging Sciences, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Cancer cachexia affects quality of life, response to chemotherapy, and survival in many advanced cancer patients. The cachexia index (CXI) was originally developed for assessment of the degree of cachexia and has demonstrated its correlation with prognosis in non-small cell lung cancer. The aim of this study was to evaluate the prognostic value of pretreatment CXI in patients with advanced hepatocellular carcinoma (HCC) treat-

ed with lenvatinib.

Methods: Patients with advanced HCC treated with lenvatinib between October 2018 and October 2020 were retrospectively studied. The CXI was calculated as (L3 skeletal muscle index) × (serum albumin) / (neutrophil-to-lymphocyte ratio). The association with treatment response and early adverse events within the first two months of lenvatinib therapy was investigated. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method with log-rank test. Multivariable Cox regression was used to identify the predictors of survival.

Results: A total of 128 enrolled patients (median age: 60) were divided into two groups: high CXI (≥62, n=78) and low CXI (<62, n=50). Patients with low CXI had a significantly lower disease control rate (68.0% vs. 87.2% *P*=0.013) and a shorter OS (9.5 vs.13.2 months, *P*=0.001) than those with high CXI. In multivariable analysis, low CXI was independently associated with shorter OS (HR: 1.97, 95% CI: 1.02-3.80, *P*=0.04). Of note, during the first two months of lenvatinib therapy, anorexia developed more frequently among patients with low CXI than those with high CXI (44% vs. 16.7%, *P*=0.001).



Conclusions: The CXI may be a useful clinical index for predicting the prognosis in patients with advanced HCC receiving lenvatinib treatment.

Keywords: Cachexia, Sarcopenia, Lenvatinib, Hepatocellular carcinoma

FV-120

Evaluation of FIB-4 and APRI in Predicting the Prognosis of Hepatocellular Carcinoma Patients after Hepatic Resection

Sang Oh YUN[1], Jong Man KIM[*2]

[1]Surgery, Korean Armed Forces Capital Hospital, Korea; [2]Surgery, Samsung Medical Center, Korea

Aims: For the APRI and FIB-4 index, which are one of the non-invasive methods of examining the degree of liver fibrosis, our paper aims to examine the implications for predicting the prognosis in hepatocellular carcinoma patients undergoing hepatectomy.

Methods: Between 2006 and 2013, total 973 patients were underwent hepatic resection due to hepatocellular carcinoma and 871 patients were enrolled in our study after adjusting exclusion criteria. Statistics were performed by calculating the optimal cut off values for the recurrence free survival and overall survival of each group which are categorized by etiology and multivariate analysis were performed for evaluating the performance of index.

Results: Among the causes of HCC patients, HBV (n=629, 72%) was the most common, and men were dominant in all groups. In each group divided by etiology, the area under the receiver operating characteristics of APRI and FIB-4 for recurrence free survival and overall survival were relatively higher in HCV patients than in other groups. After setting the cut-off value through the Youden index, univariate analysis and multivariate analysis for RFS and OS of all groups were performed, and the results of APRI values for RFS in each group were statistically significant (HBV: OR= 1.849, p-value=0.001; HCV: OR=6,548, p-value=0.010; Alcohol: OR=3.393, p-value=0.004)

Conclusions: The significance of this study is that these simple laboratory findings are meaningful in revealing the prognosis of HCC patients, which can be predicted accurately only after the pathologic staging after surgery.

FV-121

Liver Transplantation Versus Hepatic Resection for Hepatocellular Carcinomas with High Risk-MR Findings: A Propensity Score Matched Study

Dong Ik Cha[1], Woo Kyoung Jeong[1], Jong Man Kim[2], Nam-Joon Yi[3], Dong Hyun Sinn[4]

[1]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro Gangnam-gu, Seoul, Republic of Korea; [2]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: To compare recurrence-free survival (RFS) between liver transplantation (LT) hepatic resection (HR) for hepatocellular carcinomas (HCC) with high risk imaging findings on pre-operative gadoxetic acid-enhanced magnetic resonance imaging (MRI).

Methods: This multicenter retrospective study was approved by the institutional review boards. Patients who underwent primary LT or HR for HCC between January 2009 and January 2017 were compared for RFS with Kaplan-Meier method by propensity score matching with a 1: up to 2 ratio. Only HCCs eligible for HR were included. Two radiologists evaluated MRI findings associated with high risk of recurrence including peritumoral arterial enhancement, tumor shape irregularity, and peritumoral hypointensity on hepatobiliary phase. Subgroup analysis was conducted according to the presence of the high risk imaging findings.

Results: Matching yielded 57 LT patients and 99 HR patients. Median follow-up period was 64.8 months (range 0.5~132 months), with 56 events (recurrence 51 and death 20). RFS

in the total patients was significantly higher with LT than HR (*P*=0.008). Imaging analysis showed that there were 95 patients with high risk imaging findings (LT 30, HR 65). In the subgroup analysis, RFS was also significantly higher with LT than HR for patients without high risk findings (*P*=0.016). In patients with high risk imaging findings, RFS was not significantly different between LT and HR (*P*=0.182).

Conclusions: RFS for HCCs with high risk findings on pre-operative MRI was not significantly different between HR and LT.

Keywords: Gadoxetic acid, Magnetic resonance imaging, Hepatocellular carcinoma, LIver transplantation, Resection

10. Liver Transplantation

FV-122

Hepatic Artery Reconstruction Using Mid-Colic Artery in LDLT

Jae Geun Lee[1], Eun Jin Kim[1],Dong Jin Joo[1], Dai Hoon Han[1], Gi Hong Choi[1], Jin Sub Choi[1], Myoung Soo Kim[1], Soon Il Kim[1]

Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: In situation not available native hepatic artery or gastroepiploic artery, to find alternative artery for anastomosis.

Methods: Complication of hepatic artery after LDLT is a lethal complication, with incidence ranging from 2.5% to 9%. Although we attempt to meticulously dissect the hepatic artery without any injury, the native hepatic artery is sometimes unavailable because of repeated transarterial chemoembolization, radiation therapy, intra-arterial (iA) chemotherapy (CTx) or concurrent chemo-radiation therapy (CCRT). In this difficult situation, for obtaining the hepatic arterial source, instead of the native HA, the right gastroepiploic artery is mostly preferred because of its ease of access and adequate length. In situation not available gastroepiploic artery, however next choice of recipient artery is not established

Results: Herein, we reported Hepatic artery anastomosis from recipient mid-colic artery to graft Rt. hepatic artery. 66 old years man had 10cm diffuses infiltrate HCC (B-viral) with portal vein tumor thrombosis and treated by two times iA CTx in CCRT and 9 times iA 5FU/DDP CTx after CCRT. After CCRTx, He underwent LDLT because of liver failure using recipient mid-colic artery.

Conclusions: Mid-colic artery can be considered alternative hepatic artery reconstruction in situation

Keywords: Liver transplantation, Hepatic artery, Reconstruction

FV-123

Early Use of Everolimus Improved Renal Function after Adult Deceased Donor Liver Transplantation

Jaehun YANG, Sunghae PARK, Young Ju OH, Sang Oh YUN, Manuel LIM, Ji Eun KWON, Eun Sung JEONG, Jinsoo RHU, Gyu-Seong CHOI, Jong Man KIM*, Jae-Won JOH

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Tacrolimus (TAC) is a main therapy for liver transplantation (LT) patients to maintain graft function and to balance low acute rejection. Dose-related side effects of TAC were associated with acute and chronic renal dysfunction, neurotoxicity, increased malignancies, cardiovascular disease, and metabolic disorders. The purpose of this study was to retrospectively compare the renal function between a TAC group and a combination of everolimus and reduced TAC (EVR-TAC) group after deceased donor liver transplantation (DDLT).

Methods: We reviewed a retrospectively collected database of the records of all adults who underwent DDLT between January 2013 and April 2018 at our institution; during that time, 278 adult DDLTs were performed at our institution. Patients were excluded according to the following criteria: living donor LT, retransplantation, use of cyclosporin and/or antimetabolite monotherapy, discontinuation of EVR, history of continuous renal replacement therapy on the waiting list, history of proteinuria or hyperlipidemia, synchronous multiple organ transplants, pediatric LT (age <18 years), receiving a split graft, receiving a liver graft after donor cardiac death, and incomplete medical records. Patients who died from transplantation until May 2020 or received hemodialysis or kidney transplantation because of renal failure until May 2020, were also excluded. 131 patients were included in our study. They received TAC or EVR-TAC after DDLT. EVR was introduced between one and six months after DDLT.

Results: Thirty-six of 131 patients (27.5%) received EVR-TAC. The incidence of chronic kidney disease (CKD; estimated glomerular filtration rate, <60 mL/1.73 m2) in the EVR-TAC group was higher than in the TAC group (25% vs. 8.4%; *P*=0.019) (Tabel 1). Increasing serum creatinine (n=23, 63.9%) was the most common cause for adding EVR to treatment of the post-transplant patients. There were no statistical differences in acute rejection and CKD between the two groups(Figure 1). The TAC trough level was significantly lower in the EVR-TAC group than in the TAC group, and the renal function of the EVR-TAC group was worse than that of the TAC group until one year after DDLT. However, the renal function of the EVR-TAC group improved and became similar to that of TAC group at 3 years posttransplant(Figure 2 and Figure 3).

Conclusions: According to our study, renal function gradually recovered in patients who added EVR treatment between 1 and 6 months after DDLT. There was no statistical difference in acute rejection between the two groups. The present study suggests that EVR should be introduced as soon as possible after DDLT

to reduce exposure to high doses of TAC to improve the renal function.

Table 1. Baseline recipient characteristics Values are presented as number (%) or median (range)

Variable	TAC (n=95)	EVR-TAC (n=36)	P-value
Sex (male)	59 (62.1)	22 (61.1)	0.917
Age (yr)	53 (28–77)	51 (20–68)	0.453
Body mass index	24.9 (14.9–38.0)	23.0 (17.5–37.9)	0.014
Hypertension	15 (15.8)	6 (16.7)	0.932
Diabetes	24 (25.3)	5 (13.9)	0.238
Diagnosis			0.713
Alcoholic	32 (33.7)	8 (22.2)	
Hepatitis B virus	41 (43.2)	14 (38.9)	
Hepatitis C virus	4 (4.2)	4 (11.1)	
Non B, non C	8 (8.4)	5 (13.9)	
Autoimmune	3 (3.2)	1 (2.8)	
Toxic	3 (3.2)	2 (5.6)	
Hepatitis A virus	2 (2.1)	1 (2.8)	
Others	2 (2.1)	1 (2.8)	
Coexistence of HCC	25 (26.3)	8 (22.2)	0.822
MELD	33 (7–40)	37 (13–40)	0.135
Child-Pugh class			0.129
A	5 (5.3)	0	
B	21 (22.1)	6 (16.7)	
C	69 (72.6)	30 (83.3)	
CKD pretransplant	8 (8.4)	9 (25.0)	0.019
eGFR pretransplant (mL/1.73 m^2)	67.4 (6.4–123.7)	54.2 (5.9–114.4)	0.054
Cr pretransplant (mg/dL)	1.05 (0.31–3.08)	1.24 (0.44–3.80)	0.086

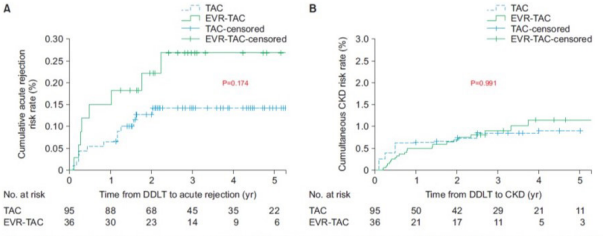


Figure. 1. The risk for developing acute rejection (A) and chronic kidney disease (CKD) (B). TAC, tacrolimus; EVR-TAC, everolimus and reduced tacrolimus; DDLT, deceased donor liver transplantation.

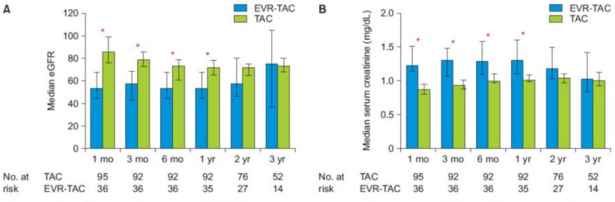


Figure. 2. Renal function change after DDLT. (A) Estimated glomerular filtration rate (eGFR) and (B) serum creatinine. *P<0.05.

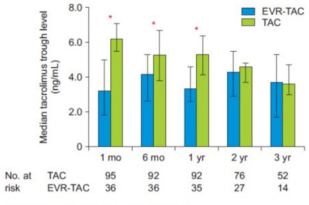


Figure. 3. TAC trough level. *P<0.05.

Keywords: Liver transplantation, Renal function, Calcineurin inhibitors, Mammalian target of rapamycin inhibitor, Immunosuppression

FV-124

Renoportal Anastomosis in Adult-to-Adult Living Donor Liver Transplantation for Patients with Portal Vein Thrombosis in Single Center Experience

Deok-Bog MOON*, Sung-Gyu LEE, Young-In YOON

Division of Hepatobiliary Surgery and Liver Transplantation,, Asan Medical Center, University of Ulsan College of Medicine, Korea

Aims: The anastomosis between the left renal vein and graft portal vein is one of the crucial options in patients with end-stage liver disease with portal venous thrombosis and a previous splenorenal shunt. However, especially in living donor liver transplantation (LDLT) practice, limited cases are published in the literature.

Methods: Between January 2006 and December 2019, a total of 14 patients underwent adult LDLTs with renoportal anastomosis (RPA). The long-term outcomes were evaluated by reviewing the medical records of the 14 patients.

Results: Of the 14 patients who received adult LDLTs with RPA, 2 patients underwent end-to-end (E-to-E) RPA using left renal vein(LRV), 5 patients underwent side-to-end (S-to-E) RPA, and the rest underwent E-to-E RPA using LRV connected IVC cuff. Except two patients who died from cerebral hemorrhage and graft failure came from acute cellular rejection, twelve patients has maintained normal graft function and a patent RPA at a median follow-up of 42 months (range, 1-155 months).

Conclusions: RPA can be performed safely and effectively in LDLT as an acceptable and life-saving procedure for patients with end-stage liver disease with portal venous thrombosis and a previous splenorenal shunt. According to our experience, E-to-E RPA using LRV connected IVC cuff is the best option considering feasibility and safety.

FV-125

Early Experience of Pure Minimally Invasive Donor Hepatectomy by Junior Surgeon

Dai Hoon HAN[1], Jae Geun LEE[2], Dong Jin JOO[2], Gi Hong CHOI[1], Jin Sub CHOI[1]

[1]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, Korea; [2]Division of Transplantation Surgery, Department of Surgery, Yonsei University College of Medicine, Korea

Aims: Although the pure minimally invasive donor hepatectomy (PMIDH) has been increasingly performed, it is still reported by experienced surgeons. Here we reported the early experience of PMIDM by junior surgeon.

Methods: From April 2019 to November 2020, PMIDHs were

performed for 19 patients by single novice surgeon (H.D.H) at Yonsei University College of Medicine. Clinical characteristics, perioperative outcomes of donors and clinical features of recipients were analyzed.

Results: 18 of 19 donors had pure laparoscopic liver resection. Right, left hemihepatectomies and left lateral sectionectomies were performed for 15, 1 and 3 donors, respectively. Mean total operation time was 460.63 ± 70.89 minutes and median operative bleeding was 200 mL (50 ~ 1600mL). Median hospital stay was 8 (7 ~ 11) days. In terms of laparoscopic donor right hemihepatectomy, mean total operation time was 464.21 ± 43.52 minutes. Median amount of bleeding during operation was 225 mL (50 ~ 1600mL). Mean estimated total liver volume was 1228.26 ± 217.01 (935.80~1584.90) and mean real graft weight was 764.86 ± 153.46 (529.00~1077.00). The robotic donor right hemihepatectomy was performed for one donor. Total operation time was 663 minutes with 550 mL of operative bleeding. There was no conversion to open surgery. Only the first donor had transfusion during operation. There was no severe perioperative complication more than grade III according to classification of Clavien-Dinido surgical complication.

Conclusions: Although the PMIDH may need high level of surgical skill, it appears to be a safe and feasible procedure by junior surgeon in properly selected donors.

FV-126

Liver Transplantation from Discarded Liver Grafts: Expanding the Donor Liver pool in Mexico

Carlos FLOREZ-ZORRILLA[1], Karina MENDOZA-GALLO[2], Miguel CHARCO-CRUZ[1]

[1]HPB and Liver Transplantation, Centro Medico Nacional 20 de noviembre-ISSSTE, Mexico; [2]Pediatrics, Hospital General Regional 46-IMSS, Mexico

Aims: Extended criteria donors (ECD) in liver transplantation has become a common policy because the shortage of optimal organs . Most of liver transplantation groups agree that prolonged cold ischemia, obesity, steatosis, age, hipernatremia, inotropic support, non heart beating donors (NHBD), split livers are related to primary non-function (PNF) of the liver graft with high morbidity and mortality. Discarded liver grafts by contrast accounts every year for more than two-fold the liver transplants done in Mexico. Poor donor characteristics such as steatosis >40%, severe hyponatremia, alcohol abuse and obesity are frequently cause of declination by most transplant teams.

Methods: A five year period was observed from january 2015 to january 2020. Donor variables such as severe hipernatremia (>165 Meq/l), moderate steatosis (>40%), BMI (>30 kg/m2), alcohol abuse and cold ischemia time (CIT) more than 8 hr were recorded and considered risk factors for PNF. Delayed graft function (DGF), PNF and complications were evaluated. All liver donors were discarded by at least three main liver transplant centers in Mexico City.

Results: 155 LT were done. Marginal donors 60 (38.7%). Discarded livers 40 (66.6%). Severe hypernatremia (165-188 Meq/l), 19 (47.5%), obesity (30-45 kg/m2), 30 (75%) and moderate to severe steatosis (40-76%), 21 (52.5%), alcohol abuse 2 (5%). There were no differences in PNF rate, when three factors coexists DGF rate were slightly higher than control group. No differences in 1-year mortality.

Conclusions: Discarded livers are an acceptable choice to expand liver pool donors. Moderate steatosis, severe hypernatremia and obesity seems to be good candidates for LT.

FV-127

How to Reduce Biliary Complication in Living Donor Liver Transplantation?

Eun-Kyoung JWA, Joo Dong KIM, Dong Lak CHOI

Division of hepatobiliary pancreas surgery and liver transplantation, Daegu Catholic University College of Medicine, Korea

Aims: Biliary complication is Achilles in LDLT. Many studies have studied risk factors associated with biliary tract complications. We review our two year LDLT data and find ways to reduce the biliary complications

Methods: Institutional LT database was searched from 2015.01.01 to 2016.12.31. Their medical records and imaging studies were reviewed.

Results: Between 2015-2016 we did 126 Liver transplanatation. (LDLT 106 DDLT 20) In LDLT, total 19 patient suffered from biliary complication. (17.9%) Two patients suffered from bile leak and 16 patients suffered form biliary stricture and 1 patient suffered from both leakage and stricture. Almost Among the patients who suffered from biliary stricture only one patient treat ERCP the others treated with PTBD insertion. In biliary complication group's 5-year graft survival was 78.9% which was lower then non biliary complication group(83.9%) but no significant difference. Compared to the biliary complication group and non biliary complication groups, only ABO incomplete factor was significant risk factor. Interestingly, duct anastomosis, stent types, duct size were not significant risk factors.

Conclusions: Still biliary complication incidence is common complication in LDLT. There was no significant differences between stent types, duct anastomosis method, duct size. We should try to reduce biliary complication. we could design a prospective study to reduce biliary complications.

FV-128

Per-Cutaneous Trans-Splenic Vein Thrombolysis for Acute Portal Vein Thrombosis in Post Liver Transplant Recipient: A Unique Experience

Kaleem ULLAH, Abdul wahab DOGAR, Shams UDDIN, Yousaf MEMON, Skindar AFRIDI

Liver Transplant Department, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences, Pakistan

Aims: Acute Portal venous thrombosis (PVT) is a rare complication in post-liver transplant recipients, with reported incidence of 1-4%. PVT can occur early within a month or late after a month of transplantation. Early PVT has a poor prognosis, leading to graft failure in majority of the cases. Post Liver transplant, Acute PVT is not easy to treat, because of difficult alternative portal hepatic inflow establishment.
Methods: 17 years old male, who underwent liver transplantation for chronic liver disease secondary to budd chiari syndrome, develop massive acute portal vein thrombosis on 8th post-operative day. He was discussed in multi disciplinary meeting and ultrasound guided per-cutaneous trans-splenic vein thrombolysis was decided. Percutaneous portal vein access was successfully achieved. First angiography was performed which showed thrombosis of main portal vein with extension into intrahepatic branches. A, 6 Fr, sheath was placed into the splenic vein over a guide wire and a catheter passed into the main portal vein and moved forward towards to the bifurcation and thrombolytic therapy was given.
Results: Intravascular thrombolytic therapy given in this patient showed complete resolution of thrombosis with out any side effects. And hence, graft failure was avoided. Patient was fine on long term follow.
Conclusions: This case report highlights the importance of the trans-splenic access for Portal vein cannulation in specific post-liver transplant recipients, because it provides easy and clear access to the Portal vein and avoiding liver graft injury and any other complications.

FV-129

Primary Biliary Cirrhosis in a 5 Years Old Female Child: A Unique Case Report

Shams UDDIN, Kaleem ULLAH, Abdul wahab DOGAR, Syed Hasnain ABBAS

Liver transplantation, Pir Abdul Qadir shah institute of medical sciences., Pakistan

Aims: Primary biliary cirrhosis (PBC) is a chronic and progressive autoimmune liver disease with no known etiology, and usually with Positive Anti-mitochondrial antibodies (AMA) in approximately 90 % of cases. So, in patients with negative AMA, typical histopathology features on biopsy has key role in diagnosis of PBC. This disease is mainly characterized by granulomatous destruction of intrahepatic biliary ducts, severe peri-portal inflammation, and ultimately liver fibrosis and cirrhosis with passage of time. The incidence of PBC is 2.7–3.5 cases per 10, 0000 people per year, and predominantly affects middle aged females between 30 to 50 years of age. Here, we report a five year old girl with PBC, who presented to us with end stage liver disease for liver transplantation.
Methods: A 5 year old female child presented with End stage live disease with history of jaundice, and hepatic encephalopathy for the last six months. On examination, she was icteric .Liver profile showed serum Bilirubin level of 17.2 mg/dl with high level of direct bilirubin. Alkaline Phosphatase level was 5 times of normal .She under went living donor liver transplantation. Explanted liver showed granulomatous destruction of intrahepatic biliary ducts.
Results: Our patient's histopathology findings were favorable, and were having increased serum alkaline phosphatase and serum bilirubin levels. All these supported the diagnosis of PBC according to the guidelines by AASLD.
Conclusions: The natural history and exact incidence of PBC in childhood is not known. There is need of increased awareness in cases of Pediatric PBC, so that further pediatric cases could be reported.

FV-130

Impact of Graft Weight Change during Perfusion on Hepatocellular Carcinoma Recurrence after Living Donor Liver Transplantation

Manuel LIM, Jaehun YANG, Ji Eun KWON, Eun Sung JEONG, Jinsoo RHU, Gyu-Seong CHOI, Jong Man KIM*, Jae-Won JOH

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Aims: Inadequate liver volume and weight is a major source of morbidity and mortality after adult living donor liver transplantation (LDLT). The purpose of our study was to investigate HCC recurrence, graft failure, and patient survival according to change in right liver graft weight after histidine-tryptophan-ketoglutarate (HTK) solution perfusion in LDLT.
Methods: Two hundred twenty-eight patients underwent LDLT between 2013 and 2017. We calculated the change in graft weight by subtracting pre-perfusion graft weight from post-perfusion graft weight. Patients with increased graft weight were defined as the positive group, and patients with decreased graft weight were defined as the negative group.
Results: After excluding patients who did not meet study criteria, 148 patients underwent right or extended right hepatectomy. The negative group included 89 patients (60.1%), and the positive group included 59 patients (39.9%). Median graft weight change was -28g (range; -132 – 0g) in the negative group and 21g (range; 1-63g) in the positive group (P<0.001). Median hospitalization time was longer for the positive group than the negative group (27 days vs. 23 days; P=0.048). There were no statistical differences in tumor characteristics, postoperative complications, early allograft dysfunction, or acute rejection between the two groups. Disease-free survival, death-censored graft survival, and patient survival were lower in the positive group than the negative group. Additionally, the positive group showed strong association with HCC recurrence, death-censored graft survival, and patient survival in multivariate analysis.
Conclusions: This study suggests that positive graft weight change during HTK solution perfusion indicates poor prognosis in LDLT.

FV-131

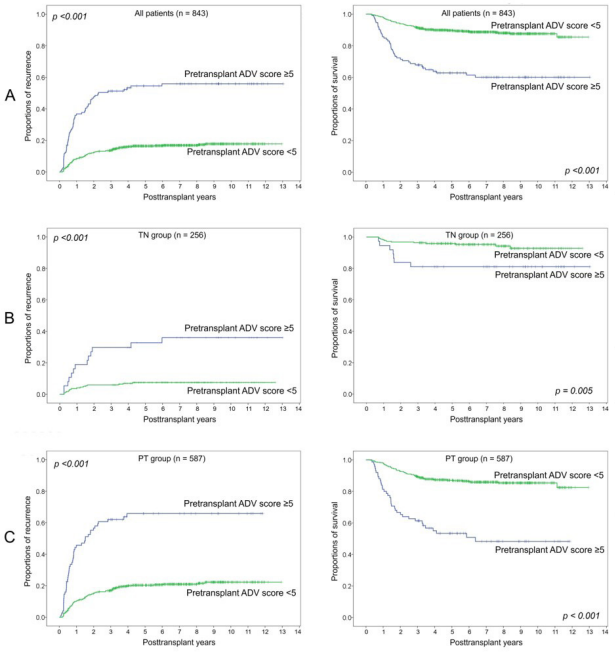
Quantitative Prognostic Prediction Using ADV Score for Hepatocellular Carcinoma Following Living Donor Liver Transplantation

Shin Hwang, Gi-Won Song, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Sung-Gyu Lee

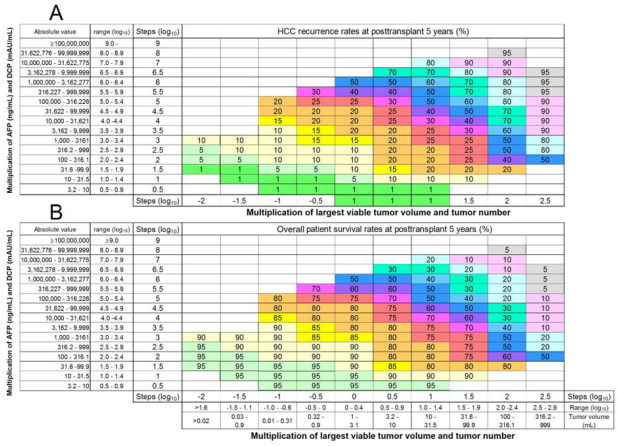
Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: We assessed the prognostic impact of the ADV score (α-fetoprotein [AFP]–des-γ-carboxyprothrombin [DCP]–tumor volume [TV] score) for predicting hepatocellular carcinoma (HCC) recurrence and patient survival after living donor liver transplantation (LDLT).

Methods: This study included 843 HCC patients who underwent LDLT between January 2006 and December 2015 at Asan Medical Center. These cases were divided into treatment-naïve (TN, n=256]) and pretransplant-treated (PT, n=587 [69.6%]) groups.



Results: There were weak or nearly no correlations among AFP, DCP and TV. There existed high correlations between the pretransplant and explant findings regarding tumor number, size and ADV score. Right lobe grafts were implanted in 760 (90.2%) patients. HCC recurrence and all-cause patient death occurred in 182 (15.9%) and 126 (15.0%) respectively during the follow-up period for 75.6±35.5 months. The 5-year tumor recurrence (TR) and overall patient survival (OS) rates were 21.5% and 86.2%, respectively. The PT group showed higher TR (P<0.001) and lower OS rates (P<0.001). TR and OS were closely correlated with both pretransplant and explant ADV scores in the TN and PT groups. The ADV score enabled further prognostic stratification of the patients within and beyond the Milan, UCSF and Asan Medical Center criteria. Compared with the 7 pre-existing selection criteria, ADV score with a cutoff of 5log showed the highest prognostic contrast regarding TR and OS.



Conclusions: Our prognostic prediction model using ADV scores is an integrated quantitative surrogate biomarker for posttransplant prognosis in HCC patients and can provide reliable information that assists the decision-making for LDLT.

Keywords: Hepatocellular carcinoma, Recurrence, Tumor biology, Prediction

FV-132

The Correlation between Preoperative Volumetry and Actual Graft Weight of Liver According to the Donor Age

Eun Jin Kim, Jae Geun Lee, Dae-Hoon Han, Gi Hong Choi, Myoung Soo Kim, Soon Il Kim, Yu Seun Kim, Dong Jin Joo

Departments of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

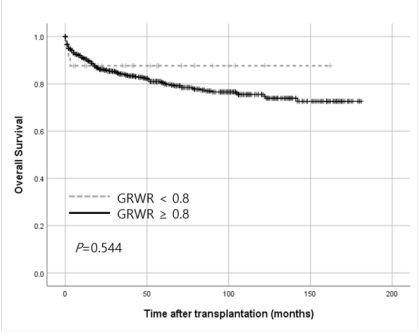
Aims: Liver volume assessment is essential to provide adequate graft volume to recipients and ensure safety to donors in living donor liver transplantation. This study aims to compare the graft volume (GV) calculated by preoperative liver volumetry and the graft weight(GW) measured during surgery according to the donor age and investigate the influence of graft-to-recipient weight ratio (GRWR) mismatch on patient survival.

Methods: Data from 771 living donors between 2005 to 2020 in Severance hospital were reviewed. We defined graft weight mismatch as a discrepancy ≥ 10% between preoperatively estimated and actually measured GRWR. Donors were divided into 6 groups based on ten-year age interval and data were compared according to the age groups. Recipient survival outcomes were analyzed in accordance with the GRWR mismatch.

Results: The proportion of GRWR mismatch donors was not different across the donor age groups (47% vs. 43% vs. 48% vs. 44% vs. 39% vs. 60%; P=0.765). However, actual GRWR was

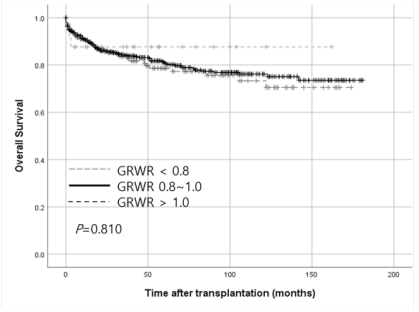
significantly smaller than estimated GRWR as donor was younger (*P*=0.001). Total 29 (3.7%) recipients received liver whose GRWR<0.8 and 24% of them (n=7) underwent portal flow modulation (splenic artery ligation, splenectomy, or renal vein ligation) during transplantation surgery. Overall survival did not differ between GRWR<0.8 and ≥0.8 groups (*P*=0.544).

Overall survival according to GRWR (2 groups)



No difference of survival rate according to the GRWR group

Overall survival according to GRWR (3 groups)



No difference of survival rate according to the GRWR group

Conclusions: Actual liver graft weight tends to smaller than estimated graft volume as donor is younger. GRWR mismatch was not affect overall survival of recipients.

Keywords: GRWR, Volumetry, Donor age

FV-133

Living Donor Liver Transplantation for Polycystic Liver Disease: A Case Report

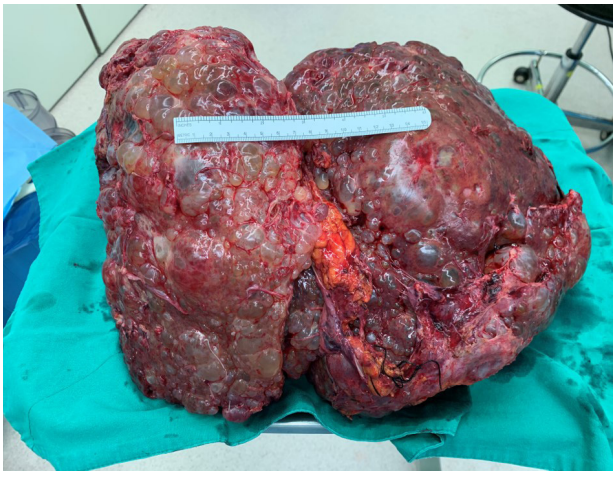
Hyun Jeong Kim, Dong Jin Joo

Department of Surgery, Yonsei University College of Medicine, Korea

Aims: Polycystic liver disease(PLD) can progress to massive hepatomegaly resulting in impaired performance status and quality of life. In PLD patients with diffuse liver cysts with few areas of normal parenchyma, liver transplantation(LT) can be the only curable treatment. But LT can be extremely challenging due to difficulty in resecting a massive native liver. We report our case of liver transplantation for massive hepatomegaly due to symptomatic PLD.

Methods: A 53-year-old man was diagnosed with autosomal dominant polycystic kidney disease(ADPKD) in 1998. After 11 years, he was diagnosed also with PLD. The patient developed end stage renal disease(ESRD), stating hemodialysis(HD) in 2011. He was firstly listed for a kidney transplantation(KT). While waiting for deceased donor, abdominal discomfort aggravated due to huge size of kidney. So he underwent bilateral nephrectomy sequentially. In July 2020, due to an enlargement of liver cysts and massive hepatomegaly, the patient developed severe clinical symptoms; abdominal discomfort due to abdominal distension, dyspepsia, poor oral intake. He was listed for combined LT and KT in September 2020.

Results: Because of his low The Model for End-stage Liver Disease(MELD) score (21) and preserved liver function, the probability of liver transplantation in brain death was too sparse. So he decided to proceed with living related LT first in February 2021. At LT, the graft mobilization was too hard not only because of the size, weight, and hardness of the organ, but also because of inflammation and adhesion due to previous several operations. Careful dissection around the liver was done but the liver was not able to be mobilized. After hilar dissection and all the vasculatures were ligated, the IVC was exposed and could be dissected up to right hepatic vein. However, the hepatic veins were not able to be identified due to the huge liver. Liver parenchyma was resected by anterior approach and right, middle and left hepatic veins were isolated. And the recipient's liver was weighed 10,134 g.



Conclusions: Most PLD patients usually preserve the liver function and show low MELD score. Therefore, the main indications for LT in PLD patients are related to performance status and impaired quality of life. The LT for PLD patients has high mortality rate and the operation is demanding. Nevertheless, this case shows that even recipients with a massive liver weighing more than 10 kg can also undergo surgery.

Keywords: Liver transplantation, Polycystic liver disease

FV-134

Hepatitis B Immunoglobulin in Hepatitis B Core Antibody-Positive Liver Grafts

Kyeong Deok Kim, Jong Man Kim, Sunghae Park, Young Ju Oh, Ji Eun Kwon, Manuel Lim, Jaehun Yang, Eun Sung Jeong, Okjoo Lee, Jinsoo Rhu, Gyu-Seong Choi, Jae-Won Joh

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: Hepatitis B core antibody (anti-HBc) positive donors are used as an extended donor pool, and current guidelines recommend the usage of nucleos(t)ide analogues (NAs) as prophylaxis for preventing de novo hepatitis B virus infection (DNH). In this study, we analyzed the long-term outcomes of a large cohort of liver transplantation (LT) patients receiving anti-HBc-positive grafts, and evaluated the risks of DNH when HBIG monotherapy was used as prophylaxis. In addition, we compared the cost-effectiveness of HBIG and NAs.

Methods: We retrospectively reviewed 457 patients (33.7%, 457/1355) with anti-HBc-positive grafts and 898 patients (66.3%, 898/1355) with anti-HBc-negative grafts who underwent LT at Samsung Medical Center in Seoul, Korea, between January 2001 and December 2018. The comparison of recipient characteristics according to the anti-HBc status of the donor was done. Also, the cost was compared between using NAs for the rest of one's life and using HBIG to maintain hepatitis B surface antibody titers above 200 IU/L.

Results: The 1-, 5-, and 10-year patient survival rates were 87.7%, 73.5%, and 67.7%, respectively in patients with anti-HBc-positive grafts and 88.5%, 77.4%, and 70.3%, respectively in patients with anti-HBc-negative grafts (*P*=0.113). Among 457 recipients with anti-HBc-positive grafts, 117 (25.6%, 117,457) were non-HBV recipients. The overall incidence of DNH was 0.9% (1/117). When using HBIG, the cumulative cost was higher compared with using NA continuously.

Conclusions: The anti-HBc-positive graft itself does not affect patient survival or graft survival. HBIG monoprophylaxis has good outcomes for preventing DNH, but is high in cost.

Keywords: Liver transplantation, Hepatitis B virus, Hepatitis B core antibody, De novo HBV, Hepatitis B immunoglobulin

FV-135

Real-World Experience of mTOR Inhibitors in Liver Transplant Recipients in a Region where Living Donation Is Predominant

Pil Soo Sung[1,2,†], Ji Won Han[1,2,†], Chang Ho Seo[3], Joseph Ahn[3], Soon Kyu Lee[1,2], Hee Chul Nam[1,2], Ho Joong Choi[3], Young Kyoung You[3], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2,*]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea; [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Surgery, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Mammalian target of rapamycin (mTOR) inhibitors, such as everolimus and sirolimus, may be efficacious in preserving renal function in liver transplantation (LT) recipients while preventing hepatocellular carcinoma (HCC) recurrence. In this study, we retrospectively evaluated the safety, efficacy, and renoprotective effects of mTOR inhibitors in LT recipients.

Methods: We retrospectively evaluated the safety, efficacy, and renoprotective effects of mTOR inhibitors in LT recipients. This retrospective observational study initially screened 500 patients who underwent LT at Seoul St. Mary's Hospital between November 2012 and October 2020. Among them, 91 patients received everolimus or sirolimus as immunosuppressants. After excluding 3 patients without information for explant liver and 4 patients with short-term use of mTORi (< 2 months), 84 patients were finally enrolled in the subsequent analyses.

Results: Among the 84 patients enrolled, mTOR inhibitor was commenced a mean of 269 days after LT. Regarding the type of mTOR inhibitor, everolimus was used in 71 patients and sirolimus in 13 patients. Concomitant tacrolimus was used in 63 patients (75.0 %). A significant improvement in kidney function was observed in the eGFR < 60 mL/min/1.73 m^2 group (n = 19) 12 months after initiation of mTOR inhibitors, for both patient groups with early+mid starters (n = 7, stating within 1 year after LT) and late starters (n = 12, starting over 1 year after LT). mTOR inhibitors were safely administered without serious adverse events that led to drug discontinuation.

Conclusions: Overall, this is the first real-world report of mTOR inhibitor application in Korea, where hepatitis B virus (HBV) infection is the principal cause of HCC and living donor LT is predominant. We demonstrated that patients with renal impairment showed significant improvement in renal function regardless of the timing of mTOR inhibitor start, suggesting that switch to mTOR inhibitors are required when renal function declines.

Keywords: Liver transplantation, MTOR inhibitor, Kidney function, Hepatocellular carcinoma

FV-136

Comparing the Closure of Hepatocaval Ligament Using Stapler or Suturing in Liver Surgery

Imam bakır BATI[1], Umut TÜYSÜZ[*2]

[1]Departman of Transplant surgery, Faculty of Medicine, Acıbadem Unıversity,İstanbul, Turkey; [2]Departman of hepatopancreatobiliary surgery and liver transplantation, Şişli Etfal Hamidiye Training and Research Hospital,İstanbul, Turkey

Aims: HCL is localized on the posterior and lateral side of the retrohepatic IVC, above the right adrenal vein. Bleeding due to retro-hepatic cava injury could sometimes occur during the dissection and closure of hepatocaval ligament (HCL).We aim

to determine closing methods of HCL in terms of cost, ease of application and safety.

Methods: The study population included 90 recipient hepatectomy patients who had cadaveric and live-donor liver transplantation at Organ Transplant Center of Acıbadem Hospital between 2017 and 2019. The patients were divided into two groups. The first group contained 40 patients who were closed with 25 mm EndoTA 30 stapler. The second group contained 50 patients who were closed by continuous double-layer suturing with propylene 5/0.

Results: In the group closed by endovascular stapler, reinforcement suturing was performed in eight patients (20%) using 5/0 propylene suture due to mild blood leakage in the closing line. In two patients (5%), on the other hand, the staple device could not be used due to the fact that HCL was very close to the right hepatic vein and the distance between the liver and the v. cava was short. There were no perioperative and postoperative HCL-associated liver and V. cava bleeding complications in both groups. However, the cost was significantly higher in the stapler group than in the suturing group.

Conclusions: The present study is the first to compare the stapler or suturing techniques for closing HCL in the receiver hepatectomy of liver transplantation. The results indicated that the closure with suturing was more

FV-137

Intraoperative Hepatic Artery Thrombosis in Living Donor Liver Transplantation Despite Immediate Reconstruction Increases Risk of Graft Failure

Su young HONG[1], Nam-Joon YI[*1], Kwangpyo HONG[1], Eui Soo HAN[1], Sanggyun SUH[1], Jeong-Moo LEE[1], Suk Kyun HONG[1], YoungRok CHOI[1], Ung Sik JIN[2], Hak CHANG[2], Kwang-Woong LEE[1], Kyung-Suk SUH[1]

[1]Department of Surgery, Seoul National University College of Medicine, Korea; [2]Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Korea

Aims: Post-transplant hepatic artery thrombosis (HAT) can lead serious complications of are derived from long arterial ischemic time. However, there has been few reports regarding fate of intraoperative HAT during adult living donor liver transplantation (ALDLT).

Methods: From 2000 to 2019, 1,355 recipients underwent ALDLT in Seoul National University Hospital. All patients with no intraoperative arterial flow were managed by redoing hepatic artery anastomosis. Survival outcomes and the rates of biliary complication of patients with intraoperative HAT were compared with others without HAT and with postoperative HAT. Median follow-up period was 89 months.

Results: Intraoperative HAT was developed in 45 cases (3.3%). Hepatic artery reanastomosis was performed once in 33 cases (73.3%), for more than 2 times in 12 cases (26.6%). Among 45 patients with intraoperative HAT, postoperative HAT was detected in 6 cases (13.3%). All patients underwent redo arterial reconstruction, but technical success rate was 50.0%. Overall graft survival rates were lower in patients with intraoperative HAT (93.3%) than others without HAT (98.0%) (P=0.026), but higher than in patients with postoperative HAT (88.9%) (P=0.001). However, patient survival rates were similar among three groups (P=0.269). There was no difference in biliary complication between patients with intraoperative HAT (33.3%) and the others without HAT (32.1%) (P=0.945), lower than patients with postoperative HAT (55.5%, P=0.011).

Conclusions: Intraoperative HAT after ALDLT did not affect biliary complication and patient survival, but is significantly associated with recurrent postoperative HAT and graft failure. Patients with intraoperative HAT in ALDLT should be intensively monitored for HAT and graft dysfunction.

FV-138

Eversion Technique: A Safe Anastomosis Method of Bile Duct in Living Donor Liver Transplantation without Internal or External Biliary Stent

Seok-Hwan KIM

Surgery, Chungnam National University Hospital, Korea

Aims: Biliary stricture (BS) is still a major concern after bile duct anastomosis in living donor liver transplantation (LDLT), even after the technical refinements using a microscope. This study aims to describe our eversion technique without stent insertion of biliary anastomosis and its effects on the incidence of biliary complications.

Methods: This was a single-center retrospective study of 52 adult LDLT recipients between December 2011 and June 2020. Group 1 consisted of the first 20 patients for whom the standard technique of biliary anastomosis (minimal hilar dissection during donor duct division, high hilar division of the recipient bile duct, and preservation of the recipient duct periductal tissue) was used. Group 2 consisted of 32 patients for whom biliary anastomosis was done with the addition of corner-sparing sutures and mucosal eversion of the recipient duct to the standard technique. Primary outcome measures included biliary complications (biliary leaks and strictures).

Results: Biliary complications occurred in 4/20 patients in group 1 (20.0%) and 2/32 patients in group 2 (6.25%). The technical factors mentioned above are aimed at preserving the blood supply of the donor and recipient ducts and hold the key for minimizing biliary complications in adult-to-adult LDLT.

Conclusions: The application of eversion technique could be a key for preventing BAS in duct-to-duct biliary reconstruction in LDLT.

FV-139

The Left Graft May Be the "Right" Graft: A Comparative Study of Using the Right versus Left Graft in Adult-to-Adult LDLT

Hye-Sung JO, Young-Dong YU, Dong-Sik KIM*

Surgery, Korea University College of Medicine, Korea

Aims: Adult-to-adult living donor liver transplantation (LDLT) has been a dominant type of liver transplantation, especially in Asian countries where deceased donors are extremely scarce. Several centers have been attempted to use left liver graft because it could reduce the postoperative risk to the donor. This study retrospectively compared clinical outcomes between right and left liver grafts in adult-to-adult LDLT.

Methods: All consecutive 116 patients who underwent adult-to-adult LDLT between 2010 and 2020 were enrolled in this study. The study cohort comprised of 94 patients in the right liver (RL) group and 22 in the left liver (LL) group. When both hemiliver grafts meet the selection criteria, LL graft was preferred. Prospectively collected clinicopathologic characteristics, perioperative outcomes, and survival were evaluated.

Results: In terms of donor variables, median actual graft-to-recipient weight ratio was higher in the RL group than in the LL group (1.01 [0.66–1.66] vs. 0.85 [0.63–1.50], *P*=0.030). Total bilirubin level and prothrombin time on postoperative day 5 were worse in the RL group, but it did not reach statistical significance. In terms of recipient variables, hepatic venous pressure gradient after reperfusion was comparable between the groups. The 90-day complication (above Clavien–Dindo grade IIIA) and 1-year graft survival rates were not different between the RL and LL groups (35.9% vs. 56.2%, *P*=0.123 and 91.3% vs. 93.8%, *P*=0.744, respectively).

Conclusions: This study demonstrated comparable donor and recipient outcomes between the RL and LL groups. In an effort to minimize potential donor risk, LL graft is worth considering when both grafts meet the selection criteria.

FV-140

The Effect of Intraductal Transanastomotic Stent in Reducing Biliary Complication after Duct-to-Duct Biliary Reconstruction in Living Donor Liver Transplantation: Single Center Experience

Changho SEO, Ho Joong CHOI*, Sung Eun PARK, Joseph AHN, Tae Ho HONG, Young Kyoung YOU

Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

Aims: Despite of the innovations in surgical and postoperative surgical treatment of donors and recipients, biliary complication is still considered to be a technical "Achilles' heel" of living donor liver transplantation (LDLT) due to the high incidence, requiring long-term interventional treatment, and potential risk for graft failure. The purpose of this study was to evaluate the effect of intraductal transanastomotic stent in reducing biliary complications after LDLT.

Methods: From August 2015 to February 2020, 201 adult LDLTs using right liver were enrolled. The intraductal transanastomotic stent was a silicone tube of various diameters considering the duct size. Two hundred one patients were divided into non-stent group (n=101) and stent group (n=100). By dividing biliary complication into bile leakage and stricture, the risk factor and effect of stent were analyzed.

Results: In all patients with LDLT, biliary complications occurred in 54 (26.9%) patients and anastomosis site leakage occurred in 9 (9.5%) patients. Of the 201 patients, non-stent group was 101 (50.2%) patients and stent group was 100 (49.8%) patients. Anastomosis site leakage was higher in the non-stent group (n=15, 14.9%) than in the stent group (n=4, 4.0%, *P*=0.005). Biliary stricture was also higher in the non-stent group (n=30, 29.7%) than in the stent group (n=17, 17.0%, *P*=0.03)). In multivariate analysis, hepatic artery thrombosis (*P*<0.001) and intraductal stent (*P*=0.01)

Conclusions: Intraductal transanastomotic stent can reduces biliary complications including anastomosis leakage and stricture. Further large-scale analyses of clinical data or randomized controlled trial are required to support this study.

FV-141

Elderly Living Liver Donors in Korea

Jong Man KIM[1], Nam-Joon YI[2], Dong Jin JOO[3], Young Kyoung YOO[4], Shin HWANG[5], Je Ho RYU[6], Doo Jin KIM[7], Hee Chul YU[8], Yang Won NA[9], Myoung Soo KIM[3]

[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea; [2]Department of Surgery, Seoul National University College of Medicine, Korea; [3]Department of Surgery, Yonsei University College of Medicine, Korea; [4]Department of Surgery, College of Medicine, Catholic University of Korea, Korea; [5]Department of Surgery, Asan Medical Center, College of Medicine University of Ulsan, Korea; [6]Department of Surgery, Pusan National University College of Medicine, Korea; [7]Department of Surgery, Gachon University Gil Medical Center, Gachon University College of Medicine, Korea; [8]Department of Surgery, Chonbuk National University School of Medicine, Korea; [9]Department of Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Korea

Aims: Old donors have gradually been used as an alternative living liver donor to alleviate the organ shortage or avoid offspring donation. The aim of the present study is to determine the impact of elderly donors more than 60 years in living donor liver transplantation (LDLT) on donor safety and recipient outcomes compared with donors from fifty to fifty-nine years

Methods: We retrospectively identified 209 patients at nine centers from 2005 to 2017 in Korea.

Results: Sixty group represented 10.0% (n=21) of the patient donors. The incidence of male donor in the sixty group was higher than in the fifty group (61.9% vs. 37.8%; *P*=0.039).

Postoperative complications were more common in the sixty group. There was no in-hospital mortality and no mortality was reported during the observation period. There were no statistically significant differences in operation time, blood loss, intraoperative and postoperative transfusion rate, postoperative total bilirubin, and hospitalization between the two groups. In recipient operation, median blood loss, transfusion rates during operation, and postoperative bleeding control operations were more than in the fifty group. Postoperative total bilirubin and hospitalization in the sixty group were higher and longer in the fifty group. Cumulative patient survival rate in the fifty group was better than in the sixty group (P=0.011). Sixty group was predisposing factor for recipient death in multivariate analysis.
Conclusions: Present study suggests that highly selected elderly living donors (≥ 60 years) can safely donate, but their recipient outcomes are worse compared with the fifty group.

11. Biliary and Pancreatic Diseasee

FV-142

Analysis Risk Factors and Consequences Toward Hepatolithiasis Disease in Indonesia

Anna FARHANA[1], Destriyani DESTRIYANI[2]

[1]Animal of Science, Universitas Gadjah Mada, Indonesia; [2]Public of Health, Universitas Gadjah Mada, Indonesia

Aims: Hepatolithiasis is the presence of gallstones in the biliary duct of the liver with 20-30% cases in Indonesia and gallstones located in all bile ducts from the periphery to the junction of the right and left hepatic ducts. Risk factors such as gender, age, genetics, environmental, family history, diet and smoking habits can affect of Hepatolithiasis. The purpose of this study was to analyze various risk factors and consequences of the incidence of Hepatolithiasis that occurred in Indonesia.
Methods: This study used electronic database as a methode by reviewing some previous article published in the last five years, from 2015 to 2020. Literature review begins with topic selection, through several reputable published journals.
Results: Based on the similarity of the dependent variables there are various risks factors of Hepatolithiasis disease that occur in Indonesia, the result showed that there is a correlation between age, genetics, environmental, diet and smoking habits toward Hepatolithiasis. While gender factor did not have a significant correlation. The finding showed that in Indonesia, The incidence of hepatolithiasis is reported in 20-30% of patients undergoing gallbladder surgery.
Conclusions: It can be concluded that in Indonesia, age, genetic, environmental, family history, diet and smoking habits factors have significant correlation toward Hepatolithiasis disease. Hepatolithiasis is still rare in Indonesia. Complete diagnosis requires a combination of imaging modalities. Surgery remains the main definitive treatment option.

FV-143

How Mutations in Pancreatic Cancer are Treated- Is Surgery the Only Option?

Tanvi GUPTA, Wen- Pin SU*

Institute of Clinical Medicine, National Cheng Kung University, Tainan, Taiwan, Taiwan

Aims: Pancreatic cancer is a lethal disease having a worst five-year overall survival rate of 2% -9% compared to other cancer types. The occurrence of pancreatic cancer is rising due to numerous factors such as intake of alcohol, smoking, obesity, dietary factors, and Helicobacter pylori infection. Most of the pancreatic cancers have gene mutations includes BRCA1, BRCA2, CDKN2A, ATM, PALB2, TP53, SMAD4, KRAS, etc. and from these BRCA1/2 have found to be more prevalent among the patients.
Methods: The treatment options for the pancreatic cancer are Pancreatico-duodenectomy includes pre-operative biliary drainage, an anastomotic technique, invasive surgery, vascular resection, and adjuvant as well as neo- adjuvant treatment. The metastatic cancer can be taken care by control of symptoms, management of jaundice and with favoured chemotherapy-mFOLFIRINOX with 5- fluorouracil.
Results: The patients treated with adjuvant gemcitabine after the surgery showed five- year overall survival rate of 20.7% against the surgery alone with 10.4%. The dual therapy of gemcitabine and capecitabine showed the median overall survival to be 28 months compared to gemcitabine alone to be 25.5 months. The other chemotherapy way by mFOLFIRINOX compared with gemcitabine alone showed 21.6 months versus 12.8 months for the disease free survival and 54.4 months versus 35 months overall survival.
Conclusions: As we know pancreatic cancer turns out to be fatal with poor overall survival rate, so there is need to explore more treatment options. Many studies are ongoing to find the standard of care for patients whether it would be or not be combinations of cytotoxic with targeted

FV-144

Presence of Fatty Liver Disease Leads to Unusual Rise of Liver Enzymes in Patients with Common Bile Duct Colic

UA BUDDHIKA[1], DS EDIRIWEERA[1], L PARANAHEWA[2], CS EKANAYAKE[1], SB TILLAKARATHNE[1], RC SIRIWARDANA[1]

[1]Department Of Surgery, Faculty of medicine, University of Kelaniya, Sri Lanka; [2]Department Of Radiology, Asiri Surgical Hospital, Sri Lanka

Aims: This study compares liver enzymes, inflammatory markers and bilirubin levels in patients with and without fatty liver disease (FLD) presenting with common bile duct (CBD) obstruction.

Methods: CBD colic was diagnosed based on clinical, radiological and biochemical criterion. Presence of FLD was diagnosed by ultra sound scan and the macroscopic appearance of liver during surgery. Liver enzymes, inflammatory markers and bilirubin levels were prospectively assessed and compared between the two groups.
Results: Out of 42, there were 22 (52.3%) patients with FLD. Median body mass index was 26.9 (24.1 – 30.8) in fatty liver group compared to 25.7 (23.5 – 26.2) in others. Individuals with FLD showed high AST (558.5 vs. 247.0, *P*=0.005), ALT (467 vs. 228.5, *P*=0.005) and bilirubin (3.8 vs. 2.2, *P*=0.015) levels compared to those without FLD. According to multiple linear regression models, high AST and ALT levels showed significant associations with FLD after adjusting for age, gender, BMI, amylase and CRP levels. The median enzyme level at two weeks did not show a difference among patients with and without FLD.
Conclusions: Presence of FLD causes unusual rise of AST and ALT levels in patients with CBD stones. This rise is transient.

FV-145

Continuous Suture Hepaticojejunostomy Is Economical Eith Similar Long Term Results as Interrupted Suture Technique: An Audit of a Prospective Database of 556 Hepaticojejunostomies

Rajan SAXENA*, Nalini Kanta GHOSH, Saurabh GALODHA

Department of Surgical Gastroenterology and Center for Hepatobiliary Diseases and Transplantation, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, India

Aims: Hepaticojejunostomy (HJ), a standard method of bilioenteric anastomosis, is done with interrupted sutures by most surgeons. This audit of a prospective database compares the safety, economics, short term and long term outcome of continuous (CSHJ) and interrupted suture hepaticojejunostomy (ISHJ).
Methods: An audit of a prospecrive database of all HJ performed between January 2014 and December 2018 after IEB approval. Patients with type IV or higher biliary strictures, duct diameter < 8 mm and/or associated vascular injury and liver transplant recipients were excluded. Patient demographics, diagnosis, pre-operative parameters, intra-operative findings, type and number of sutures, suturing time, and postoperative morbidity (Clavien Dindo) were recorded, and patients followed upto 60 months. McDonald's Grade A and B were considered as good outcome. Cost of suture (Polydioxanone) 3-0/5-0 mean cost- ₹686/length, polyglactin 3-0, 4-0 mean cost- ₹486/length), operating room time (₹5000/hour) were considered for comparison of economics of both techniques. Statistical analysis done on SPSS 22 software.
Results: 556 eligible patients - 468 with ISHJ and 88 with CSHJ analyzed. 258(54 %) had benign and 300 (46%) had malignant pathology. The groups were similar. PDS sutures dominated in CSHJ. Number of sutures, cost, time, and postoperative bile leak was significantly more in ISHJ group. 54 patients had bile leak (6 CSHJ and 48 ISHJ). There were 16 mortalities (3 CSHJ, 13 ISHJ) due to septic shock. Morbidity was comparable according to Clavien Dindo grading. Anastomotic stricture rate was comparable.
Conclusions: CSHJ is safe, economic and worthy of routine practice.

FV-146

Qulaity of Life after Reapir (Hepatico-Jejunostomy) for Post-Cholecysyectomy Bile Duct Injury

Rohit DHAWAN, Vinay KAPOOR*

Surgical gastroenterology, SGPGI, LUKNOW, India

Aims: Health-related quality of life(QoL), physical component score (PCS) and mental component score (MCS), was assessed for bile duct injury sustained at cholecystectomy
Methods: using SF-36 in 119 patients at least 24 months after repair (hepatico-jejunostomy),50 patients who underwent uneventful cholecystectomy at least 24 months ago were controls. Effect of age, sex, type (laparoscopic, open, laparoscopic converted-to-open) of cholecystectomy, pre-repair interventions, endoscopic, and surgical, number of pre-repair interventions, Bismuth type of biliary stricture, post-repair complications, need for intervention in the follow up, total number of operations required, total duration of hospitalization on QoL was studied.
Results: Age >50 years(n=25) (PCS, MCS 44,51 vs 66,70 in<30 vs 61,62 in 30-50; *P*<0.001,0.018),need for pre-repair intervention (n=102) (MCS 61 vs 75; *P*=0.01), post-repair Clavien-Dindo III, IV complications (n=8) (PCS, MCS 46,50 vs 64, 68; *P*=0.03, 0.04), need for post-repair surgical intervention (n=28) (PCS, MCS 49,54 vs 60,63; *P*=0.004, 0.01) and need for reHJ in follow up(n=16) (PCS 44 vs 59; *P*=0.12) adversely affected QoL. Patients (n=15) who did not require pre-repair intervention, did not have post-repair complication and did not require intervention in follow up had better QoL (PCS 63 vs 51, MCS 82 vs 56, *P*<0.03) than those (n=32) who required pre-repair intervention, had post-repair complication, required intervention in follow up
Conclusions: QoL is compromised,even after repair of BDI at biliary center; Older patients, those who required pre-repair (HJ) interventions, had post-repair (HJ) complications, required post-repair (HJ) surgical intervention and required reHJ in follow up.

FV-147

Post-Operative Serum Procalcitonin vs C Reactive Protein as a Marker of Post-Operative Infectious Complications in Pancreatic Surgery – A Systemic Review and Meta-Analysis

Bhavin VASAVADA, Hardik PATEL

Hepatobiliary and liver transplant, Consultant hepatobiliary and liver transplant, India

Aims: The aim of this meta-analysis was to compare the diagnostic accuracy of C reactive Protein and Procalcitonin between postoperative days 3 to 5 in predicting infectious complications

post pancreatic surgery.
Methods: A systemic literature search was performed using MEDLINE, EMBASE, and SCOPUS to identify studies evaluating the diagnostic accuracy of Procalcitonin (PCT) and C-Reactive Protein (CRP) as a predictor for detecting infectious complications between postoperative days (POD) 3 to 5 following pancreatic surgery. A meta-analysis was performed using the random-effect model and pooled predictive parameters. Geometric means were calculated for PCT cut-offs.
Results: After applying inclusion and exclusion criteria 15 studies consisting of 2212 patients were included in the final analysis according to PRISMA guidelines. Pooled sensitivity, specificity, Area under the curve, and diagnostic odds ratio (DOR)for day 3 C-reactive protein were respectively 62%,67% 0.772, and 6.54. Pooled sensitivity, specificity, Area under the curve, and diagnostic odds ratio (DOR)for day 3 procalcitonin was respectively 74%,79%,0.8453, and 11.03. Sensitivity, specificity, Area under the curve and Diagnostic odds ratio for day 4 C-reactive protein were respectively 60%,68%, 0.8022, and 11.90. Pooled sensitivity, specificity, and diagnostic odds ratio of postoperative day 5 procalcitonin level in predicting infectious complications were respectively 83%,70%, and 12.9. Pooled sensitivity, specificity, AUROC, and diagnostic odds ratio were respectively 50%,70%, 0.777, and 10.19.
Conclusions: Post-operative procalcitonin is better marker to predict post-operative infectious complications after pancreatic surgeries and post-operative day 3 procalcitonin has highest diagnostic accuracy.

FV-148

Routine use of Feeding Jejunostomy in Pancreaticoduodenectomy: A Metaanalysis

Bhavin VASAVADA, Hardik PATEL

Hepatobiliary and liver transplant, Consultant hepatobiliary and liver transplant, India

Aims: The primary aim of our study was to evaluate morbidity and mortality following feeding jejunostomy in pancreaticoduodenectomy compared to the control group. We also evaluated individual complications like delayed gastric emptying; postoperative pancreatic fistula, superficial and deep surgical site infection.
Methods: The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and MOOSE guidelines. Heterogeneity was measured using Q tests and I2. The random-effects model was used.
Results: Four studies including a total of 1639 patients were included in the analysis. Total 843 patients were included in the Feeding jejunostomy group and 796 patients included in the control group without feeding jejunostomy. Overall morbidity was significantly higher in the feeding jejunostomy group. (P=0.001). There was no significant difference between both groups. (P=0.07). Delayed gastric emptying was significantly higher in the feeding jejunostomy group. [P=0.021]. There was no significant difference in the development of pancreatic fistula between the two groups. Deep surgical site infection was significantly higher in the feeding jejunostomy group. (P=0.013). The hospital stay was significantly more in the feeding jejunostomy group (P<0.0001). There was no significant difference between readmission; TPN requirement and time to start the oral feed.
Conclusions: Feeding jejunostomy seems to be associated with increased morbidity and increased length of stay.

FV-149

Volvulus of the Gallbladder : Beware of Aberrant Biliary Anatomy

Dhanushke FERNANDO, Suresh NAVADGI, Ruwan WIJESURIYA

General Surgery, St John of God Midland Public & Private Hospitals, Australia

Aims: Gallbladder volvulus (GBV) is an uncommon differential in the acute surgical abdomen, which may incur significant morbidity if missed. Less than 500 cases have been reported in the literature, with few diagnosed pre-operatively. It is defined as the rotation of the gallbladder on its mesentery along the axis of the cystic pedicle, although cases of torsion of the gallbladder fundus itself have been reported.
Methods: An 82 year old lady presented with a worsening 5 day history of right upper quadrant pain with associated nausea, anorexia. She had worsening pain and noticed a 'lump' in her abdomen, along with subjective fevers. On examination, her abdomen was tender, with a non-pulsatile mass in the RUQ with voluntary guarding. The CT Abdo-Pelvis revealed a distended gallbladder extended up to the pelvis with multiple gallstones. Stranding of fat around the gallbladder was noted, with wall thickening up to 7mm at the fundus - with overall appearances consistent with acute cholecystitis.
Results: An open cholecystectomy was performed, with the intraoperative finding of GBV . There were multiple small arteries supplying the gallbladder, with no definitive cystic artery. The extra-hepatic biliary anatomy was aberrant with a long-cystic duct exiting through the cystic plate. Post-operatively recovery was uncomplicated.
Conclusions: GBV is an important differential of RUQ pain, requiring immediate intervention. It is often misdiagnosed as cholecystitis. Imaging is variable in detecting GBV, and early surgical intervention remains the mainstay of both diagnosis and treatment. However, surgeons should beware that unrecognized aberrant biliary anatomy can result in higher morbidity.

FV-150

Analysis of Ineffective Attempts of Endoscopic Treatment of Benign Diseases of Common Bile Duct Complicated by Mechanical Jaundice

Boyko V.V.[1,2], Avdosyev Yu.V.[2], Yevtushenko D.O.[1], Sochnieva A.L.[1],

Minukhin D. V.[1], Shevchenko O.M.[1]

[1]Kharkiv National Medical University, Ukraine; [2]SI "Institute of General and Emergency Surgery. V.T. Zaitseva National Academy of Medical Sciences of Ukraine", Ukraine

Aims: The aim of the study is the analysis of ineffective attempts of endoscopic treatment of benign diseases of common bile duct complicated by mechanical jaundice.
Methods: The study included 118 patients with diseases of CBD complicated by mechanical jaundice (MJ), who were treated at the clinical base of the Department of Surgery № 1 of Kharkiv National Medical University - SI "Zaycev V.T. Institute of General and Emergency surgery of the NAMS of Ukraine". In 15 (12.7%) cases endoscopic treatment was ineffective.
Results: There are the following complications directly related to the implementation of ERCP: ascending cholangitis due to duodeno-biliary reflux, with an unsuccessful attempt to remove the calculus with a diameter greater than the diameter of the CBD, distal to the site of obstruction – 4 (21.1%) patients. Transient hyperamylasemia was observed in 3 (15.8%) patients. These phenomena were stopped on the 1st–2nd day after the application of therapeutic doses of protease inhibitors. Acute pancreatitis developed in 2 (10.5%) patients – also all attacks were stopped by conservative methods. Bleeding from a papillotomy wound was observed in 1 (5.26%) patient. The causes of bleeding in this case, in addition to the size of the incision, are a violation of the coagulating properties of blood on the background of prolonged MJ. Dormia basket wedge was noted in 5 (26.3%) cases – choledocholithotomy, Holsted-Pikovsky choledoch drainage was performed on the first day after ERCP. No lethal outcomes have been reported in patients after this procedures.
Conclusions: Analyzing ineffective attempts of ERCP, it can be concluded that the implementation of minimally invasive endoscopic interventions requires a differentiated approach to their use.
Keywords: Benign common bile duct diseases, Mechanical jaundice, Endoscopic treatment

FV-151

Relationship between Biliary Tract Cancer and Coffee Consumption in Urban Population

Sumit Rajput, PA Joshi

Department of Physiology, B V Deemed University, India

Aims: To investigate the relationship between coffee consumption, biliary tract cancers and gallstone disease.
Methods: A population-based case-control study was conducted in urban Delhi city from 1 Feburary 2019 to 31 January 2020 involving interviews with 627 new cases of biliary tract cancers (including 368 cases of gallbladder cancer, 191 cases of extrahepatic bile duct cancer and 68 cases of cancer of the ampulla of Vater) aged 35 to 74 years and 959 population controls frequency-matched to cases by gender and age in five-year group. 1037 patients of gallstone disease were selected from the same hospital. All subjects were interviewed in person by trained interviewers by use of a structured questionnaire. Unconditional logistic regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence interval (CI).
Results: Compared with coffee non-drinkers, current coffee consumption was inversely associated with risk of gallbladder cancer, extrahepatic bile duct cancer and gallstone disease among females with OR of 0.57 (95% CI: 0.34-0.96), 0.53 (95% CI: 0.27-1.03) and 0.71 (95% CI: 0.51-0.99), respectively. OR declined with younger age at initiation of coffee drinking and with longer duration of coffee consumption (P for trend < 0.05). Among males, the corresponding OR were mostly below one, although not statistically significant.
Conclusions: Coffee consumption may decrease the risk of cancers of the gallbladder and extrahepatic bile duct among females. The protective effect appears to be independent of gallstone disease.
Keywords: Biliary tract cancers, Gallstone disease, Coffee consumption, Relationship

FV-152

Study of Relationship between Cadmium Exposure and Pancreatic Cancer in Experimental Studies

Rohit Kumar, Ashutosh, N K Tiwari

Department of Pharmacology, Memorial Institute of Engineering and Technology, India

Aims: Aim of this study was to investigate the role of this environmental pollutant cadmium (Cd) in pancreatic cancer (PC) development by conducting human observational, experimental and *in vitro* studies.
Methods: The case-control study included 72 patients with a histologically based diagnosis of exocrine PC subjected to radical surgical intervention as cases and 69 accidental fatalities or subjects who died of a nonmalignant illness as controls. Animal study included two treated groups of Wistar rats (25 and 50 mg Cd/kg b.w) and untreated control group, sacrificed 24 h after single oral exposure. In *in vitro* study pancreas hTERT-HPNE and AsPC-1 cells were exposed to different Cd concentrations corresponding to levels measured in human cancerous pancreatic tissue.
Results: Cd content in cancer tissue significantly differed from the content in healthy controls. Odds ratio levels for PC development were 2.79 (95% CI 0.91-8.50) and 3.44 (95% CI 1.19-9.95) in the third and fourth quartiles of Cd distribution, respectively. Animal study confirmed Cd deposition in pancreatic tissue. *In vitro* studies revealed that Cd produces disturbances in intrinsic pathway of apoptotic activity and the elevation in oxidative stress in pancreatic cells.
Conclusions: This study presents three different lines of evidence pointing towards Cd as an agent responsible for the develop-

ment of PC.

Keywords: Pancreatic cancer, Human observational, Pollutant cadmium, Vitro studies

FV-153

Bacteria of Secondary Sepsis from Hepatic Disease and Cholestasis

LE THI THU HIEN[1], LÊ QUỐC TUẤN[2], NGUYEN QUANG DUAT[3]

[1]Department of Internal Medicine, Thai Nguyen University of Medicine and Pharmacy, Thai Nguyen, Vietnam; [2]Department of Internal Medicine, Thanh Ba Hospital, Phu tho, Vietnam; [3]Department of Internal Medicine, 103 Military Hospital, Ha Noi, Vietnam

Aims: Background: Biliary stasis and increased intraductal pressure are central to the pathogenesis of acute cholangitis. Biliary stasis inhibits the continuous flushing activity of bile and the bacteriostatic effect of bile salts, which help maintain bile sterility. Elevated intraductal pressure favors translocation of bacteria and toxins out of the ducts and into the systemic circulation, which can result in sepsis. Sepsis is among the most common causes of mortality for hospitalized patients worldwide, and its incidence is steadily increasing.Aims: to characterize bacteria of secondary sepsis from hepatic disease and cholestasis.

Methods: We conducted a prospective study of 38 patients with secondary sepsis from hepatic disease and cholestasis at the 108 Military Central Hospital from January 2018 to August 2019. Contributions of the history, physical examination, laboratory investigation and subclinical in making diagnoses. PCR-based Sepsis@Quick test is for identifcation of sepsis-causative pathogens.

Results: Men (63.2%) accounted for a higher rate than women (36.8%). The mean age was 64.8 ± 12.7. Causes of septicemia: Escherichia Coli (55.3%) and Klebsiella pneumoniae (31.6%). Causes of biliary tract: biliary tract cancer (28.9%), gallstones (28.9%), liver cancer (13.2%). Patients receiving Aminoglycoside (86.8%) and Beta lactam (84.2%) accounted for the highest percentage. Hospitalization 15-21 days had the highest rate, accounting for 39.5%, followed by 8-14 days, accounting for 34.2%. The number of cure cases accounts for 89.5%, the number of deaths accounts for 5.3%.

Conclusions: The most common causes of sepsis are Escherichia Coli and Klebsiella pneumoniae. The most common causes of biliary obstruction are cholangiocarcinoma, gallstones, and liver cancer. Using Aminoglycoside and Beta lactam is appropriate to improve treatment efficiency.

Keywords: Bacteria, Cholestasis, Hepatic, Sepsis

FV-154

Positive Intraoperative Pancreatic Parenchymal Resection Margin : Is it a True Indication of Completion Total Pancreatectomy for Pancreatic Ductal Adenocarcinoma?

Ji Hye JUNG, Sokyung YOON, So Jeong YOON, Sang Hyun SHIN, Jin Seok HEO, In Woong HAN*

Division of Hepatobiliary-Pancreatic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Aims: Total pancreatectomy (TP) has being performed to achieve radicality. In the cases that negative margin (R0) are achieved by performing intraoperative completion TP (cTP), we aimed to identify if they showed better outcomes compared to the cases that negative margin were not obtained despite cTP and the cases that R0 were confirmed after pancreaticoduodenectomy (PD).

Methods: 718 pancreatic ductal adenocarcinoma (PDAC) patients underwent elective PD or TP at Samsung Medical Center from 1995 to 2015. We reviewed cases that cTP was performed due to positive pancreatic margin. There were 21 cases that R0 were confirmed [cTP R0 group] and 4 cases that other positive margin were confirmed [cTP R1 group]. In order to compare with cTP R0 group, 39 cases that R0 were confirmed after PD were selected through matching [PD R0 group]. We compared postoperative outcomes between cTP R0 group and cTP R1 group, and between cTP R0 group and PD R0 group.

Results: In two comparative analysis, there were no significantly meaningful differences in clinical, operative, pathologic characteristics, and short-term postoperative outcomes classified Clavien-Dindo classification and hospitalization. The survival rate of cTP R0 group was higher than that of cTP R1 group, but the difference was not significant. The survival rate of cTP R0 group was lower than that of PD R0 group, which was significant.

Conclusions: In our center, we have not shown evidence that cTP for safe margin has significant benefit in survival. It cannot be concluded that cTP is unnecessary, and further research is needed in the future.

FV-155

Unsupervised Clustering of Multi-Omics Molecular Layers Reveals Consensus Molecular Subtypes Showing Potential Therapeutic Opportunities for Pancreatic Cancer

Sung Hwan LEE[1], Jiyeon PARK[2], Hye Jung CHO[1], Incheon KANG[1], Sung Hoon CHOI[1], Sunyoung LEE[3], Ju-Seog LEE[4]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Korea; [2]Department of Life Sciences, McMaster University, Canada; [3]Department of Gastointestinal Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, USA; [4]Department of Systems Biology, Division of Basic Sciences, University of Texas MD Anderson Cancer Center, USA

Aims: Pancreatic cancer is a lethal disease showing dismal prognosis and therapeutic resistance. Previous molecular subtypes from genome or transcriptome did not show clinical relevance regarding precision strategy for optimal therapeutic options followed by precise patient classification. This study aims to uncover consensus molecular subtypes from cancer-specific multi-omics data showing clinically relevant therapeutic opportunities.

Methods: We performed comprehensive analyses using the data-

set from the cancer dependency map (DepMap) project, including cancer-specific molecular characterization with multi-omics data, genome-wide loss-of-function screening using the CRISPR-Cas9 system, and cancer drug sensitivity. The subtype-specific molecular signatures were validated in independent translational cohorts (TCGA-PAAD; n=150, ICGC-PACA-AU; n=461, ICGC-PACA-CA; n=317).

Results: Integrative profiling of multi-omics molecular layers (Mutational signature, Copy number alteration, Transcriptome, MicroRNA, Chromatic profile, Proteome, and Metabolome) from pancreatic cancer cell lines (n=59) from the Cancer Cell Line Encyclopedia (CCLE) revealed a total of three cancer-specific molecular subtypes showing distinct tumor biology through all omics layer as well as clinical relevance with unique molecular dependency. Major molecular features of each subtype were reproducible in the validation cohorts. Subtype-specific molecular biomarkers, including mutational signature and metabolites, were identified. Finally, the target drug with subtype-specific genetic dependency was analyzed to provide precision strategy according to distinct subtypes' molecular characterization.

Conclusions: Integrative profiling from multi-omics molecular layers revealed precision strategies based on cancer-specific molecular subtypes of pancreatic cancer in terms of tumor classification and discriminative therapeutic opportunities. Prospective translational studies companion with clinical trials based on cancer-specific molecular subtypes is mandatory to establish the precision strategy for managing pancreatic cancer.

FV-156

Integrative Multi-Omics Profiling of Resectable Pancreatic Cancer Reveals Clinically Relevant Molecular Subtypes with Precision Strategies Beyond the Clinical Staging System

Sung Hwan LEE[1], Hye Jung CHO[1], Incheon KANG[1], Sung Hoon CHOI[1], Sunyoung LEE[2], Ju-Seog LEE[3]

[1]Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Korea; [2]Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, USA; [3]Department of Systems Biology, University of Texas MD Anderson Cancer Center, USA

Aims: Even though the current clinical staging system for resectable pancreatic cancer has validated major clinicopathologic factors in multiple clinical cohorts, there is still an unmet need for integrative consideration using multi-omics data to stratify the patients with pancreatic cancer elaborately.

Methods: We performed a comprehensive analysis and profiling using genomic, transcriptomic, and proteomic data from TCGA-PAAD (n=150) and other translational cohorts (4 cohorts, n=340). Molecular features and major subtypes were analyzed mutually with clinical and pathologic factors to discover a clinically relevant translational staging system.

Results: The correlation analysis for each 50 cancer-specific molecular pathways with the clinical staging system revealed no remarkable pattern of the association. The mutational pattern of KRAS and several transcriptomic pathways, such as epithelial-mesenchymal transition and DNA repair, were differently presented in each clinical stage from the 8th AJCC TNM staging system. From the cluster of cluster analysis, we identified three consensus molecular subtypes, specifically SUBTYPE A was remarkably correlated with previously known aggressive subtypes, Basal, Mesenchymal, and Squamous subtypes, and SUBTYPE B and C were correlated with other subtypes regarding classical, exocrine, immunogenic, progenitor and ADEX subtypes. This consensus subtypes were validated at the independent pancreatic cancer genomics cohorts. Our in-silico prediction revealed subtype-specific biomarkers and potential therapeutics, including molecular target agents as well as immunotherapeutic options.

Conclusions: Our comprehensive multi-omics analysis reveals prognostically significant consensus subtypes showing distinct tumor biology with unique therapeutic opportunities including biomarkers with high performance. This study provides exact needs for clinical trials based on translational approaches to establish precision surgical oncology.

FV-157

Is It Worthy to Perform Elective Total Pancreatectomy Considering Morbidity or Mortality?: An Experience from a High-Volume Center

Ji Hye JUNG, So Kyung YOON, So Jeong YOON, Sang Hyun SHIN, Jin Seok HEO, In Woong HAN*

Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Aims: Total pancreatectomy (TP) is mostly performed for diseases involving the entire pancreas including various pathology. However, there is still a reluctance to perform TP due to high postoperative morbidity or mortality, and life-long endocrine and exocrine pancreatic insufficiency. This retrospective study aimed to evaluate postoperative outcomes in a high-volume center and identify the risk factors affecting major morbidity and mortality after TP.

Methods: From 1995 to 2015, a total of 142 patients who underwent elective TP at Samsung Medical Center were included in this study. One-stage TP was defined as elective primary TP, and in whom an intraoperative decision to extend the planned resection to TP, whereas 2-stage TP was elective completion TP due to recurred tumor. Patients who underwent TP in an emergency setting were excluded. Postoperative mobidity or pancreatectomy-specific complication was defined according to Clavien-Dindo classification (CDC) or ISGPF classification.

Results: There were no statistically significant differences between 1-stage TP (n= 128) and 2-stage TP (n= 14) in clinical, operative, pathologic variables. Overall major morbidity more than CDC $\geq$ 3 or ISGPF grade B/C were occurred in 25 patients

(17.6%). The readmission rate within 90-day including DM control was 20.4%. There was no in-hospital mortality among all enrolled patients. Multiple underlying diseases (OR 3.350, 95% CI 1.244- 9.019, *P*=0.017) and longer operative time (OR 1.005, 95% CI 1.000- 1.010, *P*=0.041) were identified an independent risk factors for major morbidity after multivariable analysis.
Conclusions: TP are safe and feasible procedures with satisfactory early surgical outcomes when performed at high-volume center.

FV-158

A Study of Biliary Microbiota in Patients with Biliary Tract Disease

MIN-SU PARK, BUMSOO KIM, SANGMOK LEE

Surgery, Kyunghee University, Korea

Aims: Biliary tract disease is associated with many factors: genes, environment, infection, etc. The current changes in biliary flora are thought to be involved in the formation of many gastrointestinal tract diseases. Therefore we want to investigate whether the biliary tract disease has a certain correlation with biliary microecology, and to detect specific strains.
Methods: Patients who were diagnosed with pancreaticobiliary cancer or benign inflammation were enrolled in this study. Mucosa from specimen or bile samples from Endoscopic retrograde cholangiopancretography was utilized to collect for DNA extraction and 16S rRNA gene sequencing, followed by analysis of bile microbiota composition.
Results: A total of 52 adults were enrolled, of whom 8 with pancreaticobiliary cancer, 13 with acute inflammation, and 31 with chronic inflammation. We found that pancreaticobiliary cancer patients and bening inflammation patients shared similar stable and permanent dominant species and showed apparent differences in their biliary microbial composition and gene function. We discovered that lactobacillaceae may potentially play a role in pancreaticobiliary cancer progression.
Conclusions: Our data suggested that changes in the microbiota between pancreaticobiliary cancer and benign inflammation may help deepen our understanding of the complex spectrum of different microbiotas involved in the development of pancreaticobiliary cancer.

12. Surgery,Technical Issues

FV-159

Feasibility of Using the Homologous Parietal Peritoneum as a Vascular Substitute for Venous Reconstruction during Abdominal Surgery: An Animal Model

Seok-Hwan KIM

Surgery, Chungnam National University Hospital, Korea

Aims: The interest in vascular substitutes has recently increased. We evaluated the feasibility of using a homologous parietal peritoneum (HPP) as a vascular substitute for venous reconstruction during abdominal surgery.
Methods: The inferior vena cava was replaced with an HPP after cross-linking with glutaraldehyde in 15 rabbits. At 7, 14, and 28 days, the patency rate, outer and inner graft diameters, histology, and immunohistochemistry were evaluated.
Results: Both the 7- and 14-day groups maintained vascular patency. Vascular patency was maintained in three rabbits in the 28-day group. The inner diameters of the anastomotic sites were 6.12 ± 0.20, 5.63 ± 0.14, and 2.22 ± 0.23 mm in the 7-day, 14-day, and 28-day groups, respectively. The mid-point inner diameters of the HPP grafts were 6.21 ± 0.13, 5.82 ± 0.16, and 2.12 ± 0.24 mm in each group, respectively. Endothelial cell proliferation on the HPP graft surfaces in all groups was based on the histological findings from the first group. Multiple neo-vascularizations of the HPP graft were found in the 14- and 28-day groups, indicating neo-media formation. Acute inflammation appeared to progress to the entire layer of the HPP graft without an intraluminal thrombus, but the graft was patent in the 14-day group. In the 28-day group, two rabbits showed near-total occlusion and a thrombus formed in the HPP graft at the anastomosis site with severe stricture; however, the rabbits were alive and had collateral vessel formation.
Conclusions: Use of the HPP is feasible for venous reconstruction in abdominal surgery.

FV-160

Robotic Single Port (Plus One) Unroofing of Multiple Liver Cysts using the DaVinci SP System

Joohyun LEE, Hye-Sung JO, Dong-Sik KIM, Young-Dong YU*

Department of Surgery, Korea University College of Medicine, Korea

Aims: Unroofing or marsupialization of liver cyst is performed for symptomatic case or growing cysts. Laparoscopic approach is widely used but few reports describe robotic approach for this procedure. Nowadays, single-port robotic surgery is adopted for various surgical procedures. We present a case of robotic single port (plus one) unroofing of multiple liver cysts using the DaVinci SP system.
Methods: A 53-year-old female was referred for multiple liver cysts which were diagnosed 6 years ago. Albeit asymptomatic, surgical resection was decided for enlarging cysts and subsequent pancreatic duct dilatation. Robotic port was inserted through transumbilical incision and an additional 5-mm-port was placed on the left side of the DaVinci SP system for energy device and suction/irrigation. Unroofing was done for most cysts and a drain was placed through the additional port.
Results: The operation time was 90 minutes, including 2 minutes of docking time and 57 minutes of console time, with negligible intraoperative blood loss. The drain was removed on the fifth postoperative day and the patient discharged on the ninth

postoperative day without acute complication. Postoperative CT scan 3 months later confirmed decreased size of liver cysts and no evidence of pancreatic duct dilatation.

Conclusions: We report our experience of robotic single port (plus one) unroofing of multiple liver cysts using the DaVinci SP system. To our knowledge, this is the first report in Korea using the DaVinci SP system for unroofing of liver cyst. We believe that this approach is superior to laparoscopic approach while achieving similar safety outcome with fewer incisions.

FV-161

Surgical Challeneges in Portocaval Shunt for Budd Chiari Syndrome

ROHITH MUDADLA

Institute of surgical gastroenterology and liver transplantation, Stanley medical college, The tamilnadu DR. MGR university of medical sciences, India

Introduction: The budd chairi syndrome caused by occlusion of the major hepatic veins often of unknown etiology, typically characterized by massive ascites, hepatomegaly, abdominal pain due to congestion of liver . The long term outcome of medical with out an improper management . In a significant proportion of patients, surgical decompressive procedures (shunt operations) are effective in decongesting the liver and improving the survival before onset of cirrhosis .SSPCS-side to side direct portocaval shunting procedure, proved to be the most widely applied and durable

Case Report: A 26 year old male presented with chief complaint of pain in progressive abdominal distension and loss of appetite since 1 months in our department . he was evaluated as a case of chronic budd chairi syndrome and planned for side to side portocaval shunt .after approximation. due to extensive caudate lobe hypertrophy IVC -PV could not be approximated .in such a case he was planned for partial / complete caudate lobe excision, during which there was torrential bleed from reterperitoneal collaterals, and procedure to do caudate lobe excision was abounded, Portocaval interposition shunting was performed using PTFE graft porto caval interposition shunting was done after few episodes of paracentesis, though SSPCS has best outcome for BCS in studies interposition graft patency has almost 52% in 5 years. post shunting portal venous pressure and IVC pressure is lowered and ascites gradually settled in one month, on 8 month follow up there is no ascites and patient is

FV-162

Modified Liver Hanging Maneuvers to Facilitate Various Difficult Types of Hepatectomy: A Single Center Experience

Giang NGUYEN, Anh PHAM, Trong NGUYEN, Hung NGUYEN, Ha NGHIEM, Duc PHAM

HBP Surgery Department, Vietnam National Cancer Hospital, Vietnam

Aims: The liver hanging maneuver (LHM) is a useful technique enabling a safe anterior approach. Since the first time described by Belghiti, it has been modified many times by different surgeons to be more effective. Thus, we aim to evaluate the short term results of using some modified liver hanging maneuvers (mLHM) for difficult types of Hepatectomy.

Methods: From February 1 to September 30, 2020, we perform 3 modified techniques of LHM for 4 patients with HCC. mLHM 1: A tape was placed upon the fossa ductus venosi, its cranial tip was passed to the right behind the common trunk of LHV and MHV and its caudal tip passed behind the left Glissonean pedicle to the hepatic hilum. mLHM 2: After transect the caudal part of S1R about 2cm, a tape was passed through the hepatic hilum and the RHV-MHV pocket along the right border of the paracaval portion. mLHM 3: Instead of a tape, we used 2 fingers to create the tunnel and push the liver forward.

Results: Among 4 patients, there were 2 right hepatectomy and caudate lobectomy, 1 left hepatectomy and caudate lobectomy, 1 right anterior sectionectomy with reconstruction right hepatic vein for huge tumor. The modified LHMs were performed successfully in all patients, provide adequate cut planes without complications.

Conclusions: The LHM is a safe and effective technique which can be modified to adapt with many types of hepatectomy.

FV-163

Initial Experience of Laparoscopic Liver Resection in a Community Hospital: A Case-Series

LEE HO YIN HENRY, CHU WAI YIN ANGUS, MAK CHI CHUEN CLARENCE, FAN NING, LUI KA WING KEITH

Surgery, Yan Chai Hospital, Hong Kong

Aims: Laparoscopic liver resection is quickly becoming the standard method to perform liver resection in recent decade. However, the role of laparoscopy remains a matter of development to be further assessed. In Hong Kong, laparoscopic major and anatomical hepatectomy has been performing in tertiary center with convincing outcome. Aim of this study is to evaluate the feasibility and efficacy of laparoscopic major and anatomical hepatectomy to be established in a community hospital.

Methods: It is a retrospective analysis between Jan 2019 - Dec 2020, 20 patients underwent laparoscopic major or anatomical liver resection in Yan Chai Hospital for various indications. There are 13 cases of hepatocellular carcinoma, 6 cases of intrahepatic choledocholithiasis, 1 cases colorectal liver metastasis. Among the 20 cases, hilar dissection was performed in 10 cases of hemihepatectomy; while direct vascular control was performed in segmental pedicle in another 10 cases of anatomical monosegmentectomy.

Results: There were no 30 days mortality reported in our series.

3 cases required open conversions for difficult haemostasis by laparoscopic method. The average blood loss is ___ml and __ out of 20 requires blood transfusion. The operative time was _hours _mins. There are 2 cases of post-operative collection requiring IR-guided drainage. The average discharge time was 7 days. There was no major clinical difference observed whether hilar dissection was performed or not.

Conclusions: Laparoscopic anatomical hepatectomy is safe and feasible in both tertiary and community center. Laparoscopic anatomical hepatectomy should be considered as a standard approach whenever possible.

FV-164

Extended Hepatectomies: Our Experience from Low Volume Center

RAMESH SINGH BHANDARI

Department of GI and General Surgery, T U Teaching Hospital, Kathmandu, Nepal

Aims: Improved perioperative care combined with proper training has helped in achieving excellent outcomes following liver surgery even in low volume centers. Extended resections require additional surgical skills as well as perioperative care and when done in proper has equally good results. Here, we present the outcome of extended liver resections performed in developing HPB unit of low volume center.

Methods: Retrospective review of the medical records of all the patients undergoing extended hepatectomies were analyzed.

Results: Total 86 liver resections were performed, out of which 61 were major liver resections (Three or more segments) performed over 6 years period. Out of them, total 11(18% of major liver resections) extended hepatectomies have been performed. All were right extended hepatectomies only. For liver augmentation, 2 underwent successful right side and segment 4b portal vein embolization, 2 patients had open right side portal vein ligation and one had ALPPS procedure. Rest of the patients didn't require any augmentation procedures. Postoperatively, 1 patient had grade 3 PHLF, 2 grade 2 PHLF and resolved, 2 bile leaks and resolved. Patient with ALPPS procedure had grade 3 PHLF has died on 3rd postoperativ week. Rest 10 patients were discharged on average of 12 hospital days.

Conclusions: Better patient selection combined with proper training and improved perioperative care, extended hepatectomies can also be safely performed with acceptable outcomes even in low volume centers of developing nations.

FV-165

PTBD in the Treatment of Patients with Alveococcus of the Liver, Complicated by Mechanical Jaundice

Edir Surov

Department of Hospital surgery of Kurgyz-Russian Slavic University

Aims: To improve the results of treatment of patients with obstructive jaundice of alveococcal etiology by optimizing the tactics of surgical treatment using percutaneous, transhepatic interventions. To estimate the number of patients who need PTBD for obstructive jaundice of alveococcal genesis and its effectiveness in relieving obstructive jaundice.

Methods: Of the 280 patients who were hospitalized at the clinic of I.K. Akhunbaeva NG MH KR for the period from April 2009 to April 2016, 31 (11%) were admitted with obstructive jaundice.

Results: In 21 patients, the level of bilirubin was more than 124 μmol/l, in this regardthey were held hCGH and CCHC. Of these, 12 women (57.1%), men 9 (42.9%) aged 16 to 62 years old, the average age of patients was 33.2 ± 9 years. The average level of bilirubin at admission was 252.4 ± 35 μmol max-543, min- 124. In the postoperative period, the improvement in the general condition was observed already for 2 days, and the average level of bilirubin in the postoperative period was 149 ± 24 mmol / l with a tendency to decrease with further dynamic, and in the subsequent and dispensary observation. The hospital stay was 4 days - 2 patients, 7 days - 6 patients, 10 days - 9 patients, 20 days - 2 patients. Due to cholangitis, the patients stayed for more than 10 days. Subsequently, after reducing the level of bilirubin to normal numbers, four patients underwent radical liver resection.

Conclusions: Percutaneous transhepatic cholangiostomy is one of the widely spread, widely used and effective methods of surgical treatment of patients with mechanical jaundice of alveococcal genesis, which allows to achieve adequate drainage of the bile ducts. At the moment, the operation is one of the stages of treatment of patients with alveococcosis of the liver. In the first case, this is preparation before a radical liver resection, in the second case, it is a palliative operation in inoperable patients who are prescribedto have a liver transplant.

Keywords: PTBD, ALVEOCOCCUS, LIVER

FV-166

Anti-Inflammatory and Protective Effect of Citrullus Colocynthis Seed Extract on Rat Peritonitis Model

Ankush Kumar, P Mishra

Department of Basic Sciences,, DAV, A State University, India

Aims: Citrullus colocynthis is one of the folk medicinal plants found in India, Bangladesh, and Sri Lanka. C. colocynthis contains large amounts of phenolics and flavonoids that have antioxidant activity in its seed extract. In this study, our research aims to analyze the antibacterial, anti-inflammatory, and antioxidant effect of Cucurbitacin, especially a natural phenol catechin present in the seed hydro-ethanol extract of C. colocynthis (CA) in a rat peritonitis model.

Methods: Rats were divided into five groups: (1) Control group, (2) CA group, (3) peritonitis group (P), (4) peritonitis + CA group (P + CA), and (5) peritonitis + antibiotherapy group (P + Ab). Ultrafiltration (UF) rates were determined and colony and leukocyte counts were calculated in the dialysate. Glucose, blood

urea nitrogen (BUN), creatinine levels, and alanine transaminase (ALT) activities were studied in blood. Glucose, interleukins (IL-1β, IL-6), and prostaglandin E2 (PGE2) were studied in dialysate and peritoneal tissue for the assessment of the anti-inflammatory effect. Copper/zinc superoxide dismutase (Cu, Zn-SOD), malondialdehyde (MDA), and nitric oxide (NO) were also investigated in peritoneal tissue.

Results: C. colocynthis increased the UF rate and lowered leukocyte numbers in the peritonitis group. There was no significant difference in blood and dialysate glucose, BUN, creatinine levels and ALT activity among control and CA groups. CA decreased IL-1β, IL-6 and PGE2 in peritonitis, showing good anti-inflammatory effect. CA showed antioxidant effect on the chosen antioxidant parameters Cu, Zn-SOD, MDA, and NO.

Conclusions: It was concluded that, C. colocynthis extract might be used in peritonitis for its probable UF increasing, anti-inflammatory, and antioxidant effects.

Keywords: Citrullus colocynthis, Rat peritonitis model, Anti-inflammatory, Antioxidant

FV-167

Laparoscopic Major (>2 Segments) Hepatectomy in Greece

Ioannis HATZARAS, Nikolaos ARKADOPOULOS

Surgery, National and Kapodistrian University of Athens, Greece

Aims: Objectives: Despite gaining traction around the world, laparoscopic approach to major hepatectomy, defined as resection of at least two neighboring hepatic segments, has not been fully adopted in Greece. We sought to describe our growing experience.

Methods: Data: Data on six patients who underwent major hepatic resection in the last year in two major urban hospitals.

Results: Findings: The predominant indication for hepatectomy in these patients were metastatic disease to the liver. Three patients had colorectal metastases, one patient had metastatic melanoma, and two patients had benign pathology. There were two males and four females, with an average age of 59 (range: 52-71 years). Four patients had a solitary lesion and two had two lesions. Four patients had received pre-hepatectomy disease-specific chemotherapy or immunotherapy. The median size of the lesion was 5cm (range: 3.5 – 12cm). Two patients underwent a right hepatic lobectomy, one a left hepatic lobectomy together with a right colectomy, and three patients underwent right anterior sectorectomy. All operations were done purely laparoscopic except one, where a hand port was employed due to the size of the lesion. Median operative time was 190 minutes and median stay at the hospital was 2 nights. No patient required intensive care unit monitoring. There was no 30-day mortality.

Conclusions: Conclusion: Major laparoscopic hepatic resection can be accomplished safely in well selected patients in the current Greek health system. Patients who have a laparoscopic hepatectomy benefit from a short hospital stay, without jeopardizing the safety of the operation.

FV-168

Laparoscopic Management of Perihilar Cholangiocarcinoma

Min-Su PARK, Bumsoo KIM, Sangmok LEE

Surgery, Kyunghee University, Korea

Aims: Surgical management of perihilar Cholangiocarcinoma remains the only available treatment option with curative intent and potential influence on overall survival. Complete laparoscopic resection of perihilar cholangiocarcinoma with biliary reconstruction is a challenging procedure.

Methods: A sixty-eight-year-old man was presented with a history of fever and abdominal pain. He had a clinical and biochemical picture of obstructive jaundice with a direct bilirubin of 25mg/dl and alkaline phosphatase of 422. His Ca 19-9 values were raised. CT scan showed an irregular wall thickening of proximal common bile duct with dilatation of upstream bile ducts (Bismuth type I). A preoperative per-cutaneous transhepatic biliary drainage was done to correct hyperbilirubinaemia.

Results: The laparoscopic resection of perihilar cholangiocarcinoma was performed with 5 trocars. The procedure included hepatoduodenal lymphadenectomy, common bile duct resection and hepaticojejunostomy. Intraoperative frozen section was performed to confirm negative resection margins. The operative time was 210min with an estimated blood loss of 150 ml. Final histopathology revealed a perihilar cholangiocarcinoma of size 1.7x1.6x1.3 cm, moderately differentiated adenocarcinoma invading beyond the wall of the bile duct and nodes free of tumor (0/7), with positive lymphovascular emboli. The patient was discharged on the 9th postoperative day with no complications.

Conclusions: The patient was discharged on the 9th postoperative day with no complications. Based on our experience, laparoscopic management of perihilar cholangiocarcinoma can be technically safe and feasible.

FV-169

Robotic Pancreatoduodenectomy for Large Solid Pseudopapillary Tumor of the Pancreas Using Precise and Systematic Vascular Control Technique

Kalayarasan RAJA

Surgical Gastroenterology, JIPMER, India

Aims: Large tumors in the head of the pancreas pose technical challenges during resection in minimally invasive pancreatoduodenectomy (PD). The precise and systematic vascular control of the pancreaticoduodenal branches of the superior mesenteric artery and vein during robotic PD for a large solid pseudopapillary tumor of the pancreas is described in this video.

Methods: A 16-year-old female presented with a lump in the abdomen, early satiety, and epigastric pain of 3 months du-

ration. Contrast-enhanced computed tomography abdomen revealed 7.1 x 6.2 cm solid mass with cystic areas in the head of the pancreas. The tumor was compressing the portal vein with dilated pancreaticoduodenal veins. In the present technique, the anterosuperior pancreaticoduodenal vein is controlled first, followed by the superior pancreaticoduodenal artery (by ligating Gastroduodenal artery). This is followed by the control of inferior pancreaticoduodenal veins and arteries. The posterosuperior pancreaticoduodenal vein is ligated at the end to prevent vascular congestion of the uncinate region.

Results: The duration of surgery and intraoperative blood loss were 440 minutes and 200 mL, respectively. The patient had an uneventful postoperative course and discharged on the sixth postoperative day. Histopathological examination confirmed the diagnosis of the solid pseudopapillary tumor. At nine months follow-up, the patient remains asymptomatic with no recurrence.

Conclusions: A stepwise precise vascular control described in this report could minimize intraoperative bleeding during robotic PD for large tumors in the head of the pancreas.

FV-170

Laparoscopic Anatomical Subsegmentectomy for Hepatocellular Carcinoma using Indocyanine Green Fluorescence Imaging

Hye-Sung JO, Young-Dong YU, Dong-Sik KIM

Surgery, Korea University College of Medicine, Korea

Aims: Recently, various types of laparoscopic anatomical liver resection for hepatocellular carcinoma has been actively performed in many centers. Indocyanine green (ICG) fluorescence imaging technique has been increasingly used to visualize biliary anatomy and demarcation of the transected area. We demonstrate laparoscopic anatomical subsegmentectomy for hepatocellular carcinoma using indocyanine green fluorescence imaging technique.

Methods: A 70-year-old female patient with chronic hepatitis B virus-associated hepatocellular carcinoma underwent laparoscopic S5 subsegmentectomy. We identified and divided the Glisson's pedicle to the tumor with intraoperative ultrasonography. Then, ICG 5mg (0.1 mg/kg) was administered via the intravenous route. After several seconds, future liver remnant territory was counterstained under a fluorescent microscope (Olympus, Tokyo, Japan). Then, the ventral portion of S5 was transected along with the demarcation line.

Results: ICG fluorescence was well accumulated in the future liver remnant. It provided clearer demarcation than the conventional demarcation technique. The operation time was 200 minutes, and intraoperative blood loss was negligible. All surgical resection margins were confirmed to be negative for tumor cell. She was discharged on the seventh postoperative day without any complication.

Conclusions: Laparoscopic anatomical subsegmentectomy using indocyanine green fluorescence imaging was a feasible procedure. It could contribute to better identification of subsegment indicated by conventional demarcation technique.

13. Others

FV-171

Bone Mineral Density and Muscle Strength In Post-Menopausal Women: Role of Pharmacological Therapy

Minakshi Sarswati, A K Gaur

Department of Alternative Medicine, Ayush diabetes research foundation, India

Aims: Osteoporosis is a systemic disease of the skeleton characterized by a reduction in bone mass and alterations in microarchitecture accompanied by increase in fracture risk, with a relevant decline in quality of life and important social, economic, and health implications, representing one of the most common causes of disability and a major financial item of health cost in many Countries. The best therapy for osteoporosis is prevention, consisting in measures to avoid or slow the onset of the disease. Treatment includes measures aimed at osteoporotic individuals, with or without previous fractures and a high risk of a first or additional fracture.

Methods: We enrolled thirty post-menopausal osteoporotic women, allocated in the first group underwent a 6-month personalized drug therapy and focused mechanoacoustic vibration (2 sessions per week, each lasting 15 minutes); women allocated in the second group underwent only 6-month personalized drug therapy. Patients were evaluated performing dual-energy X-ray absorptiometry (DXA) and isokinetic machine evaluation, and administration of Tinetti scale and ECOS-16 questionnaire.

Results: Show improvement of bone mineral density (BMD) and T-score at the lumbar spine and femoral neck, handgrip strength and isokinetic strength of the knee estensors, balance and gait, and quality of life.

Conclusions: Hence, the combined treatment with focused mechano-acoustic vibration and pharmacological therapy has a beneficial effect on BMD and T-score as well as on the muscle strength and quality of life of osteoporotic subjects.

Keywords: Pharmacological therapy, Muscle strength, Post-menopausal women, Bone mineral density

FV-172

Therapy of Cardiovascular Disease Through Bavachin: Biological Importance and Therapeutic Benefit in the Medicine

Dinesh Kumar Patel, Kanika Patel

Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj 211007, Uttar Pradesh, India

Aims: Heart related disorders are very common complication of human being now day as the cases of stroke related disorders have been reached up to 15 million cases every year in the different region of the world and cause many number of death every year. Fruits, nuts, vegetables and medicinal plants are rich source of phytochemical in the nature and have been used for the extraction and separation of various bioactive phytochemical. Vascular calcification is an important factor which involved in the cardiovascular disorders and chronic renal failure. Bavachin is a natural bioactive compound found to be present in the Psoralea corylifolia.

Methods: In order to know the effectiveness of bavachin in the medicine for the treatment of cardiovascular disorders, here in the present investigation anti-arteriosclerosis effect of bavachin have been investigated through scientific data analysis of various literature works. Detailed pharmacological properties of of bavachin have been investigated through literature data analysis to know their effectiveness in the medicine against various form of Heart related disorders. Biological importances in the medicine for the treatment of cardiac disorders have been also investigated through literature data analysis.

Results: Literature data analysis revealed the medicinal importance and therapeutic benefit of bavachin in the medicine for the treatment of cardiovascular disorders. Bavachin have biological potential due to effectiveness against vascular calcification. Literature data analysis revealed that, bavachin reduced the level of calcium ions and expression of calcification-related proteins dose-dependently, which further signified their effectiveness in the medicine.

Conclusions: Literature data analysis of different research works in the present investigation signified the biological potential of bavachin for the treatment of cardiovascular disorders.

Keywords: Cardiovascular disorders, Bavachin, Medicine, Calcification

FV-173

A Pulse Check on General Public's Knowledge, Awareness, and Attitudes towards Liver Health in South Korea

Hye Won Lee[1], Jin Youn[2], Megan Kim[2], Shikha Singh[3], Sang Hoon Ahn[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Gilead Sciences, Hong Kong SAR, China; [3]Kantar Health, Singapore

Aims: The 2013 Korean Liver Association Survey revealed a suboptimal level of awareness and knowledge among the general public towards liver health and diseases, sparking progressive reform of policies and education efforts in South Korea. This study aims to assess the current status of the public's awareness, knowledge, and attitude towards liver-related diseases.

Methods: A self-reported, cross-sectional study among 1,000 adult individuals (age and gender reflective of the national population) was conducted between February-March 2020. Items assessing knowledge, awareness, and attitudes towards liver-related health and diseases were administered via a 30-minute web-based questionnaire.

Results: About half knew untreated/chronic viral hepatitis could lead to liver cirrhosis/fibrosis, liver failure and/or cancer, and liver cirrhosis/fibrosis being key determinants of liver disease progression. Majority agreed regular screening (96%) and getting vaccinated (90%) were ways to protect liver health. This contrasted with 76% self-reported attended health screening within recent 2 years, 67% knowing hepatitis B virus (HBV) is preventable by vaccination (43.3% self-reported being vaccinated in 2013), and 16% aware hepatitis C virus (HCV) cannot be prevented by vaccination. Misperceptions pertaining to transmission risks hint at the presence of stigma and discrimination within the community. About one-quarter rightly identified dining with an infected individual could not transmit HBV. Apart from cost-related concerns, reasons for low urgency towards seeking medical consultation upon risk-factor exposure or diagnosis included perceptions of being healthy or the condition is not life-threatening. Furthermore, only 22% were aware of available treatments for curing HCV infection.

Conclusions: The findings highlighted a possible deterioration of public's knowledge towards liver-related health and diseases in South Korea. The limited public's knowledge towards liver diseases potentially accounts for the low urgency towards seeking medical consultation, therefore implying an unmet need for more efforts to address misperceptions and dispel stigma, encouraging screening among high-risk populations, within the community.

Keywords: HBV, Awareness, Public, Liver disease, Survey

FV-174

How Much Acute Liver Failure in India Is Related to Pregnancy

Rahul Kumar, Anjali Kanojia

Department of Zoology, J K College, Bihar, India

Aims: Acute liver failure (ALF) in pregnancy is associated with significant maternal and fetal morbidity and mortality. The Acute Liver Failure Study Group (ALFSG) registry includes patients with ALF and acute liver injury (ALI, severe injury without encephalopathy). We sought to review presentations and outcomes of all pregnant women enrolled in the ALFSG registry that met standard entry criteria for ALF/ALI.

Methods: Between January 2018 and November 2019, 5000 subjects were registered with ALF or ALI and 209 of these subjects were pregnant or postpartum at the time of enrollment. Subjects were reviewed for demographics, cause of liver disease, lab values, and outcomes at 21 days: death, liver transplant (LT) or spontaneous survival (SS). Testing for acetaminophen (APAP) protein adducts was performed on selected subjects to confirm

a suspected diagnosis of APAP.

Results: The median age of enrollees was 30 with 54.8% Maharashtrians, 29.9% Biharis, 4.2% Assamese, 4.2% other and 2.8% Islandic. Specific pregnancy-associated acute liver diseases (PAALD; hemolysis, elevated liver enzymes, low platelets [HELLP], pre-eclampsia, or acute fatty liver of pregnancy, [AFLP]) represented nearly 55% of cases—all PAALD patients were enrolled post-partum indicating that obstetrical services recognize PAALD and deliver patients appropriately. APAP toxicity was observed in 40% of cases with other etiologies such as autoimmune hepatitis, drug-induced liver injury, HSV, cancer (adenocarcinoma and lymphoma), thyroid disease, comprising the remainder; no hepatitis A, B, C, or E cases were identified. The median gestational age of presentation by etiology was PAALD 37 weeks, APAP 30 weeks, and other 30 weeks. Overall 21-day status was 57.6 % SS, 28.9% LT, and 10.7% died. When outcomes per etiology were considered separately, PAALD: 74% SS, 11% LT, 15% died; APAP: 90% SS, 4% LT, 6% died; Other: 40% SS, 23% LT, Died 37%. Fetal outcomes also differed greatly between groups with survival rates of PAALD 96%, APAP 55%, and other 43%.

Conclusions: Overall, in this population of ALF associated with pregnancy, more than half the cases were non-PAALD, with APAP toxicity being the most frequent other cause. HSV hepatitis and other causes are associated with worse outcomes but are less common. PAALD, occurring as it does near term, is associated with very good fetal survival and fair maternal overall mortality.

Keywords: Acute liver failure, Pregnancy, Patients, Spontaneous survival

FV-175

Mental Health Problems, Digital Aging, and Risk Mitigation in the Older People with Liver Disease

Rosinta Hotmaida Pebrianti Purba

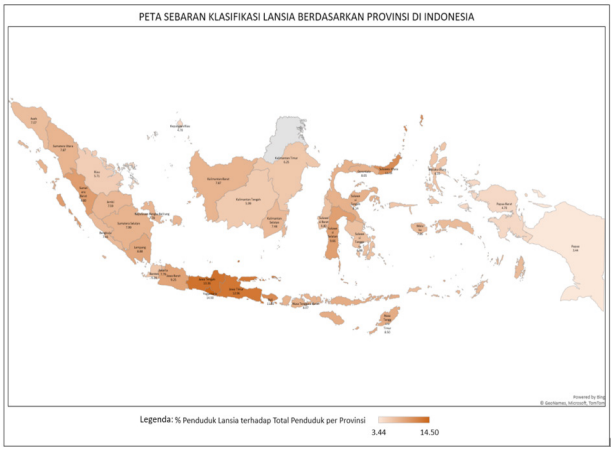
Poverty Alleviation and Community Empowerment, The Ministry of National Development Planning, Republic of Indonesia, Indonesia

Aims: Indonesia is entering Ageing Society with an older people population reaching 26.82 million people or 9.92% of the total population in 2020 and it is predicted that around one-fifth of Indonesia's population in 2045 will be older people. The senior citizen is the COVID-19 most at risk due to comorbidities and low digital literacy.

Methods: Using data from the 2014 Indonesia Family Life Survey (IFLS), this study aims to analyze mental health problems and mobile phone ownership in older adults (60+) with liver disease.

Results: The analysis shows that 16.78% of the older people with liver disease experienced mental health problems. They report feeling not trying enough, sleeping restless, bothered by things, hopeless, unable to concentrate, and feeling unhappy. The least disturbance felt by them was feeling afraid. The socioeconomic status of the elderly in Indonesia has a fairly diverse distribution between provinces. As much as 39% of the elderly with liver disease have mobile phones, this is because almost 60% of caregivers are working families. Even though, as many as 73% of Indonesian elderly with liver disease are still working. Nearly half of older people's education attainment is elementary school, which reaches 46.05 percent. Although 40.8% of the elderly with liver disease seek treatment at a community health center (Puskesmas), 18.36% tend to go to traditional practitioners.

Conclusions: Mental health problems increase the risk of fatalities due to Covid-19 because the older adults in Indonesia are not yet a priority for vaccine recipients. Strategies are needed to mitigate mental health problems in the elderly by utilizing the existing community-based integrated service system such as Puskesmas. Improving the welfare of the elderly requires a multidisciplinary and inter-sectoral approach. Mainstreaming the issue of digital aging can help various information and services needed by the elderly to be healthier, independent, and with dignity.



Chronic Conditions	Lansia Muda	%	Lansia Madya	%	Lansia Tua	%	Total	%
Hypertension	450	29,20	105	27,63	0	0	555	28,56
Diabetes or high blood sugar	**117**	**7,59**	**24**	**6,32**	**0**	**0**	**141**	**7,26**
Tuberculosis (TBC)	26	1,69	25	6,58	0	0	51	2,62
Asthma	**63**	**4,09**	**16**	**4,21**	**0**	**0**	**79**	**4,07**
Other lung conditions	23	1,49	11	2,89	0	0	34	1,75
Heart attack, coronary heart disease, angina, or other heart problems	**104**	**6,75**	**14**	**3,68**	**0**	**0**	**118**	**6,07**
Liver	49	3,18	0	0,00	0	0	49	2,52
Stroke	**63**	**4,09**	**16**	**4,21**	**0**	**0**	**79**	**4,07**
Cancer or malignant tumor	23	1,49	11	2,89	0	0	34	1,75
Arthritis/rheumatism	**216**	**14,02**	**73**	**19,21**	**11**	**50**	**300**	**15,44**
High Cholesterol (Total or LDL)	102	6,62	20	5,26	0	0	122	6,28
Prostate illness	**33**	**2,14**	**5**	**1,32**	**0**	**0**	**38**	**1,96**
Kidney disease (except for tumor or cancer)	29	1,88	5	1,32	0	0	34	1,75
Stomach or other digestive disease	**163**	**10,58**	**55**	**14,47**	**11**	**50**	**229**	**11,79**
Emotional, nervous, or psychiatric problems	49	3,18	0	0,00	0	0	49	2,52
Memory-related disease	**31**	**2,01**	**0**	**0,00**	**0**	**0**	**31**	**1,60**
	1541	**100**	**380**	**100,00**	**22**	**100**	**1943**	

Keywords: Mental health, Covid-19, Older people, Digital ageing

FV-176

Clinical Experience of Somatostatin for the Treatment of Severe Posthepatectomy Liver Failure

Hye-Sung JO, Young-Dong YU, Dong-Sik KIM*

Surgery, Korea University College of Medicine, Seoul, Korea, Korea

Aims: Posthepatectomy liver failure (PHLF) is a major cause of morbidity and mortality after major liver resection. Postoperative excessive portal pressure could cause shear stress to the small remnant liver leading to a PHLF. This study aimed to report the clinical experience of somatostatin for portal modulation in patients with severe PHLF.

Methods: This retrospective study enrolled 15 patients who received somatostatin for the treatment of PHLF between 2016 and 2019. When the patients fulfilled the 50-50 criteria (serum bilirubin >2.9 mg/dL and prothrombin time <50%) on or before postoperative day 5, somatostatin (3.5 ug/kg/h) was administered by continuous infusion. The discontinuation criteria were as follows: serum bilirubin <2 mg/dL and prothrombin time ≥50%. Prospectively collected clinical characteristics, laboratory tests, postoperative morbidity and mortality were evaluated.

Results: The study cohort consisted of 8 patients with hepatocellular carcinoma, 6 with cholangiocarcinoma, and 1 with colon cancer liver metastasis. Seven patients (46.7%) had underlying liver cirrhosis, and 14 (93.3%) underwent major hepatectomy. The median start time of somatostatin was postoperative day 1 (range 1–19), and the median duration of administration was 9 (2–29) days. There was no obvious side effects or hypersensitivity related to the somatostatin. The median hospital stay was 37 (21–249) days. The 30-day and 90-day mortality were both 6.7% (1 of 15 patients).

Conclusions: Administration of somatostatin in the early postoperative period is considered to be effective for the treatment of PHLF. Further prospective comparative clinical trials are needed to validate this finding.

FV-177

Laboratory Diagnostic Parameters and Factors Associated Among suspected liver Patient Attending Tertiary Care Hospital in Nepal

Ganga Sagar Bhattarai

Prithivi Narayan Campus, Tribhuvan University, Nepal

Aims: Aspartate Aminotransferase (AST or SGOT), Alanine Aminotransferase (ALT or SGPT) and alkaline phosphatase are one of the significant indicators of liver damage. The study aimed to determine the level of AST, ALT and alkaline phosphatase; and AST/ALT ratio among suspected liver patients attending at tertiary care hospital of Nepal.

Methods: Blood samples were collected from suspected liver patients visiting Tertiary care hospital. The samples were collected from November, 2020 to January 2021. Enzyme kinetics method was used to process the serum samples. Descriptive statistics and chi-square test were computed at 5% level of significance

Results: Of total 166 suspected liver patients, 60.02% patients had high AST or SGOT, 48.8% had high ALT or SGPT and 5.4% had high alkaline phosphatase. The prevalence of SGOT and SGPT and was higher among males (70% Vs 30%), (67.90% Vs 32.09%) respectively. Regarding alkaline phosphatase, there was only 5.4% high. Ethnicity and Alcoholic behavior was statistically associated with high SGOT in the study (P<0.05); it was highest among alcoholic group. However, there was no statistical association of high SGOT with sex. Similarly Age, Alcoholic behavior and ethnicity was statistically associated with high SGPT in the study (P<0.05).

Conclusions: The study shows high prevalence of AST, ALT among suspected liver patients attending tertiary care hospital of Nepal. Ethnicity, Alcoholic behaviour and sex were found statistically significant.

Keywords: AST, ALT, ALP, Nepal

FV-178

Therapeutic Benefit and Biological Application of Tectorigenin in The Medicine for the Treatment of Various Forms of Lungs Disorders and Complications

Dinesh Kumar Patel, Kanika Patel

Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj 211007, Uttar Pradesh, India

Aims: Phytochemicals have been utilized by human being due to their medicinal value and therapeutic benefit in the medicine and other allied health sectors and some of the best examples are vincristin, vinblastin and quinine. Tectorigenin is an important class of flavonoidal natural drugs found to be present in various plant materials and their derived products.

Methods: Biological potential and therapeutic benefit of tectorigenin for the treatment of numerous human complications have been investigated in the medicine for their health beneficial aspects. Numerous literature databases have been searched to collect all the needed information of tectorigenin in order to explore their therapeutic benefit in the medicine. Biological activities of tectorigenin for their effectiveness against various form of vascular complication were studied in the present investigation through scientific data analysis of various literature works.

Results: Literature data analysis revealed that tectorigenin is the active phytochemical of the natural drug and found to be present in the rhizomes of Iris tectorum. Literature data analysis signified the biological importance and therapeutic benefit of tectorigenin in the medicine. Analysis of different literature data signified the biological potential of tectorigenin in the medicine due to their numerous biological activities and pharmacological benefit. Scientific data analysis of various research works revealed the biological importance of tectorigenin against pulmonary fibroblasts.

Conclusions: Literature data analysis revealed the biological importance and therapeutic benefit of tectorigenin in the medicine.

Keywords: Tectorigenin, Pulmonary fibroblasts, Medicine, Phytochemical

FV-179

Study of Liver Enzymes in Patient with Cardiovascular Diseases: A Hospital Based Study

Naval Kishor Yadav[1], Daya Ram Pokharel[1], Dinesh Sharma[2]

[1]Department of Biochemistry, Manipal College of Medical Sciences, Pokhara, Nepal, [2]School of Health and allied Sciences, Glocal University, UP, India

Aims: Cardiovascular diseases are major causes of morbidity in developed and developing countries. Mortality is manifested as acute myocardial infarction, cerebral vascular accident, angina or sudden death in male age between 50-60 years and in female between 60-70 years.The risk factors of cardiovascular diseases include dietary habbits, physical inactivity, tobacco use, diabetes mellitus, hypertension, obesity and high blood lipid. The aim of study was to study liver enzymes in patients with cardiovascular diseases in hilly region of Nepal.

Methods: This is a hospital based case control study. A total of 350 individuals were enrolled, out of which 250 were case and 100 were healthy control. The patients visited to cardiology and emegerncy unit of Manipal Teaching Hospital, Pokhara, Nepal were included. The cardiovascular diseases were diagnosed on the basis of cardiac profile and ECG finding. The liver enzymes were analysed using dry chemistry analyser in biochemistry laboratory. The data were analysed using SPSS version 16.

Results: The mean age of case and control were 63.38±12.15 and 47.78±16.82 respectively. The mean ± SD of liver enzymes in case were aspartate aminotransaminase (AST) (159.67±161.13), alanine aminotransaminase (ALT) (71.53±49.25) and alkaline phosphatase (ALP) (97.35±112.73). Similarly, mean±SD in healthy control group were AST (27.65±6.15), ALT (32.13±6.32) and ALP (78.10±19.84). Serum level of AST (p value 0.000) and ALT (p value 0.000) were statistically significant. The level of ALP were higher in cardiovascular patients in compare to healthy control but it was statistically insignificant (p value 0.151).

Conclusions: The liver enzymes were higher in patients with cardiovascular diseases in relation to healthy control. Liver eanzymes can be use as supportive indicatior of cardiovascular diseases along cardiac markers.

Keywords: Liver enzyme, Cardiovascular diseases, Hospital based study

FV-180

Role of Laughter Yoga and Clapping Exercise on Hepatic Functions and Quality of Life in Patients Suffering from Chronic Liver Disease in East Delhi Metro Population

Rakesh Rajput, V K Sharma

Applied Sciences, Shri Mahamayta Vaishnav Devi Mandir Research Institute, India

Aims: To study new methods of chronic liver disease (CLD) rehabilitation complications by laughter yoga and clapping exercise program in south Delhi metro population.

Methods: Fifty-six patients (subject) between 45–65 years old with CLD were studied and divided into two groups (laughter yoga and clapping exercise group and control group) to see the effect of laughter yoga and clapping exercise group in CLD for 30 days. Using a cross-sectional design, which includes age, family history of CLD patients, exercise status and waist circumference, fasting glucose & insulin, glucose tolerance test (GTT), liver ultrasonography, regular monitoring of blood pressure, liver function, requirement of a number of dialysis, serum creatinine level and glycosylated hemoglobin (HbA1c) and quality of life (QOL) indicators were done CLD patients. A 30-minute lecture was followed by 30-minute intense clapping workout for those participants who had laughter yoga included in the program.

Results: Present study showed that after three month treatment there were a significant reduction of systolic and diastolic blood pressure, blood glucose levels, glycosylated haemoglobin levels, significant reduction in blood urea and serum creatinine levels, and significant improvement in physical and psychological domain compare to normal levels with changes in life style. Present study highlight that the successful treatment of CLD patients not only requires drugs; but also family care, life style education, harmonised mind-body-soul, awareness, psychological support, preventive approach toward activity of daily living.

Conclusions: Our study indicated the importance of daily opportunities for laughter yoga and and clapping exercise in patients with CLD patients.

Keywords: Chronic liver disease, Laughter yoga, Clapping exercise, Liver ultrasonography

FV-181

Study on Childhood Obesity and Various Possible Causes and Effects on Liver in Study Area of Mau, Chitrakoot (U.P)

Sukrat Sinha

Department of Zoology, Nehru Gram Bharati,Prayagraj, U.P, India

Aims: Childhood obesity is one of the most serious public health challenges of 21st century. The problem is global and is steadily affecting many low and middle income countries, particularly in urban settings. Overweight is multifactorial condition linked to an energy imbalance and also affecting liver. India is gaining weight. Traditionally known for malnutrition (Kalra and Unnikrishnan, 2012), Indians now report more and more frequently with overweight, obesity, and their consequences. The present study was done to analyse the overweight and obesity

in the area of Mau, Chitrakoot, U.P, India.
Methods: A pilot study was done on the schools in this area. A prestested questionnaire was prepared, schools in the area were approached and with informed consent of students data was collected, BMI was calculated and analysed. Total 150 students were selected in the age group of 9to12yrs. The present study found overall prevalence of overweight as 62 students of which 11 were found obese as having more BMI. It indicates that the study area (Mau-Chitrakoot) has more overweight children than obese
Results: It has been found that boys are more overweight than girls as boys are more careless than girls so don't pay their attention towards their health. Children having rich family background are having high in number of overweight and obesity as compared to middle and lower class . The students attending government school were less prone than of private school students due to luxuries provided at home. Children paying more time in mobile and T.V screen and less time in physical activity along with compromising their sleep are more susceptible to obesity. Parents having obesity have more chances of having their child obese
Conclusions: Obesity has to be controlled. Parents, teachers and peer groups have the responsibility to tackle this problem which is not so easy to solve else it would lead to an increase in liver associated diseases.
Keywords: Liver, Obesity, Childhood,

FV-182

Clinico-Metabolic Characterization Improves the Prognostic Value of Histological Growth Patterns in Patients Undergoing Surgery for Colorectal Liver Metastases

Ali BOHLOK[1], Ivan DURAN DERIJCKERE[2], Hugues AZEMA[1], Valerio LUCIDI[3], Sophie VANKERCKHOVE[1], Alain HENDLISZ[4], Jean Luc VAN LAETHEM[5], Serge GOLDMAN[6], Patrick FLAMEN[1], Denis LARSIMONT[7], Pieter DEMETTER[7], Luc DIRIX[8], Peter VERMEULEN[9], Vincent DONCKIER[*1]

[1]Surgical Oncology, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium; [2]Nuclear Medicine, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium; [3]Abdominal Surgery, Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium; [4]Digestive Oncology, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium; [5]Hepato-Gastroenterology, Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium; [6]Nuclear Medicine, Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium; [7]Pathology, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium; [8]Translational Cancer Research Unit (CORE), Gasthuiszusters Antwerpen Hospitals, University of Antwerp, Wilrijk, Antwerp, Belgium; [9]Translational Cancer Research Unit, GZA Hospitals & CORE, MIPRO, University of Antwerp, Antwerp, Belgium

Aims: Selection for surgery in patients with colorectal liver metastases (CRLM) remains poorly personalized. We evaluated whether the combination of clinico-metabolic characteristics with the histological growth pattern (HGP) of CRLM could improve the prognostication in individual cases.
Methods: In a series of 108 patients undergoing resection of CRLM, the HGP of CRLM was scored according to international guidelines. A baseline metabolic-Clinical Risk Score (mCRS) was calculated by adding the 18FDG-PET/CT scan data as a parameter to the traditional Memorial Sloan Kettering CRS.
Results: In patients with desmoplastic HGP (DHGP) CRLM (20% of all patients), 5- and 10-years OS and DFS were 66% and 43% and 37% and 24.5%, as compared with 35% and 21% and 11% and 11% in the non-DHGP group (*P*=0.07 and 0.054). Among DHGP patients, those with a low-risk mCRS had significantly improved postoperative outcomes, 5- and 10-years OS and DFS reaching 83.3% and 62.5% and 50% and 33%, as compared with 18% and 0% and 0% and 0% in high-risk mCRS patients (*P*=0.007 and 0.003). In contrast, mCRS did not influence the postoperative survivals in non-DHGP patients.
Conclusions: Combining the clinico-metabolic characteristics with the HGP may improve prognostication in patients undergoing surgery for CRLM.

FV-183

A Glimpse to the Resident Life in a HBP Team

Mara MARDARE[1], Alina PUSCASU[1], Victor BURLOIU[1], Andrei VACARASU[1], Irina BONDOC[1], Andrada SPANU[1], Razvan IOSIFESCU[1], Marius ZAMFIR[1], Niculae IORDACHE[1], Octav GINGHINA[1], Radu GHENADE[1], Camelia CALIN[2]

[1]General Surgery, St John Emergency Hospital, Bucharest, Rumania; [2]Anesthesiology, St John Emergency Hospital, Bucharest, Rumania

Aims: What does hepato-biliary-pancreatic (HBP) surgery mean and how does the life of the resident in a young team practicing such surgery in a developing country look like?
Methods: Surgical residents interested in acquiring advanced training in HBP surgery should take a fellowship in this kind of surgery, spending at least four years in a specialized center.
Results: The pre and postoperative management of patients is a core function of a junior doctor, but they have to be involved in every step of the journey represented by complex HBP surgery: from establishing anesthesia routine to training team and taking part in tumor board meetings. Mentorship is also a key factor in promoting and maintaining fulfillment in surgical practice.
Conclusions: In a young HBP team, bidirectional growth – both mentors and residents is crucial to developing this king of surgery. Working hard, studying and training every day are very important steps in order to build a career as a HBP surgeon.

FV-184

Celiac Disease Associated Liver Dysfunction: Study of the Histological Features and Co-Localisation Patterns of IgA and IgG Anti-Tissue Transglutaminase Antibody (TTG-2) in Liver Biopsies

Rimlee DUTTA[1], Prasenjit DAS[1], Siddhartha DATTAGUPTA[1], Govind MAKHARIA[2]

[1]Pathology, All India Institute of Medical Sciences, India; [2]Gastroenterology and Human nutrition, All India Institute of Medical Sciences, India

Aims: Celiac disease(CeD) associated liver dysfunctions (CALD) have wide range of manifestation ranging from milder symptoms alleviating on gluten free diet(GFD), to pathological conditions such as autoimmune hepatitis, cirrhosis etc. However, characteristic histopathological signatures diagnostic of this entity have not been described yet. Diagnosis relies solely on clinical suspicion due to co-occurrence of two pathologies. The aim of this study is to elucidate histological features of CALD and demonstrate IgA/ IgGanti-tTG colocalization patterns as a hypothetic evidence towards etiology.

Methods: 28 formalin fixed paraffin embedded(FFPE) core liver biopsies from patients with treatment naïve CeD with associated liver dysfunction and another 5 FFPE liver core biopsies from patients with other proven pathologies and normal serum anti-tTG titres, were retrieved and IgA/ IgGanti-tTG colocalization was carried out both by dual immunohistochemistry(IHC) and dual confocal immunofluorescence(IF) techniques. After a period of GFD, clinically indicated liver biopsies from 5 of these 28 patients were obtained and subjected to repeat testing via the same techniques.

Results: Histopathological examination in CALD revealed the following spectrum: steatohepatitis 4(14.2%), autoimmune hepatitis 4(14.2%), non-cirrhotic portal venopathy 1(3.5%), secondary hemochromatosis 1(3.5%), steatohepatitis with necrotising granuloma 1(3.5%), cirrhosis 3(10.7%), irregular sinusoidal dilatation 14(50%). In CALD, IgA/ IgGanti-tTG colocalization was noted in 85.6%cases by dual IHC technique and in 92.8%cases by dual IF technique. Follow up biopsies in 5 CeDcases showed no co-localisation.

Conclusions: Deposition of the circulating IgA/IgGanti-tTG antibodies in suspected patients of CALD seems to be a sensitive and specific technique for diagnosing their celiac association, thereby opening up newer insights into management protocols.

The Liver Week 2021

E-Poster Exhibition

PE-001~PE-020	Hepatitis B Virus
PE-021~PE-026	Hepatitis C Virus
PE-027	Autoimmune Liver Disease
PE-028~PE-030	Alcoholic Liver Diseas
PE-031~PE-034	Drug and Toxic Injury
PE-035~PE-046	Fibrosis/Liver Cirrhosis
PE-047~PE-059	Nonalcoholic Fatty Liver Disease
PE-060~PE-082	Liver Cancer
PE-083~PE-092	Liver Transplantation
PE-093~PE-107	Biliary and Pancreatic Disease
PE-108~PE-113	Surgery, Technical Issues
PE-114~PE-128	Others

1. Hepatitis B Virus

PE-001

Seroprevalence of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus Infections among Blood Donors in India: A Retrospective Study (2016–2020)

Ashok Kumar Sah, Poonam Kumari, Ganesh Singh Rawat, Geet Aggarwal Aseem Kumar Tiwari

Department Pathology & Laboratory Medicine, Medanta -The Medicity, Gurugram, HR, India

Aims: Infection with the hepatitis B virus (HBV), the hepatitis C virus (HCV), and the human immunodeficiency virus (HIV) are all serious global public health issues. In terms of disease burden, the WHO reports that over 350 million and 170 million people, respectively, are chronic carriers of HBV and HCV. Infection with chronic hepatitis B is a major public health concern around the world, with India falling into the intermediate zone of prevalence. The aim of this study is to investigate the prevalence of HBV, HCV, and HIV infections in donations at a tertiary healthcare hospital in India's National Capital Region between 2016 to 2020 by performing confirmatory tests through modern technology at a blood bank.

Methods: Confirmatory assays were used to validate all reactive donor samples. Western blot for HIV; Strip Immuno Blot Assay (RIBA) / HCV RNA for HCV; HBsAg ES confirmatory assay for HBsAg. Donor samples that were reactive in both the antibody/antigen test and the NAT testing were considered confirmed reactive. For contrast, the student t-test was used.

Results: A total of 107011 blood donors were screened during the study period. The average age of blood donors was 36.5 years, and 91.2% were male in the study. A total of 1959 (1.83%) donor samples were found to be serologically reactive. HBV, HCV, and HIV infection rates were 0.58%, 0.15%, and 0.03%, respectively in yearly.

Conclusions: This is an excellent method for investigating hepatitis infection in healthy individuals. The efficacy of screening methods and the selection of eligible donors is shown by current trends in the incidence of blood-borne infections. Male, married, low-educated, first-time donors, and donors referred to mobile centers have a higher prevalence of blood product-transmitted infections, which necessitates different preparation in these groups.

Keywords: Blood donors, HBV, HCV, HIV, Blood test

PE-002

Performance Evaluation of Highly-Sensitive Hepatitis B Surface Antigen and Core-Related Antigen in the Clinical Practice

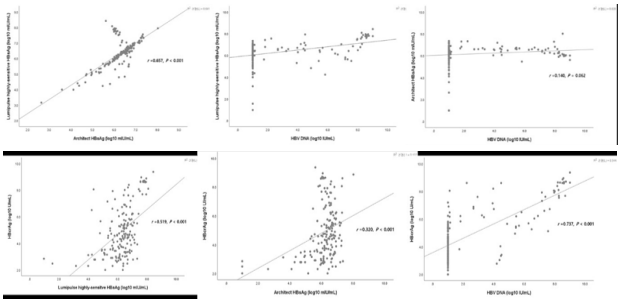
Sunghwan Yoo, Hye Young Chang, Jung Il Lee, Kwan Sik Lee, Hyun Woong Lee*

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Aims: Both serum hepatitis B virus core–related antigen (HBcrAg) and highly-sensitive hepatitis B surface antigen (HBsAg) are emerging markers for diagnosis, monitoring, and prognosis in patients with CHB. We evaluated the linearity of highly-sensitive HBsAg assay and conventional HBsAg assay and the correlation of highly-sensitive HBsAg, HBcrAg, and HBV DNA levels.

Methods: A total of 178 serum samples from patients with chronic hepatitis B were tested. Conventional HBsAg levels were determined by using the Architect (Abbott Laboratories, Abbott Park, IL), and highly-sensitive HBsAg level was measured by a two-step sandwich immunoassay method on the LUMIPULSE G1200 (Fujirebio, Tokyo, Japan). HBcrAg was measured by chemiluminescence immunoassay on the Lumipulse G12000 automated analyzer (Fujirebio, Tokyo, Japan).

Results: Both conventional HBsAg and highly-sensitive HBsAg assays showed linearity from 2.7 to 8.0 $\log_{10}$ mIU/mL and correlated well (r = 0.657, P<0.001). HBV DNA level was more correlated with Highly-sensitive HBsAg levels (r = 0.397, P<0.001) than that of conventional HBsAg levels (r = 0.140, P=0.062). HBcrAg was more correlated with Highly-sensitive HBsAg levels (r = 0.519, P<0.001) than that of conventional HBsAg levels (r = 0.320, P<0.001). HBcrAg was also correlated with HBV DNA (r = 0.737; P<0.001).



Conclusions: HBcrAg, and highly-sensitive HBsAg assays provide the possibility for further research to validate the clinical usefulness in real-world practice.

Keywords: Hepatitis B virus, Core-related antigen, Surface antigen, HBV DNA

PE-003

Current Status of Diagnosis and Follow-up Patterns of Inactive Chronic Hepatitis B: Experience of a Single Health Care Center in Korea

Jae-Jun Shim, Gi-Ae Kim, Chi Hyuck Oh

Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea

Aims: More than half of patients with chronic hepatitis B (CHB) are known to be immune-inactive at the time of diagnosis.

However, optimal managements are still lacking for the majority of patients. We investigated current status of initial diagnosis process and follow-up patterns of patients with inactive CHB in a single health care center.

Methods: From 2010 to 2016, we found 141 patients (40 to 79 years) with serum HBV DNA less than 2,000 IU/mL and normal alanine aminotransferase (ALT) (male < 30 U/L, female < 19 U/L) in a single health care center. Patients with HBsAg negative (N=16), concurrent antiviral therapy (N=35), poor medical information (N=9), active malignancy (N=2), and hepatitis C (N=1) were excluded. A total of 78 patients with tentative inactive CHB were enrolled. The confirmatory test for inactive CHB was defined as two or more serial HBV DNA and ALT tests since initial diagnosis. True inactive CHB was defined as HBsAg positive, persistently normal ALT levels and HBV DNA less than 2,000 IU/mL during 1 year or more. Patients who achieved HBsAg loss during follow-up were also considered as inactive CHB even if the confirmatory tests were lacking.

Results: Mean age of enrolled patients was 55.4 years. Cirrhosis was observed only in two patients (2.6%). Among enrolled patients, only 25 (32.1%) received the confirmatory tests during follow-up. Fifty one patients (65.4%) were initially diagnosed by hepatologists and 21 (41.2%) received the confirmatory tests. Among 27 patients cared by non-hepatologists, only 4 (14.8%) received the tests (P=0.0176). Among 45 men, 19 (42.2%) performed serial tests, while only 6 out of 33 women (18.2%) received the confirmatory tests (P=0.0246). Patients who received regular follow-up (two or more visits annually) were only 14 (17.9%). Nine patients (11.5%) followed-up less than one annually. Twenty one (26.9%) patients were poorly followed-up and 34 (43.6%) were never followed-up since initial diagnosis. Finally, 38 out of 78 patients (48.7%) were confirmed as truly inactive CHB, two (2.5%) were HBeAg negative CHB, and the remaining 38 (48.7%) failed to confirm their CHB status. During follow-up, 9 patients achieved HBsAg loss and one progressed to cirrhosis. None developed hepatocellular carcinoma.

Conclusions: Majority of patients with inactive CHB remained undiagnosed and under insufficient management. Considering that not a small number of hepatocellular carcinoma occurs among the patients with inactive CHB, more innovative approaches to achieve accurate diagnosis and optimal follow-up are required in Korea.

Keywords: Hepatitis B, Chronic, Cirrhosis, Follow-up studies

PE-004

HBcrAg and highly-Sensitive HBsAg: Useful Biomarker to Detect the Presence of Hepatitis B Virus Proteins before Rituximab Treatment

Jae Hyun Jeon[1], Sunghwan Yoo[1], Hye Young Chang[1], Jung Il Lee[1], Kwan Sik Lee[1], Jong Hoon Kim[2*], Hyun Woong Lee[1*]

[1]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, [2]Department of Dermatology, Cutaneous Biology Research Institute, Gangnam Severance Hospital, Seoul, Korea

Aims: Rituximab can lead to HBV reactivation in patients with occult HBV infection as well as in HBV carriers. To prevent HBV reactivation-related hepatitis, when HBsAg-negative and anti-HBc-positive patients treated with rituximab, HBV prophylactic antiviral treatment is being performed regardless of HBV DNA detection or HBsAg seroconversion. This study aimed to investigate whether hepatitis B core-related antigen (HBcrAg) and highly-sensitive HBsAg are more effective than conventional HBsAg test in assessing the presence of HBV proteins before rituximab treatment.

Methods: From June 2014 through October 2020, autoimmune bullous disease patients with HBsAg-/HBcAb+ who received rituximab were included. Medical records including hepatitis B serology (conventional HBsAg, anti-HBc, anti-HBs) and HBV-DNA titer, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST) levels were reviewed. Using stored sample, HBcrAg, and highly-sensitive HBsAg titer were checked at baseline before Rituximab therapy.

Results: In our study, all 16 autoimmune bullous disease patients who treated with Rituximab were HBsAg-/HBcAb+. At baseline, Among the 16 patients, 12.5% (2/16) of the patients were 6% (1/16) was seropositive for HBcrAg, seropositive using the highly-sensitive HBsAg assay. Based on this result, at least 3 patients were confirmed to have HBV proteins in serum that were not detected by conventional HBsAg test.

Conclusions: HBcrAg and highly-sensitive HBsAg assay are useful biomarkers to detect the presence of hepatitis B virus proteins before rituximab treatment. It might be considered that all HBsAg-/anti-HBc+ patients are not unnecessarily given prophylactic antiviral treatment, but only in the case of seropositive for HBcrAg or highly-sensitive HBsAg.

Keywords: HBcrAg, Highly-sensitive HBsAg, Useful biomarkers, The presence of hepatitis B virus, Before rituximab treatment

PE-005

HBcrAg, Highly-Sensitive HBsAg: Useful Biomarker to Discriminate Chronic Infection and Chronic Hepatitis In Treatment Naïve Patients with HBeAg Positive

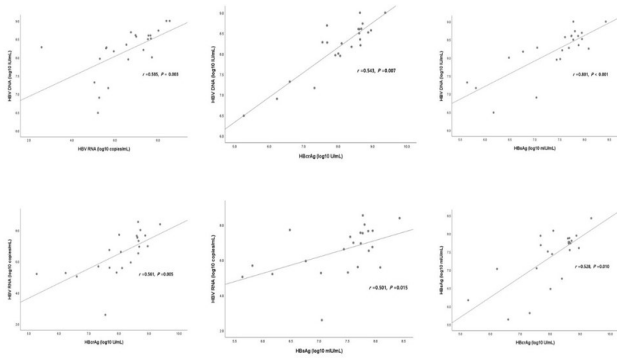
Sunghwan Yoo, Hye Young Chang, Jung Il Lee, Kwan Sik Lee, Hyun Woong Lee

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Aims: The correlation between serum HBcrAg, HBV RNA, highly-sensitive HBsAg and serum HBV DNA is rarely reported in patients with chronic hepatitis B infection. This study aimed to assess the correlation of HBcrAg, HBV RNA, highly-sensitive HBsAg, and HBV DNA, and investigate whether serum HBcrAg, HBV RNA and highly-sensitive HBsAg is useful biomarker to discriminate chronic infection and chronic hepatitis in treatment naïve patients with HBeAg positive.

Methods: Treatment naïve HBeAg positive 25 patients from January 2018 to December 2019 were included. Patients were classified into 2 clinical phases according to ALT levels. (1) HBeAg positive chronic infection (EPI) group consisted of patients with HBeAg positive and normal ALT (KASL guideline, ALT ≤ 34 IU/L in men and ALT ≤ 30 IU/L in women) (2) HBeAg positive hepatitis (EPH) group consisted of HBeAg positive patients with elevated ALT levels. serum HBcrAg, HBV RNA and highly-sensitive HBsAg titer were measured at baseline.

Results: HBcrAg was correlated positively with highly-sensitive HBsAg (r=0.528, *P*=0.01), and HBV RNA (r=0.561, *P*=0.005), and HBV DNA (r=0.543, *P*=0.007). Highly-sensitive HBsAg was correlated positively with HBV RNA (r=0.501, *P*=0.015), and HBV DNA (r=0.801, *P*<0.001). In EPI group, HBcrAg, and highly-sensitive HBsAg titer were significantly higher than those in EPH group (HBcrAg, 8.5±0.4 vs. 7.7±1.2 $\log_{10}$ U/mL, *P*=0.047; HBsAg, 7.8±0.2 vs. 7.0±0.8 $\log_{10}$ mIU/mL, *P*=0.007). However, HBV RNA level is similar between two groups (7.0±0.9 vs. 6.1±1.7 $\log_{10}$ copies/mL, *P*=0.143).



Conclusions: HBcrAg, HBV RNA and highly-sensitive HBsAg were correlated with serum HBV DNA at baseline in treatment naïve HBeAg positive patients (Figure). HBcrAg and highly-sensitive HBsAg assay are useful biomarkers to discriminate EPI and EPH group.

Keywords: HBcrAg, highly-sensitive HBsAg, HBeAg positive chronic infection, HBeAg positive hepatitis

PE-006

Long-Term Effects of Entecavir and Tenofovir Treatment on the Fibrotic Burden in Patients with Chronic Hepatitis B

Yong Eun Chon[1#], Seung Up Kim[2,3#], Yeon Seok Seo[4], Hye Won Lee[2,3], Han Ah Lee[4], Mi Na Kim[1], Yun Ho Roh[5], Jun Yong Park[2,3], Do Young Kim[2,3], Sang Hoon Ahn[2,3], Won Young Tak[6], Soo Young Park[6*], Beom Kyung Kim[2,3*]

[1]Department of Internal Medicine, Cha Bundang Medical Center, Cha University, Seongnam, Republic of Korea; [2]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea; [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea; [5]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea

Aims: Antiviral therapy (AVT) induces fibrosis regression in patients with chronic hepatitis B (CHB). We investigated the long-term effects of entecavir (ETV) versus tenofovir (TDF) on the fibrotic burden.

Methods: Treatment-naïve CHB patients who had begun ETV or TDF therapy were recruited from 4 academic teaching hospitals. The aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on 4 factors (FIB-4) were used to determine fibrotic burden.

Results: In the entire population (n=3,277), although patients treated with ETV had higher baseline APRI (1.71 vs. 1.07, *P*<0.001) and FIB-4 (3.60 vs. 2.80, *P*<0.001) than those treated with TDF, significant fibrosis regression was identified during 6 years of AVT in both ETV (APRI, mean 1.71→0.48, *P*<0.001; FIB-4, mean 3.60→2.21, *P*<0.001) and TDF groups (APRI, mean 1.07→0.43, *P*<0.001; FIB-4, mean 2.80→2.19, *P*<0.001). In patients without cirrhosis (n=2,366), baseline APRI was significantly higher in ETV group than in TDF group (1.72 vs. 0.97; *P*<0.001), however, they became similar after 6 months (all *P*>0.05). Similarly, baseline FIB-4 was significantly higher in ETV group than in TDF group (3.25 vs. 2.35; *P*<0.001), but became similar in both groups from 4 to 6 years (all *P*>0.05). In patients with cirrhosis (n=911), baseline APRI (1.70 vs. 1.34; *P*<0.001) and FIB-4 (4.62 vs. 3.91; *P*=0.005) were higher in ETV group than in TDF, respectively. However, both parameters became statistically similar from 6 months to 6 years of AVT (all *P*>0.05).

Conclusions: Significant regression of APRI and FIB-4 was observed during long-term AVT using ETV and TDF. Despite higher baseline fibrotic burden in ETV group, fibrotic burden between the groups eventually converged through significant fibrosis regression after 1 to 4 years of AVT.

Keywords: APRI, Entecavir, FIB-4, Tenofovir

PE-007

Safety and Efficacy of Switching to Tenofovir Alafenamide in Chronic Hepatitis B Patients with Hepatic Impairment: Week 48 Results

Young-Suk Lim[1], Jeong Heo[2], Chun-Yen Lin[3], Ho Bae[4], Wan-Long Chuang[5], Aric Josun Hui[6], Chun-Yen Lin[7], Magdy Elkhashab[8], Huy Trinh[9], Susanna Tan[10], Grace Zhao[10], John F. Flaherty[10], Megan Kim[10], Tak Yin Owen Tsang[11], Stephen Ryder[12], Harry Janssen[13]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Pusan National University School of Medicine, Pusan National University Hospital, Busan, South Korea; [3]Chang Gung University College of Medicine, Taoyuan City, Taiwan; [4]Asian Pacific Liver Center, St. Vincent Medical Center, Los Angeles, California, USA; [5]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsi-

ung City, Taiwan; [6]Alice Ho Miu Ling Nethersole Hospital, Hong Kong; [7]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan City, Taiwan; [8]Toronto Liver Centre, Toronto, Ontario, Canada; [9]San Jose Gastroenterology, San Jose, California, USA; [10]Gilead Sciences, Inc., Foster City, California, USA; [11]Princess Margaret Hospital, Hong Kong; [12]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK; [13]Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto

Aims: Chronic Hepatitis B (CHB) patients with impaired hepatic function who switch to TAF maintain viral suppression with stable or improved bone/renal safety at Week 24. Here we evaluated the efficacy and safety 48 weeks after switching to Tenofovir Alafenamide (TAF).

Methods: In this phase 2 study (NCT03180619), all patients were switched to TAF 25 mg QD and were to be treated for 96 weeks. Safety assessments including changes in bone (hip/spine BMD), eGFRCG, viral suppression, and biochemical responses were assessed at Week 48.

Results: 90% of 31 patients completed 48 weeks of treatment. At baseline, 74% were ≥50 y, 68% male, 81% Asian, 90% were HBeAg-negative, with median fibrotest (FT) score 0.81, median CTP and MELD scores of 6 and 10, respectively, median eGFRCG 98 mL/min, and 19% had osteoporosis at spine. Prior use of TDF and entecavir was reported by 68% and 45%, respectively. By missing equals failure analysis, all patients had HBV DNA <20 IU/mL, 81% had normal ALT and CTP, MELD scores were stable. After switching to TAF in this population with liver impairment, CTP, MELD, and FT scores were unchanged while bone and renal parameters were stable. Few Grade 3 or 4 AEs (4 patients); no serious AEs related to study drug, and 1 patient discontinued, unrelated to TAF.

Conclusions: CHB patients with hepatic impairment who were switched to TAF from TDF or other OAV showed high rates of viral suppression, normal ALT and bone and renal safety were stable at Week 48.

Keywords: HBV, TAF, Hepatic impairment, Decompensated cirrhosis, Switch

PE-008

96-Week Efficacy and Safety of Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide Switch vs. Continued TDF Treatment among Virologically-Suppressed HepatitisB Patients of Asian Ethnicity

Sang Hoon Ahn[1], Young-Suk Lim[2], June Sung Lee[3], Seung-Kew Yoon[4], Yoon Jun Kim[5], Quan Soo Byun[6], Seung Woo Paik[7], Jia-Horng Kao[8], Scott Fung[9], Wan-Long Chuang[10], Chi-Yi Chen[11], Edward Tam[12], Ho Bae[13], Xiaoli Ma[14], Leland J. Yee[15], Shalini Sethi[15], John Flaherty[15], Yang Zhao[15], Anuj Gaggar[15], Hie Won Hann[16], Henry LY Chan[17,18], Pietro Lampertico[19]

[1]Yonsei University College of Medicine, Seoul, Republic of Korea and Efficacy of Switching to Tenofovir Alafenamide in Chronic Hepatitis B Patients with Hepa; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [3]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea; [4]Catholic University Liver Research Center, The Catholic University of Korea, Seoul, South Korea; [5]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [6]Divisions of Gastroenterology and Hepatology Oncology and Hematology, Department of Internal Medicine, Korea University Medical Center, Seoul, Korea; [7]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [8]Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [9]Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; [10]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [11]Division of Gastroenterology and Hepatology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan; [12]Liver and Intestinal Research Centre, Vancouver, Canada; [13]Asian Pacific Liver Center, St. Vincent Medical Center, Los Angeles, USA; [14]Hahnemann University Hospital, Philadelphia, PA, USA; [15]Gilead Sciences, Foster City, CA, USA; [16]Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; [17]The Chinese University of Hong Kong, Hong Kong, China; [18]Union Hospital, Hong Kong, China; [19]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy. CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Aims: Study 4018, an international Phase 3 study, previously demonstrated switching to tenofovir alafenamide (TAF) vs continued tenofovir disoproxil fumarate (TDF) in suppressed chronic hepatitis B (CHB) patients has noninferior efficacy (TAF vs TDF) with superior bone/renal safety. We analyzed the efficacy and safety of switching in AE patients in Study 4018.

Methods: CHB patients on TDF for ≥48 weeks with HBV DNA <LLOQ for ≥12 weeks and <20 IU/mL at screening were randomized to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 48 weeks in a double-blind (DB) fashion followed by all patients receiving open-label (OL) TAF 25 mg QD for an additional 48 weeks.

Results: 400/488 (82%) were AE patients who received at least 1 dose of study drug, with 195 in the TAF-TAF arm and 205 in the TDF-TAF arm. Virologic suppression was similarly maintained at 96-wks in both groups (95% for TAF and 94% for TDF). Higher percent changes in BMD from baseline (both hip and spine) were seem among the TAF-TAF [1.2 (3.0 SD) for hip and 2.5 (4.0 SD) for spine] vs TDF-TAF (0.12 (2.8 SD) for hip and 1.5 (3.8) for spine]. $eGFR_{CG}$ increased over 2 years in the TAF-TAF group and from Week 48 to 96 in the TDF-TAF group and no study drug-related treatment-emergent grade 3 or 4 AEs or SAEs.

Conclusions: Following TDF-TAF switch, viral suppression was maintained, with improved bone and renal safety parameters through 96 weeks in AE patients.

Keywords: HBV, TAF, 96, Aisan

PE-009

Coadministration Without or with Food on the 96-Week Efficacy and Safety of Tenofovir Alafenamide in Switched from Tenofovir Disoproxil Fumarate

Sang Hoon Ahn[1], Jia-Horng Kao[2], June Sung Lee[3], Edward Tam[4], Ho Bae[5], Huy Trinh[6], Charles Phan[7], Scott K. Fung[8], Leland Yee[9], Grace Chee[9], Megan Kim[9], John Flaherty[9], Grace Zhao[9], Susanna Tan[9], Anuj Gaggar[9], Seung Kew Yoon[10], Wan-Long Chuang[11], Henry LY Chan[12,13]

[1]Yonsei University College of Medicine, Seoul, South Korea; [2]Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Gyeonggi-do, South Korea; [4]Liver and Intestinal Research Centre, Vancouver, BC, Canada; [5]St. Vincent Medical Center, Asian Pacific Liver Center, Los Angeles, CA, USA; [6]Silicon Valley Research Institute, San Jose, CA, USA; 7Gastrointestinal and Liver Disease Consultants, Sugarland, TX, USA; [8]Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; [9]Gilead Sciences, Inc., Foster City, CA, USA; [10]Department of Internal Medicine, The Catholic University Liver Research Center, College of Medicine, the Catholic University of Korea, Seoul, Republic of Korea; [11]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [12]The Chines University of Hong Kong, Hong Kong, China; [13]Union Hospital, Hong Kong, China

Aims: TAF has shown noninferior efficacy to TDF with superior bone and renal safety in a virally suppressed switch population of CHB patients taking TDF long-term. Unlike the registrational trials, switch study patients were permitted to take their study drug without or with food. This sub-analysis evaluates the impact of TAF once daily with/without food.

Methods: In Phase 3 Study 4018 (NCT02979613), CHB patients virally-suppressed on TDF were randomized (2:1) to switch to TAF or remain on TDF for 48 weeks, after which patients received open-label TAF for an additional 48 weeks. Efficacy and safety were assessed over 96 weeks for patients taking study drug without vs with food

Results: Of 488 patients randomized and treated, 162 (33%) continued taking study drug without food (n=81 each for the TAF-TAF and TDF-TAF groups). Antiviral efficacy was maintained at Week 96, in those taking study drug without vs with food. Adverse events (grade 3 or 4 and SARs) were generally comparable for those taking drug without vs with food. In patients who took TAF without food for 96 weeks (TAF-TAF) or for 48 weeks (TDF-TAF), improvements in $eGFR_{CG}$ and in hip and spine BMD were observed.

Conclusions: In CHB patients taking TAF without food for up to 96 weeks, antiviral efficacy was maintained, renal and bone parameters improved, and safety and tolerability were comparable to those receiving TAF treatment with food. These results lend support for the administration of TAF without regard to food.

Keywords: HBV, Food effect, TAF, Without food

PE-010

Efficacy and Safety of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF) in Chronic Hepatitis B Patients of Asian Ethnicity: 5-Years Treatment

Young-Suk Lim[1], Hyung Joon Kim[2], Ki Tae Yoon[3], Won Young Tak[4], Sang Hoon Ahn[5], Kwan So Byun[6], Wai Kay Seto[7], Ting-Tsung Chang[8], Abhijit Chowdhury[9], Chi-Yi Chen[10], Mustafa Kernal Celen[11], Mang Ma[12], Ajay Duseja[13], Wan Cheng Chow[14], Leland Yee[15], Gregor Weber[15], Megan Kim[15], John F. Flaherty[15], Anuj Gaggar[15], Bing Gao[15], Tetshuro Inokuma[16], Edward J. Gane[17]

[1]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Department of Internal Medicine, College of Medicine, Chung-Ang University, Seoul, South Korea; [3]Department of Internal Medicine, College of Medicine, Pusan National University, Pusan National University Yangsan Hospital, Yangsan, South Korea; [4]School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea; [5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; [6]Divisions of Gastroenterology and Hepatology Oncology and Hematology, Department of Internal Medicine, Korea University Medical Center, Seoul, South Korea; [7]LKS Faculty of Medicine, The University of Hong Kong, Peoples Republic of China; [8]National Cheng-Kung University Hospital, Tainan, Taiwan; [9]Institute of Post Graduate Medical Education And Research, Kolkata, India; [10]Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan; [11]Dicle Üniversitesi Hastanesi Enfeksiyon Hastaliklari Anabilim Dali, Diyarbakir, Turkey; [12]Zeidler Ledcor Centre, Edmonton, Canada; [13]Postgraduate Institute of Medical Education & Research, Chandigarh, India; [14]Singapore General Hospital, Singapore; [15]Gilead Sciences, Inc., Foster City, CA, US; [16]Kobe City Medical Center General Hospital, Kobe, Japan; [17]Auckland Clinical Studies, Grafton, New Zealand

Aims: Pivotal studies GS-US-320-0108 (HBeAg-negative) and GS-US-320-0110 (HBeAg-positive), demonstrated non-inferior antiviral efficacy of TAF vs. TDF with superior renal/bone safety through 5-yrs; after up to 3-yrs of double-blind (DB) treatment, open-label (OL) TAF was available through Year 8. We analyzed TAF efficacy and safety among patients of Asian Ethnicity in Studies 108/110.

Methods: Efficacy was assessed by individual study and included virologic, biochemical, and serologic assessments. Safety data were pooled including estimated GFR (by Cockcroft-Gault method; $eGFR_{CG}$) and hip and spine bone mineral density (BMD) changes.

Results: Among 1298 patients randomized and treated, 591 (45.5%) were Asian (TAF n=401, while n=84 and n=106 received TDF-OL-TAF-3 years and TDF-OL-TAF-2 years, respectively. Virologic control was achieved and maintained in patients receiving TAF (95%) and for TDF-OL-TAF-3 years (100%) and TDF-OL-TAF-2 years (98%). ALT normalization rates were comparable among groups (TAF: 79%, TDF-OL-TAF-3 years: 80%; TDF-OL-TAF-2-years: 79%). HBeAg loss/seroconversion was similar (TAF: 38.6%/27.4%, TDF-OL-TAF-3 years: 46.9%/37.5%; TDF-OL-TAF-2-years: 47.1/29.4%). Rates of HBsAg loss/sero-

conversion were similar in all groups (≤1%). Rates of Grade 3/4 adverse events (AEs) and AEs leading to discontinuation were low (<1.5%) among all 3 groups. After experiencing declines in $eGFR_{CG}$ and in hip/spine BMD over 2 or 3 years of TDF treatment, renal and bone outcomes were improved following the switch to OL TAF.

Conclusions: After 5 years of treatment, virologic suppression remained high, and TAF was safe and well tolerated with improved renal and bone safety among patients of Asian Ethnicity switching from TDF.

Keywords: TAF, TDF, Asian ethnicity, HBV

PE-011

Awareness of Immunization against HBV among the Health Care Workers in Mongolia

Naranzul N[1,2], Enkhjargal A[2], Burmaajav B[3,4], Nandintsetseg T[2], Munkh-Orshikh D[4], Enkhtuvshin B[5], Sarangua G[6], Azzaya O[7], Jargalmaa B[2], Khurelbaatar N[8], Batzaya M[9], Baatarkhuu O[1,10]

[1]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]Academy of Medical Professionals, Ulaanbaatar, Mongolia; [3]Ach Medical University, Ulaanbaatar, Mongolia; [4]Department of Surgery, School of Medicine, Mongolian National University of Medical Sciences Ulaanbaatar, Mongolia; [5]Department of Laboratory, School of Medicine, Mongolian National University of Medical Sciences Ulaanbaatar, Mongolia; [6]Department of Laboratories, National Center for Communicable Diseases, Ulaanbaatar, Mongolia; [7]City Health Authorities, Ulaanbaatar, Mongolia; [8]Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [9]Department of laboratory, Proliance LLC, Ulaanbaatar, Mongolia; [10]Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia

Aims: Background/aim: We examined the participants' level of knowledge about hepatitis B virus infection and prevention is related to their education, type of organization, level of care, profession, and training in this field.

Methods: This is a cross-sectional hospital based survey. A total of 1,135 HCWs were involved in the study. Specially developed questionnaire was used for defining a KAP of survey participated

Results: The best-known question of the respondents was "Did you know that complete protection comes after three doses of hepatitis B vaccine?" and 95.4% of them knew the correct answer. In addition, 73.6% of the participants are aware of that the hepatitis B vaccine is effective in preventing the disease. However, 47.7% of the participants knew the benefits of vaccination correctly. For "Does higher doses of hepatitis B vaccine or repeated doses of HBV vaccine three times have side effects?" 24.3% responded correctly. The majority of respondents did not know how long the HBV was resistant to the external environment, or 15.6% of them knew the correct answer. 31.24% of the respondents correctly identified medical professionals and HCWs as the highest risk group. The most common source of information was at work, while 17.9 percent said they received information when they were students.

Conclusions: There is lack of knowledge among HCWs about hepatitis B virus infection, its prevention and post-exposure prevention, and there is a high risk for HCWs to get exposure.

Keywords: Vaccine, B virus infection, Work

PE-012

Clinical Characteristics and Outcomes of Acute Hepatitis Delta in Mongolia

Badamnachin Batsukh[1,2,4], Munkhchuluun Batzaya[3,4], Ganbold Sarangua[4], Ochir Chimedsuren[5], Oidov Baatarkhuu[1,4,6]

[1]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]Department of Emergency Medicine, National Center for Communicable Diseases, Ulaanbaatar, Mongolia; [3]Department of Laboratory, Proliance LLC, Ulaanbaatar, Mongolia; [4]Mongolian Association for the Study of Liver Diseases, Ulaanbaatar, Mongolia; [5]Ministry of Health, Ulaanbaatar, Mongolia; [6]Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia

Aims: Infection with hepatitis B and delta virus is a public health problem in Mongolia. Aim of this study was to determine the clinical and laboratorical features in patients with acute hepatitis delta in adult patients.

Methods: This prospective cohort study was conducted at National Center for Communicable Diseases in Ulaanbaatar city in Mongolia. Patients were prospectively enrolled 77 patients from 2016 to 2018. All patients were informed of the study and gave written consent to participate.

Results: A total of 77 participants (45 male, 32 female) enrolled, 72(93.5%) patients with acute hepatitis Delta (AHD) super infection and 5(6.5%) patients with acute hepatitis D co-infection. Average age of participants was 29.9±7.4. Fatigue, loss appetite and vomiting were present in more than 68% of the cases. Symptoms resolved within 6 months in 100% of the patients with acute hepatitis co-infection and by the 12 months 98.6% of the patients with acute hepatitis delta super infection. On admission, the median TBIL, ALT and AST values were similar in the two groups. At the final follow-up, a patients with AHD super infection had significantly higher ALT (85.5±125.8 vs 13.8±6.5, *P*=0.008) and AST (63.4±67.1 vs 19.7±9.6, *P*=0.04) compared with patients AHD co-infection. At the time of admission, the HBsAg positive rate was 100% in both groups. At final follow-up, the HBsAg positive rate was significantly higher in AHD super infection patients than in AHD co-infection patients. 40% AHD co-infection patients and 94.4% AHD super infection patients developed chronic HBV infection (*P*=0.0001).

Conclusions: The clinical manifestation and biochemical results of all patients had significantly improved. 6.7% of acute AHB infections and 90.9% of AHD developed into chronic hepatitis. 40% of AHD co-infection and 5.6% of AHD super-infection were recovered.

Keywords: Hepatitis delta virus, Co-infection, Super infection, Follow-up

PE-013

Clinical Implication of HBs Ag Quantification in Chronic Hepatitis B Patients Treated with TDF or ETV

Jung Hyun Lim[1], Jung Hwan Yu[1], Young Ju Suh[2], Jin-Woo Lee[1], Young-Joo Jin[1]

[1]Department of Internal Medicine and Division of GI and Liver Diseases, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea; [2]Department of Pathology, Inha University Hospital, Incheon, South Korea

Aims: This study evaluated the clinical implications of hepatitis B surface antigen quantification (qHBs Ag) in chronic hepatitis B (CHB) patients treated with entecavir (ETV) or tenofovir (TDF) and identified the association between qHBs Ag and the risk of hepatocellular carcinoma (HCC) in these patients.

Methods: Between January 2007 and December 2018, the qHBs Ag and clinical data of 183 CHB patients who initially received ETV (n=45, 24.6%) or TDF (n=138, 75.4%) were analyzed.

Results: The mean follow-up period of the 183 CHB patients was 45.3 months, of which 59 (32.2%) patients showed a reduction in qHBs Ag by more than 50% after one year of antiviral treatment. The HCC development (*P*=0.179) or qHBs Ag reduction (*P*=0.524) were similar in the ETV and TDF groups. Patients with a 50% or more decrease in qHBs Ag had a significantly lower incidence of HCC or decompensated cirrhosis complications than those with a less than 50% decrease or rather an increase in qHBs Ag (*P*=0.005). Multivariate analysis showed that a more than 50% reduction of qHBs Ag (hazard ratio [HR] 0.085, *P*=0.018) and the presence of cirrhosis (HR 3.32, *P*=0.016) were independent factors predicting the development of HCC.

Conclusions: Patients whose qHBs Ag value decreased more than 50% at 1 year after antiviral treatment for CHB showed a significant decrease in HCC or decompensated cirrhosis events. A reduction in qHBs Ag could be used as a predictive factor of HCC development or critical complications in CHB patients treated with TDF or ETV.

Keywords: Chronic hepatitis B, Entecavir, HBs Ag quantification, Hepatocellular carcinoma

PE-014

Epidemiological and Clinical Follow-Up Study Among Patients with Acute Viral Hepatitis B in Mongolia

Badamnachin Batsukh[1,2,4], Munkhchuluun Batzaya[3,4], Ganbold Sarangua[4], Ochir Chimedsuren[5], Oidov Baatarkhuu[1,4,6]

[1]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]Department of Emergency Medicine, National Center for Communicable Diseases, Ulaanbaatar, Mongolia; [3]Department of Laboratory, Proliance LLC, Ulaanbaatar, Mongolia; [4]Mongolian Association for the Study of Liver Diseases, Ulaanbaatar, Mongolia; [5]Ministry of Health, Ulaanbaatar, Mongolia; [6]Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia

Aims: Following the introduction of infant HBV immunization in 1991 in Mongolia, dramatic decline in the reported annual incidence of acute hepatitis demonstrating the remarkable impact of mass immunization. Nevertheless, incidence of HBV remains moderate among unvaccinated adults. Aim of this study was to determine the clinical and laboratorical features and the rate of development to chronic infection in adult patients with acute hepatitis B.

Methods: A prospective study was conducted (2017-2019) in 105 adult patients diagnosed with acute HBV and hospitalized in NCCD, to understand risk factors and clinical features of acute HBV infection and its natural course. All patients were informed of the study and gave written consent to participate.

Results: The infection rate was highest among the age group of 21-30 (67,6%), mean age 25.2±6.0. Study of HBV infection risk factor in the last six months denotes several behavioral and health care services are related, counting 12.5% for dental treatment, 4 (3.85%) for tattoos, and 3 (2.9%) for ear piercings. Liver function tests showed a steady decrease in bilirubin, ALT, and AST. Serological tests showed HBsAg remained positive in 7.6% of the patients after six months and 6.7% within a year.

Conclusions: Risk factors for acute hepatitis B virus include dental treatment, unprotected sex, and shared nail clipper. Follow-up studies demonstrated that 93.3% of acute HBV patients were recovered, 6.7% developed chronic HBV and 71.4% of the patients who developed chronic HBV are tested positive with Delta virus infection.

Keywords: Acute, HBsAg, ALT, Mongolia

PE-015

Long-Term Renal Function Changes in Patients Receiving Tenofovir vs. Entecavir In Chronic Hepatitis B Patients: A Multicenter Study

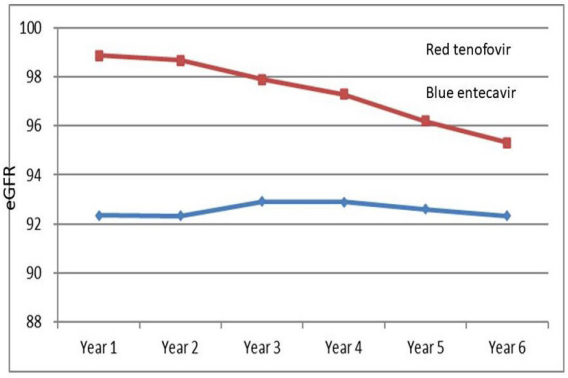
Yong Eun Chon[1#], Seung Up Kim[2,3#], Yeon Seok Seo[4], Hye Won Lee[2,3], Han Ah Lee[4], Mi Na Kim[1], Yun Ho Roh[5], Jun Yong Park[2,3], Do Young Kim[2,3], Sang Hoon Ahn[2,3], Won Young Tak[6], Soo Young Park[6*], Beom Kyung Kim[2,3]

[1]Department of Internal Medicine, Cha Bundang Medical Center, Cha University, Seongnam, Republic of Korea; [2]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea; [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea; [5]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea

Aims: Renal safety is a critical issue in chronic hepatitis B (CHB) patients with long-term antiviral therapy (AVT). We investigated the long-term effects of entecavir (ETV) and tenofovir (TDF) on the renal function in patients with CHB.

Methods: Treatment-naïve CHB patients who started ETV or TDF and continued more than 1 year were recruited. eGFR (estimated glomerular filtration rate) by CKD-EPI equation was used to determine the renal function .

Results: In the entire population (n=3,033), baseline eGFR (mean, 92.8 *vs.* 98.6 ml/min/1.73m^2, *P*<0.001) was statistically lower in patients treated with ETV compared to TDF. During 6 years of AVT, patients treated with ETV showed similar eGFR from 1 to 6 years (all *P*>0.05). Patients treated with TDF showed similar eGFR from baseline to 2 years, however, eGFR significantly decreased annually after 2 to 6 years of AVT (mean, 98.7 → 97.9 → 97.3 → 96.2 → 95.3 ml/min/1.73m^2, all *P*<0.001 compared to baseline). During long-term AVT, baseline eGFR < 60 mL/min/1.73 m^2, hypertension, serum albumin < 3.5mg/dL, and TDF use (HR, 1.65; 95% CI, 1.29-2.09; *P*>0.001) were risk factors for time-averaged percent eGFR change > 3%.



Conclusions: Compared to patients treated with ETV having similar renal function over 6 years, those treated with TDF experienced slow but progressive renal dysfunction. Although the annual eGFR change is minimal, careful monitoring of renal function should be performed in patients with long-term TDF therapy.

Keywords: Hepatitis B, Entecavir, Tenofovir, Renal insufficiency

PE-016

Treatment Efficacy of Nucleos(t)ide analogues in Treatment-Naïve Chronic Hepatitis B Patients with Liver Cirrhosis

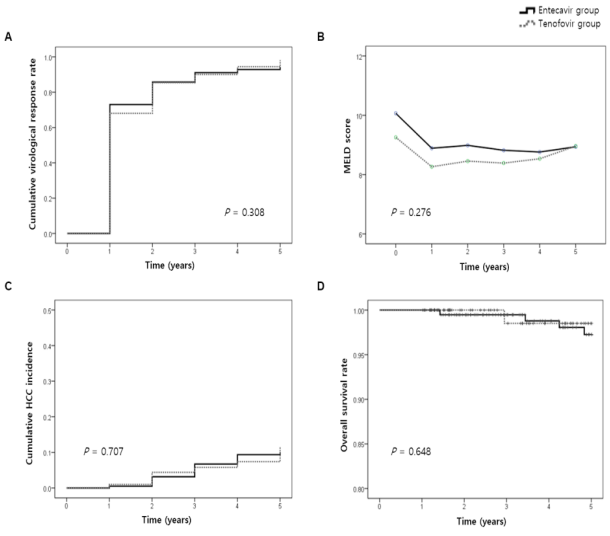
Chang Hun Lee[1], Yun Chae Lee[1], Yeon Soo Lee[2], So Min Jeong[2], Jong Oh Park[2], Ji Hun Lee[2], Han Eum Ju[2], Seung Young Seo[1], Seong-Hun Kim[1], Sang Wook Kim[1], Seung Ok Lee[1], Soo Teik Lee[1], In Hee Kim[1,*]

[1]Department of Internal Medicine, Jeonbuk National University Medical School and Research Institute of Clinical Medicine of Jeonbuk National University Hospital-Jeonbuk National University Medical School, [2]Jeonbuk National University Medical School, Korea

Aims: To investigate the clinical effects of oral nucleos(t)ide analogue therapy in patients with hepatitis B virus-related liver cirrhosis.

Methods: We retrospectively reviewed data from treatment-naïve chronic hepatitis B patients who had started antiviral therapy from 2007 to 2018 at Jeonbuk national university hospital. Eligible patients were diagnosed with liver cirrhosis and maintained antiviral therapy for more than a year. Patients diagnosed with hepatocellular carcinoma (HCC) or other malignant tumors before treatment or within six months of treatment were excluded. There were 236 entecavir (ETV) and 100 tenofovir (TFV) users and we performed a propensity score matched analysis with a 2:1 ratio based on age, sex, and initial MELD score. Demographic and clinical characteristics were analyzed.

Results: The patients had a mean age of 54.5 ± 10.6 years, and 198 patients were men (66.0%). The annual virological response (VR) rate over the five years after treatment was 73.0%, 85.7%, 91.0%, 2.8%, and 94.2% in ETV group and 68.0%, 85.4%, 90.0%, 94.5%, and 98.2% in TFV group, respectively. Initial MELD score was 10.1 ± 3.6 in ETV group and 9.7 ± 3.6 in TFV group and repeated-measures two-way ANOVA was performed for evaluating within-subjects and between-subjects factors. In the analysis of within-subjects factor, antiviral agents significantly altered MELD score during the treatment period in both groups (*P*<0.001). However, for between-subjects factor, the alteration of MELD score was not different according to the type of antiviral agents (*P*=0.276). We additionally evaluated the cumulative HCC incidence and overall survival. HCC was detected in 32 (10.7%) patients and there was 5 (1.7%) non-survivors during the follow-up period. Cumulative incidence of VR and HCC analyzed by life-table method with Wilcoxon test was not significantly different between two groups. In terms of overall survival, there was no significant difference using Kaplan-Meier analysis with log-rank test.



Conclusions: Antiviral therapy revealed high VR rate and significant MELD improvement in treatment-naïve hepatitis B virus-related liver cirrhosis patients. Depending on the type of antiviral agent, there were no differences in VR, MELD improvement, HCC incidence, and survival.

Keywords: Hepatitis B, Chronic, Liver cirrhosis, Antiviral agents, Treatment outcome, Mortality

PE-017

A Study on Knowledge, Attitude and Practice towards Hepatitis B and C among Adolescents in Kaski, Nepal

Mani Neupane

Transcultural Psychosocial Organization Nepal

Aims: Hepatitis B is the world's most common chronic infectious liver disease, with severe consequences. Universal vaccination and improved awareness and attitudes about disease transmission will help to prevent infection. Adolescence is a period of struggles and opportunities for self-discovery in a social setting. Infectious diseases such as hepatitis B and C are more common in adolescents. Any educational program must begin with an assessment of the target group's baseline awareness. A cross-sectional study has been conducted among adolescents of kaski, Nepal to ascertain their knowledge, Attitude, and practices regarding hepatitis B and C.

Methods: 120 adolescents completed a self-administered questionnaire that included questions about their understanding, attitudes, and practices about hepatitis B and C infection. Statistical Package for Social Sciences (SPSS) software version 25 was used to enter and analyze the data.

Results: Males made up 58.4 percent of the 120 respondents, while females made up 41.6 percent. Just 59.6% of adolescents were aware of the causative agent, and only 58.3% were aware of vaccine prevention. Minority, 32.6 percent, 30.0 percent, and 62 percent, respectively, knew about transmission by unsterilized needles, mother to infant during pregnancy, and blood and blood products. Just 20.4 percent of respondents agreed that the situation could be asymptomatic. Hepatitis B and C can be avoided by properly disposing of needles and sharp instruments, according to more than half of adolescents. About 75% of adolescents are aware that it can be avoided by preventing multisexual relationships. Likewise, 51.6%, 48.0% adolescent respond that Hepatitis B can be severe and fatal, and can persist in body lifelong. The majority of the adolescents stated that they did not use gloves when handling various bodily fluids and that they did not properly dispose of needles and sharps. Just 21.3 percent have experienced a needle stick injury in the past. In total, 32 percent of teenagers had ever been tested for hepatitis B or C, and 15% had requested a new needle during piercing or tattooing. Just 17 percent asked the barber for a new razor, 18.6% asked the medical staff for a new syringe, and 26.5 percent asked the dentist for a sterilized instrument. Similarly, 88 percent had used others tooth brush or razor, and 91 percent had used earrings or nail clippers.

Conclusions: The majority of adolescents were unaware of the existence of hepatitis B and C. There was a lack of knowledge and practice about the mode of transmission and preventive steps.

Keywords: Hepatitis, Knowledge, Adolescent, Kaski

PE-018

Prevalence and Disease Burden of Chronic Kidney Disease and Hepatitis B, C Co-Infection among HIV Infected Population: A Meta-Analytic Synthetic Evidence Using Real World Studies

Md Azharuddin[1*], Manju Sharma[2]

[1]Department of Pharmaceutical Medicine, Division of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India; [2]Department of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India

Aims: Chronic kidney disease (CKD) is a major health concern for HIV-infected population, has become an important cause of morbidity and mortality. Therefore, CKD and hepatitis B, C co-infection remains an important comorbid condition in the HIV-infected population. We aimed to conduct a systematic literature review and meta-analysis to estimate the exact prevalence of CKD and hepatitis B, C co-infection among HIV infected population in the Asian countries.

Methods: A systematic literature search was performed in PubMed, Embase, and Web of Science using pairing relevant keywords to identify English language articles from inception to February, 2021. The eligible studies determine the prevalence of CKD among HIV positive population in geographical area of the Asian continent. Subgroup analysis was performed by the stratification of the country and equation used to define CKD. Heterogeneity was assessed by using Cochrane Q test statistic and inconsistency index (I^2). The random effects model was used to calculate the pooled estimate. A meta-analysis was performed with random effect model using "meta" package through R 3.5.0. Software.

Results: A total of 11 studies with 53656 participants were included in this study. The mean age of participants was 41.28 years. CKD was defined as estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2 by using the equation Modification of Diet in Renal Disease (MDRD) in 7 studies, Chronic Kidney Disease Epidemiology (CKD-EPI) in 3 studies and Cockcroft-Gault (CG) in one study. The prevalence of hepatitis B and C co-infection ranges from 1.6% to 16% and from 3.3% to 33.4% respectively. The overall prevalence of CKD was 9.5% (95%CI: 6.2-14.3%), (I^2= 99%, P< 0.01) with high degree of heterogeneity. Subgroup analysis was reported the highest prevalence in japan, 13.65% (95%CI: 17.4- 25.4%), followed to china 11.76% (95%CI: 15.3-24.7%), Taiwan, Australia, and Vietnam. The CKD prevalence was observed 9.6% (95%CI: 7.6-11.8%) with MDRD, 6.2% (95%CI: CI 2.5-6.8.1%) with CKD-EPI and 10.7% (95%CI: 9.4-11.7%) with CG. There was no significant publication bias was observed (P=0.97).

Conclusions: The current finding suggests that people with HIV infection have a high burden of CKD, especially in Japan. Moreover, HIV treatment programs should consider early screening for CKD and hepatitis B, C co-infection among HIV-infected populations to prevent and delay the progression of comorbidity.

Keywords: Prevalence, Disease burden, Hepatitis B, C co-infection, Meta-analytic synthetic evidence

PE-019

Herbal Plants That Can Treat Hepatitis in Indonesia

Indra SUARDI

Midwifery, Hasanuddin University, Indonesia

Aims: Hepatitis is inflammation of the liver or liver. Hepatitis can be caused by a viral infection, it can also be caused by other conditions or diseases, such as alcohol consumption, use of certain drugs, or autoimmune diseases. If caused by a viral infection, hepatitis can be contagious. Therefore, it is necessary to immediately treat hepatitis patients, one of which is by utilizing herbal plants.

Methods: The Method used is studying secondary data from published journals. Of the several collected, 6 articles were selected. The search for articles includes the following criteria; the articles should be published in the last 10 years from 2011 to 2021 and the samples of hepatitis patients are conducted in Indonesia.

Results: Based on the similarity of the dependent variable, found 5 herbal plants that can overcome hepatitis. These herbs are Moringa Aloifera Lamk, Artocarpus altilis, Curcuma zedoaria, Euphorbia Milli Ch Des Moulins, Eucalyptus Globulus. Other studies have shown that health promotion to parents regarding clean and healthy living behaviors can prevent hepatitis.

Conclusions: The people can use herbal plants as an early treatment for hepatitis patients because the use of herbal plants does not require a large fee, is often found in the community, and has minimal side effects.

PE-020

Survey on Hepatitis B Vaccination Coverage among Mongolian Healthcare Workers

Batzaya M[1], Naranzul N[2], Munkh-Orshikh[3], Enkhtuvshin B[4], Baatarkhuu O[2,5]

[1]Department of laboratory, Proliance LLC, Ulaanbaatar, Mongolia; [2]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [3]Department of Surgery, School of Medicine, Mongolian National University of Medical Sciences Ulaanbaatar, Mongolia; [4]Department of Laboratory, School of Medicine, Mongolian National University of Medical Sciences Ulaanbaatar, Mongolia; [5]Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia

Aims: Mongolia has a large burden of viral hepatitis, especially chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which are associated with cancer and cirrhosis. The occupational risk for transmission of HBV, HCV and HIV among healthcare workers (HCWs) is well recognized. To study HBV vaccination coverage among Mongolian healthcare workers.

Methods: This is a cross-sectional hospital based survey which will be conducted among healthcare workers to evaluate HBV vaccination coverage and KAP towards to the HBV infection and vaccination. In total, 1200 health care workers were attended to the survey.

Results: More than half of survey respondents were had full 3 doses of HBV vaccination. About 4.5% of them had infected with HBV. About 64.0% of them were health workers who are currently working at risk position and most of them had contact with blood, blood products and other body fluids, as well as the risk of needle-stick injuries. 40.0% of respondents who had full doses of HBV vaccination and 56.9% of them had immune due to natural infection. Whereas, 16.7% of respondents who did not received full doses of HBV vaccination were had immune due to natural infection. In general, 1 of 2 respondents had immune due to natural infection.

Conclusions: The HBV vaccination coverage among health workers are relatively sufficient. However, already infected percentages of among health workers are high in Mongolia.

Keywords: HBV clinical

2. Hepatitis C Virus

PE-021

Impact of Acute Kidney Injury on Survival in Patients With Chronic Hepatitis C

Hankyu Jeon[1,3], Jae Heon Kim[1,3], Sang Soo Lee,[*1-3], Hee Jin Kim[1-3], Ra Ri Cha[1-3], Hyun Chin Cho[1-2], Jae Min Lee[1-3], Chang Yoon Ha[1-2], Hyun Jin Kim[1-3], Tae Hyo Kim[1,2], Woon Tae Jung[1,2], Ok-Jae Lee[1,2]

[1]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea [3]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

Aims: Acute kidney injury (AKI) is expected to occur commonly in patients with chronic hepatitis C. In addition, AKI may affect the survival of patients with chronic hepatitis C. However, few studies are available on this topic. We aimed to evaluate the incidence of AKI in patients with chronic hepatitis C and investigate the factors related to overall mortality.

Methods: Between January 2005 and December 2018, 1252 patients with chronic hepatitis C virus (HCV) infection were retrospectively enrolled at two centers. Of them, 1008, 123, and 121 patients had chronic hepatitis (CH), compensated cirrhosis (Com-LC), and decompensated cirrhosis (Decom-LC) or hepatocellular carcinoma (HCC) at entry, respectively.

Results: Over a mean follow-up period of 5.2 years, 285 patients

developed AKI, with an incidence rate of 4.35 per 100 person-years. The incidence of AKI increased gradually with progression of chronic hepatitis C: CH (3.32 per 100 person-years), Com-LC (5.86 per 100 person-years), and Decom-LC or HCC (17.28 per 100 person-years). Patients without AKI showed a better survival rate than patients with AKI (P<0.001). In multivariate Cox regression analysis, AKI (hazard ratio, 6.66; 95% confidence interval, 4.26–10.41) remained an independent risk factor for overall mortality.

Conclusions: AKI is common in patients with chronic HCV infection and is associated with significant overall mortality. Therefore, clinicians should carefully monitor the occurrence of AKI, which is an important predictor of mortality in patients with chronic hepatitis C.

Keywords: Hepatitis C virus, Mortality, Incidence, Acute kidney injury

PE-022

Virological Efficacy and Safety of Ledipasvir and Sofosbuvir in Patients with Chronic Hepatitis C Virus Genotype 2 Infection: Real-World Experience from Korea

Ju-Yeon Cho[1], Jae Hyun Yoon[2]

[1]Department of Internal Medicine, Chosun University Hospital, School of Medicine, Gwangju, South Korea; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chonnam National University Hospital, School of Medicine, Gwangju, South Korea

Aims: Genotype 2 (GT2) hepatitis C virus infection is the one of the two most common genotypes in Korea. While ledipasvir/sofosbuvir (LDV/SOF) is approved for the treatment of GT2 HCV infection in Taiwan, Japan, and Korea, the real-world experience of Korea is not well known. The aim of the study is to evaluate the efficacy and safety of LDV/SOF in patients with GT2 chronic hepatitis C infection in Korea.

Methods: From June 2019 to March 2021, 17 consecutive HCV GT2 patients who received LDV/SOF at 2 university-based hospitals were retrospectively included for analysis. HCV RNA was measured at baseline, 12 and 24 weeks after the first dose to determine the end of treatment response (ETR) and sustained virologic response at 12 weeks off-therapy (SVR12). The effectiveness of the treatment was determined by the SVR12 response.

Results: Among the 17 HCV GT 2 patients treated with LDV/SOF, 1 patient was still on treatment and 3 patients were lost to follow up before the assessment of SVR 12. In the remaining 13 patients, the overall SVR12 rate was 100%. Five males and 8 females were included in the study. The mean age of the patients was 58-years old. Liver cirrhosis assessed with abdominal imaging which included ultrasonography, computed tomography or fibroscan was present in 61.5% (8/13) patients. All the patients had no prior treatment history with pegylated interferon or other direct-acting antiviral agents. No severe adverse events were reported and there was no drug interruption due to adverse events.

Conclusions: Treating GT2 chronic hepatitis C patients with LDV/SOF in Korea was safe and resulted in excellent efficacy regardless of the presence of liver cirrhosis.

Keywords: Hepatitis C virus

PE-023

Clinical Features of Hepatitis C Virus-Related Acute-On-Chronic Liver Failure in a Korean Population

Jae Heon Kim[1,3], Jung Woo Choi[1], Jin-Kyu Cho[1], Sang Soo Lee[*1-3], Hankyu Jeon[1,3], Hee Jin Kim[1-3], Ra Ri Cha[1-3], Jae Min Lee[1-3], Hyun Jin Kim[1-3]

[1]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea; [3]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

Aims: Acute-on-chronic liver failure (ACLF) is a widely recognized concept in which acute decompensation (AD) in patients with cirrhosis results in organ failures and high short-term mortality. However, few studies reflecting the various etiologies of cirrhosis are available. We aimed to investigate the clinical features of patients with hepatitis C virus (HCV)-related ACLF.

Methods: Between January 2005 and December 2018, 109 HCV-related cirrhosis patients who were hospitalized for AD (ascites, hepatic encephalopathy, gastrointestinal hemorrhage, and/or bacterial infection) were enrolled for ACLF defined by European Association for the Study of the Liver (EASL).

Results: ACLF developed in 35 patients (32.1%) on admission. Eight patients had ACLF grade 1, eight had ACLF grade 2, and 19 had ACLF grade 3. The 28-day and 90-day mortality rates were very low (2.7% and 5.4%, respectively) in patients without ACLF and very high (60.0% and 74.3%, respectively) in those with ACLF. In patients with HCV-related ACLF, the prevalence of liver failure was very low (17.1%), whereas that of kidney failure was very high (71.4%) compared to previous studies on hepatitis B virus-related ACLF and alcohol-related ACLF. Compared with all other prognostic scores, Chronic liver failure Consortium Organ Failure score most accurately predicted 90-day mortality, with an area under the receiver operator characteristic of 0.921.

Conclusions: HCV-related ACLF has unique clinical characteristics that are distinct from hepatitis B virus-related and alcohol-related ACLF. ACLF defined by EASL can be useful in predicting short-term mortality in HCV-related cirrhosis.

Keywords: Acute-on-chronic liver failure, Hepatitis C virus, Mortality, Organ failures, Acute decompensation

PE-024

Implications of Pretreatment HCV RNA Level on Sustained Virological Response in Hepatitis C Virus-infected Patients Receiving Glecaprevir and Pibrentasvir

Hong Jae Jeon, Byung Seok Lee, Hyuk Soo Eun, Eaum Seok Lee, Seok Hyun Kim

Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine

Aims: Combination therapy with glecaprevir and pibrentasvir has high efficacy in HCV-infected patients across HCV genotypes 1-6. There are limited data on the implications of pretreatment RNA level on sustained virological response (SVR) in patients receiving glecapreivr and pribrentasvir. We aimed to determine whether pretreatment HCV RNA level predicts sustained virological response in patients receiving glecaprevir/pibrentasvir.

Methods: Patients who received at least one dosage of treatment between December 2018 and February 2021 were enrolled. Demographic, clinical, and laboratory data were collected through a review of medical records. Patients were grouped into the following two categories, based on pretreatment RNA level: ≥ 600,000 copies/mL; and <600,000 copies/mL. The rate of SVR were examined for each group.

Results: A total of 122 patients received glecaprevir and pibrentasvir during study period. There was no serious adverse event leading to drug discontinuation, so all patients complete treatment except for four patients on treatment. Most common adverse events were fatigue and itching sense. In overall patients, the proportion of patients who showed end of treatment response was 99.0% and SVR at 12 weeks after end of treatment (SVR_{12}) reached to 97.4%. The proportion of patients who have more than 600, 000 HCV RNA copies/mL was 74.3%. The probability of SVR_{12} was similar between high and low pretreatment RNA groups after adjustment for other baseline characteristics

Conclusions: Glecaprevir/pibrentasvir combination therapy is an efficacious and safe treatment for HCV-infected patients, and pretreatment HCV RNA level does not influence the probability of SVR_{12}.

Keywords: Hepatitic C virus, Gecaprevir and pibrentasvir, HCV RNA level, Sustained virologial response

PE-025

Safety and Effectiveness of HARVONI® (Ledipasvir/Sofosbuvir, LDV/SOF) from the 5th Year Post-Marketing Surveillance (PMS) Data in Korea

Ju Hyun Kim[1], YoungMi Hong[2], ByungHoon Han[3], Sung Won Lee[4], Yan Zhong[5], Soon Koo Baik[6], SoYoung Kwon[7], Jung Hyun Kwon[8], Sang Bong Ahn[9], DaeWon Jun[10], Hyoung Su Kim[11], Kwon Yoo[12], Ji Hoon Kim[13], Dong Joon Kim[14], Jin-Woo Lee[15], Hyun Chin Cho[16], Eileen Laurel Yoon[17], HeeSeung Park[18], HyungJoon Kim[19], SooYoung Park[20], MoonSoo Koh[21], Mimi Won[5], Jeong Heo[22], JungGil Park[23], Kyung min Kwon[5]

[1]Gachon University Gil Medical Center; [2]Pusan National University Yangsan Hospital; [3]Kosin University Gospel Hospital; [4]The Catholic University of Korea, Bucheon ST. Mary's Hospital; [5]Gilead Science Korea; [6]Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital; [7]Konkuk University Medical Center; [8]The Catholic University of Korea Incheon ST. Mary's Hospital; [9]Nowon Eulji Medical Center, Eulji University; [10]Hanyang University Hospital; [11]Kangdong Sacred Heart Hospital; [12]Ewha Womans University Mokdong Hospital; [13]Guro Hospital, Korea University Medical College, Korea; [14]Hallym University Chuncheon Sacred Heart Hospital, Korea; [15]Inha University Hospital, Korea; [16]Gyeongsang National University Hospital; [17]Inje University Sanggye Paik Hospital; [18]Busan ST. Mary's Hospital; [19]Chung-Ang University Hospital; [20]Kyungpook National University Medical Center Chil-Gok; [21]Dongguk University Ilsan Hospital; [22]Pusan National University Hospital; [23]Yeungnam University Medical Center

Aims: Harvoni®(LDV/SOF) is a treatment regimen for HCV infected patients, which is currently approved for the treatment of genotype 1, 2, 4-6 HCV infections in adults and adolescents aged 12 to <18 years in Korea. The 5th PMS data of LDV/SOF was analyzed. We identified the incidence proportion of adverse event (AE), adverse drug reaction (ADR), serious adverse event (SAE) within post-treatment week 12, and sustained virologic response (SVR) rate at post-treatment week 12.

Methods: In this open-label, non-interventional study, case report forms of 180 patients were collected by 22 physicians at 22 sites from 13 October 2019 to 12 October 2020. 169 patients were included in the safety analysis set and 131 patients were included in the effective analysis set.

Results: Of the 169 patients included in the safety analysis, 92.3% (159/169) of patients were infected with HCV genotype 1, 7.7% (13/169) were infected with genotype 2. 49.7% (84/169) were male patients and 42.0% (71/169) of patients were above age 60. 10.1% (17/169) of patients had previous HCV treatment experience. 26.6% (45/169) were 'Compensated cirrhosis', and 3.6% (6/169) were 'Decompensated cirrhosis'. 92.3% (156/169) of patients were treated with LDV/SOF only and 7.7% (13/169) of patients were treated with LDV/SOF+RBV. 61.0% (103/169 patients) have taken at least one concomitant medication. The incidence proportion of AE from start date to 12 weeks after administration completion or discontinuation was 30.8% (52/169, 95 events). The AE incidence proportion was higher in LDV/SOF+RBV group (61.5%, 8/13 patients, 17 events) compared to LDV/SOF only group (28.2%, 44/156 patients, 78 events). The incidence proportion of ADR was 13.6% (23/169, 35 events) and SAEs was 4.14% (7/169 patients, 8 events). The incidence proportion of SADR was 0.6% (1/169 patient, 1 event), presented as fatigue in a patient with underlying CKD. The causality between LDV/SOF and this event was assessed as 'possible'. Among 131patients in the effectiveness analysis set, the SVR rate was 98.5% (129/131).

Conclusions: In conclusion, the 5th PMS on Harvoni® has proven its safety and efficacy in Korean patients.

Keywords: LDV/SOF, Harvoni, HCV, Korea

PE-026

The Genotypic Association of Hepatitis C Associated Oral lichen planus and its Response to Direct Acting Antivirals

Priyanka Rozario, Dexton Antony Johns

National Medicity Hospital

Aims: Oral Lichen Planus (OLP) is one of the extraneous manifestation of hepatitis C infection. Various genotypes may be associated with OLP. The genotypes vary in pathogenicity and response to direct-acting antivirals (DAAs). The study was done to assess the various genotypes linked with hepatitis C associated OLP.

Methods: Lichen Planus refractory to conventional steroid treatment was considered as an oral manifestation of HCV and it was confirmed by anti-HCV by ELISA (third generation). Genotyping was done using genotype specific core primers in nested polymerase chain reaction, NS5B sequencing and 5′ non coding region based PCR restriction fragment length polymorphism. Eighteen patients with HCV-related OLP received Sofosbuvir with ribavirin for 24 weeks. Out of eighteen, ten were males with a mean age of 64. The patient response were assessed before and after treatment using escudier scoring system.

Results: Most common genotype associated with OLP was 3(65%) followed by 1(25%) and 4(15%).In our sample the other genotypes were not seen. Sustained virological response was observed in all patients irrespective of the genotype OLP was associated with.There was no worsening of lichen planus in any of the treated patients. Clinically refractory lichen planus resolved with DAAs treatment.

Conclusions: HCV associated OLP responded to DDAs irrespective of the genotype corresponding to a reduction in escudier score.

Keywords: Hepatitis C, Lichen planus

3. Autoimmune Liver Disease

PE-027

Increasing Prevalence and Incidence of Primary Biliary Cholangitis in South Korea from 2009 to 2018

Kyung-Ah Kim[1], Hwa Youg Choi[2], Moran Ki[2], Eun Sun Jang[3], Sook-Hyang Jeong[3]

[1]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, [2]Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

Aims: As a rare disease, only a few population-based epidemiology studies of primary biliary cholangitis (PBC) have been reported. PBC has been designated as a rare disease since 2009 in South Korea,. This study aimed to elucidate the trends of prevalence and incidence of PBC in South Korea from 2009 to 2018.

Methods: The Korean National Health Service database and Rare Intractable Disease registration data on PBC, identified with the International Classification of Diseases 10 code of K74.3*, were obtained from 2009 through 2018. The age and gender-specific prevalence and incidence rates of PBC were calculated. The trends of PBC prevalence and incidence were estimated using Joinpoint regression analysis.

Results: A total of 3,983 patients over 20 years old were identified as an incident PBC in 2009~2018 (female-to-male ratio 5.1, median age 58 years). The age and sex-adjusted incidence from 2009 to 2018 was 9.9 per million per year on average, and has significantly increased from 10.26 to 11.92 with the average annual percent change (APC) of 3.9% (95% confidence interval 1.1-6.8, $P<0.05$). The increasing tendency of PBC incidence was consistent in both female and male, and patients aged ³ 40 years. The age and sex-adjusted prevalence from 2009 to 2018 was 79.1 per million on average and has also significantly increased from 44.0 to 114.4 per million with the average APC of 11.0% (95% incidence interval 10.6-11.6, p-value<0.001). The increasing tendency of PBC prevalence was consistent regardless age and sex, and more prominent as age increases. The prevalence of PBC demonstrated remarkable intranational geographic variation. The adherence to UDCA treatment from 2009 to 2015 was 90.9% on average and increased from 88.9% to 95.8%.

Conclusions: During 2009-2018, the incidence of PBC was 9.9 per million per year, and the prevalence of PBC was 79.1 per million population with significantly increasing trends in South Korea, which suggests increased occurrence or detection of PBC and improved outcomes with UDCA treatment. However, remarkable geographic disparity of epidemiology warrants further nationwide efforts for enhancing awareness and diagnosis.

Keywords: Primary biliary cholangitis, Prevalence, Incidence, Trend

4. Alcoholic Liver Disease

PE-028

Histone Deacetylase 8 Inhibition Attenuates Ethanol-Induced Hepatic Steatosis and Inflammation

Chang Hun Lee, Song Yi Yu, Seung Young Seo, Seong-Hun Kim, Sang Wook Kim, Seung Ok Lee, Soo Teik Lee, In Hee Kim*

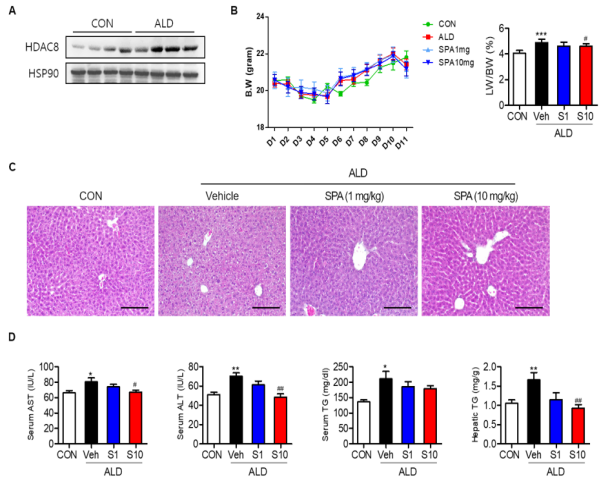
Department of Internal Medicine, Jeonbuk National University Medical School and Research Institute of Clinical Medicine of Jeonbuk National University Hospital-Jeonbuk National University Medical School, Korea

Aims: Histone deacetylases (HDACs) are known to be involved in

the progression of fibrosis in various organs and a recent study has shown that HDAC8 inhibition alleviates cholestatic liver injury and fibrosis. We aimed to investigate the pathogenic role of histone deacetylase 8 (HDAC8) in alcoholic liver disease.

Methods: A selective HDAC8 inhibitor SPA3014 (1 mg/kg and 10 mg/kg) was administered once a day intraperitoneally in chronic-plus-binge ethanol diet mouse model (NIAAA model).

Results: Hepatic HDAC8 protein expression was elevated in ethanol-fed mice. Although body weight of ethanol-fed mice was not different from that of SPA3014-treated mice, liver-to-body weight (%) was significantly diminished in mice administered 10 mg/kg of SPA3014. H&E staining of livers revealed prominent fat accumulation and neutrophil infiltration in ethanol-fed mice and SPA3014 treatment remarkably ameliorated the inflammation and steatosis. Additionally, elevated serum AST, ALT, and hepatic TG levels were significantly attenuated by SPA3014 treatment. To determine the hepatoprotective role of SPA3014 on alcohol induced liver inflammation, mRNA levels of pro-inflammatory mediators were analyzed which were markedly upregulated by ethanol diet, but they were suppressed by SPA3014 treatment. Next, we evaluated the potential mechanism of SPA3014 on hepatic steatosis. Western blotting showed that the protein expression of CPT1, p-AMPKα, and PPARα was significantly downregulated in ethanol-fed mice, but was restored by SPA3014 administration.



Conclusions: Administration of HDAC8 inhibitor in chronic-plug-binge ethanol-fed mice alleviated alcohol-induced hepatic steatosis and inflammation.

Keywords: HDAC8, Drug therapy, Liver diseases, Alcoholic, Fatty liver, Alcoholic

PE-029

The Role of Matrix Metalloproteinase-9 in Alcoholic Fatty Liver Disease

Yu-Hsiang Liao[1], Chien Huang[1], Leang-Shin Wu[1], De-Shien Jong[1], Chih-Hsien Chiu[1], Yi-Fan Jiang[2]

[1]Laboratory of Animal Physiology, Department of Animal Science and Technology, National Taiwan University, Taipei, 10617, Taiwan; [2]Graduate Institute of Molecular and Comparative Pathobiology, School of Veterinary Medicine, National Taiwan University, Taipei, 10617, Taiwan

Aims: The incidence and mortality of chronic liver disease have increased year by year, which has become an essential issue that people cannot ignore. Previous research showed that matrix metalloproteinase-9 (MMP9) played an important role in liver fibrosis and cirrhosis. However, the role of MMP9 in alcoholic fatty liver disease (AFLD) has not been cleared yet. In this study, we aimed to examine whether MMP9 has a role in the spectrum of AFLD.

Methods: C57BL/6 wild type (WT) male mice and B6.FVB(C-g)-*Mmp9*^{tm1Tvu}/J (MMP9$^{-/-}$, MMP9 KO) male mice were fed with Lieber-DeCarli EtOH liquid diet or liquid control diet for 4 weeks to establish AFLD animal models. HE and Oil Red O staining were used to examine liver tissue morphology and detect lipid accumulation respectively. qRT-PCR (quantitative real time polymerase chain reaction) was used for investigate expression of mRNA of lipid metabolism and proinflammatory markers.

Results: When fed with EtOH liquid diet, the MMP9 KO group accumulate more triglyceride and appear more lipid droplets in the liver slice. Furthermore, higher mRNA expression of lipid uptake gene (*Pparγ* and *Adrp*) and lower mRNA expression of the β-oxidation gene (*Pparα*) are found in the MMP9 KO group. Lastly, MMP9 KO/EtOH group express more pro-inflammatory genes (*Tlr4*, *Mcp-1*, *Il6*, and *Tnfα*), followed by higher expression of plasma IL-6 concentration, suggesting that MMP9 KO mice develop severe inflammatory response than WT mice when fed with EtOH liquid diet.

Conclusions: Our results show that MMP9 KO mice develop more severe steatosis than WT mice with long-term alcohol consumption, which may go through regulation of lipid metabolism or inflammatory response. This study demonstrates that MMP9 plays a role in AFLD and provides a novel perspective about the progression of AFLD.

Keywords: MMP9, Alcoholic fatty liver, Lipid metabolism, Inflammation

PE-030

Association of Alcoholic Liver Disease and Periodontitis using Alkaline Phosphatase as a Marker

Dexton Antony Johns

National Medicity Hospital, Malapuram

Aims: Alcoholic hepatitis are usually associated with an elevation in the level of alkaline phosphatase enzyme (ALP).Increased ALP level is associated with an increase in periodontitis and alveolar bone loss. The aim of the case control study was to assess whether alcoholic liver disease is associated with periodontitis.

Methods: The case study included 50 cases and 150 controls and participants were smokers. A full mouth periodontal examina-

tion was performed using probing depth, clinical attachment loss, bleeding on probing and plague index. The alveolar bone level was assessed using an orthopentamogram. The ALP level was determined by kinetic method (R.A 50).The association of risk variables were done using univariate analysis and multivariate logistic regression.

Results: A higher prevalence of periodontitis were seen in cases (68.7%) compared to controls (43.5%).Individuals with alcoholic hepatitis have a higher prevalence of periodontitis (OR =2.45; 95%CI 1.41-3.98, *P*<0.001) .The level of bone loss was also higher in the test group; aided by the higher level of ALP level (40.31+/-4.2compared to 24.67+/-2.19) which has bone resorbing activity. We also found higher the age in the cases have more periodontitis.

Conclusions: Eliminating a potential confounding factor smoking we could find a positive correlation between ALP increase seen in alcoholic hepatitis and periodontitis

Keywords: Alcoholic liver disease, Periodontitis

5. Drug and Toxic Injury

PE-031

Drug Rehabilitation

Muhammad irzaq[1], Dewayan Ekowanti[2]

[1]Department of Education, Padang State University, Padang- Indonesia, [2]Department of Health Behavior and Medicine, Gadjah Mada University, Yogyakarta-Indonesia

Aims: Drug users in Indonesia have continued to increase in the last two years, based on data compiled by the National Narcotics Agency (BNN) from 2017 to 2019. mistakes of young people in choosing their social environment. With the increase in drug cases, it is undoubtedly very detrimental and very worrying. To reduce drug addiction, it is necessary to carry out a comprehensive rehabilitation of young people addicted to drugs. According to one study, rehabilitation is a relatively effective way of eliminating this addiction's effects, including changing the mindset. Young people about the dangers of drug use make young people aware that drug addiction is a habit that will endanger themselves and damage the future of young people.

Methods: We collected articles from 2010-2020 from an electronic database. To answer the purposes of the study, we reviewed as many as ten selected articles to answer the purpose of this study.

Results: Rehabilitation of drug users will significantly affect the patient's brain system, and this is done because rehabilitation uses therapy to eliminate the effects of addiction in the patient's brain. So that if a person with drug addiction follows rehabilitation regularly and regularly, they will slowly stop using drugs, then they are trained. To be disciplined and self-controlled so that they can overcome potential recurrences. Also, they can manage their social functions. One of the dangerous diseases that drug users will experience is the liver; one of the studies states that rehabilitation is a process of retraining brain function, which is disturbed by addiction. It will have a very different impact if drug users are only punished by imprisonment or other punishment because a drug addict needs to be rehabilitated to restore brain function that the drug's destructive effect has damaged.

Conclusions: The success of patients who are addicted to drugs will significantly impact liver disease to avoid the disease. What must be done is to prevent the patient from experiencing drug addiction. This addiction can be eliminated with therapy or rehabilitation, where rehabilitation is eliminating bad habits to form cells. New tissue in the brain to get a new habit to be more disciplined and avoid liver disease and other disorders caused by drugs.

Keywords: Drug, Rehabilitation, Toxic, Liver

PE-032

Analysis of Chemical Compounds in Red Fruit (Pandanus Conoideus) as a Traditional Cancer Cure

Rikab Darwis[1], Jumriani Jumriani[2]

[1]Department of Public Health, Institute of Health Science Bina Bangsa Majene; [2]Department of Public Health, Institute of Health Science Bina Bangsa Majene

Aims: The red fruit (Pandanus Conoideus) is one of Indonesia's traditional fruits. Traditionally, red fruit is consumed by the public because it is believed to be efficacious to cure various diseases, such as: treating eye diseases, intestinal worms, skin, cancer and restoring stamina. This study aims to determine the chemical content in red fruit (Pandanus Conoideus) so that it can cure various diseases, especially cancer.

Methods: The method in this research was literature study by examining various scientific studies related to red fruit (Pandanus Conoideus). 15 Research journals that examine the chemical content of this fruit are then analyzed and summarized in order to obtain data on the various chemical contents contained in the fruit.

Results: The results of research related to red fruit (Pandanus Conoideus) showed that in the form of juice, red fruit contains antioxidants with an average content of: carotene (12,000 ppm), beta-carotene (700 ppm) and tocopherol (11,000 ppm). In addition, several other substances contained in these fruits include: oleic acid, linoleic acid, omega 3, and omega 9, all of which are active compounds that prevent the formation of free radicals in the body. Betakaroten functions to slow down the buildup of spots in the arteries so that blood flow to the heart and brain goes well without blockage. Interaction with protein increases the production of antibodies thereby increasing the number of natural killer cells and multiplying T helpers and lymphocytes.

Conclusions: The conclusion from the research results obtained

is that there are various kinds of active compounds in red fruit (Pandanus Conoideus), especially beta-carotene substances that can help the body produce natural disease-fighting cells. Increasing natural cells suppress the presence of cancer cells because they are effective in neutralizing free radicals from carcinogenic compounds that cause cancer.

Keywords: Red fruit (pandanus conoideus), Betakaroten, Cancer

PE-033

Dipeptidyl Peptidase-IV Inhibitor and Antioxidant Properties from Alkaloid Rich Fraction of Withania Somnifera Improve Liver Dysfunction in Type 2 Diabetic Mellitus

ANAND KRISHNA

Institute of Science Shri Vaishnav Vidyapeeth Vishwavidyalaya, Indore

Aims: Dipeptidyl peptidase-IV inhibitor (DPP-IV) from alkaloid extract of *Withania somnifera* (WS) might have the pleiotropic effect because of a receptor of incretin hormones in various tissue, including liver. We examined whether DPP-IV inhibitor with antioxidant capacity affects non-alcoholic fatty liver function in Type 2 Diabetic Mellitus (T2DM) in a rat model.

Methods: The T2DM model was induced in Wistar rats with high sucrose diet along with dexamethasone. Biochemical, toxicology, and histological variable were evaluated between all the groups. Apart from serum DPP-IV inhibition, glycosylated hemoglobin, hepatic lipid peroxidation, and endogenous antioxidant in tissue were measured with serum lipid profiles to correlate with antiperoxidative effects of alkaloid fraction of WS. In *ex-vivo*, hepatic lipid peroxidation, erythrocytes hemolysis was performed

Results: DPP-IV inhibitor reduced the level of aminotransferases i.e SGOT & SGPT and alkaline phosphatase by increasing the level of insulin and decrease HbA1c. Triglyceride and cholesterol levels also significantly in the normal range as compared to the control group.WS plant extract has shown a better antioxidant capacity to protect lipid peroxidation and reduced erythrocytes hemolysis of RBC. The histoarchitectural of the liver also relevant good result after treatment of DPP-IV inhibitor.

Conclusions: DPP-IV inhibitors improve insulin sensitivity and help to improve liver dysfunction in T2DM. Additionally, plant isolated DPP-IV inhibitors with their antioxidant properties reduced the toxic effect by scavenging the free radicals

Keywords: Dipeptidyl peptidase-iv, Antioxidan, Diabetic mellitus, Incretin hormons

PE-034

Chemical Compounds of Telang Flowers (Clitoria Ternatea) as a Hepatoprotective Drugs for Liver Injury: A Literature Review

Andi Nursanti[1], Danang Ari Krisnadi[2], Irwan Fitriyanto[2]

[1]Department of Chemistry, Gem Institute of Technology and Health Sciences Indonesia, [2]Herbalist, Ash Shikhah, Yogyakarta, Indonesia, Department of Public Health, Gadjah Mada University

Aims: Until now, some communities still have local knowledge about traditional medicine, mainly made from plants that have been passed down from generation to generation through oral tradition. Rural communities in Indonesia recognize and use plants as medicine to treat various health problems. Telang flower (*Clitoria ternatea*) is one type of ornamental plant and is quite popular for use in traditional medicine. This study aims to describe the chemical content of *Clitoria ternatea* has a hepatoprotective effect.

Methods: In writing this review is done by using the meta-analysis method by collecting from several scientific journals both national and international which are trusted as data primer downloaded online. From some of these journals, it is used as a comprehensive review so that it can be used as useful scientific information about *Clitoria ternatea* and Hepatoprotective.

Results: The results showed that *Clitoria ternatea* contains compounds, namely terpenoids, (triterpenoids, saponins tocopherols, phytosterols), alkaloids, and phenols (flavonoids, phenolic acids, tannins, and anthraquinones, among these compounds that provide hepatoprotective effects, namely phenols and flavonoids. The hepatoprotective activity of *C. ternatea* flowers can be caused by the activity of free radical scavengers and antioxidants resulting from the presence of phenolic compounds in the flower extract. They were given *C. ternatea* extract to mice that were induced excess acetaminophen so that it was damaged. Hepatoprotective activity was evaluated by monitoring levels of the enzymes aspartate aminotransferase and alanine aminotransferase, as well as levels of bilirubin and glutathione through histopathological analysis. The results showed that the rats given the *C. ternatea* extract (200 mg/kg) had decreased levels of the four indicator compounds of liver damage. The results of other experiments showed a dose of 300-500 mg/kg rats were still in normal doses even at a dose of 3000 mg/kg at the root showed no signs of toxicology or death.

Conclusions: Hepatoprotective drugs for liver injury come from the chemical content of phenolic compounds which function as antioxidants in *C. Ternatea*.

Keywords: Chemical compounds, Clitoria ternatea, Hepatoprotective

6. Fibrosis/Liver Cirrhosis

PE-035

Evogliptin, Dipeptidyl Peptidese-4 Inhibitor, Attenuates Liver Fibrosis

So-Hee Lee[1,2], Hye-Young Seo[1,2], Ji-Ha Lee[1,2], Jae Seok Hwang[1], Mi-Kyung Kim[1,2], Byoung Kuk Jang[1,2*]

[1]Department of Internal Medicine, Keimyung University School of medicine, Daegu, South Korea; [2]Institute for Medical Science, Keimyung University School of Medicine, Daegu, South Korea

Aims: Evogliptin, a dipeptidyl peptidase 4 inhibitor, is an anti-diabetic drug. Several studies have shown anti-fibrotic effects of DPP-4 inhibitors in a variety of organ systems, including the heart, lungs, liver, and kidneys. However, few reports have described the effect of evogliptin on liver fibrosis. Therefore, in this study, we investigated whether evogliptin reduces liver fibrosis in primary hepatocytes and primary hepatic stellate cells.

Methods: We isolated primary hepatic stellate cells and primary hepatocyte from C57BL/6 mice and primary hepatocyte from hepatocyte-specific ATG7 knockout (ATG7f/f-Cre+) mice. The expression levels of αSMA, CTGF, collagen, LC3 and Samd3 were evaluated by western blot analysis. LC3 puncta was observed with a fluorescence staining microscope.

Results: Evogliptin reduced the expression of αSMA and collagen in primary hepatic stellate cells, thus confirming that activation of hepatic stellate cells inhibited. And evogliptin inhibited TGF-β-induced CTGF and phospho-Smad3 in primary hepatocytes, and increased LC3 II conversion, formation of LC3 puncta and autophagy flux. However, evogliptin did not decrease CTGF expression in primary hepatocytes of $ATG7^{f/f}$-Cre+ mice. Therefore, it was confirmed that an increase in autophagy of evogliptin was associated with a decrease in the expression of CTGF.

Conclusions: In our study, evogliptin attenuates liver fibrosis by preventing hepatic stellate cell activation. In addition, evogliptin decreases CTGF expression by inducing autophagy in hepatocyte. These results suggest that evogliptin may be a new agent to treat liver fibrosis.

Keywords: Evogliptin, DPP-4 inhibitor, Liver fibrosis

PE-036

Mitochondrial Regulation of Human Bone Marrow Derived Mesenchymal Stem Cells in Liver Cirrhosis

Seong Hee Kang[1,2*], Su-Jung Park[2], Jin Suk Lee[2], Moon Young Kim[1,2], Soon Koo Baik[1,2]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea, [2]Regenerative Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

Aims: Mesenchymal stem cells (MSCs) transplantation is an emerging therapy for treating chronic liver diseases. However, only modest improvements have been seen, because of the limited feasibility of transplanted cells. Hypoxic preconditioning is thought to enhance the therapeutic potency and duration of survival of engrafted MSCs. We investigated the effect of administration of hypoxic pre-conditioned bone marrow-derived MSC (hBMSCs) of patients with cirrhosis and control.

Methods: Control hBMSCs were purchased from the American Type Culture Collection and hBMSCs of patients with cirrhosis were obtained from Pharmicell. Cobalt chloride (CoCl2) imitates hypoxia *in vitro*. hBMSCs cells were preconditioned in both normoxia and hypoxia with CoCl2. Potentials of proliferation and differentiation and mitochondrial activity of BMSCs were analyzed. The expression levels of cytoprotective factors and biological effects in hypoxia were studied.

Results: The multifunctional cytoprotective gene, HGF, and the proangiogenic gene, VEGF were significantly overexpressed in hypoxic preconditioning hBMSCs. To study the effects of hypoxic preconditioning on H2O2-induced cytotoxicity, there were significant degrees of protection against H2O2-induced cell death in hypoxic preconditioning hBMSCs compared with normoxia in assays measured by annexin V/PI staining. To determine the mitochondrial functions, the mitochondrial membrane potential in MSCs was assessed using membrane-permeant dual emission potential-sensitive JC-10 dye and flow cytometry analysis. The results showed an about 20% higher red fluorescence signal in hypoxic preconditioning hBMSCs when compared with that in normoxia. However, changes in mitochondrial morphology and dynamics are mediated by mitochondrial biogenesis marker (PGC1, MTCO1), fission (Fis1, Drp-1), and fusion (Mfn1, Opa-1) regulators, which were evaluated by q-RT-PCR are not significant. Moreover, bioenergetic profiles by measuring real-time O2consumption (OCR) showed that basal and maximal uncoupled OCR were significantly lower in hypoxic preconditioning hBMSCs.

Conclusions: Although hypoxic preconditioning hBMSCs possessed better cytoprotective abilities and promoted cell proliferation, hypoxia could reduce the mitochondrial function of hBMSCs.

Keywords: Mesenchymal stem cells, Hypoxia, Liver cirrhosis

PE-037

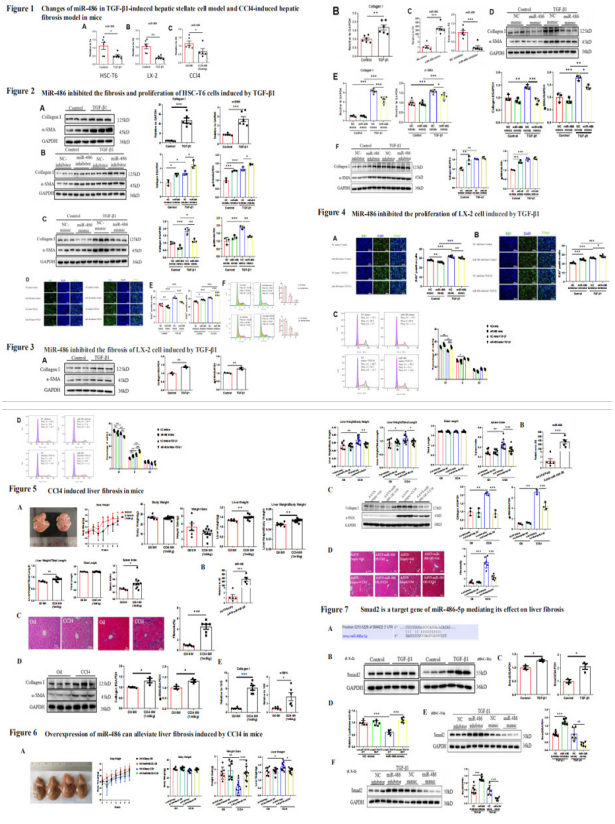
MiR-486-5p Suppresses Hepatic Stellate Cells Activation Liver Fibrosis by Targeting Smad2

Beiyong Cui[1], Xiya Lu[2], Meiyi Song[2], Changqing Yang[2]

[1]Division of Gastroenterology and Hepatology, Digestive Disease Institute, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China, [2]Division of Gastroenterology and Hepatology, Digestive Disease Institute, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China

Aims: Liver fibrosis is a reversible stage in the progression of liver injury to cirrhosis. This study aims to investigate the effects of miR-486-5p on the biological behaviors of hepatic stellate cells (HSCs) during hepatic fibrosis, and to explore the underlying molecular mechanisms.

Methods: MiRNA expression of active hepatic stellate cells (HSC-T6, LX-2) and CCl_4-induced mouse liver fibrosis model was detected by Real-time Quantitative polymerase chain reaction(qPCR). Cell proliferation was assessed using the EdU. Cell cycle were analyzed by a flow cytometer (FCM). The expression of collagen Ia1 and α-SMA in hepatic stellate cells and liver fibrosis tissues was detected by Western blot. Targetscan 7.2 was used to predict the potential targets of miR-486-5p and the target gene was further confirmed by dual-luciferase reporter assay.



Results: MiR-486-5p was significantly down-regulated in TGF-β1-induced hepatic stellate cells activation and CCl4-induced mouse liver fibrosis model. Overexpression of miR-486-5p can markedly inhibit the proliferation and matrix formation of HSCs, but down-regulation of miR-486-5p has the opposite effects. MiR-486-5p overexpression protected mice from liver fibrosis induced by CCl_4. Target gene prediction, Western blotting and dual-luciferase reporter assay confirmed that Smad2 is a target gene of miR-486-5p mediating its effect on liver fibrosis.

Conclusions: MiR-486-5p may inhibit the proliferation and activation of HSCs by targeting Smad2 during liver fibrosis. miR-486-5p is a potential treatment for liver fibrosis.

Keywords: Liver fibrosis, Hepatic stellate cells, Cell proliferation, miR-486-5p

PE-038

Endoscopic Sclerotherapy for Bleeding from the Duodenal Third Portion Varices

Ji Yoon Kwak, Hyeon-Uk Kwon, Choi Jung Woo, Chang Min Lee, Chang Yoon Ha, Woon Tae Jung, Ok-Jae Lee, Hyun Chin Cho

Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Korea

Aims: Duodenal variceal bleeding is rare and difficult case to make diagnosis and bleeding control because of its anatomical position. About two-thirds of duodenal varices caused by portal venous hypertension due to liver cirrhosis. It is presented with hematemesis or lower gastrointestinal bleeding and often massive volume of bleeding result in high mortality. Several treatment modalities are performed to achieve duodenal variceal bleeding control including endoscopic therapy, radiologic intervention and surgery but the optimal treatment for patients with bleeding duodenal varices is unclear.

Methods: We retrospectively evaluated two patients who visited the emergency room for gastrointestinal bleeding.

Results: A 60-year-old man was admitted to the emergency room with massive hematochezia and hypotension. Angiography for radiologic intervention was tried but failed due to tortous vessel. Esophagogastroduodenoscopy(EGD) was performed and confirmed variceal bleeding in duodenal 3rd portion. Endoscopic injection of cyanoacrylate was successfully performed (Figure 1 (A) (B)). A 58-year-old man was admitted to the emergency room melena. EGD was performed, and variceal bleeding was confirmed in the duodenal 3rd portion. The hemoclip was applied to the bleeding site (Figure 2(A)). However, there was rebleeding afterwards, endoscopic injection of cyanoacrylate was performed (Figure 2(B)). In both patients, there were no more bleeding findings after endoscopic sclerotherapy.

Conclusions: To detect a bleeding source in a portal hypertensive patient, duodenal varices should be carefully investigated. Endoscopic sclerotherapy is a good choice to control duodenal variceal bleeding, but the patient should be warned of fatal complications such as pulmonary embolism or duodenal perforation.

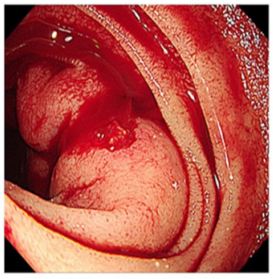


Figure 1(A). Reperformed EGD showed spurting blood from duodenal third portion varices.

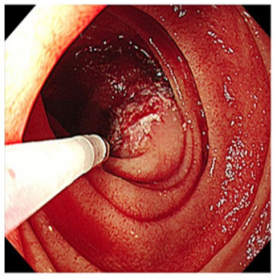


Figure 1(B). Endoscopic injection of cyanoacrylate and lipiodol was successfully performed.

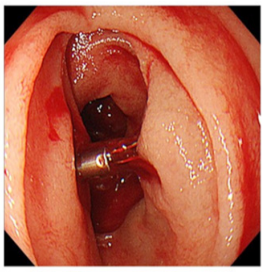


Figure 2(A). Endoscopic injection of cyanoacrylate and lipiodol was successfully performed.

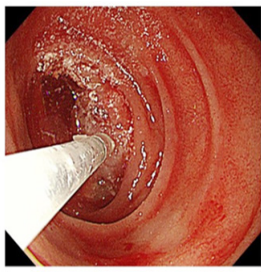


Figure 2(B). Endoscopic clipping was performed.

Keywords: Endoscopic sclerotherapy, Duodenal third portion varices, Gastrointestinal bleeding

PE-039

Safety Performance of Sedative Drugs for Cognitive Impairment in the Patients with Liver Cirrhosis

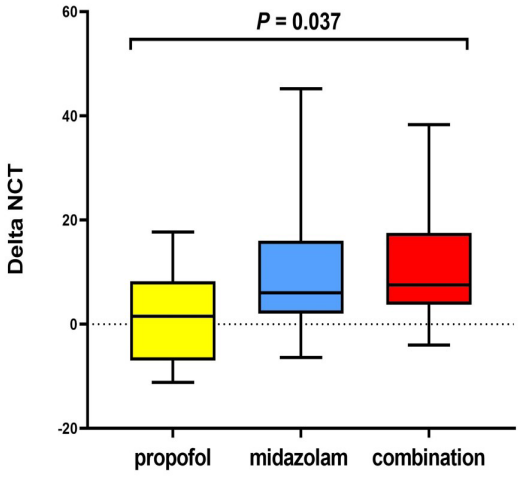
Hyun Joon Park, Kwang Il Seo, Sang Uk Lee, Byung Hoon Han, Byung Cheol Yun, Yeonsu Kim, Jeonghwan Noh

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Aims: Selection of appropriate drugs for endoscopic sedation in liver cirrhosis (LC) patients is still challenging for many reasons, including the risk of cognitive impairment. We aimed to evaluate the safety of sedative drugs for hepatic encephalopathy (HE) in LC patients.

Methods: From April 2018 to November 2020, results of number connection test (NCT) of LC patients admitted to Kosin University Gospel Hospital were analyzed. NCTs were performed prior to endoscopic sedation and 2 hours after endoscopy. The results of NCT were graded as minimal hepatic encephalopathy (MHE) (<30 sec), grade 1 (30-50 sec), grade 2 (50-80 sec), grade 3 (80-120 sec) and grade 4 (>120 sec). We divided the study population into three groups (propofol, midazolam, combination), thereby compared the three groups.

Results: A total of 107 LC patients were enrolled. The mean (±SD) age of the patients was 56.4 (±9.71) years and proportion of males was 71.0%. Thirty-two (29.9%) patients were positive for HBsAg, and 19 (17.8%) patients were positive for anti-HCV. Seventy-six (71.0%) patients were alcoholics, and 45 (42.1%) patients were decompensated LC. The results of NCT grade revealed MHE in 10 (9.3%) patients, grade 1 HE in 56 (52.3%), grade 2 HE in 34 (31.8%), grade 3 HE in 7 (6.5%). The mean (±SD) of delta-NCT was 8.53 (±17.49) sec, and 34 (31.8%) patients deteriorated HE after endoscopy. The propofol group included 38 (35.5%) patients, midazolam group included 27 (25.2%) patients, and combination group included 42 (39.3%) patients. The mean (±SD) delta-NCT of the propofol, midazolam, and combination groups were 2.72 (±14.28) sec, 11.12 (±18.55) sec, and 12.11(±18.45) sec, respectively (P=0.037). The number of patients who deteriorated HE in the propofol, midazolam, and combination groups was 8 (21.1%), 10 (37.0%), and 16 (38.1%) patients, respectively.



Conclusions: Propofol may be relatively safe for cognitive impairment in patients with LC.

Keywords: Conscious sedation, Sedative drug, liver cirrhosis, Number connection test, Hepatic encephalopathy

PE-040

Nutritional Status Assessment and Sarcopenia in Liver Cirrhosis Patients

Hyung Jun Kim, Kwang Il Seo, Sang Uk Lee, Byung Hoon Han, Byung Cheol Yun, Hyun Joon Park, Yeonsu Kim, Jeonghwan Noh

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Aims: Nutritional status assessment is important for predicting the prognosis of liver cirrhosis (LC) patients. The Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT) is a well-validated and simple screening tool to assess the nutritional status of LC patients. Sarcopenia is also a major problem related to poor prognosis of LC patients. The aim of this study was to assess the nutritional status of LC patients using RFH-NPT, as well as the correlation with RFH-NPT and muscle mass.

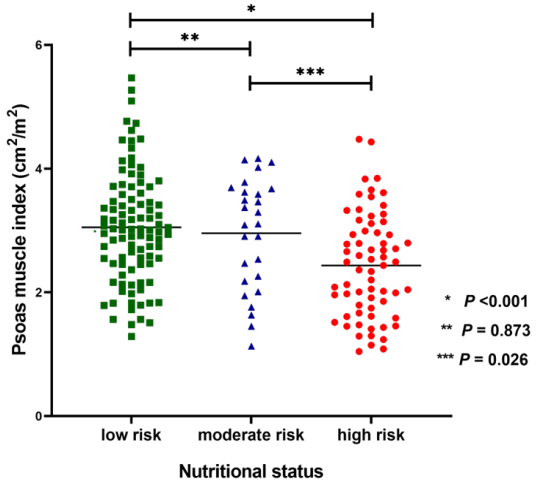
Methods: We conducted the RFH-NPT to LC patients in Kosin

University Gospel Hospital from January to July 2020. The Psoas Muscle Index (PMI) was measured using abdominal CT scan performed within 3 months. The RFH-NPT were conducted in 201 LC patients. Ten patients who did not perform abdominal CT scans within the last 3 months were excluded, and then a total of 191 patients were enrolled.

Results: The mean (±SD) age of study population was 62.6 (±10.31) years and the proportion of male was 79.5%. Seventy-eight (40.8%) patients were positive for hepatitis B virus, 37 (19.4%) patients were positive for hepatitis C virus, and 108 (56.5%) patients were alcoholics. One hundred twenty-seven (66.5%) patients had Child-Pugh grade A, 42 (22.2%) patients had grade B, and 22 (11.5%) patients had grade C. The mean (±SD) BMI of study population was 24.0 (±4.06) kg/m^2, the PMI was 2.8 (±0.92) cm^2/m^2. The results of RFH-NPT showed low risk in 98 (51.3%) patients, moderate risk in 27 (14.1%), and high risk in 66 (34.6%), respectively. The Child-Pugh grade (P<0.001), BMI (P<0.001), albumin (P<0.001), total cholesterol (P<0.001) and PMI (P<0.001) showed significant differences according to nutritional status of RFH-NPT. In addition, RFH-NPT score was significantly correlated with PMI (rho = – 0.327, P<0.001).

Conclusions: Based on the results of RFH-NPT, 34.6% of LC patients needed nutritional support. High-risk patients were significantly associated with sarcopenia.

Keywords: Liver cirrhosis, RFH-NPT, Nutrition, Psoas muscle index, Sarcopenia



PE-041

Epidemiologic Change of Hepatitis B Related Cirrhotic Patients Combined with or Without Alcoholic Liver Disease during Ten Years in South Korea

Jeong Han Kim[1], Jae Hyun Yoon[2], Chung Hwan Jun[2], Eileen L Yoon[3], Byung Seok Kim[4], Jeong Eun Song[4], Ki Tae Suk[5], Moon Young Kim[6], Seong Hee Kang[6]

[1]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Chonnam National University Hospital School of Medicine, Gwangju, Korea; [3]Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea; [4]Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Korea; [5]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea; [6]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

Aims: Cirrhosis is a leading cause of death worldwide. Hepatitis B virus (HBV) is the most common etiology and alcoholic liver disease (ALD) is the second in South Korea. HBV-related cirrhosis combined with ALD is also common but data about these patients is limited. We aimed to investigate epidemiology and change during ten years of these patients.

Methods: This is a cross-sectional epidemiologic study and we retrospectively reviewed medical records of HBV related cirrhotic patients visited six tertiary hospital from 2008 to 2017. Changing trends were analyzed via Poisson regression

Results: Total 6,788 visit records (mean 679 patients each year) of 4,704 patients were included in this analysis. Mean age was 52.7-57.8 years and male was predominant (64.9-69.9%). Prevalence of patients combined with ALD was decreased during ten years (total P=0.003, male P=0.015, female P=0.015) and more common in male (P<0.001) and younger age. New diagnosis of hepatocellular carcinoma was more common in ALD than HBV alone (P<0.001) and incidence was not changed during ten years. Overall mortality and liver-related mortality were both higher in ALD (P<0.001) and rate was not changed. Prevalence of decompensated cirrhosis was more common in ALD (P<0.001) and incidence was only decreased in HBV alone during ten years (P=0.045).

Conclusions: Prevalence of HBV-related cirrhotic patients combined with ALD was decreasing, but clinical status of these patients has not been improved. Strategic management approach for these patients was warranted.

Keywords: Liver cirrhosis, Hepatitis B, Alcoholic liver disease, Hepatocellular carcinoma, Mortality

PE-042

A Case of Portal Vein Thrombosis in a Patient with Breast Cancer

Yujin Kim

Department of Internal Medicine, Cheju Halla General Hospital

Aims: Portal vein thrombosis is an uncommon complication in a patient with breast cancer. Malignancy and several drugs are known to have prothrombic effects. We introduce a case of a female patient with history of metastatic breast cancer under treatment with aromatase inhibitor, and developed ascites and esophageal varices due to portal vein thrombosis.

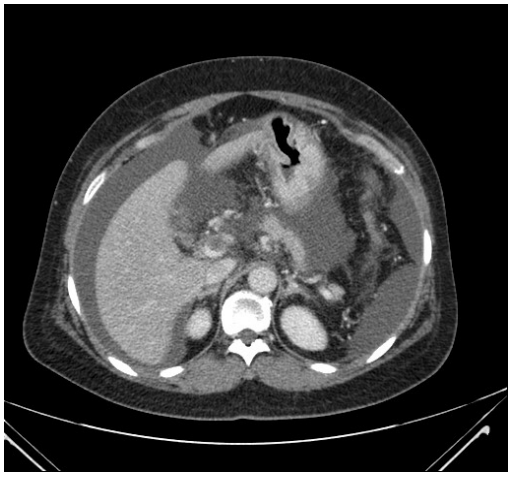
Methods: A 47-year-old female patient was referred from the oncology department with six months of abdominal distension. She has been treated for breast cancer for 6 years with surgery, chemotherapy, and radiotherapy. An aromatase inhibitor, letro-

zole has been used for years. Physical examination revealed distended abdomen and shifting dullness. Abdominal CT showed large amount of ascites and a portal vein thrombosis involving main portal vein and proximal superior mesenteric vein. Initial blood test revelaed platetet count 90,000/mL, AST/ALT 34/17 U/L, albumin 3.1 g/dL, and prothrombin time 13.4 sec. Serology test for hepatitis B and C virus infection was negative. No abnormal result related with thrombophilia was found . F2 esophageal varices without red color signs were seen on gastrscopy. Diagnostic paracentesis was performed to define the characteristics of the ascites. The serum-ascites albumin gradient was 2.5 g/dL, and ascites protein level was 1.1 g/dL. No malignant cell was found from the ascites.

Results: The patient was diagnosed with pre-hepatic portal hypertension due to portal vein thrombosis associated with breast cancer. Diuretics including furosemide and spinorolactone was given to control ascites.

Conclusions: Malignancy is a hypercoagulable state. An aromatase inhibitor also can raises the risk for venous thromboembolism. A development of portal vein thrombosis should be an important differential diagnosis when patients with history of malginancy and under treatment of drugs raise thromboembolic event developed new onset ascites.

Keywords: Portal vein thrombosis, Breast cancer, Portal hypertension, Ascites



PE-043

Association between New-Onset Liver Cirrhosis and Suicide Risk in South Korea: A Nationwide Cohort Study

Suk-Yong JANG[1], Woo Sun ROU[2,3], Seok Hyun KIM[2,3], Byung Seok LEE[2,3], Hyuk Soo EUN[2,3]

[1]Department of Preventive Medicine, Eulji University College of Medicine, Jung-gu, Daejeon, South Korea; [2]Department of Internal Medicine, Chungnam National University School of Medicine, Junggu, Daejeon, South Korea; [3]Department of Internal Medicine, Chungnam National University Hospital, Jung-gu, Daejeon, South Korea

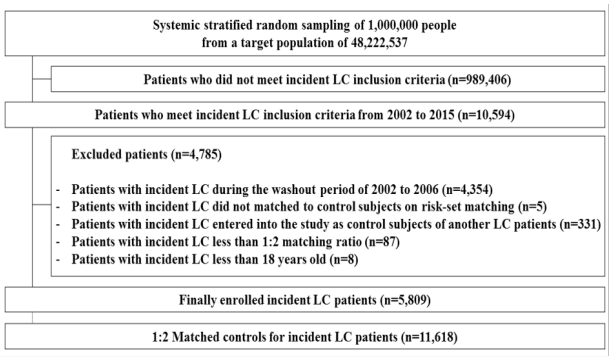
Aims: Current evidence suggests that liver cirrhosis (LC) causes severe psychological stress and depression, which are risk factors for suicide. Although previous studies reported the association between LC and suicidal thoughts, little is known of its effect on suicidal deaths. Therefore, this study was undertaken to investigate the effect of new-onset LC on suicide.

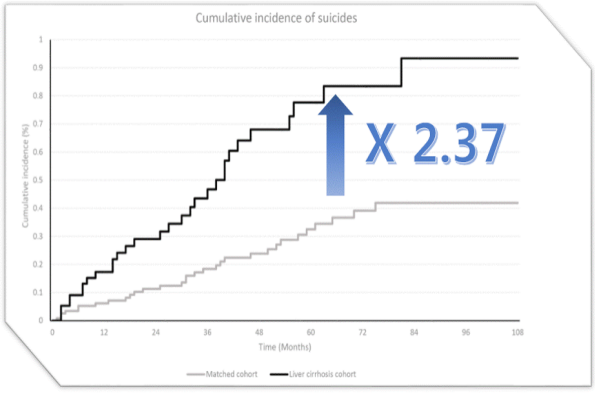
Methods: From the National Health Insurance Service-National Sample Cohort of South Korea, 5,809 incident LC patients and 11,618 risk-set controls matched by propensity score were selected for follow-up. The incidence rate of suicide was estimated using a generalized estimating equation with a Poisson distribution. Effect size was presented as a hazard ratio (HR) using Cox's proportional hazards model.

Results: The incidence rate of suicide was 143.3 cases per 100,000 person years (95% confidence interval [CI] 100.2–205.1) among the LC cohort. The LC patients were 2.37 times more likely to commit suicide compared with matched controls (HR 2.37, 95% CI 1.44–3.88). Increased suicide risk was evident within the first two years of the follow-up period (HR 2.59, 95% CI 1.20–5.60) and among the 18–49-year-old age group (HR 3.72, 95% CI 1.45–9.56)

Conclusions: Our study found increased risk of suicide in patients with new onset LC, especially during the early period following diagnosis and in younger patients. To decrease this suicide risk, a regular and continuous social support system is required.

Keywords: Liver cirrhosis, Suicide, Risk, Psychological distress





PE-044

Formulation and Evaluation of Novel Self Nano Emulsifying Formulation of Furosemide: A Drug Used in Portal Hypertension

Pankajkumar Yadav

Sam Higginbottom University of Agriculture Technology & Sciences

Aims: Poor water solubility is one of the reasons for erratic absorption after oral administration of furosemide (FSM), an antihypertensive loop diuretic. Aim of this study was to utilize Self nano emulsifying drug delivery system (SNEDDS), a novel drug delivery system, for improvement of water solubility, permeability and ultimately bioavailability of FSM.

Methods: FSM solubility was determined in various vehicles oils, surfactants and co surfactants. Self emulsification region for the rational design of SNEDDS formulations was identified by pseudoternary diagrams. Developed formulations were characterized by zeta potential determination, droplet size analysis, dilution test, viscosity determination, *in vitro* dissolution studies and *in vivo* pharmacodynamic evaluation.

Results: A remarkable increase in dissolution was observed for the optimized SNEDDS when compared with the plain FSM and marketed formulation by *in vitro* dissolution studies. The pharmacological effect of FSM was improved by SNEDDS formulation as compared to plain FSM.

Conclusions: The study confirmed that SNEDDS formulation can be used as a possible alternative to traditional oral formulations of FSM to improve its bioavailability.

Keywords: SNEDDS, Bioavailability

PE-045

Parenting Stress: Psychological Condition of Parents with Children with Cirrhosis of The Liver

Ardela Iga Pratiwi

Department of History, Universitas Gadjah Mada, Indonesia

Aims: Cirrhosis of the liver is common in someone who has had liver damage for years, but it can also occur in children. The daily life of children with cirrhosis of the liver, both physical and psychosocial will be disrupted, so that the child becomes more dependent on their parents. However, often parents are not ready to accept the child's condition. This study was to describe the psychological condition of parents who care children with cirrhosis of the liver.

Methods: This study used electronic data base as a method by reviewing some articles published since 2007 to 2017.

Results: The results showed that the doctor's initial diagnosis of their child with liver cirrhosis was an initial problem that caused uncomfortable feelings in parents, such as shock, resistance, sadness, confusion, and anger. Parents feel responsible for their child's illness, which causes feelings of guilt and despair. The uncertainty of the child's condition or the potential that will happen to their child in the future is the biggest stressor for parents. The stress level will increase during transplant preparation and transplantation. In conditions of increase stress levels, not seldom create tension in the relationship between father and mother.

Conclusions: Parents who have children with cirrhosis of the liver faced more complex challenges than parents who have healthy children. They must prepare themselves for the doctor's diagnosis, progression of disease, need for treatment at an uncertain time, transplantation and also potential cure. In these conditions, having a good quality relationship between husband and wife is important to deal with the impact of problems with children with liver cirrhosis. In addition, parents need to seek social support from interdisciplinary health professionals for dealing with each stage of the stressor.

Keywords: Parents, Psychological condition, Chlidren with cirrhosis of the liver

PE-046

Quality of Life in Patients with Primary Biliary Cirrhosis and Sclerosing Cholangitis By SF-36 Health Survey: A Literature of Review

Derizal[1], Ade Kartikasari Sebba[2]

[1]Economics, STATE ISLAMIC INSTITUTE OF BUKITTINGGI, Indonesia; [2]Public Health, Universitas Gadjah Mada, Indonesia

Aims: Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC) are part of the family of cholestatic liver disease. Therapies or transplantation are using increase and make improvement of patient survival. However, healing or control of the disease is often not accompanied by a full recovery of quality of life (QoL). This study aimed to reviews analyze various of the quality of life of patients Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC).

Methods: This study used journal which published from 2001-2020. Ten articles were selected based on the articles using the Short Form Health Survey 36 (SF-36) in measuring the quality of life of patients. The collection of mean score for result SF-36 indicator in each article was used to see the factors that significantly influence the quality of life of patients.

Results: The results showed there were 8 indicators that showed the quality of life of patients based on SF 36. The Bodily Pain, Mental health, Role Emotion, and Social have a high value was marked by the mean score of patients satisfaction of QoL over 70. The mean score of General Health, Physical Health, Role Physical and vitality is marked lower in all which are indicated by the mean score of patient satisfaction between 40-65.

Conclusions: The mean of two summary scores of SF-36 show that Physical Component Summary (PCS) is lower than Mental Component Score (MCS). The doctors and medical personnel must take quick action to improve the quality of life in the form of physical recovery.

Keywords: Primary biliary cirrhosis (PBC), Primary sclerosing cholangitis (PSC), Quality of life, SF-36

7. Nonalcoholic Fatty Liver Disease

PE-047

Genetic Predisposition to NAFLD in Yakut Population

Aleksandra T. Diakonova[1], Khariton A. Kurtanov[1], Nadezhda I. Pavlova[1]

Yakut Science Center of Complex Medical Problems [1] Yakutsk, the Republic of Sakha (Yakutia), Russia

Aims: The aim of our research was to study the distribution of alleles and genotypes of the FTO rs9939609 SNP, the PNPLA3 rs738409 SNP, and the TM6SF2 rs58542926 SNP in the Yakut population

Methods: The study of the FTO rs9939609, SNP the PNPLA3 rs738409 SNP, and the TM6SF2 rs58542926 SNP was carried out in the Department of Molecular Genetics at YSC CMP. For the study, we used DNA samples from the collection of biomaterials of the YSC KP using the UNU "Genome of Yakutia" (reg. No. USU_507512). A total of 85 DNA samples from the population were tested. the population were tested. The inclusion criteria for the study were Yakuts by ethnicity, living in Yakutia, without liver damage by chronic viral hepatitis. Exclusion criteria: autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hereditary hemochromatosis, Wilson-Konovalov disease, and alcohol abuse (>30g/l).

Results: An analysis of the frequency distribution of alleles and genotypes of the FTO rs9939609 SNP in the study group did not reveal significant differences. An analysis of the frequency distribution of alleles and genotypes of the PNPLA3 rs738409 SNP revealed that in men and women the G allele and the homozygous GG genotype prevailed. The results of the analysis of the frequency distribution of alleles and genotypes of the TM6SF2 rs58542926 SNP showed the predominance of individuals with the C allele (89% in men and 90% in women) with statistical significance in women. We previously found a high frequency of the PNPLA3 (rs738409) [G] allele in the Yakut population (72%-73%).(30,31) The accumulation of triglycerides in hepatocytes, associated with the PNPLA3 p.I148M variant, was probably an adaptation to a cold climate; this accumulation is not needed in the modern world, but leads to NAFLD among the Yakut population. As noted by many domestic and foreign researchers, carriers of the PNPLA3 G allele are more susceptible to liver diseases (NAFLD, NASH) with a high risk of developing cirrhosis and hepatocellular carcinoma.(20) Undoubtedly, further studies with a larger sample size are required to detect the features of the distribution of alleles and genotypes of the FTO rs9939609 SNP and the TM6SF2 rs58542926 SNP in that population.

Conclusions: The further studies with a larger sample size are required to detect the features of the distribution of alleles and genotypes of the FTO rs9939609 SNP and the TM6SF2 rs58542926 SNP in that population

Keywords: Nonalcoholic fatty liver disease, Genome-wide association study, Single nucleotide polymorphism, Yakuts

PE-048

EWSR1 Deficiency Impaired Mitochondrial Fatty Acid Oxidation and Lipid Homeostasis *In Vitro* and *In Vivo*

Wonhee Hur, Gil Won Lee, Byung Yoon Kang, Sung Min Kim, Seung Kew Yoon

The Catholic University Liver Research Center & WHO Collaborating Center of Viral Hepatitis, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea

Aims: Non-alcoholic fatty liver disease (NAFLD) with accumulated fat in the liver is a common cause of chronic liver disease in the developed/Western world. Previous studies have shown that *Ewing sarcoma breakpoint region 1* (EWSR1) is essential for classical brown fat development as well as a possible role in beige fat cell formation. However, there have been no studies on the role of EWSR1 during NAFLD progression.

Methods: EWSR1 expression was analyzed in *in vitro* and *in vivo* NAFLD model by qRT-PCR and Western blot. To explore the biological processes in liver of EWSR1 knockout mice, functional pathway enrichment and protein–protein interaction (PPI) network analyses were performed on the DEGs from cDNA microarray. To further validate the molecular mechanisms of EWSR1, we silenced or overexpressed the expression of EWSR1 by lentivirus or plasmid vector in palmitic acid-induced hepatocytes or mice model of high fat diet (HFD)-induced NAFLD.

Results: EWSR1 protein levels were significantly downregulated in PA-induced hepatocytes, and liver tissue of HFD-induced NAFLD mice model. Furthermore, the DEGs using the analysis of biological function and PPI network were mainly involved in fatty acid metabolism, lipid metabolism and PPARa signaling pathways. The EWSR1 depletion inhibited lipid oxidation (PPARα and CPT-1α) and increased hepatic lipogenesis (ACC and FASN). Then we further examined expression of transcription factors which are critically involved in liver lipid metabolism. SREBP and ChREBP mRNA expression levels were decreased by 30 and 80% in EWSR shRNA hepatocyte, respectively. Nile red staining demonstrated a robust accumulation of lipid droplets on EWSR shRNA hepatocyte. In contrast, overexpression of EWSR1 significantly decreased hepatic lipid accumulation via AMPK/ACC/CPT-1A and SREBP-1c/FAS signaling pathways in hepatocyte. Especially, PPARa expression was efficiently activated by EWSR1 expression in hepatocyte.

Conclusions: These results suggested that EWSR1 expression may modulate hepatic lipid via AMPK/ACC/CPT-1A and SREBP-1c/FAS signaling pathways. This study may provide a new thought for the treatment of NAFLD.

Keywords: Non-alcoholic fatty liver disease, Ewing sarcoma breakpoint region 1, Fatty acid metabolism, PPAR signaling

PE-049

Hepatic Steatosis Is a Significant Factor for Breast Cancer Recurrence after Curative Surgery

Se Ryun Bae[1], Young-Sun Lee[2], Su Min Bang[2], Yoon Seok Lee[2], Ji Hoon Kim[2], Sun Young Yim[2], Young Kul Jung[2], Yeon Seok Seo[2], Hyung Joon Yim[2], Jong Eun Yeon[2], Soon Ho Um[2], Kwan Soo Byun[2]

Department of Internal Medicine, Korea University College of Medicine, Korea

Aims: Many kinds of cancer are associated with NAFLD. Breast cancer is the most common cancer among women worldwide, and it is a main cause of death in women. As with breast cancer, metabolic components are important risk factors for the development of nonalcoholic fatty liver disease (NAFLD).In this retrospective cohort study, we aimed to determine the prevalence of NAFLD in patients with breast cancer and the impact of NAFLD on the prognosis of breast cancer.

Methods: Patients with breast cancer were enrolled in the study from January 2007 to June 2017. Hepatic steatosis was evaluated using hepatic steatosis index (HSI). hepatic steatosis index (HSI) is calcaulated by 8 x(ALT/AST ratio)+BMI (+2, if female; +2, if diabetes mellitus). It was divided into NAFLD group over 36 at HSI and control group under 30 at HSI .

variable	Control(n=447)	NAFLD 1(n=400)	Total(N=1587)	P-value
Age, median (IQR),	46.0 (41-53)	54 (47-62.00)	50 (44-58)	0.000
BMI, median (IQR),	21.04 (19.81-21.97)	27.83 (26.24-29.71)	23.71 (21.85-26.22)	0.000
DM(N)	8(1.79%)	111(27.75%)	184(11.59%)	0.000
HTN(N)	41(9.17%)	164(41%)	406(25.58%)	0.000
AST, median (IQR), IU/L	20 (17-23)	23 (18-29)	21 (18-25)	0.000
ALT, median (IQR), IU/L	12 (10-14)	23 (17-32)	16 (12-22)	0.000
ALP, median (IQR), IU/L	58 (49-71)	71.50 (58.00-86.00)	64 (53-80)	0.000
Hb, median (IQR), g/dL	12.90 (12.20-13.60)	13.300 (12.600-14.000)	13.100 (12.300-13.800)	0.000
PLT, median (IQR), X 10^3/μL	238 (204-274)	250.00 (221.00-301.00)	243.00 (210.00-283.00)	0.000
Bilirubin, median (IQR), mg/dL	0.5100 (0.3800-0.7000)	0.4800 (0.3500-0.6375)	0.4800 (0.3700-0.6600)	0.001
Albumin, median (IQR), g/dL	4.400 (4.200-4.500)	4.400 (4.200-4.500)	4.400 (4.200-4.500)	0.547
PT, median (IQR), INR	0.9800 (0.9400-1.0200)	0.9500 (0.9100-0.9900)	0.9600 (0.9300-1.0100)	0.000
BUN, median (IQR), mg/dL	12.300 (10.000-14.900)	13.900 (11.400-17.000)	13.000 (10.800-16.100)	0.000
Cr, median (IQR), mg/dL	0.6000 (0.5400-0.6700)	0.6300 (0.5700-0.7300)	0.6100 (0.5500-0.6800)	0.28
Glucose, median (IQR), mg/dL	101.00 (93.00-109.00)	110.00 (100.00-130.00)	104.00 (95.00-117.00)	0.000
Cholesterol, median (IQR), mg/dL	183.00 (161.00-203.00)	196.00 (171.25-223.00)	188.00 (166.00-213.00)	0.000
Mortality	26(5.82%)	38(9.50%)	124(7.81%)	0.044
Recurrence	35(7.83%)	52(13.00%)	154(9.70%)	0.040

Results: Total 1587 patients were enrolled from January 2007 to June 2017. The prevalence of NAFLD in patients with breast cancer was 25.21% (400/1587). 28.17% of breast cancer patients (447/1587) was classified into non-NAFLD group. The number of mortality in NAFLD group was 38/400(9.50%) and it was higher than the number of mortality in non-NAFLD group (26/447, 5.82%).The number of recurrence in NAFLD group was 52 (13.00%) and it was higher than the number of recurrence in non-NAFLD group (35/447, 7.83%). Overall survival was significantly lower in NAFLD group comparing with non-NAFLD group (*P*=0.044). Moreover, the cumulative incidience of recurrence of breast cancer was higher in NAFLD group comparing with non-NAFLD group (*P*=0.040).

Conclusions: Breast cancer patients with NAFLD had higher mortality rate than non-NAFLD group. Moreover, breast cancer patients with NAFLD showed poor prognosis in terms of recurrence. Therefore, diagnostic evaluation to determine whether or not NAFLD would be important in managing patients with breast cancer.

Keywords: Hepatic steatosis index (HSI), NAFLD, Breast cancer, Survival and recurrence

PE-050

Low Skeletal Muscle Mass Is a Novel Risk Factor in Patients with Lean Non-Alcoholic Fatty Liver Disease

Min Kyu Kang, Jung Gil Park

Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, Korea

Aims: Recently, low skeletal muscle mass (LSMM) has emerged as a potential risk factor for non-alcoholic fatty liver disease (NAFLD). However, the association between LSMM and lean NAFLD are not well-known. We investigated the association between LSMM and lean NAFLD in patients with NAFLD.

Methods: Lean-NAFLD was defined as a body mass Index (BMI) ≤ 23 kg/m^2 with NAFLD. Fatty liver was defined using ultrasound and appendicular skeletal muscle mass (ASM) was adjusted by the height^2 using bioelectrical impedance analysis. LSMM was based on 1SD below the sex-specific mean for young healthy adults (cut-off values of 7.0 kg/m^2 for men and 5.8 kg/m^2 for women).

Results: Of 8,905 NAFLD patients, 3,670 (41.2%) were diagnosed with lean NAFLD. Lean NAFLD group were younger (45.0 vs 49.0 years, *P*<0.001), more likely to be women (66.3 vs. 34.2 %, *P*<0.001), had a lower waist circumference (74.0 vs 85.0 cm, *P*<0.001), had lower prevalence of diabetes (3.1 vs. 7.4 %, *P*<0.001), hypertension (4.2 vs. 15.2 %, *P*<0.001), metabolic syndrome (3.7 vs. 17.3%, *P*<0.001), and higher proportion of low skeletal muscle mass (28.0 vs. 2.2%, *P*<0.001) than non-lean NAFLD group. The presence of LSMM was associated with lean NAFLD in patients with NAFLD (odd ratio [OR] = 7.02, *P*<0.001) using stepwise adjusted models for age, sex, diabetes, hypertension, waist circumference, HOMA-IR, alanine aminotrasferase, platelet count, triglyceride, and high sensitivity C-reactive protein.

Adjusted odds ratio of low skeletal muscle mass for lean non-alcoholic fatty liver disease in patients with non-alcoholic fatty liver disease

	Low skeletal muscle mass	
	OR (95% CI)	*P*-value
Total NAFLD population (n =8,905), OR for lean NAFLD		
Unadjusted	17.30 (14.25-21.20)	<0.001
Multivariate model 1	18.86 (15.34-23.40)	<0.001
Multivariate model 2	6.79 (5.20-8.97)	<0.001
Multivariate model 3	6.88 (5.26-9.09)	<0.001
Multivariate model 4	7.02 (5.37-9.28)	<0.001

OR, odds ratio; CI, confidential interval; NAFLD, non-alcoholic fatty liver disease

Low skeletal muscle mass was defined as the appendicular skeletal muscle mass divided by the square of the height (mm^2/m^2) using bioelectrical impedance analysis, with sex-specific cut-off values of <7.0 mm^2/m^2 for men and <5.7 mm^2/m^2 for women.

Model 1 was adjusted for age and sex.

Model 2 was adjusted diabetes, hypertension, and waist circumference inclusive of model 1.

Model 3 was adjusted for presence of insulin resistance, C-reactive protein inclusive of model 2.

Model 4 was adjusted for serum alanine aminotransferase, triglyceride, and platelet count inclusive of model 3.

Conclusions: LSMM may be a potential risk factor for lean NAFLD patients compared with non-lean NAFLD patients independently of classic metabolic factors.

Keywords: Non-alcoholic fatty liver disease, Metabolic factor, Lean, Skeletal muscle mass

PE-051

Effects of Metabolic Syndrome on Developing Cirrhosis in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease: A Preliminary Study Using a Common Data Model

Woo Ram Han[1], Hyun Phil Shin[1,2], Ha Il Kim[1]

[1]Division of Gastroenterology, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Korea; [2]Division of Gastroenterology, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea

Aims: Metabolic syndrome (Met) is associated with progressive liver disease in patients with fatty liver disease. We aimed to assess the effects of each component of metabolic syndrome whether differently affects nonalcoholic fatty liver disease (NAFLD) and alcohol-related fatty liver disease (AFLD).

Methods: We performed a cohort study of standardized Common Data Model data from Kyung Hee University at Gangdong between 2006 and 2013. The incidence and demographic properties were extracted and divided into NAFLD and AFLD. The 4 components of Met were analyzed: type 2 diabetes mellitus, hypertension, dyslipidemia, and Obesity (body mass index [BMI] ≥ 25 kg/m^2). We also analyzed the subgroup that divided into simple steatosis and Met-associated steatosis of the liver. The study outcome defined the occurrence of cirrhosis and primary liver cancer.

Results: We analyzed data from 736 AFLD and 3,436 NAFLD patients. At cohort entry, 323 (42.9%) AFLD and 1,472 (42.8%) NAFLD had no component of Met. From these simple steatosis, 26 (8.0%) AFLD and 101 (7.4%) NAFLD had more than one Met component within 3 years. During the 4.4 and 6.8 median follow up year simple and Met-associated steatosis group, the incidence of cirrhosis was 9/219 (4.1%) and 6/981 (0.6%) for simple AFLD and NAFLD, respectively, and 12/339(3.5%) and 11/1547 (0.7%) for Met-associated AFLD and NAFLD, respectively. In study periods, more than two-thirds of new cirrhosis from the simple steatosis group were newly diagnosed patients with no Met components within 3 years. In addition, all the primary liver cancer cases that of simple steatosis group arose in patients who were not diagnosed Met component within 3 years.

Conclusions: Although the incidence of cirrhosis and primary liver cancer were higher in AFLD than NAFLD, liver-related outcomes could not be accelerated by the component of Met both AFLD and NAFLD in the study period. Liver fibrosis or carcinogenesis for fatty liver disease may not largely depend on Met.

Keywords: Metabolic syndrome, Nonalcoholic fatty liver disease, Alcohol-related fatty liver disease, Cirrhosis, Primary liver cancer, Common data model

PE-052

Clinical Correlation between Coronary Artery Disease and Nonalcoholic Fatty Liver Disease Using Coronary Calcium Scan

Kyoung Min Sohn

Hansol Hospital

Aims: Coronary artery disease (CAD) and nonalcoholic fatty liver disease (NAFLD) are two of the most prevalent diseases in today's developed country. The link between NAFLD and CAD has been explored with coronary angiography and has shown a significant relationship between severe NAFLD and increased cardiovascular disease (CVD) risk. This study aims to determine if positive coronary calcium scan(CCS) that are used to determine CAD severity in asymptomatic populations can help predict the presence of NAFLD.

Methods: Retrospective cross-sectional study of patients from 2018 to 2020 with positive CCS and liver imaging with CT or ultrasound of the abdomen. Patients were excluded if they had consumed greater than 7 or 14 drinks per week for a woman or man respectively or had chronic viral hepatitis. CCS scores and findings of NAFLD were correlated by chi-squared analysis. Age, gender, weight, blood pressure, liver function tests panel, lipid panel, and hemoglobin A1c were extracted and correlated to CAD severity and NAFLD by chi-squared analyses and logistic regression.

Results: 63 patients met inclusion criteria for the study. Median age of 64 years, 68% male, BMI 26.5, and 9% diabetes. CAD severity was not associated with presence of hepatic steatosis

(*P*=0.36). Multivariate logistic regression showed statistically significant findings were between hepatic steatosis, CAD severity, BMI over 28 (*P*=0.02), and diabetes history (*P*=0.01). There were associations between hepatic steatosis and triglycerides over 160 (*P*=0.03) and CAD severity with AST over 45 (*P*=0.02). CAD severity was not statistically significant when compared to gender (*P*=0.12), triglycerides (*P*=0.64), total cholesterol (*P*=0.054), HDL (*P*=0.15), LDL (*P*=0.28), BMI (*P*=0.64), diabetes (*P*=0.91), hypertension (*P*=0.72), ALT (*P*=0.88), ALP (*P*=0.71), and total bilirubin (*P*=0.18). Hepatic steatosis was not statistically significant when compared to gender (*P*=0.88), total cholesterol (*P*=0.42), HDL (*P*=0.42), LDL (*P*=0.35), hypertension (*P*=0.75), AST (*P*=0.65), ALT (*P*=1), ALP (*P*=0.19), and total bilirubin (*P*=0.36).

Conclusions: In patients with CAD detected using a positive CCS, we determined that BMI over 28 and diabetes were markers of increased NAFLD risk. Further prospective studies are needed.

Keywords: NAFLD, CAD, Coronary Calcium scan

PE-053

Association between Non-Alcoholic Fatty Liver Disease and the Risk of Early-Onset Dementia in Middle-Aged Adults: A Nationwide Cohort Study

Gi-Ae Kim,[1] Chi Hyuk Oh,[1] Jung Wook Kim,[1] Su Jin Jung,[2] In-Hwan Oh[2], Jin San Lee[3], Key-Chung Park[3], Jae-Jun Shim[1]

[1]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea; [2]Department of Preventive Medicine, Kyung Hee University School of Medicine, Seoul, Korea; [3]Department of Neurology, Kyung Hee University School of Medicine, Seoul, Korea

Aims: Non-alcoholic fatty liver disease (NAFLD) and early-onset dementia are emerging health burdens among the middle-aged. Given that hepatic steatosis is one of the abnormal fat metabolisms in the body and fat dysregulation in the brain is related to dementia, we aimed to investigate whether NAFLD is associated with the risk of developing early-onset dementia focusing on the middle-aged.

Methods: We conducted a nationwide cohort study involving subjects aged 40 to 64 years who had two or more health checkups provided by the National Health Insurance Service in Korea between January 2004 and December 2007. Based on the hepatic steatosis index (HSI), the subjects were categorized into non-NAFLD (HSI <30 at all health checkups) and NAFLD (HSI > 36 once or more). The development of early-onset dementia, which was defined as dementia with onset before 65 years of age, was assessed using the Diseases Codes and the prescription of any anti-dementia drug until December 2017 or until the age of 65. Cox proportional hazards regression models analyzed the dementia risk of each group.

Results: Of 3,451,801 subjects, 88,293 (2.6%) developed dementia. Compared with the non-NAFLD group, the NAFLD group was associated with a higher risk of dementia (hazard ratio [HR] 1.22; 95% CI 1.20–1.24; *P*<0.001). With the demographic and metabolic factors adjusted, NAFLD showed a strong association with a higher risk of dementia (HR 1.18; 95% CI 1.15–1.20; *P*<0.001). The association between NAFLD and dementia risk was more prominent among females (HR 1.34; 95% CI 1.30–1.38; *P*<0.001). The association between NAFLD and the risk of dementia was stronger among non-obese NAFLD (BMI <25 kg/m^2).

Conclusions: This study showed that NAFLD was associated with an increased risk of early-onset dementia in the middle-aged population. The association between NAFLD and dementia risk was stronger among females and non-obese NAFLD.

Keywords: NAFLD, Dementia, Early-onset, Middle-aged

PE-054

Bariatric Surgery Improved Hepatic Steatosis and Fibrosis in Obese Patients with Non-Alcoholic Fatty Liver Disease

Mu Jin Son, Kwang Il Seo, Sang Uk Lee, Byung Hoon Han, Byung Cheol Yun, Hyun Joon Park

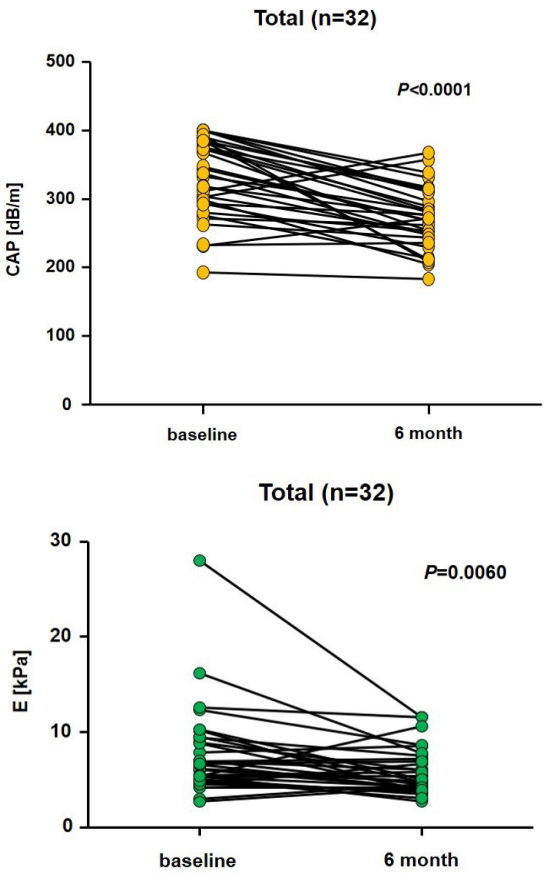
Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Aims: Non-alcoholic fatty liver disease (NAFLD) is an emerging and increasing chronic liver disease able to progress to cirrhosis and hepatocellular carcinoma. The most important and proven treatment strategy of NAFLD is a weight reduction. The purpose of this study is to investigate whether bariatric surgery could improve the hepatic steatosis and fibrosis in obese patients.

Methods: Among the patients who underwent bariatric surgery at the Kosin University Gospel Hospital from January 2019 to June 2020, 83 patients underwent fibroscan before surgery, and 32 patients underwent follow-up fibroscan 6 months after surgery. We compared the result of fibroscan before and after bariatric surgery.

Results: The average age of 32 participants in the study was 37.6 years old, 15 males and 17 females. The average BMI before surgery was 39.3 and BMI after 6 months of surgery was 32.1. Of the 32 participants in the study, 21 underwent sleeve gastrectomy and 11 underwent Roux-en-Y bypass surgery. The average of the controlled attenuation parameter (CAP) score at baseline was 331 (dB/M), and the average of E score was 7.7 (kPa). In 6 months after surgery, the average CAP score was 272 (dB/M) and E score was 5.8 (kPa), which was reduced by 18% and 25% respectively. In 21 patients who received sleeve gastrectomy, the average preoperative CAP score was 331 (dB/M) and E score was 7.7 (kPa). After sleeve gastrectomy, CAP score was 272 (dB/M) and E score was 5.8 (kPa), respectively. In 11 patients who received Roux-en-Y bypass (11 patients), the average preoperative CAP score was 336(dB/M) and E score was 7.8(kPa). After roux-en-Y bypass, CAP score was 271(dB/M) and E score was 5.7(kPa), respectively.

Conclusions: Bariatric surgery has been shown to be effective not only in weight loss but also in improving the hepatic steatosis and fibrosis in obese patients with NAFLD.



Keywords: Bariatric surgery, Non-alcoholic fatty liver disease, Fibroscan, Steatosis, Fibrosis

PE-055

Does Superimposed Fatty Liver Affect Antiviral Response and Incidence of Hepatocellular Carcinoma in Chronic Hepatitis B on Potent Nucleot(s)ide Analogue?

Jaewon Park*, Eun Sun Jang*, Sangmi Jang, Chan Young Jeong, Heaeun Kim, Gwang Hyeon Choi, Jin-Wook Kim, Sook-Hyang Jeong

*These 2 authors contributed equally to this study

Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Aims: In chronic hepatitis B patients (CHB), the effect of superimposed fatty liver is not clear. Thus, we aim to compare virologic response and hepatocellular carcinoma (HCC) incidence between CHB with and without fatty liver detected on ultrasonography or non-contrast CT images.

Methods: We retrospectively enrolled treatment-naïve CHB patients who started entecavir or tenofovir between January 2014 and August 2019 in a tertiary hospital and their virological response within 48 weeks of therapy and HCC development were investigated.

Results: Among 789 CHB patients on entecavir or tenofovir (median age of 48 years, 59% of male), 135 (17.1%) patients had fatty liver. The superimposed fatty liver (FL) group showed significantly younger, higher male proportion, higher body mass index (BMI) with many other metabolic indices and lower proportion of liver cirrhosis than CHB alone group. However, pretreatment HBV DNA level, AST and ALT levels were not different. The complete virologic response rate was significantly lower in FL group (60.9%) than CHB alone group (75.6%), however, presence of FL was not an independent factor for virologic response on the multivariable analysis. During median follow-up of 38 months, 7 patients (5.2%) in FL group and 35 patients (5.4%) in CHB alone group developed HCC. After propensity matching based on age, sex, HBV viral load, hepatitis B e antigen positivity and presence of liver cirrhosis, cumulative HCC incidence was not different between FL group and CHB alone group.

Conclusions: Among CHB, 17% had superimposed FL showing younger age, higher male proportion, higher BMI group and lower proportion of liver cirrhosis than CHB alone group. However, superimposed FL was not an independent factor for either virological response or for HCC development. Further validation study with long term follow-up is warranted.

Keywords: Fatty liver, Chronic hepatitis B, Antiviral response, Hepatocellular carcinoma

PE-056

Development of mHealth Application Based Self-Management Program (SMART-Liver®) for Patients with Non-Alcoholic Fatty Liver Disease

Oh Young Kwon[1], Yeonsoo Jang[1,2*], Mi Kyung Lee[3], Hyerang Kim[4], Hye Won Lee[5], Jae Seung Lee[5]

[1]College of Nursing and the Brain Korea 21 FOUR Project, Yonsei University; [2]Mo-Im Kim Nursing Research Institute, Seoul, Republic of Korea; [3]Department of Sport and Leisure Studies, Yonsei University, Seoul, Republic of Korea; [4]Department of Nursing Science, Howon University, Gunsan, Republic of Korea; [5]Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea

Aims: Self-management for patients with non-alcoholic fatty liver disease (NAFLD) is a key to promote health outcome. The mHealth technologies may offer the potential to provide effective and efficient healthcare to facilitate the self-management behaviors. The SMART-Liver® is the personalized coaching program for changing lifestyles using mHealth. The purpose of this study was to develop the mobile phone application program to improve self-management behaviors for patients with NAFLD.

Methods: This study was designed with methodological research using ADDIE model. The SMART-Liver® was developed by the investigators and consisted of the contents based on NAFLD guidelines and literature reviews. The validity of contents was evaluated using Content Validity Index by 7 clinical experts who were physicians and nurses in Liver center of

Severance hospital, Seoul, Korea. In addition, usability test for SMART-Liver® was evaluated using Health Care Smart Phone Application Evaluation Tool by five patients with NAFLD.

Results: SMART-Liver® consisted of education for NAFLD management, self-monitoring of diet and physical activity, coaching session based on patients' records, and feedback message for 6 months. After initial goal setting with professionals, the app allows participants for self-monitoring of intake records using a food diary logging AI system, and provides feedback message every week. The weekly educational clip such as etiology, diagnosis and treatment, and monthly exercise video are delivered. The investigators analyze compliances and give participants feedback regarding diet, physical activity, and healthy lifestyles every 4 weeks. The primary outcomes are the improvement of BMI, liver fat score, and the level of self-management using NAFLD Self-Management Questionnaire.

Conclusions: This SMART-Liver® was developed to improve self-management with personalized coaching of diet and physical activity using mobile phone application. It may be effective non-pharmacological intervention to achieve health outcomes of patients with NAFLD.

Trial Registration: CRIS registry, KCT0005549, Registered on 29 October 2020.

Keywords: Non-alcoholic fatty liver disease, Self-management, mHealth

PE-057

Correlation of Longitudinal Changes in Hepatic Steatosis with Adiposity after Lifestyle Intervention in Potential Living Liver Donors with Nonalcoholic Fatty Liver

Sunyoung Lee[1], Kyoung Won Kim[2]

[1]Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Korea; [2]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Aims: This study aimed to investigate the relationship of changes in hepatic steatosis (HS) evaluated by liver biopsy with changes in body composition indices assessed by computed tomography (CT) measurements in potential living liver donors with nonalcoholic fatty liver (NAFL), and determine the factors associated with resolution of NAFL after lifestyle intervention.

Methods: This retrospective study included 115 potential living liver donors (mean age, 30.5 ± 7.5 years; 101 men) with NAFL who underwent paired liver biopsies and abdominal CT before and after lifestyle intervention between January 2011 and December 2018. Anthropometry, laboratory parameters, body composition, and HS were evaluated before and after lifestyle intervention.

Results: Anthropometry, laboratory parameters, body composition, and HS were significantly decreased after lifestyle intervention (all, $P<0.001$). Relative changes in HS were significantly correlated with relative changes in visceral fat area (VFA) ($r = 0.278$; $P=0.003$) and SFA ($r = 0.382$; $P<0.001$) but not with body weight, body mass index, or skeletal muscle area. Subjects with resolved NAFL after lifestyle intervention had significantly lower VFA at follow-up than those with persistent NAFL (69.8 ± 39.1 vs. 91.5 ± 41.4 cm^2; $P=0.014$). Multivariable logistic regression analysis demonstrated that VFA (odds ratio, 0.987; 95% confidence interval, 0.981–0.992; $P<0.001$) was an independent factor associated with resolved NAFL after lifestyle intervention.

Conclusions: In potential living liver donors with NAFL, body fat reduction is correlated with a decrease in HS, and VFA is an independent factor associated with resolved NAFL after lifestyle intervention.

Keywords: Hepatic steatosis, Lifestyle intervention, Body composition, Adipose tissue

PE-058

Effect of Herbal Medicines on NFLD in Metabolic syndrome Subjects

Senthil Kumar Subramani[1,2], Pratiba Chauchan[1], Rohit Sharma[2], GBKS Prasad[1*]

[1]Centre for Translational Research, SOS in Biochemistry Jiwaji University, Gwalior, India; [2]Department of Biotechnology, Tropilite Foods Pvt. Ltd, Gwalior, India

Aims: Non-alcoholic fatty liver disease (NAFLD) is the term for a range of conditions caused by a accumulation of fat in the liver. It's usually seen in people who are metabolic syndrome. Herbal medicines have been used in the treatment various disease for a long time in folk system. In the present study, we evaluate some anti-diabetic herbal medicines effect on NAFLD.

Methods: Seventy five subjects those who have MetS were randomly selected from the week end diabetic clinic Health center, Jiwaji University. The subjects have divided in to four groups to evaluate for its antidiabetic activity and hepatotoxicity. Regimen I- Gymnemma sylvester, Regimen II- Triphala, Regimen III Triphala + Gymnemma sylvester for 3 month. Fasting and PP blood glucose and lipid profile (total cholesterol, triglycerides, HDL & LDL cholesterol) liver marker (Bilirubin, SGOT, SGPT) and oxidative stress markers (SOD, Catalase, GSH, TBARS) were also monitored in the study subjects. Paired t-test was made the compare the significance.

Results: Administration of herbal regiments regularly for 3 months resulted in significant reductions of blood glucose ($P<0.001$) and glycosylated hemoglobin levels ($P<0.001$) in all regiments. Lipid function markers level were reduced significantly ($P<0.001$) Also, liver function markers (Bilirubin levels reduced 12.5-15.6 % $P<0.05$, SGOT levels reduced 7.5 - 18.0 % $P<0.05$ and SGPT levels reduced 11.8-17.8% $P<0.05$) and the antioxidant markers were also improved significantly ($P<0.05$).

Conclusions: Herbal medicines for the treatment of NAFLD show the significant improvement in glycemic control and lipid levels. The liver functions improved in MetS subjects. It may be the

due to the anti-oxidant property of the herbal medicine.
Keywords: NAFLD, Herbal medicine, Metabolic syndrome, Liver enzymes

PE-059

The Effect of Non-Fermented and Fermented Soymilk (Glycine max) on Glucose Levels in The Dyslipidemic Rats (Rattus norvegicus) Model

Hilmi Ardian Sudiarto[1], Rafik Prabowo[1], Miranti Dewi Pramaningtyas[1]

[1]Department of Physiology, Faculty of Medicine, Universitas Islam Indonesia

Aims: Dyslipidemia is a metabolic disease that is usually interrelated with other metabolic diseases, such as diabetes. Diabetes can be characterized by increased glucose levels in the blood. There were few studies have compared the effect of non-fermented and fermented soymilk on glucose levels. The purpose of this research is to compare the effect of non-fermented and fermented soymilk on glucose levels of dyslipidemic rats model.
Methods: This study used a quasi-experimental method with pre-test and post-test control group design. This research was conducted in the laboratory of physiology, Universitas Islam Indonesia (UII) for 4 weeks. This research used male Wistar strain rats aged 1-2 months with BW of 100-150 grams. Rats were divided into four groups. All groups were given fed *ad libitum* for 4 weeks. In the first two weeks, first group, third group, and fourth group were given 5 ml/200 gram BW/day quail egg yolks (G1, G3, and G4), while second group was not given the quail egg yolks (G2). In the second two weeks, third group were given 5 ml/200 gram BW/day non fermented soymilk, while fourth group were given 5 ml/200 gram BW/day fermented soymilk. In the end of the research, glucose levels were measured. ANOVA with bonferroni post-hoc test was used in statistical analyzing.
Results: Mean of glucose levels (nmol/gr) were 166,42±2,55 (pre) and 174,43±2,06 (post) for G1; 71,05±1,48 (pre) and 72,15±0,61 (post) for G2, 170,38±1,75 (pre) and 126,50±1,83 (post) for G3, and 168,86±2,20 (pre) and 112,79±1,34 (post) for G4. Statistical analyzing shown that there were significant differences of glucose levels among the groups (P=0.00).
Conclusions: Both non fermented and fermented soymilk had the potency to reduce glucose levels (P=0.00), but fermented soymilk can reduce the glucose level on heart better than non-fermented soymilk.
Keywords: Non-frmented soymilk, Fermented soymilk, Glucose levels, Dyslipidemic rats

8. Liver Cancer

PE-060

Protective Effect of Biofabricated Trianthema Portulacastrum Silver Nanoparticles against Hepatocellular Carcinoma

Ekta Yadav

Shalom Institute of Health and Allied Sciences, SHUATS

Aims: Over the recent years, nanoparticle approach for targeted drug delivery is considered as a promising therapeutic method to improve the potential of antitumor agents. Since *Trianthema portulacastrum* (TP) leaves have been utilized as a strong hepatoprotective in Indian traditional medicinal system. Thus current study was designed to biofabricate, characterize and evaluate protective effect of TP extract mediated silver nanoparticles (AgTPNPs) against diethylnitrosamine (DEN) induced hepatocarcinoma in rat model.
Methods: AgTPNPs were synthesized by co-precipitation method and different characterization techniques confirmed the formation of spherical crystalline nanoparticles with size range of 50-80 nm. Liver damage in rats was induced with a single dose of DEN (200 mg/kg) as well as double dose of phenobarbital. Simultaneously, animals were administered with AgTPNPs at two dose levels (10 and 20 mg/kg p.o.) for 16 weeks. At the end of study, serum biomarkers, hematological status, antioxidants enzymes and proinflammatory cytokines were examined to assess the protective effect of AgTPNPs along with histopathological studies.
Results: DEN significantly induced the hepatocellular carcinoma in each group, which was significantly reversed (P<0.001) by AgTPNPs in a concentration dependent manner. A significant reduction in level of serum hepatic and non-hepatic marker enzymes, oxidative stress and different inflammatory markers via direct and indirect inhibition of NF-kB expression were observed in rats administered with AgTPNPs.
Conclusions: Collectively, results demonstrated that AgTPNPs potentially ameliorated the damaging effects of DEN induced hepatocellular carcinoma and it can be utilized as an effective nano technology based anticancer approach.
Keywords: Trianthema portulacastrum, Diethylnitrosamine

PE-061

Effect of Interleukin-7 on Radiation-Induced Lymphopenia and Its Anti-Tumor Effects in a Mouse Model

Hwa Kyung Byun, Kyoung-Jin Kim, Su Chul Han, Jinsil Seong

Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Aims: Local ionizing radiation (IR) can lead to systemic lympho-

cyte depletion, which is associated with poor survival outcomes in cancer patients. Interleukin-7 (IL-7) plays an important role in lymphocyte homeostasis; however, its role in alleviating radiation-induced lymphopenia remains unclear. Hence, we established a radiation-induced lymphopenia animal model and evaluated the effect of exogenous IL-7 administration.

Methods: C3H/HeN mice underwent X-ray irradiation of 30 Gy in 10 fractions at the right hind limbs. Next, 10 mg/kg of IL-7 was injected subcutaneously, and the lymphocyte count in blood was measured. Murine hepatocellular carcinoma (HCa-1) cells were inoculated subcutaneously into the right thighs of tumor model mice, which underwent the same treatment.

Results: In the naïve mouse model, the decreased CD45+ cell count after irradiation gradually recovered to the initial level over 3 weeks in the IR group, whereas it markedly increased to 373% of the initial level in 1 week in the IR+IL-7 group. Similar trends were observed for the CD3+, CD8+, CD4+, regulatory T cells, and CD19+ B cell counts. Similar findings were observed in the tumor mouse model. CD8+ and CD4+ T cell infiltration in tumor specimens was higher in the IL-7 and IR+IL-7 groups than in the non-treated and IR groups. Tumor growth was significantly more suppressed in the IR+IL-7 group than in the IR group. The median survival time was significantly longer in the IR+IL-7 group (not reached) than in the IR (56 days; *P*=.0382), IL-7 (36 days; *P*=.0004), or non-treated groups (36 days; *P*<.0001).

Conclusions: Administration of exogenous IL-7 after IR not only restored lymphocyte counts but also enhanced the anti-tumor effect. Exogenous IL-7 can be beneficial in overcoming radiation-induced lymphopenia and in enhancing the treatment outcome in combination with radiotherapy, which needs validation through future clinical studies.

Keywords: Radiotherapy, Lymphopenia, Interleukin-7, Hepatocellular carcinoma

PE-062

Intra-Tumoral Lymphocyte Infiltration are Associated with a Low Risk of the Recurrence of Hepatocellular Carcinoma

Sunghwan Yoo[1+], Jin Hong Lim[2+], Hye Young Chang[1], Jung Il Lee, Kwan Sik Lee[1], Hyun Woong Lee[1*], Ji Hae Nahm[3*]

[1]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, [2]Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, [3]Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Aims: In tumor tissues, lymphocyte infiltration provides a local microenvironment for generating anti-tumor cellular and humoral immune responses. It is associated with improved clinical outcomes in most solid tumors investigated to date. We aim to investigate the role of lymphocyte infiltration in tumor tissues to predict the recurrence of hepatocellular carcinoma (HCC).

Methods: Data and samples from 171 patients with HCC treated by surgical resection between Jan 2007 and Dec. 2017 were retrospectively analyzed. By pathological review, the prognostic significance of lymphocyte infiltration in a series of 171 patients with HCC treated by surgical resection in Gangnam Severance Hospital.

Results: Among the 171 patients (136 males, mean age 63.1±10.0 years) who underwent surgical resection, the median clinical follow-up was 6.2 (2.5–13.5) years. The median duration of the recurrence of HCC was 4.1 (1.0–12.9) years. Overall lymphocyte infiltration in tumor tissues was identified in 84% (144/171), with tertiary lymphoid follicles in 5.3% (9/171) of the cases. Univariate and multivariate analyses showed that lymphocyte infiltration in tumor tissues significantly correlated with a lower risk of the recurrence of HCC (hazard ratio 0.831, *P*=0.016).

Conclusions: We have shown that overall lymphocyte infiltration in tumor tissues is associated with a lower risk of the recurrence of HCC in retrospective cohorts of patients with HCC treated by surgical resection.

Keywords: Hepatocellular carcinoma, Lymphocyte, Recurrence, Lymphoid follicle

PE-063

Laparoscopic Liver Resection versus Percutaneous Radiofrequency Ablation for Single Hepatocellular Carcinoma (≤3 cm)

Ji Su Kim[1,2], Dai Hoon Han[1,2], Beom Kyung Kim[2,3], Do Young Kim[2,3], Jin Sub Choi[1,2], Gi Hong Choi[1,2]

[1]Department of Hepatobiliary and Pancreatic Surgery, Yonsei University College of Medicine, Seoul, Korea; [2]Liver Cancer Center, Yonsei Cancer Center, Severance Hospital, Seoul, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

Aims: Laparoscopic liver resection (LLR) and Percutaneous radiofrequency ablation (RFA) are ideal treatment options for single hepatocellular carcinoma (HCC). As laparoscopic technology advances, LLR is now less invasive and safer than RFA comparable. Therefore, this study aims to compare the long-term survival outcomes of the two treatment and to suggest appropriate treatment criteria.

Methods: From 2008 to 2019, a total 345 newly diagnosed patients with single HCC ≤ 3cm underwent RFA or LLR as first-line therapy. A total of 272 patients were analyzed retrospectively, excluding those with a Platelet count less than 100,000.

Results: A total of 123 and 149 patients underwent RFA and LLR, respectively. RFA showed significantly higher marginal recurrence rate than LLR. (22 versus 0, *P*<0.05). LLR has better overall survival (OS) and recurrence free survival (RFS) (*P*<0.05, *P*<0.05). Cox regression analysis found the treatment methods as the unique variable statistically significant for OS and RFS [hazard ratio (HR) 95% confidence interval (CI): 0.122-0.490, *P*<0.05; HR 95% CI: 0.201-0.627, *P*<0.05].

Conclusions: LLR showed better outcomes in overall survival and recurrence free survival. In cases where RFA is difficult to perform or if the possibility of local recurrence is high, it is recommended to consider LLR for single HCC (≤3cm).

Keywords: Hepatocellular carcinoma, Laparoscopic liver resection, Radiofrequency ablation, Hepatectomy, Laparoscopic surgery

PE-064

Clinical Usefulness of 18F-FDG PET in Patients with Hepatocellular Carcinoma Undergoing Surgical Resection

Min Ho SHIN, Nam Kyu CHOI*

Hepatobililiary Pancreas Surgery, Chosun University Hospital, Korea

Aims: the diagnosis and staging hepatocellular carcinoma (HCC) is important because of the different treatment methods and the prognosis. [18F]fludeoxyglucose positron emission tomography/computed tomography([18F]FDG-PET/CT) has been suggested as a diagnostic modality in HCC. The aim of this study is to evaluate the accuracy of [18F]FDG-PET for staging of HCC after surgical resection and histological confirmation.

Methods: We retrospectively collected data of 56 patients who underwent [18F]FDG-PET before surgical resection for HCC from March 2011 to May 2017. All of whom were suitable for resection by conventional HCC staging. The results of Maximal standardized uptake value (SUVmax) was compared with histological confirmation

Results: A larger tumor size was related with a higher SUV (≥4.9) and also serum alpha-feto protein was associated with SUV. The recurrence rate was higher in patients with a higher SUV and the patients with lower SUV had better survival rate

Conclusions: hepatocellular carcinoma, [18F]fludeoxyglucose positron emission tomography, standardized uptake value (SUV).

PE-065

Impact of the Prognostic Nutritional Index on the Recurrence of Hepatocellular Carcinoma Patients after Curative Resection

Kil Hwan KIM, Sanghyun SONG*, Sungho JO

Department of Surgery, Dankook University Hospital, Dankook University College of Medicine, Korea

Aims: The purpose of this retrospective study was to determine the association between the prognostic nutritional index (PNI) and recurrence of hepatocellular carcinoma after curative resection.

Methods: Between 2007 to 2019, 130 patients who underwent curative hepatectomy for hepatocellular carcinoma were enrolled. The PNI was calculated, and the cutoff value was identified through receiver operating characteristic curve analysis. According to the PNI, patients were divided into two groups. Univariate and multivariate analyses were performed to identify independent risk factors for recurrence.

Results: The cutoff value of the PNI was 52. In the univariate analysis, alcoholic liver cirrhosis (P=0.041), protein induced by vitamin K antagonist-II ≥ 200 (P=0.012), indocyanine green retention test (ICG R15) >10% (P=0.001), estimated blood loss ≥ 800 mL (P=0.037), tumor size (P=0.001), microvascular invasion (P=0.023), T-stage (P=0.001), and PNI < 52 (P=0.001) affected recurrence. In the multivariate analysis, alcoholic liver cirrhosis (P=0.046), ICG R15 >10% (P=0.025), T-stage (P=0.003), and PNI < 52 (P=0.046) were independent prognostic factors for disease-free survival.

Conclusions: The PNI, a nutritional and immunologic factor, is an independent prognostic factor that can predict the recurrence of hepatocellular carcinoma in patients undergoing curative resection.

PE-066

Prevalence of Live Cancer in Indonesia: A Cross Sectional Population-Basic Health Center (2011-2019)

Citra SUARDI[1], Indra SUARDI[2]

[1]Computer Science, Universitas Muslim Indonesia, Indonesia; [2]Midwifery, Universitas Hasanuddin, Indonesia

Aims: Liver-Cancer is one of the health problems in Indonesia and one of the most killers for everyone in Indonesia. The prevalence of Liver-Cancer in Indonesia is still high and has an increase. Impact of Liver Cancer is a public health problem. Many people in Indonesia suffer from liver-cancer due to a lack of awareness of the symptoms of early detection so that cancer becomes malignant and ultimately causes death. In the later stages of liver-cancer can spread to other breasts, as well as to other body organs, such as blood vessels, lymph nodes.

Methods: The data used are secondary data from Basic Health Research since 2011 until 2019. This research is an observational study using a cross sectional design. Samples were taken from Indonesian people spread throughout Indonesia.

Results: Based on data collected from the Indonesian Ministry of Health, in 2011 cancer-related deaths totaled 2433 cases where liver-cancer became the-second number of-cancer that occurred in Indonesia. The GLOBOCAN, in 2012 liver cancer patients in Indonesia were 19,4%. In 2015, 263,000 deaths from liver cancer were caused by hepatitis B. Until 2019, the Ministry of Health Republic of-Indonesia showed the most common cancer case in-Indonesia ware liver cancer at 12.4/100,000 population with an average death rate of 7.6/100,000 population.

Conclusions: Although the prevalence of liver-cancer has experienced and decreased, based on data obtained shows liver cancer has been the second-of-biggest cause of-death of-cancer-sufferers in Indonesia. Public health intervention is urgently needed to improve diagnosis, treatment, and early detection of-liver-cancer in-Indonesia.

PE-067

Preemptive Therapy for Hepatic Regenerative and Dysplastic Nodules and its Clinical Implications in Patients with Liver Cirrhosis

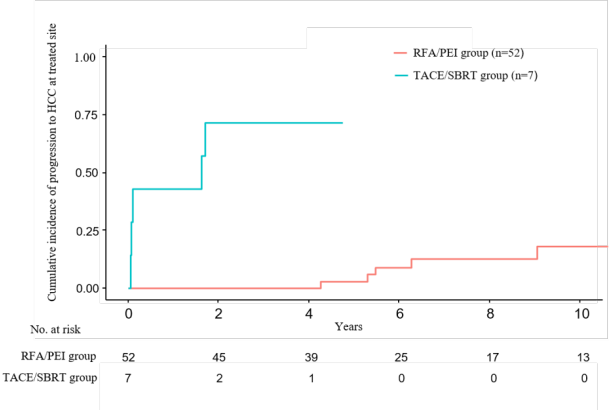
Ji Yoon Kim[1], Ji Hye Lim[1], Hyo Jeong Kang[2], Ju Hyun Shim[1]

[1]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: Clinical and molecular studies have demonstrated that hepatic regenerative nodules (RNs) and dysplastic nodules (DNs) are potential precursors of hepatocellular carcinoma (HCC). We aimed to evaluate long-term outcomes and practical impacts of RNs/DNs treated using locoregional approaches in cirrhotic patients.

Methods: This study included 59 biopsy-proven hepatic RNs or DNs in 59 cirrhotic patients, which were treated with radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), or stereotactic body radiation therapy (SBRT). We examined the development of HCC at the treated site, and explored clinical, pathological, and radiological factors related to the de novo events.

Results: Additional hepatic nodules other than a biopsied RN or DN were noted in 27 patients, among whom two had an intrahepatic HCC lesion concurrent with a high-grade DN. Of 59 hepatic nodules, 43, 14, and 2 was pathologically confirmed as high-grade DNs, low-grade DNs, and RNs, respectively. There were 48 nodules treated with RFA, 4 with PEI, 6 with TACE, and one with SBRT. The median diameter of the included nodules was 1.7 cm (range 1.4-2.0 cm), and 16 nodules (27.1%) showed arterial enhancement in CT scans. During the median follow-up of 6.4 years, de novo HCCs occurred at treated sites of the target nodule in 11 patients. Time-to-progression to HCC at the treated site was significantly longer in the RFA/PEI group, compared with the TACE/SBRT group (0% vs. 42.9% at 1 year; and 0% vs. 71.4% at 3 years, $P<0.001$: Figure 1). Multivariate cox analysis revealed that both RFA/PEI treatment and smaller size of nodules were independent predictors for a decreased risk of progression to HCC at the treated site of RNs/DNs (Ps<0.05), as was neither pathologic grade nor arterial phase enhancement.



Conclusions: We identified that preemptive ablation of hepatic RNs/DNs could effectively reduce the risk of malignant transformation in cirrhotic patients.

Keywords: Dysplastic nodule, Regenerative nodule, Radiofrequency ablation

PE-068

The Impact of Ultrasonographic Blind Spots on Detecting Early-Stage Hepatocellular Carcinoma during Surveillance

Joo hyang Chun, Hyun Phil Shin, Ha Il Kim

Kyung Hee University Hospital at Gangdong, Seoul, South Korea

Aims: Abdominal ultrasonography (US) is the backbone of hepatocellular carcinoma (HCC) surveillance. Although previous studies have evaluated clinical factors related to surveillance failure, there have been no studies on US blind spots *per se*.

Methods: We included 706 patients who underwent 6 months intervals surveillance using US and a serum alpha-fetoprotein (AFP) and eventually diagnosed with single nodular HCC. Patients were divided into two groups: US-detected group (HCC detected by US; n=484) and US-missed group (HCC detected by AFP only; n=222). "Blind spots" were comprised of four locations, including hepatic dome, caudate lobe or around inferior vena cava, beneath ribs <1 cm, and the surface of the left lateral segment.

Results: The proportion of HCCs in blind spots was higher in the US-missed group than in the US-detected group (64.0% vs. 37.8%, *P<0.001). The proportion of HCCs ≥ 2 cm detected in blind spots was higher than that in non-blind areas (10.6% vs. 26.9%, P*<0.001). The US-detected group underwent more radiofrequency ablation; otherwise, hepatectomy was performed more frequently in the US-missed group. Patients with an HCC in a blind spot in the US-detected group had better overall survival than those in the US-missed group (*P*=0.036).

Conclusions: In the current surveillance test, US blind spots affect the size of the detected HCC, even in early stages. Although the AFP test is important for detecting HCC in blind spots, it has limited efficiency in detecting HCCs <2 cm. HCC surveillance needs to be individualized when focusing on the early detection.

Keywords: Hepatocellular carcinoma, Surveillance, Ultrasonography, Blind spot, Treatment, Survival

PE-069

Clinical Characteristics of Hepatocellular Carcinoma in Patients with Inactive Chronic Hepatitis B

Gi-Ae Kim, Chi Hyuck Oh, Jae-Jun Shim

Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea

Aims: The risk of hepatocellular carcinoma (HCC) development is relatively low in patients with inactive chronic hepatitis B

(CHB). However, a large number of patients with inactive CHB are expected to significantly contribute to the development of HCC in the country. Moreover, those with inactive CHB might be likely to consider their disease as more favorable and neglect follow-up than the others. This behavior might be associated with delayed diagnosis and poorer outcomes. We investigated clinical characteristics and diagnosis process of new HCCs in patients with inactive CHB.

Methods: From January 2015 to February 2020, newly diagnosed HCC patients with CHB were retrospectively reviewed. Inactive CHB was defined as HBsAg positive, HBeAg negative, serum HBV DNA titer less than 2,000 IU/mL, and no concurrent use of antiviral agents.

Results: A total of 48 patients with HBV-related HCC were enrolled and 16 of them (33.3%) were inactive CHB at the time of diagnosis of HCC. Their mean age was 59.9 years old and 15 of them (93.8%) were male. Interestingly, 10 patients (62.5%) were non-cirrhotic. The majority of patients were aware of their infection and 14 patients knew they had been inactive hepatitis for a long time. Those who were compliant to regular medical follow-up were only two (12.5%) and their tumor stages were all very early ones. Six of the patients (37.5%) visited a hospital due to any symptoms and most of them were diagnosed as far advanced stages. A half of them were found to have HCC incidentally. Portal vein tumor thrombosis or extrahepatic metastasis were found in 7 patients (43.8%) at the time of diagnosis.

Conclusions: Among newly diagnosed HBV-related HCC, 1 out of 3 cases developed during inactive phase. Most of them were not compliant to regular follow-up and about half of them were diagnosed very lately. More innovative and cost-effective approaches are needed to detect HCCs at an earlier stage for many unmotivated patients with inactive CHB.

Keywords: Chronic hepatitis B, Inactive phase, Hepatocellular carcinoma

PE-070

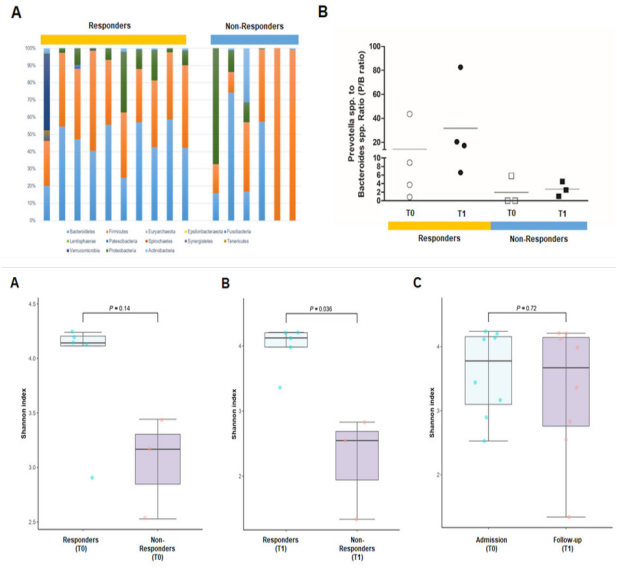
Gut Microbiome as a Prognostic Factor for Nivolumab Treatment in Advanced Hepatocellular Carcinoma Patients

Min-Woo Chung, Ji-Yun Hong, Jae Hyun Yoon, Dae Seong Myung, Sung Bum Cho, Wan Sik Lee, Young-Eun Joo, Sung Kyu Choi

Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

Aims: Immunotherapy has revolutionized the clinical outcomes of intractable cancer patients. Little is known about the intestinal nonpathogenic bacterial composition of hepatocellular carcinoma (HCC) patients treated by immunotherapy. We aimed to determine whether there is a correlation between gut bacterial composition and prognosis in HCC patients.

Methods: We prospectively collected fecal samples and examined the gut microbiome of nine advanced HCC patients treated with nivolumab. Metagenomic data from 16S rRNA sequencing were analyzed using CLC Genomics Workbench. Microbiome data were analyzed according to therapeutic response.



Results: Significant differences were observed in the diversity and composition of the gut microbiome between responders and non-responders. There was no significant difference in the diversity or composition of the patient gut microbiome according to the immunotherapy used. *Dialister pneumosintes, Escherichia coli, Lactobacillus reteri, Streptococcus mutans, Enterococcus faecium, Streptococcus gordonii, Veillonella atypica, Granulicatella* sp. and *Trchuris trichiura* were specific to non-responders, while *Citrobacter freundii, Azospirillum* sp. and *Enterococcus durans* were specific to responders. Of note, a skewed *Firmicutes/ Bacteroidetes* ratio and the low *Prevotella/ Bacteroides* ratio can serve as predictive markers of non-response, whereas the presence of *Akkermansia* species predicts a response.

Conclusions: Our study suggests a potential role for the gut microbiome as a prognostic marker of the response to nivolumab in the treatment of HCC patients.

Keywords: Microbiome, Hepatocellular carcinoma, Nivolumab, Microbiota

PE-071

Cause of Death and Cause-Specific Mortality in Primary Liver Cancer: Temporal Trends in a Hepatitis B Virus Endemic Area

Bo Hyun Kim[1,2], Dahhay Lee[1], Kyu-Won Jung[3], Young-Joo Won[1,3], Hyunsoon Cho[1,3]

[1]Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Republic of Korea; [2]Division of Gastroenterology, Department of Internal Medicine, Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang-si, Republic of Korea; [3]Division of Cancer

Registration and Surveillance, National Cancer Control Institute, National Cancer Center, Goyang, Republic of Korea

Aims: Causes of death in liver cancer patients have not been studied in detail. We aimed to investigate the causes of death and cause-specific mortality trends in primary liver cancer patients.
Methods: Causes of death and proportionate mortalities in liver cancer patients diagnosed from 2000–2016 were investigated using a retrospective cohort from nationwide cancer registry data (n=231,338). Risks of non-cancer deaths relative to the general population were compared by standardized mortality ratios (SMR). The 5-year probabilities of death were estimated under the competing risks.
Results: Of the total, 179,921 patients died. Among the deaths, 92.4%, 1.7%, and 6.0% died of primary liver cancer, cancer from other sites, and non-cancer illnesses. Proportionate mortality from liver cancer persisted high. The five-year probability of death attributed to liver cancer varied by tumor stage from 42% to 94% and remained high after ten years post-diagnosis. Mortality from other causes has continuously increased from 3.3% in 2002 to 11.7% in 2016. The most common causes of non-cancer death were liver disease (34.5%) and viral hepatitis (10.7%). Relative to the Korean general population, mortality risks due to liver disease (SMR=15.6, 95%CI: 15.1,16.1) and viral hepatitis (SMR=46.5, 95%CI: 43.9,49.2) were higher in liver cancer patients. Meanwhile, mortality risks due to suicide were also higher (SMR=2.6, 95%CI: 2.4, 2.8), suggesting an additional need for psychological support for these patients.
Conclusions: Patients with liver cancer are most likely to die from liver cancer even ten years after the diagnosis. These findings highlight a need for specialized long-term follow-up care for patients with liver cancer.
Keywords: Liver cancer, Mortality, Cause of death

PE-072

The Comparison of Effectiveness of Percutaneous RFA and Laparoscopic RFA on Recurrence-Free and Overall Survival in Patients with Hepatocellular Carcinoma

Hong Jae Jeon, Seok Hyun Kim, Hyuk Soo Eun, Eaum Seok Lee, Byung Seok Lee

Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine

Aims: Laparoscopic radiofrequency ablation (LRFA) has several advantages over percutaneous radiofrequency ablation (PRFA) for the treatment of patients with hepatocellular carcinoma (HCC) eligible for RFA. However, there are limited date on the difference in survival outcomes between patients who underwent LRFA and PRFA. We aimed to determine whether RFA method influence recurrence-free and overall survival rate in patients with HCC.
Methods: Patients who underwent LRFA or PRFA for the treatment of HCC between April 2005 and August 2020 were enrolled retrospectively in this study. The recurrence-free and overall survival rate were examined for and compared between two RFA procedure groups in total and newly diagnosed HCC patients. Inverse probability of treatment weighting (IPTW) was performed to reduce the impact of the potential confounding factors and treatment-selection bias.

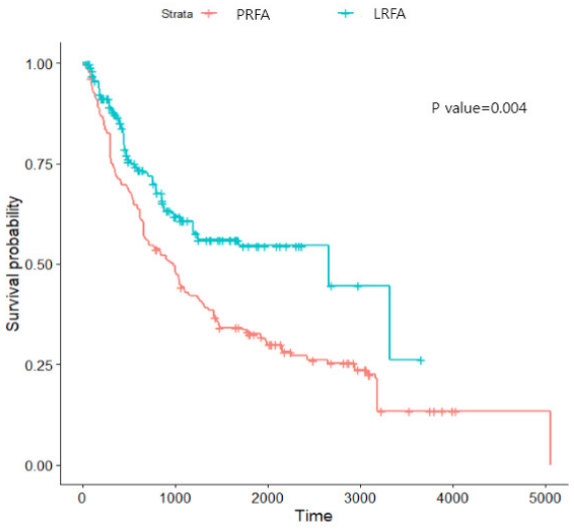


Figure 1. Survival curves comparing the cumulative recurrence-free survival rates in patients newly diagnosed with HCC who received percutaneous radiofrequency ablation (PRFA) versus those who received laparoscopic radiofrequency ablation (LRFA) for hepatocellular carcinoma.

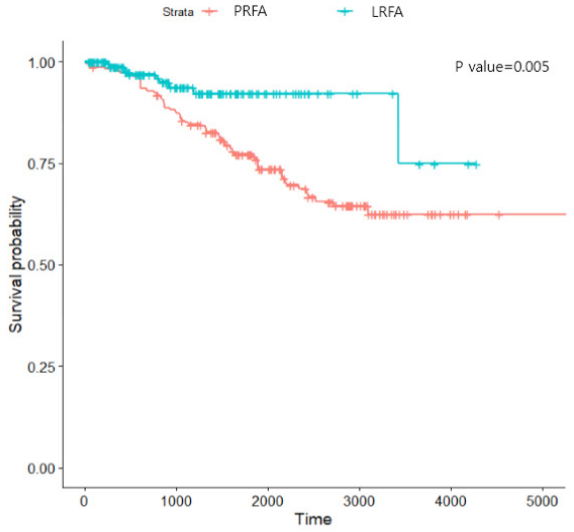


Figure 2. Survival curves comparing the cumulative overall survival in patients newly diagnosed with HCC who received percutaneous radiofrequency ablation (PRFA) versus those who received laparoscopic radiofrequency ablation (LRFA) for hepatocellular carcinoma.

Results: LRFA group showed higher proportion of male and cirrhotic patients, more tumors, and more advanced TNM stage. Univariate and multivariate analysis showed that LRFA was associated with improved recurrence-free and overall survival

rate in total HCC patients compared to PRFA. Among patients who underwent RFA as the primary therapy, LRFA group also showed superior survival outcomes compared to PRFA group. After IPTW, LRFA remained a significant factor for improved recurrence-free and overall survival.

Conclusions: LRFA seemed to be superior to PRFA for the treatment of HCC in terms of survival outcomes. Our result shows that LRFA should be considered the primary therapy in patients with HCC eligible for RFA. Well-designed, multi-centered, randomized controlled trials are required to confirm this result.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Recurrence-free survival rate, Overall survival rate

PE-073

The Predictive Value of Enhanced Liver Fibrosis (ELF) Score for the Patient with Hepatocellular Carcinoma after Liver Resection

Munseok CHOI[1,2], Alshandder Marei HUSSEIN[3], Dai Hoon HAN[1], Gi Hong CHOI[1], Jin Sub CHOI[1]

[1]Department of Surgery, Yonsei University College of Medicine, Severance Hospital, Seoul, Korea; [2]Department of Surgery, Yonsei University College of Medicine, Yongin Severance Hospital, Yongin-si, Korea; [3]Department of Surgery, King Khalid University, Saudi Arabia

Aims: The enhanced liver fibrosis (ELF) score is and extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) having good correlations with fibrosis stages in chronic liver disease. This study aimed to figure out the predictive value of ELF score for the hepatocellular carcinoma (HCC) patients having liver resection

Methods: From April 2015 to July 2020, preoperative ELF score was collected for 127 patients with HCC having curative liver resection. The patients were grouped according to ELF score as 11 and perioperative outcome was compared between two groups: high ELF (HELF, n=22) Vs low ELF (LELF, n=105). Perioperative prognostic factors were analyzed for disease-free survival after liver resection.

Results: HELF had significantly higher liver stiffness by transient elastography (8.7 ± 4.0 Vs 23.4 ± 16.4 Kpa, *P*=0.001), and higher perioperative transfusion (3.8 Vs 22.7%, *P*=0.007). Disease-free survival rates of HELF was significantly poor comparing LELF group. Tumor size more than 5cm(HR 3.559 (1.487~8.518), *P*=0.004), and HELF (HR 2.745 (1.063-7.083), *P*=0037) were the significantly poor risk factors for disease-free survival on multivariate analysis.

Conclusions: Higher ELF score may be correlated with poor liver condition correlating liver fibrosis. Moreover, ELF score was the significant prognostic factor for disease-free survival for the patient having HCC after liver resection.

Keywords: ELF, HCC, Elastography

PE-074

Role of Interleukin-7 in the Development of and Recovery from Radiation-Induced Lymphopenia: A Post-Hoc Analysis of a Prospective Cohort

Hwa Kyung Byun[1], Seung Yeun Chung[1,2], Kyoung-Jin Kim[1], Jinsil Seong[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [2]Department of Radiation Oncology, Ajou University Medical Center, Suwon, South Korea

Aims: Radiation-induced lymphopenia is associated with worse outcomes in solid tumors. We assessed the impact of interleukin-7 (IL-7), a key cytokine in lymphocyte homeostasis, on radiation-induced lymphopenia.

Methods: A post-hoc analysis was performed in a prospective cohort of 98 patients with hepatocellular carcinoma who were treated with radiotherapy in 2016–2018. Blood IL-7 levels were assayed before and at the end of radiotherapy. Acute severe lymphopenia (ASL) was defined as a total lymphocyte count of <200/μL during radiotherapy. Cox and logistic regression analyses were performed to identify predictors of survival and ASL development, respectively.

Results: Patients with ASL (n=41) had significantly poorer overall survival than those without (12.0 *vs.* 25.3 months; *P*=0.001). Patients with lymphocyte recovery showed significantly longer overall survival than those without (21.8 *vs.* 10.3 months; *P*=0.042). ASL was an independent predictor of poor survival (hazard ratio: 2.07; *P*=0.015). Patients with ASL had significantly lower pre-radiotherapy IL-7 levels (2.07 *vs.* 3.01 pg/mL; *P*=0.010). A high pre-radiotherapy IL-7 level was an independent predictor of a reduced risk of ASL development (hazard ratio: 0.40; *P*=0.004). IL-7 levels reflected a feedback response to ASL, with a higher ΔIL-7 in patients with ASL and a lower ΔIL-7 in those without ASL (0.48 *vs.* -0.66 pg/mL; *P*<0.001). Post-radiotherapy IL-7 levels were significantly positively correlated with the total lymphocyte counts at 2 months.

Conclusions: IL-7 is associated with the development of and recovery from ASL, which may impact survival. To overcome radiation-induced lymphopenia, a novel strategy using IL-7 may be considered.

Keywords: Radiotherapy, Lymphopenia, Interleukin-7, Hepatocellular carcinoma

PE-075

Multi-Institutional Retrospective Study on Effectivenss of Radiotherapy for Hepatocellular Carcinoma in the Caudate Lobe

Sung Uk Lee[1], Sang Min Yoon[2], Jason Chia-Hsien Cheng[3], Tae Hyun Kim[1,4], Bo Hyun Kim[4], Jin-hong Park[2], Jinhong Jung[2], Chiao-Ling Tsai[3], Yun Chiang[3], Joong-Won Park[4]

[1]Center for Proton Therapy, National Cancer Center, Goyang, Republic

of Korea; [2]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [4]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea

Aims: No studies evaluating the clinical outcomes of radiotherapy (RT) for hepatocellular carcinoma (HCC) in the caudate lobe have been available to date. The purpose of this study was to evaluate the effectiveness and safety of RT for HCC in the caudate lobe.
Methods: Seventy patients with HCC in the caudate lobe treated with RT from a multi-institutional database were included in this study. The median equivalent dose in 2 Gy (EQD2) was 80.0 Gy_{10} (range, 31.3 – 99.3), and freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS) rates were evaluated.
Results: The median time of follow-up was 47.9 months (range, 3.4 – 127), and the 5-year FFLP, PFS, and OS rates were 80.6% (95% confidence interval [CI], 70.8 – 91.8), 13.8% (95% CI, 7.5 – 25.4), and 51.3% (95% CI, 39.9 – 66.1), respectively. In the multivariate analysis, the radiation dose was significantly associated with the FFLP rate (hazard ratio [HR], 0.57 per 10 Gy_{10} increase, *P*=0.001), and the status of FFLP was significantly associated with OS (HR, 2.694, *P=0.014). The overall rate of ≥grade 3 adverse events was 5.7% (4 of 70), and RT-related mortality was not observed.*
Conclusions: RT for HCC in the caudate lobe showed promising FFLP and OS rates with safe toxicity profiles. These findings suggest that RT may be a promising treatment option for HCC in the caudate lobe.
Keywords: Hepatocellular carcinoma, Caudate lobe, Freedom from local progression rate, Radiotherapy

PE-076

Comparison of Hepatocellular Carcinoma Development in Patients with Liver Cirrhosis Based on Glucose Control Status

Jae Won Song[1,2], Hye Won Lee[1-3], Jae Seung Lee[1-3], Beom Kyung Kim[1-3], Seung Up Kim[1-3], Jun Yong Park[1-3], Sang Hoon Ahn[1-3], Do Young Kim[1-3]

[1]Department of Internal Medicine, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Yonsei Liver center, Severance Hospital, Seoul, Republic of Korea

Aims: Diabetes mellitus (DM) is a risk factor for hepatocellular carcinoma (HCC). However, it remains unclear whether glucose control status affects the prevalence of HCC among patients with DM, especially those with liver cirrhosis. We investigated the relationship between glucose control status and the risk of HCC development in patients with liver cirrhosis.
Methods: We retrospectively screened patients with liver cirrhosis and chronic hepatitis B virus infections who received antiviral therapy between 2006 and 2015. Patients were divided into three groups: those with well-controlled, poorly controlled, and no DM. We compared the HCC incidences of the groups and those of liver-related events reflecting hepatic decompensation.
Results: A total of 2,186 patients were ultimately included. Of these, 413 developed HCC, including 90 (25.7%), 33 (25.9%), and 290 (16.9%) in the well-controlled, poorly controlled, and no DM groups, respectively. Patients with diabetes exhibited a higher prevalence of HCC. However, there were no significant differences between the well-controlled and poorly controlled groups. Liver-related events occurred in 262 cases, including 59 (16.8%), 25 (20.4%), and 177 (10.4%) of the respective groups. (*P*<0.0001)
Conclusions: DM is a risk factor for HCC and liver decompensation in patients with liver cirrhosis. However, glucose control status did not directly affect HCC development or liver decompensation. Further investigation is needed to determine the long-term outcomes of, and risk factors for, diabetic individuals.
Keywords: Diabetes mellitus, Glucose control status, Hepatocellular carcinoma, Decompensation

PE-077

Liver-Directed Concurrent Chemoradiotherapy versus Sorafenib for BCLC Stage C Hepatocellular Carcinoma

Jina Kim, Tae Hyung Kim, Hwa Kyung Byun, Jinsil Seong

Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Although the Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC) is a heterogeneous disease entity, current guidelines recommend a uniform treatment of Sorafenib. In this study, we investigated the efficacy of concurrent chemoradiotherapy (CCRT) compared to Sorafenib in liver-confined BCLC C HCC patients presenting portal vein tumor thrombus (PVTT).
Methods: In total, 409 patients treated with Sorafenib and 637 patients treated with CCRT in 2005-2016 were reviewed. Patients with extrahepatic disease or without PVTT were excluded, resulting in 28 patients in the Sorafenib group and 448 patients in the CCRT group. Propensity score matching (PSM) was performed to minimize the difference between treatment groups. The Kaplan-Meier method was used to calculated overall survival (OS) and Cox proportional hazard model was utilized for multivariate analysis.
Results: Median follow-up duration was 73 months (ranges, 11-110). There were significant differences in PVTT type and disease extent between the treatment groups. PSM was performed according to the following factors: age, tumor size, PVTT type, and disease extent. A total of 27 patients from the Sorafenib group and 52 patients from the CCRT group were matched. After PSM, median OS was 4.0 and 8.7 months for the Sorafenib group and for the CCRT group, respectively (*P*=0.001). Cox proportional hazard model showed that CCRT

was a significant prognostic factor. Five patients (1 from the Sorafenib group and 4 from the CCRT group) were long term survivors (median OS 79.0 months), and all of them received surgical treatment of either liver transplantation or liver resection. Of the 4 patients who received CCRT followed by surgical treatment, 2 patients showed total necrotic tumor and the other 2 patients showed 95% tumor necrosis.

Conclusions: CCRT is an effective treatment option for HCC patients with PVTT. CCRT can serve as a bridge to surgical treatment, leading to prolonged survival.

Keywords: Hepatocellular carcinoma, Portal vein tumor thrombus, Concurrent chemoradiotherapy, Sorafenib, Prognostic factors

PE-078

Therapeutic Benefit and Biological Assessment of Avicularin as Potential Anticancer Agents for the Treatment of Hepatocellular and Gastric Carcinoma: an Phytotherapeutic Approach

Dinesh Kumar PATEL, Kanika PATEL

Faculty of Health Sciences, SHUATS, Payagraj, 211008, India

Aims: Flavonoidal class chemicals are one of the main plant based chemical and avicularin is a flavonoidal class chemical which have been well known for their biological potential to treat rheumatoid

Methods: In order to know the therapeutic benefit of avicularin in the treatment of various types of cancerous disorders, different scientific databases have been searched to collect all the needed information of avicularin for their huge potential against cancers. All the data's have been evaluated statistically for their anticancer potential with various models. Further it has also been considered as a potent anticancer agent, but molecular mechanism of action of avicularin on tubulin has been not investigated properly. So in the present study scientific database analysis of avicularin has been done to know the molecular mechanistic study of avicularin for the treatment of hepatocellular and gastric carcinoma.

Results: From the data analysis of various scientific researches work it was found that avicularin has anti-inflammatory, hepatoprotective, anti-allergic, anti-oxidant, and anti-tumor activities. Avicularin has positive influence on human hepatocellular carcinoma and gastric cancer. Medicinal importance of avicularin in different form of cancers has been also investigated through scientific data analysis. Data analysis of various molecular scientific research works describe the medicinal importance of avicularin in the medicine which could be used for the treatment of hepatocellular and gastric carcinoma which support the anticancer potential of avicularin for the treatment of hepatocellular and gastric carcinoma.

Conclusions: Scientific research work data analysis describes the recent developments in the health promoting properties of avicularin in cancerous disorders treatment.

PE-079

The Effect of Leaf of Buas – Buas (premna pubescens blume) Extract towards The Premalignancy Degree of Rats Liver Cancer Induced

Qurais Syihab[1], Jumriani Jumriani[2]

[1]Department of Veterinary Medicine, Airlangga University Surabaya; [2]Department of Public Health, Institute of health Sciences Bina Bangsa Majene

Aims: The liver cancer rank as the fifth most common cancer and approximately 694.000 deaths caused by liver cancer, so that liver cancer ranks third in the world as a cause of death.7,12 DMBA can be used to induce liver cancer in rats. Buas-buas (*Premna pubescens Blume*) is one of the traditional crops that are cytotoxicity against some types of cancer cells and has been widely used as anticancer. This study aims to look at the effect of Buas-buas (*Premna pubescens Blume*) leaf extract supplements against the premalignancy degree of rat liver cancer induced with 7,12 DMBA.

Methods: Experimental research using post test only with control group design was carried out ten strains of Sprague Dawley rats which were divide into two groups. Group 1 and group 2 were given intra gastric 7,12 DMBA twice a week with dose of 20 mg/kgBW for 5 weeks. Group 2, after induction is completed, were given Annona muricata leaf extract dose of 200 mg/kgBW through a gastricsonde every day for 8 weeks. At the end of the treatment, liver tissue retrieval was performed and histopathologic preparations were made and then the microscopic evaluation was performed on the histopathological picture of the liver tissue.

Results: The result was Histopathological observation indicated a change in the precancerous stage in both groups, on the first group an image of 57,8% mild premalignancy was obtained, while the second group 28,9% mild premalignancy was acquired. The results showed histopathological picture of the liver tissue group2 (treatment) differed significantly with the control group (Mann-Whitney *P*=0,005)

Conclusions: There is influence of supplementation with Buas-buas (*Premna pubescens Blume*) leaf extract towards premalignancy degrees of rat liver cancer induced with 7,12 DMBA

Keywords: Buas – Buas (premna pubescens blume) leaf extract, Liver Cancer, 7,12 DMBA

PE-080

Computational Interactions Study of Marine Organisms's Metabolites with Drug Target Kinase of Hepatocellular Carcinoma

Chakresh Kumar Jain

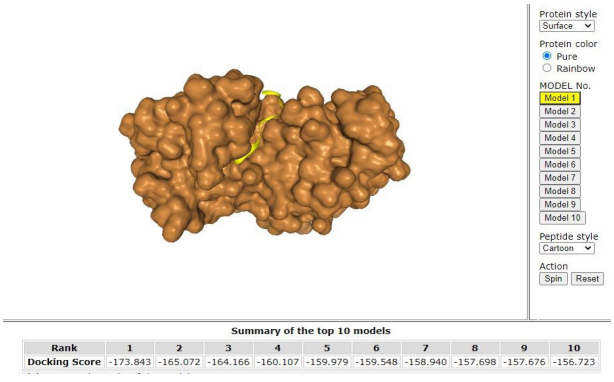
Department of Biotechology, Jaypee Institute of Information Technology NOIDA UP INDIA

Aims: Hepatocellular carcinoma (HCC), is the most common type of liver cancer and causing the high mortality rate referring the third ranking cause of death worldwide. Though there are several drug targets but Oftenly kinsase inhibitors such as Sorafenib and Lenvatinib (chemotherapeutics agents) quit commonly prescribed drugs but facing the side effects such as fatigue, loss of appetite, high blood pressure, weight loss, diarrhea, and abdominal (belly) pain etc. Therefore there is the need to find some better therapeutics agents. Peptide therapeutics provide the new dimension in the disease care. Natural peptide are comparatively less immunogenic and found to be stable could be the possible drug agent against many drug target currently many drug target are exhibiting the drug resistance or side effects for many known drugs .this raises an urgent need to investigate the new therapy. The hypothesis refers as How marine peptide therapeutics can be the new way for HCC treatment with minimal side effect

Methods: The drug target kinase (PDB ID: 3HEG.pdb) of Hepatocellular carcinoma (HCC) has been downloaded from www.rcsb.org. The peptidesequence GFFALIPGIE of Pardaxin 1 which is released by red sea fish *P. marmoratas* and *P. pavoninus* release to repel the sharks has been downloaded from uniprot (https://www.uniprot.org/uniprot/P81863). this peptide has been reported to exhibits as alpha-helical cationic anticancer potential therefore it is of great importance. Preforming the computational interaction (docking through online tool HPEPDOCK server (http://huanglab.phys.hust.edu.cn/hpepdock/.)

Results: The docking score : -173.843 of drug target -marine paptide obtained from HPEPDOCK server (http://huanglab.phys.hust.edu.cn/hpepdock/.) which is based on blind docking.

Conclusions: The peptide pardaxin 1 produced in red sea sole which is a alpha-helical cationic peptide with, helix-hinge-helix structure has shown considerably good docking score (-173.843) on computational platform and hence can be a potential for wet lab experimentation for more validations



Summary of the top 10 models

Rank	1	2	3	4	5	6	7	8	9	10
Docking Score	-173.843	-165.072	-164.166	-160.107	-159.979	-159.548	-158.940	-157.698	-157.676	-156.723

Keywords: HCC, Marine peptide, Docking, Side effect

PE-081

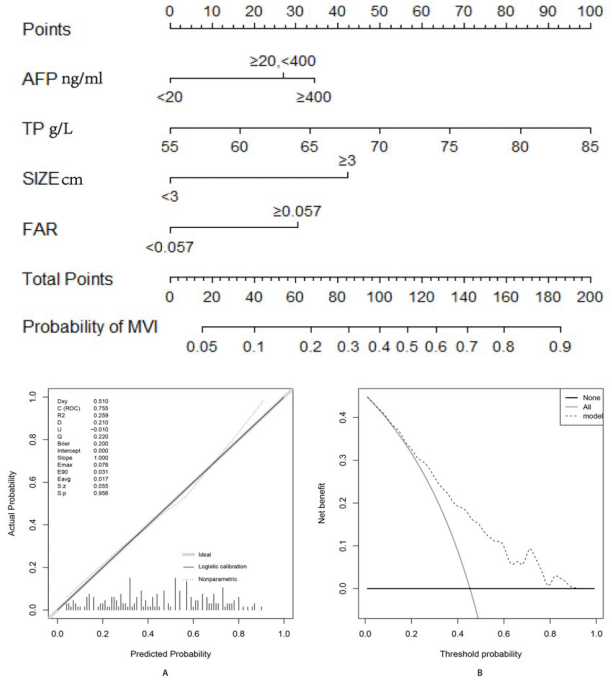
Predictive Significance of Preoperative Fibrinogen-to-Albumin Ratio in Microvascular Invasion of Hepatocellular Carcinoma

Zhen Sun, Rui Li, Zhenhua Lu, Weiwei Shao, Yangyang Zheng, Xiaolei Shi, Jinghai Song

Department of General Surgery, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences

Aims: Hepatocellular carcinoma (HCC) is a deadly disease with high postoperative recurrence and microvascular invasion (MVI) is a significant prognostic factor affecting overall survival in HCC patients after surgical resection. However, the diagnosis of MVI can only be determined by pathological examination of specimens. There is a lack of criterion in preoperative diagnosis of MVI. Accurate preoperative prediction of MVI is conducive to clinical decisions. In this study, we will develop a preoperative diagnostic model for MVI based on fibrinogen-to-albumin ratio (FAR).

Methods: Data from 193 patients with HCC who underwent surgery at Beijing Hospital between January 2013 and October 2020 were retrospectively collected. Patients were grouped according to an optimal value of FAR. Logistic regression analysis was used to identify variables significantly associated with MVI that were then included in the nomogram. And the discrimination and calibration ability of the nomogram were evaluated by using R software.



Results: MVI was confirmed in 88 (45.6%) patients by a pathological examination. Multivariate logistic regression analysis identified four risk factors independently associated with MVI:

Tumor size [odds ratio (OR) = 3.263; 95% confidence interval (CI): 1.300–6.261; *P*=0.012], serum α-fetoprotein (20–400 ng/mL, OR = 2.326; 95%CI: 1.026–5.271; *P*=0.043; ≥400 ng/mL, OR = 2.818; 95%CI: 1.214–6.542; *P*=0.016), total protein (OR = 1.107; 95%CI: 1.038–1.181; *P*=0.002), and FAR (OR = 2.600; 95%CI: 1.079–6.261; *P*=0.033). A nomogram incorporating statistically significant factors was developed and the AUROC was 0.755. Calibration curve with Unreliability test indicated favorable calibration (*P*=0.956). Decision curve analysis revealed promising clinical application of the diagnostic nomogram.

Conclusions: We have developed a preoperative prediction model for MVI in HCC patients based on FAR. The model could aid physicians in clinical treatment decision making.

Keywords: Hepatocellular carcinoma, Microvascular invasion, Fibrinogen-to-Albumin Ratio, Predication

PE-082

Cytoxic Activity of Fractions From Methanol Extract of Sisik Naga (Drymoglossum Piloselloides Presl) against Hepatocellular Carcinoma Strech HUH7IT-1 Cell Line

Jumriani Jumriani[1], Megawati Megawati[2]

[1]Department of Public Health, Institute of health Sciences Bina Bangsa Majene, [2]Department of Agribusiness, Sebelas Maret University of Surakarta

Aims: Hepatocellular carcinoma (HCC) is a malignant tumor of liver cells with prognosis can cause death within 2-3 months. Previous studies of Sisik Naga (*drymoglossum piloselloides presl*). on anti-HCV studies at concentrations of 20 µg / mL showed very high toxicity to Huh7it-1 cell line, it was indicated to have anti- cancer potential of liver cells, so this study tested the potency of anticancer activity extract methanol leaf Annona muricata L. (EMDAM) against Hepatocellular Carcinoma Huh7it-1 strain cell line with low dose.

Methods: Cells were tested with concentrations of 20, 10, 5, 2.5, 1.25, 0.6, 0.3 µg / mL for 48 hours. The EMDAM cytotoxicity of Huh7it-1 was seen with an inverted microcomputer and then measured with MTT assay [3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium].

Results: The results showed that the cells presented non-monolayer form in an inverted microscope with cytotoxicity until the lowest concentration of 0.3 µg / mL reached 84.7%, thus concentrating 50% cytotoxicity (CC50) <0.3 µg / mL.

Conclusions: The results indicate that EMDAM has the potential for anti-liver cancer activity. Further studies are needed for purification for active compounds as anticancer or target mechanisms against anti- liver cancer activity.

Keywords: Hepatocellular carcinoma, Huh7it-1, Cytotoxicity, drymoglossum piloselloides presl

9. Liver Transplantation

PE-083

A study on Differences in DDLT before and after the Introduction of the MELD System: 3 Low Volume Center, Multi Center Trial

Tae yun Lee, Yoon young Chul

Incheon St Mary's hospital

Aims: The comparative analysis before and after the introduction of the MELD score was announced at the high volume liver transplant center, but the comparative analysis has not been conducted at the low volume center in Gyeong-in area yet, so it is insufficient to conclude the effectiveness.

Methods: From June 2013 to May 2019, the study was conducted on adult patients who had undergone brain death liver transplantation at Incheon St. Mary's Hospital, Bucheon Suncheonhyang Hospital, and Gachon Gil Hospital, and a total of 87 patients were studied. Before the MELD system was introduced, before June 2016, it was named CTP group. After the MELD system was introduced, it was named the MELD group.

Results:

Conclusions: 1. Before the MELD system was introduced, liver transplantation due to HBV was the most common, but after the MELD system, alcoholic liver disease was the most common primary disease. This is the same as the results of other studies.
2. After the introduction of the MELD system, the waiting days for transplantation were shortened.

Table 1. Baseline characteristics of two groups

VARIABLE	CTP GROUP(N=39)	MELD GROUP(N=48)	P-VALUE
Recipient's age(yr)	50.846 ± 9.5574	50.604 ±11.2245	0.915
Recipient's gender, male(%)	29(74.4%)	28(58.3%)	0.118
Recipient's blood type(A:B:O:AB)	19:9:5:6	15:15:11:7	0.334
Donor's age	47.692±14.1480	49.208±14.7979	0.629
Donor's gender	29(74.4%)	30(62.5%)	0.239
Donor's blood type(A:B:O:AB)	20:9:7:3	14:14:16:4	0.183
CTP score upon registration	11.500±1.5553	11.625±1.5795	0.715
MELD score upon registration	24.079±8.4065	31.667±7.2032	<0.001
CTP score at the time of transplantation	11.590±1.5512	11.708±1.6626	0.734
MELD score at the time of transplantation	26.744±8.9376	36.000±6.0985	<0.001
Transplantation area			0.927
Region 1	25(64.1%)	32(66.7%)	
Region 2	6(15.4%)	6(12.5%)	
Region 3	8(20.5%)	10(20.8%)	
Primary disease			0.463
HBV related	18(46.2%)	14(29.2%)	
HCV related	1(2.6%)	1(2.1%)	
Alcoholic	15(38.5%)	21(43.8%)	
drug	1(2.6%)	2(4.2%)	
other	4(10.3%)	10(20.8%)	
Presence of HCC before transplantation	12(30.8%)	7(14.6%)	0.069

Table 2. Outcomes of two group

VARIABLE	CTP GROUP	MELD GROUP	P-VALUE
Drop rate(Dropped/total)	85/161(52.8%)	128/270(47.4%)	0.279
Hospitalized day	37.897±26.2075	53.750±84.4609	0.263
Waiting date for transplant	89.79±166.218	31.56±43.858	0.039
Death during hospitalization	10(25.6%)	17(35.4%)	0.327
Expire within a month	7(17.9%)	11(22.9%)	0.569

A. Due to the introduction of the MELD system, liver transplantation is being carried out to more critical ill patients (severe), and if the waiting time for transplantation is prolonged, the waiting date seems to be shortened due to the dropout due to death (the dropout rate between the two groups).
B. Alcohol-induced liver failure is more acute than HBV and HCV, resulting in shorter waiting days for transplantation.
3. There was no statistically significant difference in hospitalization period and survival rate between the two groups.
Keywords: Liver transplantation, MELD system, Low volume center

PE-084

Biliary Reconstruction Using High Biliary Radical Is Safe Option for Multiple Graft Bile Duct in Right Lobe Living Donor Liver Transplantation

JOODONG KIM, DONG LAK CHOI

Department of Surgery, Catholic University of Daegu College of Medicine

Aims: Multiple small size graft bile ducts (BDs) are related to higher incidence of biliary complications (BCs) and biliary reconstruction for multiple BDs still remains a technical challenge during living donor liver transplantation (LDLT). Especially, biliary reconstruction using high biliary radicals (right or left hepatic duct) of recipients for multiple BDs has very high probability of BCs secondary to devacularization and ischemia. Therefore, hepaticojejunostomy has been performed in cases with multiple BDs which are not close to each other although duct to duct anastomosis (DDA) has more physiological advantages.
Methods: Herein, we analyzed clinical outcomes through retrospective reviews 227 patients receiving DDA for right lobe grafts LDLT from January 2013 to September 2018. 87 LDLT using grafts with multiple BDs have been performed and 39 patients received DDA using high biliary radicals among them with minimal hilar dissection, external biliary stents and mucosal eversion technique. We compared clinical outcomes between these 39 patients and those receiving DDA using common hepatic duct of recipients for multiple BDs (CHD group).
Results: The incidence of biliary leakage and stricture were 10.3% and 12.8% and these results were not different to those in CHD group. Neither overall patient survival nor graft survival differed significantly between the two groups . Moreover, these results were comparable to those in groups using graft with single BD during the same periods.
Conclusions: The choice of high biliary radicals as the recipient BD for multiple graft BDs was not associated with higher incidence of BCs and furthermore, could be safe option for biliary reconstruction during LDLT
Keywords: Liver transplantatin, Bile duct, Multiple, Complication

PE-085

Alcoholic Liver Disease has More Bleeding Tendency during Liver Transplant Operation

Dong Jin JOO*, Mun Chae CHOI

Department of surgery, Yonsei University College of Medicine, Seoul, South Korea, Korea

Aims: Alcohol Liver Disease (ALD) includes a wide clinical spectrum from acute alcoholic hepatitis to severe cirrhosis and/or hepatocellular carcinoma. Until now, there was no report to reveal the bleeding tendency of ALD compared to other diseases in liver transplantation (LT). Thus, we analyzed the blood loss and transfusion amount during operation according to the etiologies of liver disease and MELD score.
Methods: Out of 874 recipients who underwent LT, a total of 146 patients were excluded by our exclusion criteria. We compared 728 recipient's baseline characteristics, operation time, blood loss, and transfusion amounts between ALD and Non-ALD according to MELD score.
Results: The number of patients in ALD groups was 130 (17.9%), and 598 (82.1%) in non-ALD group. ALD group showed younger age, higher MELD score, and more proportion of deceased donor liver transplantation than non-ALD group. Overall blood loss, RBC, FFP, Platelets transfusion of ALD group were significantly higher than non-ALD group. When we divided the patients into two group according to the MELD score 20, ALD group showed significant blood loss, RBC, and FFP transfusion in both higher and lower MELD groups even though there were no significant differences of INR and PLT counts between two groups in the higher MELD subgroup.
Conclusions: ALD showed more bleeding tendency than Non-ALD during LT operation. These findings imply that transplant surgeon need to prepare for blood loss during operation for ALD patients regardless of the MELD score.

PE-086

Clinical Analysis of the Outcomes after Receiving a Liver Graft That Abandoned Transplantation due to Poor Graft Conditions in the Centers Allocated as a Priority

Ho Joong CHOI, Changho SEO, Sung Eun PARK, Joseph AHN, Tae Ho HONG, Young Kyoung YOU

Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

Aims: Depending on the recipient's condition and lack of donors, even liver grafts with poor conditions may need to be transplanted. This study was conducted to analyze the outcomes after receiving a liver graft that abandoned transplantation due to poor graft conditions at the preceding centers.
Methods: From January 2010 to September 2020, Deceased-donor liver transplantation (DDLT) was performed in 161 patients in our center. Among them, 127 patients (allocated group) were preferentially allocated to our center by KONOS and the remaining 34 patients (abandoned group) received liver grafts that were abandoned by other transplant centers due to poor organ conditions. Various perioperative factors and postoperative outcomes were compared.
Results: There was no difference in recipient factors before transplantation, and the donor had a longer stay in the ICU in the abandoned group. The operation time was less in the abandoned group, but there was no statistical difference (P=0.06), and there was no difference in ischemic time or transfusion between the two groups. Postoperative ICU hospital stay was longer in the abandoned group (P=0.04), but postoperative in-hospital mortality was not different between the two groups. There was no difference between the two groups in long term survival after transplantation.
Conclusions: Even if the graft that was abandoned due to poor condition, good results can be obtained if the transplant is carried out according to the recipient state. And as a result, it is expected that the discarded graft can be reduced.

PE-087

Necrotizing Pancreatic Pseudocyst Induced by PTC & ERC for Biliary Strictures after Liver Transplantation: Case Report

Mi Rin LEE, Jae Do YANG, Sung Woo AHN, Hee Chul YU*

Department of General Surgery, Jeonbuk National University Hospital, Korea

Aims: Biliary strictures that developed after LT are managed with endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), or surgical revision. In cases where conventional endoscopic access is failed, alternative treatments should be achieved by means of the rendezvous technique, which is a hybrid technique combining PTC and ERC. We describe a rare case of necrotic pseudocyst occurring after the Rendezvous technique for treatment of post-transplant biliary strictures.
Methods: a case review has been done.
Results: A 65-year-old man who presented with hepatocellular carcinoma complicating chronic hepatitis B liver cirrhosis underwent live donor liver transplantation (LDLT) from his son. One year after, he presented mild pruritus. The serum liver enzymes and bilirubin level raised but, liver biopsy was not diagnostic of rejection. ERCP showed stricture of the biliary anastomosis and tried to PTC and ERC, but failed three times. Cannulation of a biliary stricture can be achieved by the Rendezvous technique with progressive balloon dilation and the placement of two plastic stents. The patient was readmitted 2 weeks later with pain and vomiting with fever. CT showed 17cm large pancreatic necrotic pseudocyst which was possibly a complication of previous intervention. Percutaneous drainage (PCD) of the collection yielded abscess. Despite of drainage and antibiotics management during 4weeks, symptoms and pancreatitis were not resolved. After repositioning of PCD and irrigating with saline daily, symptoms including fever have improved.
Conclusions: Necrotizing pancreatic pseudocyst has been happened rarely as a complication after post-ERCP in liver transplantation patients. and needed intensive treatments and long-term hospitalization for preventing fatal course.

PE-088

Quality of Life in Patients after Liver Transplantation: A Literature of Review

Putri AYU[1], Ade Kartikasari SEBBA[2]

[1]Economics, Andalas University, Indonesia; [2]Public Health, Universitas Gadjah Mada, Indonesia

Aims: Liver Transplantation is one of the therapies that increases every year because it contributes to the improvement of patient survival. However, healing or control of the disease is often not accompanied by a full recovery of quality of life (QoL). This study aimed to reviews analyze various of the quality of life of patients Liver Transplantation.
Methods: Ten articles were selected based on the articles which published which using the Model for End-stage Liver Disease (MELD), Short Form -36 (SF-36) Health Survey, NIDDK Liver Transplantation QOL survey, and European Organisation for Research and Treatment of Cancer QOL Questionnaire (5 studies) in measuring the quality of life of patients after transplantation. The collection of indicator in each article was used to see the factors that significantly influence the quality of life of patients.
Results: The results showed the quality of life of patients based on all analysis have improved after transplantation Liver. The global health, physical, emotional, cognitive, role and social function improved after transplantation. Indicator of financial difficulties also showed decrease after transplantation.
Conclusions: At the start of the year there were changes that improved after the transplant. However, in the long term, the quality of life of people with liver disease will decline, especially they often experience fatigue and physical weakness. so that there needs to be exercises that can be used so that the quality of life for people with liver after transplantation is getting better.
Keywords: Liver transplantation, Quality of life

PE-089

The Role of Religion in Transplanting Liver in Indonesia

Mahyuddin Mahyuddin

Institut Agama Islam Negeri Parepare

Aims: The phenomenon of transplantation in Indonesia, in particular, organ donation for the liver, is a social discourse in medical science that cannot be separated from the dimensions of religiosity. In this connection, the fact that medical technology has created a sensitive debate between medical science and religion. This study aims to investigate the role of religion on individual decisions to donate body organ especially liver.
Methods: This study used a juridical normative method that was analytical description of law sociology and normative qualitative analysis of secondary data by examining Muhammadiyah and Nahdatul Ulama agreements as well as the guidance of an order person of The Indonesian Council of Ulama in Indonesia. In order to maintain validity, the author collected books containing fatwas from these organizations and fatwa documents published on the internet and looks for relevant reading sources from both national daily news and journals that discuss topics related to transplantation and organ donation
Results: The results of this study indicate that (a) The agreement of Islamic organizations about whether or not organ transplants have given new hope to liver patients in which the scholars recommend transplantation as long as the benefits obtained are greater and do not endanger the person who receives (recipient) with the provisions of the organ in pairs (kidneys, eyes, feet, ears), not the only organs, such as the liver, brain, or heart. (b) The largest Islamic organizations in Indonesia such as MUI, NU and Muhammadiyah in general allowed this practice as long as they followed the provision of the shari'ah rules (Islam law). (c) Altruism has encouraged the behavior of Muslim liver donors to help other humans, especially fellow Muslims. The other hand, they were not receive money for their action.
Conclusions: In the past, religion became an inhibitor of liver transplant in Indonesia. However, now religion has a significant role in transplanting of body organ including liver donor. There have been many agreements and consensus of scholars (fatwa of ulema) from various conferences, institutions, Islamic organizations that allow the practice of liver transplant.
Keywords: Liver tranplantation, Religion, Islamic altruism, Indonesia

PE-090

The Practice of Liver Transplantation In Muslim Countries: A Critical Review

Mahyuddin Mahyuddin

Sociology of Religion, Institut Agama Islam Negeri Parepare, Indonesia

Aims: Currently the practice of transplantation in muslim societies is urgent. Tranplantation, especially organ donation for liver transplantation, are necessary to human life. Therefore, the need and the demand for transplants are increasing all over the world muslims. This study aims to describe the role of religion on discourses and practice of liver transplantation in muslim countries. The authors analyze the fatwas of islamic scholar (the ulama) and the attitudes of the muslim societies in responding to the fatwa of ulama about transplantation practices and organ donations including liver transplantation
Methods: This research used a critical review and it used sociology of religion perspective in explaining these phenomenon. To complement the existing data, the authors search information from previous studies through both journal articles and book references
Results: The results of this has found that there is ambivalance within discourses of tranplantation and organ donation in the world of muslim countries. Religious institutions have supported people to help others within the spirit of Islamic altruism. Conversely, religious beliefs have restricted the practice of transplantation like liver transplantation.
Conclusions: The institution of religion played a significant role to suggest transplantation of body organ for human life, however there have been many people did not yet accept it, where in particular religious concerns was an important reason why Muslim societies decline listing to donate organ.
Keywords: Liver transplantation, Muslim countries, Organ donation, Religion

PE-091

Treatment Outcomes and Prognostic Factors of Patients with Recurrent Hepatocellular Carcinoma after Liver Transplantation

Young Seob Shin[1], Sang Min Yoon[1], Young-In Yoon[2], Gi-Won Song[2], Ki-Hun Kim[2], Jinhong Jung[1], Jin-hong Park[1], Sung-Gyu Lee[2]

[1]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: Recurrent hepatocellular carcinoma (HCC) after liver transplantation (LT) is difficult to manage, and therapeutic strategy or prognostic factors have not been established. The aim of this study was to investigate patterns of recurrence, treatment outcomes, and prognostic factors in patients with HCC after LT.
Methods: We retrospectively reviewed the medical records of 922 patients who had undergone LT for HCC at the Asan Medical Center from June 2005 to May 2015. Among them, 158 (17.1%) patients were diagnosed with recurrent HCC after LT. Patterns of recurrence, treatment outcomes, and potential prognostic factors were evaluated.
Results: The median time to recurrence after LT was 10 months (range, 1–142 months). Most patients (83.5%) experienced tumor recurrences at extrahepatic sites or simultaneously at both intrahepatic and extrahepatic sites. During a median follow-up period of 15 months (range, 1–155 months), 1- and 2-year overall survival rates after recurrence were 66.5% and 39.5%, respectively. The 2-year overall survival rate of patients who had received surgery or local treatments to all lesions were significantly higher compared to other patients (57.7% vs. 30.1% for surgery; 48.4% vs. 23.7% for local treatments; $P<0.001$

for both). Multivariate analyses revealed that the time to recurrence after LT, alpha-fetoprotein level at recurrence, number of recurrent sites, number of recurrent nodules, maximal size of nodules, and neutrophil-to-lymphocyte ratio (NLR) at recurrence were significantly associated with patient survival. The receiver operating characteristic curve analysis suggested an optimal cutoff NLR of 2.0.
Conclusions: Patients with recurrent HCC after LT showed a poor prognosis. However, vigorous local treatment might improve oncologic outcomes and allow longer survival times, particularly in patients with favorable prognostic factors. NLR may be a useful prognostic marker for treatment decision in this situation.
Keywords: Carcinoma, Hepatocellular, Liver Transplantation, Recurrence, Therapeutics

PE-092

Liver Transplantation in the Era of Pandemic COVID-19

Ramlah RAMLAH

Biology, Universitas Gadjah Mada, Indonesia

Aims: Liver transplantation is considered the ultimate solution for patients with end-stage chronic liver disease. Patients with liver transplant need special care starting from preoperative preparation, surgical intervention ending with postoperative care. The effect of coronavirus disease 2019 (COVID-19) on liver transplantation programmes and recipients is still not completely understood but overall involves the risk of donor-derived transmission, health-care resource utilization and the effect of immunosuppression. The aim of this study is to describe the situation of liver transplantation in the era of pandemic COVID-19.
Methods: Data obtained from secondary data on 13 articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 2 years (2019-2020).
Results: The result showed that patients with liver disease need special attention and continuous follow-up. Similarly, transplant candidates also need special care. Restricting non-transplant elective surgical procedures, managing transplant patients in separate outpatient clinics, and in-patient wards can prevent transmission of infection both to patients and healthcare workers. Telemedicine can help in the triage of patients to screen for symptoms of COVID-19 before their regular appointment. Patients with novel coronavirus disease 2019 (COVID-19) experience various degrees of liver function abnormalities. Liver injury requires extensive work-up and continuous surveillance and can be multifactorial and heterogeneous in nature.
Conclusions: It can be concluded that in management of immunosuppressive therapy and drug-drug interactions in liver transplant recipients infected with COVID-19 should be cautiously practiced to prevent rejection and effectively treat the underlying infection.

10. Biliary and Pancreatic Disease

PE-093

Vascular involvement Assessment in Patients with Hilar Cholangiocarcinoma by 128-Row Multidetector Computed Tomography

Julia KULEZNEWA, Boris NIKITIN, Natalia ORLOVA, Konstantin LESKO

Radiology department, The Loginov Moscow Clinical Scientific Center, Russia

Aims: The purpose was to evaluate the diagnostic accuracy of multidetector 128-row computed tomography (MDCT) in tumor-vessel contact assessment for predicting vascular invasion in patients with hilar cholangiocarcinoma (HCCA).
Methods: We analyzed results of MDCT with intravenous contrast enhancement in 29 patients with MDCT-pattern of HCCA who underwent surgical treatment and verified HCCA from January 2015 to July 2019. We assessed tumor-vessel contact in degrees of the circumference and length of contact in combination and separately. Hepatic arteries (HA) and portal vein (PV) involvement assessed separately. There were 49 cases of potential HA involvement and 48 cases of potential PV involvement.
Results: We expected vascular involvement, when at least one sign was positive: tumor-vessel contact ≥180° and/or length of tumor-vessel contact ≥11 mm. Sensitivity (Sn), specificity (Sp), accuracy (Ac), positive (PPV) and negative predictive value (NPV) of combined approach were 90.3%, 66.7%, 81.6%, 82.4% and 80% for tumor-HA contact and 96.8%, 70.6%, 87.7%, 85.7%, 92.3% for tumor-PV contact, respectively. Tumor-vessel contact circumference assessment approach had Sn 83.9%, Sp 88.8%, Ac 85.7%, PPV 96.9%, NPV 76.2% for tumor-HA contact and Sn 90.3%, Sp 88.2%, Ac 89.6%, PPV 93.3%, NPV 83.3% for tumor-PV contact; tumor-vessel contact length assessment had Sn 82.1%, Sp 66.7%, Ac 76.1%, PPV 79.3%, NPV 70.6% for tumor-HA contact and Sn 78.1%, Sp 81.2%, Ac 79.2%, PPV 89.3%, NPV 65% for tumor-PV contact.
Conclusions: Combined approach was more sensitive, but less specific and accurate than tumor-vessel contact circumference assessment. Thus, tumor-vessel contact circumference assessment is more suitable than combined approach.

PE-094

Early Complications of Laparoscopic Cholecystectomy

Myltykbay RYSMAKHANOV, Bazylbek ZHAKIYEV

General Surgery, Aktobe Medical Center, Kazakhstan

Aims: The gallbladder stones as worldwide disease occurs in 10% of the world population. After laparoscopic cholecystec-

tomy (LCE) complications observed at 1% to 8,5%. The aim is to evaluate the early postoperative complications (EPC) of LCE in our medical center.

Methods: Analyzed 983 LCE, which performed in period 2014-2020 in "Aktobe Medical Center". Of these 598 patients (60,9%) had GS with acute cholecystitis, 385 (39,1%) – chronic cholecystitis. Woman – 74,2% (n=729), man – 25,8% (n=254),

Results: EPC was in 24 (2,4%) patients. Cause of EPC were: bile leakage – in 7 patients (29,2%) (in 2 patients it is stopped on their own), bleeding – 4 (16,7%), sub-hepatic infiltrate – 3 (12,5%), choleperitonitis after extrahepatic bile duct injure - 2 (8,3%), abdominal wall wound inflammatory complications - 8 (33,3%). Nine patients were undergoing reoperation in early postoperative period. Seven patients had relaparoscopy due to bile leakage from the cystic duct stump (2 case) and from Luschka duct (3 case); bleeding from cystic artery (2 cases). Reasons of early 2 laparotomies were bile leakage with choleperitonites after extrahepatic bile duct injure. In three cases with bile leakage we held suturing the bile ducts wall. Umbilical wound inflammatory complications resolved conservatively. One patient died after pulmonary artery thromboembolism – 0,1%.

Conclusions: Our analysis indicates that LCE has a low number of complications and minimal mortality. However, there are serious injuries to the bile ducts, which can be minimized by improving surgical techniques.

PE-095

Hepatolithiasis Long Term Complication of Choledochal Cyst Resection: Case Report

Ana Isabel ARGUETA, Francisco DE LEON, José CONTRERAS, Jimmy IXCAYAU, Haroldo PAIZ, Estuardo PORRAS, Erick SOTO

Surgery, 14475, Guatemala

Aims: Choledochal cysts (CCs) are uncommon with an incidence that ranges from 1 in 100,000-150,000 in Western populations, to 1- 1000 in some Asian populations. The cyst can become complicated with stone disease, pancreatitis, cholangitis and malignancy of the biliary tree, therefore it has to be treated by operative resection of the bile duct, cholecystectomy, and biliodigestive reconstruction, irrespective of the age at presentation. In the long term follow up, post operative intrahepatic stone and cholangitis present serious complications. Hepatolithiasis is likely to develop secondary to a postoperative anastomotic stricture.

Methods: We present a case report of a 23-year-old male with recurrent episodes of cholangitis and a past surgical history of complete choledocal cyst excision with bilioenteric anastomosis 16 years ago with no long term follow up. The diagnosis of anastomotic stenosis and hepatolithiasis was confirmed by magnetic resonance cholangiopancreatography. Percutaneous treatment was not possible. Patient was taken to surgery where 28 bile stones were removed from choledoco, common hepatic and left hepatic duct. Intraoperative choledochoscopy confirmed stone clearance from the intrahepatic and extrahepatic ductal system. Biopsy was taken and a hepaticojejunostomy according to Hepp-Couinaud performed.

Results: Biopsy reported negative for malignancy. Patient was discharged with no postoperative complications.

Conclusions: Close follow-up after choledochal cysts surgical treatment is important, moreover, these patients have a need for long term follow up to detect hepatolithiasis as soon as possible. Combined surgical procedure (stone extraction, on-table choledochoscopy and bilio-enteric drainage) is an acceptable option for hepatolithiasis.

PE-096

Pancreatic Solid Harmatoma Mimicking Neuroendocrine Tumor: Case Report

Jae Do YANG, Mi Rin LEE, Sung Woo AHN, Hee Chul YU*

Surgery, Jeonbuk National University Hospital, Korea

Aims: Pancreatic solid hamartoma is an extremely rare entity that shows components that are present in the normal pancreas with distorted architecture and are considered as malformative lesions. Preoperative diagnosis is difficult because the clinicopathological features of pancreatic solid hamartoma have not yet been fully clarified.

Methods: Herein, we report extremely rare case of pancreatic solid harmatoma mimicking neuroendocrine tumor.

Results: A 68-year-old male presented to our hospital for the evaluation of an incidentally detected pancreatic mass. Serum tumor marker levels were within normal limits. On delayed-phase computed tomography (CT), a homogeneous enhancing hypervascular mass measuring 1.8 cm was detected in the pancreatic head. On FDG-PET/CT, the mass showed no significant FDG uptake. As the radiologic impression was that of a neuroendocrine tumor, the patient underwent pylorus-preserving pancreatoduodectomy. Pathologic findings show that microscopically, the tumor exhibited typical features of pancreatic solid hamartoma with no evidence of neuroendocrine differentiation in the cells of the lesion.

Conclusions: n conclusion, pancreatic hamartoma may be detected incidentally, without the patient presenting with any signs or symptoms of disease. Clinical symptoms are dependent on tumor size and location, and the diagnosis of this disease primarily depends on imaging techniques, including computed tomography, MRI and EUS. However, pancreatic hamartoma is difficult to differentiate from other benign pancreatic lesions. For symptomatic patients or those with an indefinite diagnosis, a complete surgical excision is recommended.

PE-097

Intrathoracic Calculous Cholecystitis Due to Delayed Iatrogenic Diaphragmatic Hernia

Jae Do YANG, Mi Rin LEE, Sung Woo AHN, Hee Chul YU

Surgery, Jeonbuk National University Hospital, Korea

Aims: Iatrogenic diaphragmatic hernias is rare complications of abdominal or thoracic surgery. Depending on the location and size of the defect retroperitoneal or intra-abdominal organs and tissues can prolapse into thoracic cavity due to the negative intra-thoracic pressure. This can cause risk of obstruction or strangulation of abdominal contents, and may ischemia and perforation.

Methods: We present a case of delayed presentation of a patient with iatrogenic diaphragmatic herniation of liver and gallbladder with stones into the thorax.

Results: A 62-year-old female was visited our hospital for complaining of right sided thoracic back pain during 3month. The pain had not been treated with analgesics. 3 years ago, she has been diagnosed right diaphragmatic metastatic nodule from ovarian cancer. She was operated excisional biopsy of intrathoracic lymph nodes and parietal pleural by VATs(video-assisted thoracic surgery). A CT- scan showed intrathoracic displacement of her liver and chronic cholecystitis with multiple stones.The patients underwent laparotomy via an abdominal approach with subcostal incision. Intraoperative findings confirmed that right diaphragmatic focal defect and liver and gallbladder herniated into the thoracic cavity The organs were placed back into the thoracic cavity. A cholecystectomy was performed, and the defect in the diaphragm measuring 13cm X 10 cm, was repaired with a Gortex graft.

Conclusions: Postoperative recovery was uneventful. The patient was discharged seven days after the surgery without any problems.

PE-098

Surgical Outcomes in Cystic Neoplasm of the Pancreas- A 30-Year Experience ina Tertiary Care Center in Southern India

AMITH KUMAR PAKKALA, BHEERAPPA NAGARI*, ASHISH BANSAL, VENU MADHAV THUMMA, G SURYA RAMACHANDRA VARMA, NAVA KISHORE, PHANI KUMAR N

Department of Surgical Gastroenterology, Nizams Institute of Medical Sciences, India

Aims: Cystic neoplasm of the pancreas is a diverse group of lesions varying from benign to invasive malignant tumours. Though uncommon, they are diagnosed with increased frequency due to the widespread use of cross-sectional imaging for abdominal complaints.

Methods: We analysed this data from a prospectively maintained database from 1990 to 2020 at a tertiary care hospital in Southern India. Patients' demographic profile, tumour distribution, surgical procedures, and perioperative outcomes including complications were studied.

Results: A total of 146 cases underwent surgery for cystic neoplasm of the pancreas from 1990 to 2020. The median age at presentation was 37years (11-85y). The female: male ratio was 3:1. 93.8% of patients were symptomatic at presentation. The most common location was in the body and tail which was 73.9%. 72(49.3%) underwent distal pancreatico-splenectomy, 39 (26.7%) underwent pancreaticoduodenectomy, and 33 (22.6%) underwent central pancreatectomy. 17 (11.7%) patients underwent a laparoscopic/laparoscopic assisted procedure. On histopathology examination most common lesion was SPEN 83(56.8%), 29(19.9%) were serous cystic neoplasm and 11(7.5%) had mucinous cystic neoplasm. Mean hospital stay was 9.2± 4.2 days. The most common postoperative complication was POPF which was present in 39 (26.7%) and out of them, 6 were grade B/C (4.1%). 8 (5.5%) had postoperative morbidity of Clavien-Dindo grade 3a or more and out of them, 2 (1.4%) had postoperative mortality.

Conclusions: Cystic neoplasm of the pancreas is most common in the female population. In expert centres, these can be managed with acceptable postoperative morbidity and mortality.

PE-099

Empyema Gall Bladder in Cirrhotic Patient

Muhammad ZAKRIA

Surgery, Wapda Teaching Hospital, Lahore., Pakistan

Aims: Acute cholecystitis is initially managed by conservative management. Once patient is stable surgical treatment is the final solution. If stone is impacted neck of the gall bladder then we have to do surgery urgently as the conservative treatment may fail. Sometimes patient has late presentation and gall bladder is full of pus. In these conditions we have to select the surgery as our first option. This becomes more challenging if patient is cirrhotic and has other co morbid factors like diabetes mellitus. It is wise to do the immediate surgery in a cirrhotic patient or even non cirrhotic patient if he develops empyema gall bladder.

Methods: A 58 years old female patient was admitted through emergency with complaint of pain right side abdomen and radiating to back. It was associated with fever, nausea, and vomiting and tenderness right side abdomen. She was a patient of Child A, liver cirrhosis. She was diabetic but controlled on insulin. Her CT scan was showing stone in the neck of gall bladder. She underwent open surgery through right Kocher incision, pus was aspirated from the gall bladder fundus. Retrograde cholecystectomy was done. Wound was left open. After 10 days secondary suturing was done.

Results: During her stay in hospital she remained afebrile postoperatively. Recovery was uneventful.

Conclusions: Early intervention is gold standard in empyema gall bladder. Although laparoscopic cholecystectomy is very much

ideal for the gall bladder surgery but in case of massive adhesions, open surgery is safe option if laparoscopic surgery fails.

PE-100

Common Bile Duct Dilatation according to the Type of Anastomosis after Gastrectomy for Gastric cancer

Hanlim Choi[1,2], Jae-Woon Choi[1,2], Dong Hee Ryu[1,2], Kanghe Xu[1]

[1]Department of Surgery, Chungbuk National University College of Medicine, Cheongju, Korea; [2]Department of Surgery, Chungbuk National University Hospital, Cheongju, Korea

Aims: There are many studies for the increased incidence for choledocholithiasis and common bile duct dilatation after gastrectomy. However, there are few reports about the dilatation of common bile duct (CBD) according to the type of anastomosis in patients undergoing gastrectomy for gastric cancer. We compared the changes of CBD diameter after gastrectomy with various anastomosis. The aim of this study was to evaluate the degree of CBD dilation in patients who underwent subtotal gastrectomy with various anastomosis using 1-year follow-up abdominal CT scan.
Methods: From January 2012 to December 2015, 395 patients who underwent subtotal total gastrectomy for gastric cancer and had no gallstones were enrolled. We measured CBD diameter in the pancreas head by analyzing preoperative, 6-, and 12-months follow-up abdomen-pelvis enhanced computed tomography (A-P CT) scans.
Results: The CBD was dilated slightly from 4.1 mm at baseline to 5.1 mm at 6 months and 6.1 mm at 12 months after gastrectomy. The number of cases of CBD dilatation of more than 7 mm at 6 months and at 12 months after cholecystectomy were 11 (24.4%) and 9 (29.0%), respectively. Seven cases at 6 months and 5 cases at 12 months showed bile duct dilation of more than 3 mm compared to baseline. There were no cases having bile duct dilation of more than 10 mm.
Conclusions: The diameter of CBD was significantly increased after subtotal or total gastrectomy. In addition, the degree of dilation of CBD was higher after not only Billroth-II with Braun anastomosis but Roux-en Y anastomosis compared to Billroth-I. A CBD dilatation within 10 mm in patients had gastrectomy can be regarded as normal physiological change.
Keywords: Common bile duct, Dilation, Gastric cancer, Gastrectomy, Anastomosis

PE-101

Gravity Dependent and Hand Held 'Push' Injection Method of Contrast Cholangiography: A Pilot Study Comparing Outcomes and Efficacy

Neha BHATT[1], Nalini Kanta GHOSH[2], RAJAN SAXENA[*3]

[1]Surgical Gastroenterology and Center of Hepatobiliary Diseases & Transplantation, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebereli Road, Lucknow, India; [2]Surgical Gastroenterology and Center of Hepatobiliary Diseases & Transplantation, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebereli Road, Lucknow, India; [3]Surgical Gastroenterology and Center of Hepatobiliary Diseases & Transplantation, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebereli Road, Lucknow, India

Aims: Contrast cholangiograms still continue to be obtained prior to removal of intraoperatively or preoperatively placed intra-biliary tubes to look for filling defects, anastomotic leaks or stenosis, evaluation of radiological intervention or a controlled external biliary fistula. Post-cholangiogram cholangitis remains a major morbidity concern. Is it related to the technique?
Methods: An observational prospective pilot study comparing hand held push injection (PIC) and gravity dependent (GDC) techniques of cholangiography in 30 consecutive patients with in-situ biliary tubes after administration of pre-procedure antibiotic, excluding patients with active cholangitis or complete biliary obstruction. In GDC group, dye was delivered under gravity from a height of 25 cm instead of injection. Outcomes analysed included adverse reactions - minor (two or more of low grade fever, tachycardia, pain/nausea without fever, subclinical cholangitis) and major (two or more of high grade fever, chills, tachycardia, hypotension, oliguria), readmission requirement, and the efficacy (opacification of the biliary tree with the
Results: In the PIC group (n= 14), adverse reactions were minor in 6 (42.8 %) and major in 4 (28.5 %). Two patients required re-admission, and in two others discharge from the hospital was delayed. In the GDC group (n=16), adverse reactions were minor in 7 (43.7 %), with no major adverse reaction or readmission. Major adverse reactions were significantly more common in PIC as compared to GDC (28.5 % vs 0 % respectively, p value = 0.03), and translated into higher treatment costs.
Conclusions: When required, GDC, limiting rise in intrabiliary pressure, is a safer, completely efficacious and economical technique.

PE-102

Primary Pancreatic Ewing's Sarcoma: Dreadful Yet Treatable Alien

Adithya MORUMPALLE[1], Anand Vijai NATESAN[2], Palanivelu CHINNUSAMY[3], Selvakumar BALAKRISHNAN[4]

[1]Department of HPB & Minimal Access Surgery, Gem Hospital & Research Center, India; [2]Department of HPB & Minimal Access Surgery, Gem Hospital & Research Center, India; [3]Department of HPB & Minimal Access Surgery, Gem Hospital & Research Center, India; [4]Department of HPB & Minimal Access Surgery, Gem Hospital & Research Center, India

Aims: Ewing's sarcoma is a highly aggressive malignant tumour most commonly affecting long bones in children and adolescents. Primary presentation in Pancreas is considered to be an extremely rare and only a handful of cases have been published to date.Our case intensifies the importance to recognize this

rare type of tumor in young adults with a primary pancreatic lesion as there is a broad spectrum of tumours with a similar morphological and radiological presentation.

Methods: A 26-year-old man was evaluated for upper abdominal pain with cross sectional imaging studies which revealed 3x3.3 cm complex cystic lesion in head of pancreas. Serum tumor markers and other blood investigations were within normal limits.We conducted tumour board meeting and proceeded for laparoscopic pancreaticoduodenectomy.

Results: Post-operative whipple"s specimen was subjected for histopathological analysis and Immunohistochemistry which confirmed the diagnosis of Ewing's sarcoma of pancreas. Currently, the patient is receiving regular follow-up care and received 3 cycles of adjuvant chemotherapy till now and has no evidence of cancer at six months post-surgery.

Conclusions: Primary pancreatic Ewing sarcoma is a very rare highly aggressive malignant tumour that should be considered in differential diagnosis of an unusual pancreatic tumour especially in young adults. Being rare, we only have 32 reported cases up-to-date. Establishing the correct diagnosis requires a multidisciplinary approach involving close cooperation between clinical, radiological and pathological teams with accurate application of immunohistochemistry or cytogenetic analysis. Complete surgical excision with adjuvant chemotherapy and with or without radiation therapy is the standard of care.

PE-103

Cystic Metastasis From an Adenocarcinoma of Pancreas: A Case Report

Nattawut Keeratibharat

Suranaree University of Technology

Aims: A 75-year-old female was presented to our hospital due to obstructive jaundice. Computed tomography demonstrated a pancreatic head mass that causing common bile duct and intrahepatic duct dilatation without evidence of advanced disease. She was underwent pyloric-preserving pancreatoduodenectomy and they discharge without complication. Although the incidence of hepatic cystic liver metastasis from pancreatic cancer is extremely rare, care should be taken to when a cystic liver lesion was detected with pancreatic cancer.

Methods: In operative finding, we found the 1-cm liver cyst at segment 5 and excisional biopsy was done. The pathological report revealed well-differentiated adenocarcinoma of head of pancreas without nodal metastasis and cystic metastasis well-differentiated adenocarcinoma of liver.

Results: Then we reviewed the imaging study, it showed a small cystic lesion without enhancing portion at liver segment 5 that mimics intrahepatic duct dilatation and a cystic lesion at segment 6 that previously seen in preoperative imaging study. The patient underwent chemotherapy with Gemcitabine. Six months after surgery, the computed tomography revealed increase sized of cystic lesion at segment 6 and development of ascites. Ten months after surgery, the patient was dead due to severe septicemia from urinary tract infection. The previous study show a range of spectrum of hepatic cystic liver metastasis with histopathologic confirmation of diagnosis.

Conclusions: Although the incidence of hepatic cystic liver metastasis from pancreatic cancer is extremely rare, care should be taken to when a cystic liver lesion was detected with pancreatic cancer.

Keywords: Pancreatic cancer, Cystic metastasis

PE-104

Functional Neuroendocrine Tumors of Pancreas

Mallela Sai Charan Reddy[1], Prabhat Nichkaode[2], Shahji G Chavan[3], Chamakura Manichandra Reddy[4]

[1]Resident, Department of General Surgery, Dr D Y Patil Vidyapeeth, Pune, [2]Professor, Head of Unit, Department of General Surgery, Dr D Y Patil Vidyapeeth, Pune, [3] Professor, Head of department, Department of General Surgery, Dr D Y Patil Vidyapeeth, Pune, [4]Resident, Department of General Surgery, Dr D Y Patil Vidyapeeth, Pune

Aims: -To analyse the spectrum of Pancreatic Neuroendocrine Tumor.

Objectives:

-To know the specific method of investigations.

-To study the outcomes with surgical treatment.

Methods: We studied the Clinical Spectrum of Functional NET of Pancreas in medical college Hospital. As far Localization & diagnostic modalities . To analyze management & outcome. Feasibility To Undertake Such Surgeries In Hospital Without a Specialty Department. Retrospective analysis of 27 Histopathologically proven Functional NET of Pancreas – from 2000 to 2019 .Demographic data, Clinical presentation, Tumor characteristics, Management & Outcome were analyzed.

Results: The most common NET was Insulinoma, followed by other tumors like gastrinoma, and Glucaganoma. USG-Sensitivity small tumors: 10-30% Liver Mets : 90%. CT With / without Angiography. MRI. Intraoperative USG- sensitivity very High, Palpatory Method- Very Useful. PETwith C11-%HTP or C11 L Dopa, are recent investigations. General Tumor markers Chromogranin A– 90-100%, Synaptophycin, Pancreatic Polypeptide-40-60%HCG / Alpha/Beta—15-20.

Conclusions: Treatment is either enucleation or pancreatic resection depending on size of tumor. Enucleation has the Benefit of sparing normal pancreatic parenchyma as long as integrity of Pancreatic Duct is preserved. Laparoscopic resection of pancreatic endocrine tumors is becoming common, For patients with unresectable disease, New somatostatin analog – LANREOTIDE-remains biologically active for up to 2 weeks following a single injection and controls symptoms.

Keywords: Functional neuroendocrine tumor, Insulinoma, Intraoperative ultrasonography, Pancreatic resection

PE-105

Herbal And Traditional Therapies For Liver Disease: A Study with Rural Communities in Indonesia

Nuraliah

West Sulawesi Research and Empowerment Center, Indonesia

Aims: Liver disease is one of the leading causes of death in Indonesia. In 2013, it was reported that Indonesia's hepatities prevalence was 1,2 %. This study aims to describe people's experience in preventing liver disease. The authors explore the medical plants that was used by the patient to cure liver by using herbal and therapies.
Methods: This study used literature review. The author collected data from some journals to study the local knowledge of rural communities to overcome liver disease.
Results: The phenomenon learned from this treatment was not only the behavior of people who use alternative medicine to prevent various disease, but also the effectiveness of these traditional therapies. The results of this study indicate that 1) Herbs have become the main treatment choice for rural communities. 2) Therapies are chosen because it has been a treatment for generetions.
Conclusions: Base on the results of the study it can be concluded that the majority of rural people in Indonesia develop more and use herbs as alternative treatments to overcome liver. Local therapy was the main outcome measure and it had the role in reducing various disease.
Keywords: Herbal, Liver, Traditional therapies, Rural community

PE-106

The Efficacy and Safety of Laparoscopic Cholecystectomy Using Indocyanine Green Fluoroscopy

Mi-Rin Lee, Jae Do Yang, Sung-Woo Ahn, Hee Chul Yu

Departments of Surgery, Chonbuk National University Medical School and Hospital, Jeonju, Korea

Aims: Laparoscopic cholecystectomy (LCC) is now accepted as the gold standard for the management of gallbladder diseases. Currently, one of the basic techniques of general surgical residency in Korea is cholecystectomy. However, it is not easy to overcome the learning curve during fellowship period because about 150 cases are required to overcome. Intraoperative imaging using indocyanine green (ICG) might reduce learning curve and the risk of bile duct injury by improving visualization of the biliary tree. We compared the outcomes of LCC in patients with and without ICG.
Methods: We performed a retrospective review of total 300 conventional LCC cases with and without ICG performed by three surgeons who started the fellowship of hepatobiliary surgery in a single center. The outcomes of LCC with and without ICG were compared using the operation time, the rate of conversion, complications and the length of stay.
Results: The median operation time was 43.0 vs. 39.0 min (P=0.45) in the group with and without ICG, respectively. Without ICG, after the first 50 cases, operation time is gradually diminished and the mean operation time reached a plateau (average=35min). In cases of using ICG, after 30 cases experience, we reached plateau. The rate of conversion was 4.6% in the group without ICG, while 2.5% in the group with ICG. Bile duct injury occurred 1% vs 2.2% in the group with and without ICG, respectively. (P<0.05)
Conclusions: LCC with ICG enables a better visualization and identification of biliary tree and therefore should be considered as a means of increasing the safety and reducing learning curve of LCC.

PE-107

HDAC-Targeting Epigenetic Drug Screening for Biliary Tract Cancer

Christian MAYR[1,2], Tobias KIESSLICH[1,2], Sara ERBER[1], Dino BEKRIC[1], Heidemarie DOBIAS[1], Markus RITTER[1,3], Tarkan JÄGER[4], Bettina NEUMAYER[5,6], Paul WINKELMANN[5,6], Eckhard KLIESER[5,6], Daniel NEUREITER[5,6]

[1]Institute for Physiology and Pathophysiology, Paracelsus Medical University, Austria; [2]Department of Internal Medicine I, University Clinics Salzburg, Paracelsus Medical University, Austria; [3]Ludwig Boltzmann Institute for Arthritis und Rehabilitation, Paracelsus Medical University, Austria; [4]Department of Surgery, University Clinics Salzburg, Paracelsus Medical University, Austria; [5]Institute of Pathology, University Clinics Salzburg, Paracelsus Medical University, Austria; [6]Institute of Pathology, Cancer Cluster Salzburg, Austria

Aims: Although molecular insights about biliary tract cancer (BTC) increased in the last decade, new therapeutic strategy like inhibition of histone deacetylases (HDACs) could additionally improve the still dismal outcome of this tumor entity.
Methods: Therefore, we performed comprehensive investigation of HDAC expression and pharmacological inhibition in a panel of eight established BTC cell lines and in a cohort resected native BTC specimens (n=78).
Results: HDAC profiling revealed a heterogeneous expression of HDACs across the studied cell lines and the BTC cancer specimen. Cytotoxicity of six established HDAC inhibitors (HDACi) covering pan- and class-specific HDACis was dose- as well as cell line-dependent and did not show a statistical correlation with HDAC isoform expression. Romidepsin (a class II HDACi), induced the highest reduction of cell viability and apoptosis in BTC cells which was paralleled by reducing HDAC1/2 activity and increasing histone 3 lysine 9 acetylation. Furthermore, non-toxic concentrations of romidepsin could augment the cytotoxic effect of the standard chemotherapeutic cisplatin. Related to the clinical tumor specimen, HDAC expression pattern correlated with the tumor grading and the survival of BTC patients.
Conclusions: In conclusion, in-vitro-experiments provide clear evidence that the HDAC class I inhibitor romidepsin is effective for BTC alone and acts supportively in combination with standard

chemotherapeutics. Additionally, the observed HDAC expression in BTC specimens could serve as a predictive and prognostic biomarker for BTC patients.

11. Surgery,Technical Issues

PE-108

Common Bile Duct Exploration for Retrieval of Impacted Dormia Basket Following ERCP with Mechanical Failure: Case Report

Jenit GANDHI, Manish JOSHI*

Surgical gastroenterology, BGS global hospital, Banglore, India

Aims: Dormia baskets are commonly used during ERCP- endoscopic retrograde cholangiopancreatography. One of the complications is basket retention, through impaction with a gallstone or wire fracture.
Methods: We describe a case of 45-year-old female, referred from the endoscopy department for an emergency surgery. She was undergone ERCP for obstructive jaundice secondary to choledocholithiasis. She was presented to us with metallic wire seen in her oral cavity as external handle of basket snapped causing retained basket plus large gallstone impacted in CBD.
Results: She underwent an emergency laparotomy following CBD exploration for direct stone fragmentation. The basket was cut and removed; wire was withdrawn orally.
Conclusions: This case highlights mechanical failure of dormia basket and its subsequent management which required high surgical skill and full armamentarium in emergent situation for safe and feasible approach which also prevent further interventions.

PE-109

Preoperative Volume Assessment Using Bioelectrical Impedance Analysis for Minimizing Blood Loss during Hepatic Resection

Suk-Won SUH, Yoo Shin CHOI

Surgery, Chung-Ang University Hospital, Korea

Aims: Bioelectrical impedance analysis (BIA) is a method recently used for monitoring volume status, with the advantages of non-invasiveness, rapid processing, and easy handling with a portable instrument. The aim of this study was to determine whether preoperative volume assessment using BIA can be feasible for reducing cardiac preload to minimize blood loss during hepatic resection.
Methods: We investigated 149 patients who underwent hepatic resection from January 2017 to December 2020. Regression analysis showed a significant correlation between central venous pressure (CVP) and the ratio of extracellular water to total body water (ECW/TBW), measured using InBody S10 (Biospace, Seoul, Korea) that ECW/TBW value of 0.378 correlates to a CVP of 5 mmHg (R = 0.839, $P<0.001$). Patients were divided into two groups; 58 patients with ECW/TBW < 0.378 (group A) and 91 patients with ECW/TBW ≥ 0.378 (group B). Demographics and intraoperative and perioperative outcomes were compared between the groups.
Results: here were no significant differences in demographics, diagnosis, preoperative liver function, and type of hepatic resection between the groups. Estimated blood loss was significantly decreased in group A, compared with group B (324±193 mL vs. 508±321 mL, $P<0.001$). Identified predictors for estimated blood loss ≥ 500 mL were body mass index (odds ratio [OR], 1.151; 95% confidence interval [CI], 1.037-1.278; $P=0.008$) and ECW/TBW < 0.378 (OR, 0.271; 95% CI, 0.127-0.577; $P=0.001$).
Conclusions: BIA can be utilized for preoperative volume assessment to minimize blood loss during hepatic resection.

PE-110

Surgical Treatment of the Liver Alveococcosis, Complicated by the Mechanical Jaundice

Gulira Murzalieva

Department of Hospital Surgery at KRSU

Aims: To evaluate the results of surgical treatment of liver alveococcosis complicated by obstructive jaundice.
Methods: 69 patients' case histories undergoing inpatient treatment were analyzed at the Department of Surgical Gastroenterology and Endocrinology of the National Hospital under the Ministry of Health of the Kyrgyz Republic. During the period 2009 to 2019, 440 patients received surgical treatment for alveococcosis of the liver, 69 of them (15.68%) were patients with complicated mechanical jaundice form of alveococcosis, 38 of them (55.07%) were women and 31 (44, 93%) were men. The average age of patients was 37.3 ± 3 years. All patients undergoing treatment were given a blood test for liver tests, the results of which characterized the pattern of obstructive jaundice (the level of total and direct bilirubin was significantly elevated against the background of the normal level of indirect bilirubin fraction).
Results: To improve the general condition of patients, percutaneous-transhepatic drainage of the bile ducts for the purpose of decompression was performed, to resolve questions about the volume of the operation and also as a stage of preoperative preparation. After 2-3 weeks, in 90% of patients laboratory values reached the normal range, which allows for radical surgery. The choice of tactics and the volume of the operation depends on the size, localization of alveolar nodes. The choice of tactics and the volume of the operation depends on the size,

localization of alveolar nodes. 69 patients with alveococcosis of the liver complicated by obstructive jaundice, 6 of them (8.7%) underwent liver resections, with hepaticocholedochitis resection with hepaticojejunostomy on the off loop according to Ru. 6 (8.7%) extensive liver resections were performed. 2 (2, 9%) atypical resections of the liver were performed., 2 (2.9%) related liver transplantation (India)., Resection using transplant technologies: 4 (5.8%) ("invivo - insitu")., 2 (2, 9%) ("exvivo – exsitu").

Conclusions: The best option for surgical treatment of alveococcosis of the liver complicated by obstructive jaundice is decompression of the bile ducts, liver resection performed within healthy tissues. The amount of liver resection should be chosen taking into account the localization, number and extent of alveococcal nodes, as well as local conditions and the presence of complications (lack of extensive germination in the inferior vena cava, forging and portal gates of the liver). In cases of impossibility of carrying out a radical operation, it is necessary to carry out biliary tract decompression in patients with obstructive jaundice, which will improve the quality of life of patients during the period of preparation for a liver transplantation.

Keywords: Liver surgery, Liver alveococcosis, Surgical treatment

PE-111

Endoscopic Treatment of Suppurative Liver Echinococcosis

Rokiya Surova

Kyrgyz-Russian Slavic University

Aims: To study the results of treatment of patients with suppurative echinococcosis of the liver

Methods: Over the past 5 years, the clinic has treated 120 patients with suppuration echtnococcosis of the liver. There were 75 men (62.5%), 45 women (37.5%). The age of patients ranged from 24 to 82 years. In 59 (49.2%). In observations, suppurative echinococcosis of the liver was located in the right lobe of the liver, in 38 (31.7%) in the left lobe of the liver and in 23 (19.1%) cases in both lobes of the liver.

Results: With suppurative liver echinococcosis, the clinical picture of the disease in 98% of cases was dominated by signs of intoxication syndrome. Of the instrumental research methods, the most informative in terms of diagnosing suppurative liver echinococcosis were ultrasound and CT, which diagnosed the disease in 95–97% of cases. To select the method and scope of surgery for traditional or video laparoscopic intervention. They attached importance to assessing the severity of the condition of patients on the APACHE II scale. So, with suppurating liver echinococcosis and severity of the condition of patients according to APACHE II from 0 to 20 points in 74 (61.7%) cases, traditional open methods of echinococcectomy (n = 48), pericystectomy (n = 14) and liver resection (n = 12). In 46 (38.3%) cases with indicators of severity of the condition of patients according to APACHE II more than 20 points whether video laparoscopic and puncture-draining interventions under ultrasound control. After doing nii of traditional open surgical interventions postoperative complications of purulent-septic this character was noted in 27 observations, with 8 deaths, whereas after video laparoscopic interventions and puncture-draining operations postoperative complications were observed in 9 patients ents, with 1 death.

Conclusions: Video laparoscopic interventions and puncture-draining operations under ultrasound control is the operation of choice for suppurating liver echinococcosis in patients with high operational risk.

Keywords: Endoscopic treatment, Suppurative, Liver, Echinococcosis

PE-112

Laparoscopic Resection of Segment 4 and Ventral Area of Anterior Section in Cirrhotic Liver

Yang Won NAH[1], Sang Min KONG[1], Eun Ji LEE[1], Jun Ho JUNG[2]

[1]Department of Surgery, Ulsan University Hospital, Korea; [2]Department of Internal Medicine, Ulsan University Hospital, Korea

Introduction : In this video, I will describe the laparoscopic procedure where the hepatic territory supplied by the Glisson pedicles to the segment 4 and the ventral branches of the right anterior Glisson pedicle is resected.

Methods : A 48 years old male patient presented with two HCC's. Chronic hepatits B was diagnosed 20 years ago. 8 months ago a hypoechoic lesion (1.5cm) was identified in right liver. No treatment was given. On follow CT scan, 2 HCC's were identified. One tumor was 1.8cm in size and located at segment 5-6, 2 cm deep from the liver surface. The other tumor was 1.5cm in size and located at liver hilum, in between the left and right anterior Glisson pedicles and in proximity to the middle hepatic vein. The level of AFP was 3.7 ng/ml and PIVKA II 126 mAU/ml. E was 10.4 kPa on fibroscan. For the sake of preservation of liver volume, the former lesion was ablated with radiofrequency energy before the surgery. And for the latter lesion, laparoscopic resection of segment 4 and ventral area of anterior section was performed.

Results : The operation took 390 minutes. No blood product was given perioperatively. The patient was discharged 6 days after the operation without any complication. He is now tumor free 8 months after the operation.

Conclusions : Laparoscopic resection of segment 4 and ventral area of anterior section in cirrhotic liver can be performed safely and anatomically. Tumor adherent to the middle hepatic vein is a good indication for this parenchyma-sparing resection.

PE-113

Hepatolithiasis - How we Dealt

Balajiprathep Santhan, S.V. Panchabhai

Department of General Surgery, Dr. D.Y. Patil Medical College & Hospital, Pimpri, Pune, India

Aims: Presence of bile duct stones within the intrahepatic bile ducts, proximal to confluence of the right and left hepatic ducts is known as Hepatolithiasis. Rare disease in western world but seen in East Asian Countries & Pacific. The disease can occur with or without concomitant presence of cholelithiasis or choledocholithiasis.
Methods: Two subjects were admitted from surgery Opd, Dr DY Patil medical college, Pune.
Results: A 15 year male with progressive Jaundice since 6 months and pain in abdomen. On investigations -he was found to be a beta thalassemia, with USG and MRCP warranting Multiple intrahepatic stones, proximal and distal CBD calculus. Another patient was 18 years male from same family presented with similar complains. ERCP guided CBD stone extraction was tried but failed. Selective CBD cannulation done on 4th attempt. But still CBD clearance could not be achieved. Decision to go for CBD exploration and Cholecystectomy. Intra operatively complete clearance of Stones in both intrahepatic ducts, confluence, proximal and distal CBD. Ampullary stone not cleared so Roux en Y hepaticojejunostomy was done. Post surgery uneventful, follow up no jaundice, MRCP after 4 weeks no residual stone. Two years follow up – no evidence of new stones in Intrahepatic or extrahepatic biliary system.
Conclusions: Hepatolithiasis a rare disease with chances of recurrence, the newer treatments available are management via percutaneous approaches & Newer modalities for obstructive jaundice in young. PTCSL, POCSL for intra hepatic stones and transduodenal Sphincteroplasty for multiple recurrent CBD stones. As these treatments are not available we were forced to operate.
Keywords: Hepatolithiasis, Beta thalassemia, Obstructive jaundice, PTCSL

12. Others

PE-114

Evogliptin Decreases Lipopolysaccharide Induced iNOS in Primary Hepatocyte

Hye-Young Seo[1,2], So-Hee Lee[1,2], Ji-Ha Lee[1,2], Jae Seok Hwang[1], Mi-Kyung Kim[1,2], Byoung Kuk Jang[1,2*]

[1]Department of Internal Medicine, Keimyung University School of medicine, Daegu, South Korea; [2]Institute for medical Science, Keimyung University School of Medicine, Daegu, South Korea

Aims: Intestinal bacterial endotoxins, such as lipopolysaccharides (LPS), are one of the important mechanisms that cause inflammation. When LPS increase, hepatocytes express inducible nitric oxide synthase (iNOS), which causes liver damage. Evogliptin is a dipeptidyl peptidase 4 inhibitor and a treatment for type 2 diabetes. Although several studies have shown that DPP4 inhibitors improve inflammation, but the effect of evogliptin on liver has not been evaluated. In this study, we examined the effects of evogliptin on LPS-induced iNOS expression.
Methods: We isolated primary hepatocyte cells from C57BL/6 mice and hepatocyte-specific ATG7 knockout ($ATG7^{f/f}$-Cre+) mice. The expression of iNOS was evaluated by real-time RT-PCR and ELISA analysis. LC3 puncta was observed with a fluorescence staining microscope.
Results: Evolgiiptin reduced the expression of LPS-induced iNOS mRNA and iNOS activity in primary hepatocyte, and increased LC3 II conversion, formation of LC3 puncta and autophagy flux. However, evogliptin did not decrease iNOS mRNA and iNOS activity in ATG7f/f-Cre+ mice. Therefore, it was confirmed that an increase in autophagy of evogliptin was associated with a decrease in iNOS.
Conclusions: The results of this study show that evogliptin decrease LPS-induced iNOS expression and activity by increasing autophagy in hepatocyte. These results suggest that evogliptin may be a new drug to treat liver inflammation.
Keywords: Evogliptin, DPP-4 inhibitor, INOS

PE-115

Changes in the Seroprevalence of IgG Anti-Hepatitis A Virus between 2005 and 2019: Experience at Two Centers in South Korea

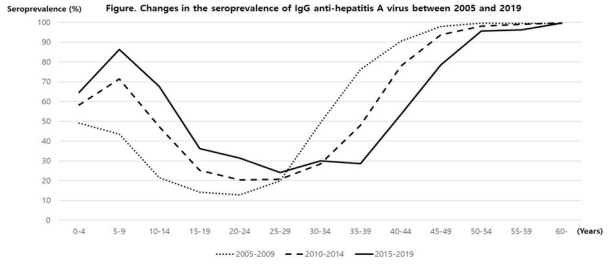
Jae Yoon Jeong[1], Seung Woo Nam[1], Jae Gon Lee[2], Joo Hyun Sohn[2], Won Sohn[3], Hyunwoo Oh[4], Eileen L Yoon[5], Tae Yeob Kim[6]

[1]Department of Internal Medicine, National Medical Center, Seoul, [2]Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, [3]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, [4]Department of Internal Medicine, Uijeongbu Eulji Medical Center, Eulji University College of Medicine, Uijeongbu, [5]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, [6]New Hope Internal Medicine Clinic, Seoul, Korea

Aims: Although universal vaccination in toddlers and in military recruit has been performed, there have been periodic nationwide outbreaks of acute hepatitis A in South Korea since late 2000s. We examined the changes in the seroprevalence of IgG anti-hepatitis A virus (HAV) over the past 15 years (2005-2019).
Methods: We collected retrospectively 15,520 subjects who underwent IgG anti-HAV test without evidence of HAV infection at two academic hospitals in South Korea between January 2005 and December 2019. The seroprevalence of HAV was analyzed according to age and compared among 13 age groups and among the following time periods: late 2000s (2005-2009),

early 2010s (2010-2014), and late 2010s (2015-2019). The chi-square test for trend was used for statistical analysis.

Results: The seroprevalence of HAV in people aged 0-24 years significantly increased over time (P<0.001). On the other hand, the seroprevalence of HAV in those aged 30-49 years decreased over time (P<0.001). In particular, those 30-39 years in late 2010s showed less than 30% seroprevalence of HAV (30.0% in 30-34 years and 28.6% in 35-39 years, respectively). Also, the seroprevalence of HAV in those aged 25-29 years was still low regardless of each period (late 2000s vs early 2010s vs late 2010s: 20% vs 20.8% vs 24.2%, P=0.254).



Conclusions: Since the introduction of universal vaccination, the seroprevalence of HAV in children and young adults has gradually increased. However, the seroprevalence of HAV in their 20s is still low and the seroprevalnce of HAV in their 30s and 40s is gradually decreasing. Therefore, a new strategy for HAV vaccination is needed for those in their 20s to 40s.

Keywords: Hepatitis A infection, IgG anti-hepatitis A virus, Seroprevalence

PE-116

Acute Hepatitis E Virus Superinfection Increases Mortality in Patients with Cirrhosis

Ho Jin Son[1,3], Jin-Kyu Cho[1], Jung Woo Choi[1], Sang Soo Lee[*1-3], Jae Heon Kim[1,3], Hankyu Jeon[1,3], Hee Jin Kim[1-3], Ra Ri Cha[1-3], Jae Min Lee[1-3], Hyun Jin Kim[1-3]

[1]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea; [3]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

Aims: Although acute hepatitis E is not fatal in healthy individuals, it is unclear whether hepatitis E superinfection increases mortality in patients with pre-existing liver disease. Thus, we investigated the prognosis of patients with acute hepatitis E according to their cirrhosis diagnosis, and the prognosis according to the development of acute-on-chronic liver failure (ACLF) in patients with cirrhosis and chronic liver disease (CLD).

Methods: This study included 74 consecutive patients who were diagnosed with acute viral hepatitis E between January 2007 and December 2019. Of them, 39 patients without CLD, 13 patients with non-cirrhotic CLD, and 22 patients with cirrhotic CLD were analyzed.

Results: Among the 74 patients with HEV infection, 7 (9.5%) died within 180 days: 5 with underlying cirrhosis (71.4%) and 2 without cirrhosis (28.6%). The 180-day mortality was significant higher for patients with cirrhosis than for patients without cirrhosis (22.7% vs. 3.8%, P=0.013). The age- and sex-adjusted proportional-hazard model revealed an approximately 8-fold increase in 180-day mortality risk in patients with cirrhosis compared to patients without cirrhosis. In addition, development of hepatitis E virus-related ACLF due to acute liver function deterioration in patients with pre-existing CLD or cirrhosis worsened the 180-day mortality rate.

Conclusions: Our findings suggest that the acute hepatitis E mortality rate was low in heathy individuals but higher in patients with cirrhosis, and especially high in those with ACLF.

Keywords: Hepatitis E virus, Chronic liver disease, Cirrhosis, Acute-on-chronic liver failure, Mortality

PE-117

Impact of Non-Hepatic Hyperammonemia on Mortality in Intensive Care Unit Patients: A Retrospective Cohort Study

Jae Heon Kim[1,3], Hankyu Jeon[1,3], Sang Soo Lee*[1-3], I Re Heo[1,3], Jung Woo Choi[1], Hee Jin Kim[1-3], Ra Ri Cha[1-3], Jae Min Lee[1-3], Hyun Jin Kim[1-3]

[1]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea; [2]Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea; [3]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

Aims: The effect of hyperammonemia on the mortality in patients with liver cirrhosis is well documented. However, little is known about the impact of hyperammonemia on mortality in intensive care unit patients without hepatic disease. We aimed to investigate factors associated with non-hepatic hyperammonemia in intensive care unit patients and evaluate the factors related to 90-day mortality.

Methods: Between February 2016 and February 2020, 972 cases in 948 intensive care unit patients without hepatic disease were retrospectively enrolled and classified as hyperammonemia grades 0 (≤80 μg/dL; n=585 (60.2%)), 1 (≤160 μg/dL; n=291 (29.9%)), 2 (≤240 μg/dL; n=55 (5.7%)), and 3 (>240 μg/dL; n=41 (4.2%)). Factors associated with hyperammonemia and 90-day mortality were evaluated by multivariate logistic regression analysis and Cox regression analysis, respectively. Kaplan-Meier survival curves for 90-day mortality were constructed.

Results: The independent risk factors for hyperammonemia were male sex (odds ratio, 1.517), age (0.984 per year), acute brain failure (2.467), acute kidney injury (1.437), prothrombin time-international normalized ratio (2.272 per unit), and albumin (0.694 per g/dL). The 90-day mortality rate in the entire

cohort was 24.3% and gradually increased with increasing hyperammonemia grade at admission (17.9%, 28.2%, 43.6%, and 61.0% in patients with grades 0, 1, 2, and 3, respectively). Additionally, non-hepatic hyperammonemia was an independent predictor of 90-day mortality in intensive care unit patients.
Conclusions: Non-hepatic hyperammonemia is common (39.8%) and associated with 90-day mortality in intensive care unit patients. Therefore, clinicians must examine serum ammonia levels in patients before admission to intensive care unit.
Keywords: Hyperammonemia, Non-hepatic disease, Intensive care unit, Acute brain failure, Mortality

PE-118

Immediate Results of Surgical Treatment of Metastasis of Colorectal Cancer of the Treatment

Erlan Murzaliev

Department of Hospital surgery of Kyrgyz-Russian Slavic University

Aims: Evaluation of the results of surgical treatment of CRS metastasis in the liver.
Methods: The results of treatment of 34 patients with metastases of colorectal cancer in the liver from 2010 to 2017 are analyzed. There were 19 men (55.8%), women-15 (44.1%). The average age of the patients was 37 ± 85 years old. There localization of metastasis are in the left lobe – 5 patients, right lobe – 24 patients and bilobate liver damage – 6 patients. According to the international mTNM classification IwatsukiS.C. with et al. 1986 metastasis of colorectal cancer in the liver patients were distributed as follows: mT2N0M0 (stage II) - 19, mT3N0M0 (III stage) - 10, mT4N0M0 (IVA stage) - 4 patients, mT4N1M1 (IVB stage) -1.
Results: The following types of liver resection were performed: PGEGE-17, LGGE-2, atypical resections-2, bisegmentectomy -8, trisegmentectomy-3, LLE-1, explorative laparotomy-1. The average loss of blood was 798 ± 256ml., minimal 200 ml. 6 patients had hepatic insufficiency in the postoperative session, received conservative therapy; All patients received adjuvant chemotherapy according to the XELOX scheme, FOLFOX. Postoperative mortality was 2.9% (1 patient).
Conclusions: The tactic of surgical treatment of metastatic liver cancer should be active, liver resection can be performed in patients with sufficient functional reserve of the organ. Performance of anatomic resections of the liver is more preferable. The closest results of treatment of this category of patients justify the proposed treatment tactics.
Keywords: Liver surgery, Liver carcer, Colorectal metastasis

PE-119

Telemedicine in Hepatology

LAWANYA RANJAN[1], AMAR RANJAN[*2]

[1]Engineering Management - Telecommunication, Service Stream Limited, Australia; [2]Cancer Institute, AIIMS, NEW DELHI, India

Aims: Telemedicine involves medical consultation through telecommunication facilities using online devices.
Methods: Literatures review has been done.
Results: Telemedicine includes following components:
Interactive (live) Medicine: It allows patients and physicians to communicate in real-time, while the two are distant locations. They share information from one computer screen to another. Communication is encrypted and transferred. Health data like heart rate, blood pressure, glucose levels are shared. Interaction is done among patient, nearby health professionals or doctors at remote areas with a specialist doctor for diagnosis and management of certain health conditions. It may be used for second opinion or for opinion of other specialities. Many subdivisions are existing even today like 'teleradiology, telepathology. Telemedicine services are evolving for almost all branched of medicine like Mental Health, Pediatric, Dermatology etc.
Specialized Mobile Health devices: In Smartphone, the person opens the app and clicks to choose a doctor. Small scopes and other peripherals can be plugged into a mobile phone. These devices transform the phone into a pocket-sized diagnosis tool, excellent for point-of-care tests. These devices are Digital stethoscope, EKG, Pulse oximeter, Ultrasound, Blood pressure cuff, Otoscope, Dermatoscope etc.
Online Medical Centres are evolving with 24/7 online medical facilities.
Setting up of telemedicine: Various Video-conferencing software like OnCall Health, DrChrono HER etc are available. Portable telemedicine kits includes a computer and mobile medical devices (ECG).
Disadvantages: No clear administrative policy is available. Data leak is of concern.
Conclusions: Telemedicine is an evolving concept and is the need of hours.

PE-120

Biological Potential of Swertisin in the Medicine: Therapeutic Benefit and Biological Potential in the Health Sectors through Current Scientific Research Work

Dinesh Kumar PATEL, Kanika PATEL

Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, India

Aims: Swertisin is a pure phytochemical found to be present in the Iris tectorum which is used in the traditional system of medicine for the treatment of numerous health complications.
Methods: In order to know the effectiveness of swertisin in the medicine against Hepatitis B virus, here in the present investigation numerous scientific research work data have been collected and analyzed from the literature work. Effect of swertisin in different cells was studied in some scientific research work and data have been collected in the present investigation to know their effectiveness for potential anti- Hepatitis B virus activity.
Results: Literature data analysis revealed the biological potential

of swertisin in the modern system of medicine for the treatment of numerous health complications due to their therapeutic benefit and important pharmacological activities. Scientific data analysis of different research work of the literature revealed the biological potential in the medicine for the treatment of numerous human disorders. Literature data analysis of different research work revealed the biological importance of swertisin against Hepatitis B virus as it showed significant inhibitory activity on Hepatitis B virus replication. Some other literature data analysis also signified the biological importance of swertisin in the medicine due to their effectiveness in the Hepatitis B virus transgenic mice model.

Conclusions: Literature data analysis of scientific research works signified the biological potential of swertisin in the medicine for the treatment of Hepatitis B virus infection and could be used for the development of better medicine in the future.

PE-121

Role of D-DIMER, and C-Reactive Protein as Inflammatory Markers in RA Patients Having Raised Liver Enzymes

Soobia Krim Ansari

Department of Biochemistry, Rajkiya Medical College, Jalaun, Orai

Aims: The Aim of this study was to asses, whether, there is association between liver enzymes, D-DIMER and C-reactive protein, as inflammatory markers, in patients suffering from Rheumatoid Arthritis.

Methods: Alanine aminotransferase (ALT), alkaline phosphatase (Alk-P) and high sensitive D-DIMER & C-reactive proteinmeasured in 150 patients. All parameters were assessed in fully autoanalyzer machine.

Results: D-DIMER and C-reactive proteinvalues were found elevated, which is significant in RA patients with raised levels in patients suffering from Rheumatoid Arthritis

Conclusions: Rheumatoid Arthritis is an inflammatory disease, D-DIMER & C-reactive protein are assessed to indicate the degree or severity of inflammation in the body.Elevation of raised values of liver enzymes is closely associated with increased D-DIMER,which in turn shows direct association with each others.

Keywords: Rheumatoid arthritis, D-DIMER, Inflammation, ALT

PE-122

Creation of a Multiaccess Database for Hepatopancreaticobiliary Surgery Using Open-Source Technology in a Country That Lacks Electronic Clinical Database Management Systems

Malaka JAYAWARDENE, Malith Sachintha NANDASENA, Upul DE SILVA, Aloka PATHIRANA

Hepatopancreaticobiliary Unit - Professorial Surgical Unit, Colombo South Teaching Hospital, Sri Lanka

Aims: State sector hospitals in Sri Lanka lack electronic database management systems. The database at the HPB unit at Colombo South Teaching Hospital was based on a rudimentary Google-Sheet that wasn't maintenance-friendly, prone to inconsistencies, and lacked data retrievability for analysis purposes.

Methods: Using cloud-based Google services and AppSheet®, a multiaccess mobile app was developed to store HPB data. The author spent 2 months studying the web platform to create a password-protected app. Consent was obtained from patients to maintain clinical data through the app using mobile devices of the HPB team members. After 25 months of use of the app, this abstract analyses the overall data.

Results: The app can record 254 data variables per patient, of which 222 are analyzable. The database has so far 1561 patients referred to and managed at the HPB unit since November 2018 in which 566 liver (M:F 2:1), 578 pancreatic (M:F 1.5:1), and 417 biliary pathologies (M:F 1:1.2) have been diagnosed. 857 have malignant pathologies, 523 have benign pathologies. 455 had a conclusive surgical management decision, 477 had a nonsurgical management decision. 74% (n=420) of liver, 37% (n=214) of pancreatic, and 53% (n=222) of biliary patients had cancers. Data on 239 HCC, 64 CRLM, 137 pancreatic adenocarcinomas, 16 pancreatic cystic neoplasms, 141 cholangiocarcinoma, and 43 gallbladder cancers are available in the database. In whom a management decision was reached, 31% of liver, 39% of pancreatic, and 49% of biliary patients were operated on.

Conclusions: This cost-free user-friendly solution can revolutionize database management for a low-income country.

PE-123

Recurrent Liver Metastasis in Ovarian Cancer

Harshita DUBEY, Amar RANJAN*

Laboratory Oncology, Dr. B.R.A IRCH, AIIMS, New Delhi, India

Aims: The most common sites of metastasis in Ovarian cancer (OC) is liver, peritoneum, and lymph nodes resulting from hematogenous spread or secondary to liver parenchymal invasion (LPI) from perihepatic peritoneal metastases.

Methods: The case was retrieved from routine reporting at our hospital.

Results: A 34 year old female presented with lump in left side of abdomen for six months. Ultrasonography (USG) showed Left complex tubo-ovarian mass. Serum level of CA125 was 19.8U/mL. Upfront surgery was done. Histopathology showed malignant lesion, positive for WT1, P53 & CK7 and negative for CK 20. Retroperitoneal lymph nodes and omentum were involved. The cases was diagnosed as epithelial ovarian cancer, high grade papillary serous cyst adenocarcinoma stage III. Three months after surgery repeat CECT showed lung and liver metastasis lymphadenopathy. Patient was given 6 cycles of paclitaxel +carboplatin to achieve complete clinical response (CR). Lesions of lung, liver & lymph node subsided. She spent 33 months of treatment free interval, after which lymph node enlargement was noticed and its FNAC showed metastasis. Patient was put

on to oral metronomic therapy (OMT) with Etoposide, Cyclophosphamide and celecoxib (COX-2 inhibitor) for 8 months, which showed CR. Again after 4 months, lesion in liver reappeared with raised CA 125, suggesting second relapse. The patient is on OMT till date with improved clinical condition.

Conclusions: This study highlights the need of early diagnosis, adjuvant chemotherapy with frequent follow up in this case. Liver is an early site for metastasis. Second relapse in also not uncommon.

PE-124

Skewing of Sodium Antimony Gluconate Mediated Therapy to Control Hepato-Splenomegaly during Visceral Leishmaniasis on Triggering CD2 Epitope

Sukrat Sinha

Department of Zoology, Nehru Gram Bharati University, Prayagraj

Aims: Visceral Leishmaniasis is a macrophage associated disorder leading to hepatosplenomegaly for the treatment of which antimony based drugs like SAG and SSG were the first choice in the recent past. The clinical value of antimony therapy is now declined against VL because increasing cases of Sodium Antimony Gluconate (SAG) resistance have reached outstanding proportion in Bihar, India. Within this context we looked into the protein sequences of ABC transporters of Leishmania spp associated with Visceral Leishmaniasis that are known to play a crucial role in the development of multidrug resistance (MDR).

Methods: Our studies consisting of ClustalW, Phylogeny and TCOFFEE have pinpointed that ABC transporters have enormously diverged during the process of evolution even within the identical species strains resulting in insignificant homology and subdued conservation amongst the aminoacid residues.We have also evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3 million parasites via-intra-cardiac route. Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, liver and spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

Results: Amino acid residues remain susceptible to mutations in evolutionary era as indicated by high frequency of variations by the variability studies. Hence we predict that during the process of evolution a series of frequent mutations might have led to changes in the ABC transporters favorable to effluxing the drug thereby making the Leishmania species prone to resistance against the efficient first line drug SAG, used for combating VL. This selection has made them to survive efficiently in the adverse circumstances of antimony based antileishmanial therapy regime.The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy (*P*=0.298) but CD2 treatment even alone significantly influenced IFN- γ production than either SAG treatment (*P*=0.045) or with CD2 adjunct SAG treatment (*P*=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. As shown, the super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Interestingly, the super-oxide generation ability remained intact in macrophage after treatment with immuno-chemotherapy even in mice infected with Leishmania resistant strain. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of L. donovani from infected macrophagesThe combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy (*P*=0.298) but CD2 treatment even alone significantly influenced IFN- γ production than either SAG treatment (*P*=0.045) or with CD2 adjunct SAG treatment (*P*=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. As shown, the super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Interestingly, the super-oxide generation ability remained intact in macrophage after treatment with immuno-chemotherapy even in mice infected with Leishmania resistant strain. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of L. donovani from infected macrophagesThe combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy (*P*=0.298) but CD2 treatment even alone significantly influenced IFN- γ production than either SAG treatment (*P*=0.045) or with CD2 adjunct SAG treatment (*P*=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. As shown, the super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Interestingly, the super-oxide generation ability remained intact in macrophage after treatment with immuno-chemotherapy even in mice infected with Leishmania resistant strain. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of L. donovani from infected macrophagesThe combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy (*P*=0.298) but CD2 treatment even alone significantly influenced IFN- γ production than either SAG treatment (*P*=0.045) or with

CD2 adjunct SAG treatment (*P*=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages. As shown, the super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Interestingly, the super-oxide generation ability remained intact in macrophage after treatment with immuno-chemotherapy even in mice infected with Leishmania resistant strain. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of L. donovani from infected macrophages.

Conclusions: . Our results indicate that CD2, which can boost up a protective Th1 response, might also be beneficial to enable SAG to induce macrophages to produce Leishmanicidal molecules and hence control the infection in clinical situation like Kala-azar. Drug resistance is the major impedance for disease control but the encouraging results obtained after infecting mice with resistant strain of the parasite strongly imply that this drug can be effective even in treating resistant cases of Visceral Leishmanaisis.

Keywords: Visceral leishmanaisis, Sodium antimony gluconate, Sodium stibo gluconate

PE-125

Traditional Medicine and Liver Prevention : Study of The Use of Curcuma Longa as Alternative Treatment for Rural Communities in West Sulawesi, Indonesia

Kadriah Kadriah[1], Nuraliah Nuraliah[2]

[1]Public Health Department, Faculty of Public Health, Al Asyariah Mandar University; [2]West Sulawesi Research and Empowerment Center

Aims: This study aims to describe people's experience in preventing liver disease. The authors explore the person in reducing liver by using alternative drugs based on curcuma longa

Methods: This study used qualitative methods with an ethnographic approach. The author collected data from the local community through interviews, observation and documentation. The phenomenon learned from this treatment was not only the behavior of people who use traditional medicine to prevent liver, but also the effectiveness of these traditional therapies.

Results: The results of this study indicate that 1) curcuma longa have become the main treatment choice for rural communities in preventing liver disease. 2) This treatment is chosen because rural communities believe that curcuma longa has many benefits for health.

Conclusions: Base on the results of the study it can be concluded that the majority of rural people in this place develop more and use herbs as alternative treatments to cure and prevent liver. They prefer to use alternative medicine (herbs) than pharmacological treatment.

Keywords: Raditional medicineT, Liver disease, Curcuma longa, Rural community

PE-126

Biochemistry

Rajiv Nehra[1], Deepti Mandsorwale[2]

[1]Department of Biochemistry, Rajkiya Medical College, Jalaun, U.P, India; [2]SHMMH Medical College, Saharanpur, U.P, India

Aims: World is facing a pandemic by novel coronavirus termed as COVID-19. Patients shows symptoms of fever, respiratory discomfort and myalgia along with liver injury and GI symptoms such as abdominal pain, nausea, vomiting and diarrhoea. GI symptoms were also common during the previous outbreak of coronavirus family. Hepatic injury was assessed with abnormal serum levels of alanine aminotransferase, aspartrate aminotransferase, total bilirubin, concentration of cytokine and acute phase protein.

Methods: 10 ml of fasting venous blood was collected from the anticubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4^0 C for biochemical and immunological investigations. The study group consisted of n=25 healthy individuals (Group I), n=25 COVID-19 (Group II) of either sex aged between 40-65 years. The diagnosis of Liver disease was done by ultrasonographic examination of liver. Serum levels of ALT, AST, Total Bilirubin, Cytokine (IL-6) and acute phase protein (hs-CRP) were estimated.

Results: Mean value of ALT 20.10 ± 5.60 and 354.35 ± 105.18**, AST 28.50 ± 7.50 and 393.15 ± 115.09** T.Bil

0.80 ± 0.15 and 7.20 ±4.10**Concentration of cytokine IL-6 9.24±1.20 and 36.76±11.56; acute phase protein hs-CRP 0.90±1.10 and 2.18±0.90 was significantly elevated in Group II as compared to Group I.

TABLE I- BIOCHEMICAL PARAMETERS AND INFLAMMATORY RESPONSE IN NORMAL AND COVID-19 POSITIVE PATIENTS.

INDIVIDUALS	ALT (IU/L)	AST (IU/L)	Total Bilirubin (mg/dl)	IL-6	Hs-CRP
Normal n=25 (Group I)	20.10 ± 5.60	28.50 ± 7.50	0.80 ± 0.15	9.24±1.20	0.90±1.10
COVID-19 Positive n=25 (Group II)	354.35 ± 105.18**	393.15 ± 115.09**	7.20 ± 4.10**	36.76±11.56	2.18±0.90

data were expressed as mean ± SD. The data was analyzed using the student's t- test. *indicates p<0.05 and statistically significant, **indicates p<0.001 and statistically highly significant

TABLE-I

With respect to biochemical parameters, Mean value of ALT 20.10 ± 5.60 and 354.35 ± 105.18**, AST 28.50 ± 7.50 and 393.15 ± 115.09** T.Bil 0.80 ± 0.15 and 7.20 ± 4.10**

Concentration of cytokine IL-6 9.24±1.20 and 36.76±11.56; acute phase protein hs-CRP 0.90±1.10 and 2.18±0.90 was significantly elevated in Group II as compared to Group I.

Conclusions: Results of the present study indicates that the levels of ALT, AST, Total Bilirubin, CRP and IL-6 increased in parallel with the progression of covid-19 positive patients which indicates COVID-19 might end with GI symptoms and hepatic injury.

Keywords: Hepatic, COVID-19, IL-6, Hs-CRP

PE-127

Bad Relation between Covid19 and Liver Disease

Fitri Kurnia

Economic Faculty, Andalas University

Aims: Covid19 changes the current living system, limited interaction activities and we even have to comply with health protocols, to prevent infection by this virus. Covid19 cannot be considered the common cold virus, because this virus can cause more severe effects, especially in sufferers who have underlying comorbidities. In Indonesia, comorbidities diseases are the leading cause of death for Covid 19 sufferers. One of the comorbidities diseases that aggravate the health conditions of sufferers of Covid19 is liver disease. For this reason, further studies are needed regarding the level of liver disease that can worsen Covid19.

Methods: Literature Review

Results: Acute liver injury have been reported and are associated with higher mortality (Jothimani, Venugopal, Abedin, Kaliamoorthy, Rela, 2020). Patients who have liver disease should receive special care because this group is a very sensitive patient group (Sahin, akbulut, Yilmaz, 2020). Covid 19 sufferers who have acute liver injury must do a complete blood check and EKG, because this because this comorbidities disease can worse covid19 (Indonesian Ministry of Health, 2020). Liver injury is a comorbidities disease that is categorized as severe, because this disease can worsen Covid19 (Wong et.al, 2020).

Conclusions: From the results of previous studies, it can be concluded that liver disease affects the severity of covid19, therefore patients with liver disease should receive special care to minimize the risk of COVID-19 severity.

Keywords: Liver injury, Comorbidities, Covid19, Liver disease

PE-128

Anti-Diabetic and Antihepatotoxicity Activity of Green Synthesized Silver Nanoparticles Using Trigonella Foenum Greacum Seed in Alloxan Induced Diabetic Rats

Poonam, A K Rao

Department of Basic and Applied Sciences, V K Singh University, India

Aims: In developing countries medicinal plants has been proven to be used in the treatment of diabetes mellitus. It was well accounted in the literature that phytofabricated Silver nanoparticle of traditional plants were found effective against diabetes mellitus. The aim of the current study is to investigate the antidiabetic activity of green synthesized silver nanoparticles of Trigonella foenum greacum ethanolic extract (TEE) in alloxan -induced diabetic rats.

Methods: We have successfully biofabricated the silver nanopartivles using ethanolic extract of Trigonella foenum greacum seed under ambient conditions. Green synthesized silver nanoparticles were characterized by using different spectroscopymethods such as UV-spectroscopy, Fourier transform-infrared spectroscopy, X-ray diffraction, transmission electron microscope, Field Emission Scanning Electron Microscope and Energy- dispersive X-ray Spectroscopy. Anti-diabetic potential of green synthesized silver nanoparticles of Trigonella foenum greacum seed extract for 30 days was assessed in alloxan -induced rats by measuring the fasting blood glucose and the peak of blood glucose level within 2 hours of oral glucose tolerance test (OGTT). Its effects on heart and liver antioxidant status and tissue glycogen contents in cardiac muscles were also measured. Statistical analyses were done via one- way analyses of variance (ANOVA) and found to be statistically significant ($P<0.05$).

Results: Variation in the colour of the plant extract from orange to dark brown supported the synthesis of silver nanoparticles (CCAgNOs) and evidenced by the UV- visible spectroscopy which showed absorbance peak at 420-450 nm. Floowing second week, green synthesized silver nanoparticles reduced the level of blood glucose in rats. Furthermore, AgNPs revealed significant enhancement in tissue glycogen contents and plasma insulin.

Conclusions: Eco-friendly synthesized silver nanoparticles of Trigonella foenum greacum seed showed potent antihyperglycemic agent by improving insulin sensitivity and may be tested in clinical tiarls. Thus, the green synthesis and application of the nanoparticles offer a novel approach in nanomedicine for diabetes management.

Keywords: Silver nanoparticles, Trigonella foenum greacum ethanolic extract (alloxan-induced diabetic rats., antihepatotoxicity)

AUTHOR INDEX

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

The Liver Week 2021

발 행 인 : 이 한 주
편 집 인 : 김 승 업

발 행 처 : 대한간학회
서울특별시 마포구 마포대로 53
마포트라팰리스 A1210호
Tel : (02)703-0051, Fax : (02)703-0071
E-mail : kasl@kams.or.kr
Website : http://www.kasl.org

인 쇄 처 : 와이디앤피
서울특별시 강서구 공항대로 213
보타닉파크타워2 713호
Tel : (02)3662-1084, Fax : (02)3664-1084
E-mail : yangks1017@naver.com

등록번호 라-7453(1995년 9월 25일)
2021년 5월 10일 인쇄
2021년 5월 13일 발행

President : Han Chu Lee, M.D.
Editor-in-Chief : Seung Up Kim, M.D.

Published by
The Korean Association for the Study of the Liver
Room A1210, Mapo Trapalace,
53 Mapo-daero, Mapo-gu, Seoul 04158,
South Korea

Printed by
Y design & printing
213, Gonghang-daero, Gangseo-gu, Seoul 07802,
South Korea

Printed on May 10, 2021
Published on May 13, 2021