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# The The Liver Week 2018 June 14-16, 2018 Grand Hyatt Incheon, South Korea

The 24th Annual Meeting of the Korean Association for the Study of the Liver The Korean Association of HBP Surgery Symposium The 21st General Symposium of the Korean Liver Cancer Association The Korean Liver Transplantation Society Symposium













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The Korean Association for the Study of the Liver



THE KOREAN ASSOCIATION OF HBP SURGERY



The K Trans



### Dear colleagues,

On behalf of the organizing committee, we would like to welcome you to The Liver Week 2018.

Since the first meeting was held in 2014, The Liver Week has become a multidisciplinary international conference hosted by the Korean Association for the Study of the Liver (KASL), in partnership with three co-hosting societies. Those societies are the Korean Association of HBP Surgery (KAHBPS), the Korean Liver Cancer Association (KLCA), and the Korean Liver Transplantation Society (KLTS).

The theme of The Liver Week 2018, "Navigating Future Advances in Hepatology", is purposed to encourage all participants to study the recent research trends and views related to liver disorders from the perspectives of eminent experts, and to facilitate the exchange of up-to-date information on liver diseases with your fellow attendees, all with the ultimate goal of revitalizing our research. The organizing committee has prepared an attractive and invaluable scientific program focused on the latest trends, issues, and advances made in various areas including hepatitis, liver cirrhosis, hepatocellular carcinoma. and more.

In particular, this year's program seeks to achieve a breakthrough change from the past. Debate sessions and various joint symposia have been organized for the discussion of major clinical issues. We have also invited the Korea Centers for Disease Control and Prevention (KCDC) to participate in the policy forum by actively participating in the shaping of future policy. On the last day, a lecture and a hands-on course for abdominal ultrasound specialist certification and relevant major education will be conducted.

We firmly believe that The Liver Week 2018 will be a worthwhile experience for all attendees.

Thank you.





**Congress President** The Liver Week 2018

Date

Joong-Won Park Congress Vice President The Liver Week 2018





The Liver Week 2018



Kim myouf Soo

Myoung Soo Kim **Congress Vice President** The Liver Week 2018



# Program at a Glance

### DAY 1 Thursday, June 14, 2018

### ■ WEST TOWER

	ROOM AB (B1)	ROOM C (B1)	ROOM D (B1)
08:00	* Postgraduate Course: Current Concept for the Optimal Management of Chronic Liver Disease		
09:00-	PG1. Current Management of Viral Hepatitis	K. Publication Forum:	
10:00-		How to Publish Good Papers (09:00-10:10)	
		Coffee Break (10:10-10:30)	
_	K	к	
11:00—	PG2. Current Management for Advanced Liver Disease (10:30-12:10)	Academic Forum: How to Win Research Grants (10:30-12:10)	
12:00—			
 13:00	LN SYM 1 [AbbVie] (12:10-13:10)	LN SYM 2 [Ildong] (12:10-13:10)	
 14:00	K PG3. Current Management in Alcoholic Liver Disease (13:10-14:50)		
15:00—		Coffee Break (14:50-15:10)	
- 16:00— -	K PG4. Current Management in Non-Alcoholic Fatty Liver Disease (15:10-16:50)		
17:00— — 20:00			CMH Workshop (Closed Meeting) (17:30-20:30)

### K : Session in Korean

### **POSTGRADUATE COURSE** "Current Concept for the Optimal Management of Chronic Liver Disease"

### Course Director's Message Sang Gyune Kim, Soonchunhyang Univ.

Now more than ever, with the rapid pace of research progress in various hepatology fields, the clinician is challenged in patient management. The integration of the latest tools in scientific education, communication of real methods for treatment, and diagnosis based on critical basic knowledge and clinical skills are an indispensable element for hepatologists to deliver the highest level of patient care. Our Scientific Program Committee has created exciting and diverse educational and scientific programs highlighting cutting edge knowledge, new clinical trends and hot topics of interest. The KASL Postgraduate Course will provide up-to-date information on a variety of interdisciplinary subjects including management of chronic hepatitis B, C, cirrhosis complications, alcoholic and non-alcoholic liver disease.

### **WEST TOWER**

### Room AB [B1]

08:30-10:10	PG1. Current Management of Viral Hepatitis [*K] Kwan Sik Lee (Yonsei Univ.), Ya	oung Oh Kweon (Kyungpook National Univ.)
08:30-08:55	When to Start and Stop Antiviral Therapy in Chronic Hepatitis B?	In Hee Kim, Chonbuk National Univ.
08:55-09:20	Optimal Choice for Antiviral Treatment in Chronic Hepatitis B: New Drug vs. Old Drug	eong Won Jang, The Catholic Univ. of Korea
09:20-09:45	Optimal Choice for Direct-Acting Antiviral for Treatment in Chronic Hepatitis ( Updated KASL Guidelines	C: Sung Jae Park, Inje Univ.
09:45-10:10	Immunological Changes after Antiviral Treatment of Chronic Hepatitis B and	C Wonseok Kang, Sungkyunkwan Univ.
10:10-10:30	Coffee Break	
10:30-12:10	PG2. Current Management for Advanced Liver Disease <sup>[*K]</sup> Sung Kyu Choi (Chonnam No	ational Univ.), Byung Cheol Yun (Kosin Univ.)
10:30-10:55	Management of Ascites and Hydrothorax	Jeong-Hoon Lee, Seoul National Univ.
10:55-11:20	Ascites-Related Complications in Cirrhosis	Moon Young Kim, Yonsei Univ. Wonju
11:20-11:45	Management of Non-Neoplastic Portal Vein Thrombosis	Danbi Lee, Univ. of Ulsan
11:45-12:10	Current Status of Liver Transplantations in Korea	Dong-Sik Kim, Korea Univ.
12:10-13:10	Luncheon Symposium 1 [AbbVie]	
13:10-14:50	PG3. Current Management in Alcoholic Liver Disease <sup>(*K)</sup> Heon Ju Lee (Yeungnam	n Univ.), Byung Ik Kim (Sungkyunkwan Univ.)
13:10-13:35	Mechanisms of Alcoholic Liver Injury: Already Known and to Be Revealed	Sung Hwan Ki, Chosun Univ.
13:35-14:00	Assessment of Alcoholic Liver Disease	Ki Tae Suk, Hallym Univ.
14:00-14:25	Medical Management of Alcoholic Liver Disease	Jae Young Jang, Soonchunhyang Univ.
14:25-14:50	Intervention Strategy for High Risk Drinking in General Clinical Setting	Hae Kook Lee, The Catholic Univ. of Korea
14:50-15:10	Coffee Break	
15:10-16:50	PG4. Current Management in Non-Alcoholic Fatty Liver Disease [*K] Joo Hyun Sohn (Ho	anyang Univ.), Han Chu Lee (Univ. of Ulsan)
15:10-15:35	Cell-Type Specific Roles of Autophagy in Nonalcoholic Steatohepatitis Progress	ion Sang Geon Kim, Seoul National Univ.
15:35-16:00	Noninvasive Assessment of Non-Alcoholic Fatty Liver Disease	Seung Up Kim, Yonsei Univ.
16:00-16:25	Optimal Management of Dyslipidemia and Hyperglycemia in Non-Alcoholic Fatty Liver Disease	Kyu Yeon Hur, Sungkyunkwan Univ.
16:25-16:50	Optimal Management of Nonalcoholic Steatohepatitis and Advanced Fibrosis	Dae Won Jun, Hanvana Univ.



K : Session in Korean

### WEST TOWER

### Room C [B1]

09:00-10:10	Publication Forum: How to Publish Good Papers $^{\scriptscriptstyle[*K]}$	So Young Kwon (Konkuk Univ.), Jin-Wook Kim (Seoul National Univ.)
09:00-09:20	Tips for Writing Papers and Good Cover Letters: How	to Do It Hyun Woong Lee, Yonsei Univ.
09:20-09:40	Tips for Responding to Reviewer Comments	Grace Lai-Hung Wong, The Chinese Univ. of Hong Kong
09:40-10:00	Things Authors Should Know: Editor's Viewpoint	Yoon Jun Kim, Seoul National Univ.
10:00-10:10	Discussion	
10:10-10:30	Coffee Break	
10:30-12:10	Academic Forum: How to Win Research Grants ${}^{({}^{\ast}{\rm K}{\rm )}}$	Kyun-Hwan Kim (Konkuk Univ.), Yong Han Paik (Sungkyunkwan Univ.)
10:30-10:50	Lecture 1: How to Win Research Grants	Goo Taeg Oh, Ewha Womans Univ.
10:50-11:10	0 Lecture 2: Collaborative Research for Clinical Unmet Needs Don Haer	
11:10-11:30	Lecture 3: How to Win Research Grants	Kwang-Lae Hoe, Chungnam National Univ.
11:30-11:50	Lecture 4: How to Win Research Grants	Soon Koo Baik, Yonsei Univ. Wonju
11:50-12:10	Discussion	
12:10-13:10	Luncheon Symposium 2 [Ildong]	

### ROOM C (B1) ROOM AB (B1) ROOM D (B1) ROOM E (2F) ROOM F (2F) ROOM A (2F) ROOM BC (2F) 07:00 EMW 1 NAFLD (07:00-08:00) 08:00-Opening Ceremony (08:15-08:30) KLTS KI CA 09:00-Symposium 1 Symposium Symposium (08:30-09:50) 1 1 (08:30-09:50) (08:30-09:50) Coffee Break (09:50-10:10) 10:00-Plenary Session 1 (10:10-11:10) 11:00-Κ Κ K Κ Hepatology KLTS General Special Associates KCDC-KASL Meeting Lecture Symposium 2 Course Joint (11:10-12:10) (11:20-12:10) (11:10-12:10) (11:10-12:10) Symposium 12:00-(11:10-12:30) General Meeting (12:10-12:25) LN SYM 6 LN SYM 3 LN SYM 4 [Bayer] [BMS] [Yuhan] LN SYM 5 [Astellas] (12:25-13:10) (12:10-13:10) (12:10-13:10) (12:10-13:10) 13:00-Κ Κ Presidential Choice (13:10-13:40) KAHBPS-KLTS-KLCA Health Policy Joint Symposium KLTS Forum Κ 14:00-(13:10-14:30) Coordinator (13:10-14:40) Session Free Paper 1 HBV Free Paper 2 Free Paper 3 NAFLD (13:10-15:10) Clinical Cirrhosis Hepatology (13:30-15:30) (13:30-15:30) (13:30-15:30) Úpdate K K KAHBPS-KLCA-NCC (13:50-15:30) 15:00-**KLTS** Joint CPG for HCC Symposium (14:40-15:30) (14:40-15:30) Poster Round Poster Round Free Paper 4 Press 16:00-Conference Liver Cancer East Tower 2F [G1-G9] East Tower 2F [G1-G9] (15:30-16:30) (15:30-16:30) (15:30-16:30) (15:30-16:30) KLCA Free Paper 8 Free Paper 5 Free Paper 6 Free Paper 7 Free Paper 9 17:00-Symposium 2 Symposium HBV Basic Surgery-Biliary Surgery-Liver (16:30-17:50) (16:30-17:50) 2 (16:30-17:50) (16:30-17:50) (16:30-17:50) (16:30-17:50) (16:30-17:50)

### DAY 2 Friday, June 15, 2018

18:00-

19:00

Faculty Dinner (18:00-20:30)

### ■ WEST TOWER ■ EAST TOWER

ROOM E (2F) EMW 2 Viral

Hepatitis

(07:00-08:00)

The Korean Association for the Study of the Liver (KASL) The Korean Liver Transplantation Society (KLTS) The Korean Association of HBP Surgery (KHBPS) The Korean Liver Cancer Association (KLCA)

### The Liver Week 2018

# Scientific Program

K : Session in Korean

### EAST TOWER

### ROOM D [2F]

07:00-08:00	Early Morning Workshop 1 [Non-Alcoholic Fatty Liver Disease]	Chia-Yen Dai (Kaohsiung Medical Univ.), Dae Won Jun (Hanyang Univ.)
07:00-08:00	Non-Alcoholic Fatty Liver Disease, What Is Next Key Question?	Donghee Kim, Stanford Univ.
		ROOM E [2F]

07:00-08:00	Early Morning Workshop 2 [Viral Hepatitis]	Oidov Baatarkhuu (Mongolian National Univ. of Medical Sciences), Byung Seok Lee (Chungnam National Univ.)
07:00-08:00	How to Optimize Chronic Hepatitis C Treatment?	Jung II Lee, Yonsei Univ.

### WEST TOWER

### Room AB [B1]

08:15-08:30	Opening Ceremony	
08:30-09:50	Symposium 1. Recent Updates in Chronic Hepatitis C You	n Jae Lee (Inje Univ.), Sook-Hyang Jeong (Seoul National Univ.)
08:30-08:50	How to Eliminate Hepatitis C Virus by 2030	Do Young Kim, Yonsei Univ.
08:50 <b>-</b> 09:10	Upcoming Direct-Acting Antivirals for Prior Treatment Failu	re Alessio Aghemo, Humanitas Univ.
09:10-09:30	Management of Special Populations: Decompensated Cirrh Chronic Kidney Disease, and Post-Transplantation	osis, Woo Jin Chung, Keimyung Univ.
09:30-09:50	Special Issue in Hepatitis C Virus Treatment: Hepatitis B Vir and Occurrence and Recurrence of Hepatocellular Carcinor	us Reactivation Chia-Yen Dai, Kaohsiung Medical Univ. na
09:50-10:10	Coffee Break	
10:10-11:10	Plenary Session 1 Soon II Kim (Yonsei Univ.), Joong-Won Park (N	lational Cancer Center), Jung-Hwan Yoon (Seoul National Univ.)
11:10-12:10	Special Lecture	Dong Jin Suh (KMP Healthcare Seoul Clinic)
11:10-11:40	Towards Hepatitis B Virus Cure and Immunology	Qin Ning, Huazhong Univ. of Science and Technology
11:40-12:10	Novel Drivers for Alcoholic Hepatitis and Alcohol-Promoter Liver Cancer	Hidekazu Tsukamoto, Univ. of Southern California
12:10-13:10	Luncheon Symposium 3 [Yuhan]	
13:10-13:40	Presidential Choice	Jin Mo Yang (The Catholic Univ. of Korea)
13:10-13:40 13:10-13:40	Presidential Choice Spread and Elimination of Hepatitis C Virus in Japan	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo
13:10-13:40 13:10-13:40 13:50-15:30	Presidential Choice Spread and Elimination of Hepatitis C Virus in Japan Clinical Hepatology Update (*K)	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.)
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update [*K]         Hepatitis B Virus	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ.
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15 14:15-14:40	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update (*K)         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ.
13:10-13:40         13:10-13:40         13:50-15:30         13:50-14:15         14:15-14:40         14:40-15:05	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update (*K)         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15 14:15-14:40 14:40-15:05 15:05-15:30	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update (*K)         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty         Liver Cirrhosis	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ.
13:10-13:40         13:10-13:40         13:50-15:30         13:50-14:15         14:15-14:40         14:40-15:05         15:05-15:30         15:30-16:30	Presidential ChoiceSpread and Elimination of Hepatitis C Virus in JapanClinical Hepatology Update [*K]Hepatitis B VirusClinical Update of Chronic C Viral HepatitisUpdate of Pharmacological Therapy in Non-Alcoholic FattyLiver CirrhosisPoster Round	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ. EAST TOWER, G1-G9 [2F]
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15 14:15-14:40 14:40-15:05 15:05-15:30 15:30-16:30 16:30-17:50	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update <sup>(*K)</sup> Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty         Liver Cirrhosis         Poster Round         Symposium 2. Recent Updates in Steatohepatitis	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ. EAST TOWER, G1-G9 [2F] Dong Joon Kim (Hallym Univ.), Young Nyun Park (Yonsei Univ.)
13:10-13:40         13:10-13:40         13:50-15:30         13:50-14:15         14:15-14:40         14:40-15:05         15:05-15:30         15:30-16:30         16:30-17:50         16:30-16:50	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update [*K]         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty         Liver Cirrhosis         Poster Round         Symposium 2. Recent Updates in Steatohepatitis         Similarities and Differences in Alcoholic Steatohepatitis and         Nonalcoholic Steatohepatitis: A Histologic Point of View	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ. EAST TOWER, G1-G9 [2F] Dong Joon Kim (Hallym Univ.), Young Nyun Park (Yonsei Univ.) So-Young Jin, Soonchunhyang Univ.
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15 14:15-14:40 14:40-15:05 15:05-15:30 15:30-16:30 16:30-17:50 16:30-17:10	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update [*K]         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty         Liver Cirrhosis         Poster Round         Symposium 2. Recent Updates in Steatohepatitis         Similarities and Differences in Alcoholic Steatohepatitis and         Nonalcoholic Steatohepatitis: A Histologic Point of View         Non-Obese vs. Obese Non-Alcoholic Fatty Liver Disease, W	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ. EAST TOWER, G1-G9 [2F] Dong Joon Kim (Hallym Univ.), Young Nyun Park (Yonsei Univ.) So-Young Jin, Soonchunhyang Univ. nat Is the Difference? Donghee Kim, Stanford Univ.
13:10-13:40 13:10-13:40 13:50-15:30 13:50-14:15 14:15-14:40 14:40-15:05 15:05-15:30 15:30-16:30 16:30-17:50 16:50-17:10 17:10-17:30	Presidential Choice         Spread and Elimination of Hepatitis C Virus in Japan         Clinical Hepatology Update [*K]         Hepatitis B Virus         Clinical Update of Chronic C Viral Hepatitis         Update of Pharmacological Therapy in Non-Alcoholic Fatty         Liver Cirrhosis         Poster Round         Similarities and Differences in Alcoholic Steatohepatitis and Nonalcoholic Steatohepatitis: A Histologic Point of View         Non-Obese vs. Obese Non-Alcoholic Fatty Liver Disease, Wi         Pharmacotherapy against Nonalcoholic Steatohepatitis und	Jin Mo Yang (The Catholic Univ. of Korea) Masao Omata, The Univ. of Tokyo Yung Sang Lee (Univ. of Ulsan), Joung-II Lee (Kyung Hee Univ.) Hyung Joon Yim, Korea Univ. Eun Young Cho, Wonkwang Univ. Liver Disease Kang Mo Kim, Univ. of Ulsan Yeon Seok Seo, Korea Univ. EAST TOWER, G1-G9 [2F] Dong Joon Kim (Hallym Univ.), Young Nyun Park (Yonsei Univ.) So-Young Jin, Soonchunhyang Univ. nat Is the Difference? Donghee Kim, Stanford Univ. er Development Sang Hoon Park, Hallym Univ.

K : Session in Korean

### WEST TOWER

### Room C [B1]

11:10-12:10	Hepatology Associates Course $^{\scriptscriptstyle [^*\mathrm{K}]}$	Myung Seok Lee (Hallym Univ.), Won Young Tak (Kyungpook National Univ.)
11:10-11:25	Management of Cirrhotic Ascites	Nae-Yun Heo, Inje Univ.
11:25-11:40	Management of Hepatic Encephalopathy	Seong Hee Kang, Yonsei Univ. Wonju
11:40-11:55	Antiviral Therapy for Chronic Hepatitis B and C	Hyun Phil Shin, Kyung Hee Univ.
11:55-12:10	Treatment for Hepatocellular Carcinoma	Sung Bum Cho, Chonnam National Univ.
12:10-13:10	Luncheon Symposium 4 [BMS]	
13:10 <b>-</b> 14:40	Health Policy Forum. Hospice and Palliative C	are for Advanced Liver Disease: Current and Future [*K] Youn Seon Choi (Korea Univ.), Young Seok Kim (Soonchunhyang Univ.)
13:10-13:20	Criteria for Hospice and Palliative Care in Korea End-Stage Liver Disease and Domestic Status	an Patients with Sung Eun Kim, Hallym Univ.
13:20-13:40	Hospice and Palliative Care in Patients with End	d-Stage Liver Disease Jeong Han Kim, Konkuk Univ.
13:40-14:00	Hospice and Palliative Care Policy in Korea	Yoon-Jung Chang, National Cancer Center
14:00-14:20	Classification and System of Hospice and Pallia	tive Care in Korea In Kyu Song, National Cancer Center
14:20-14:40	Referral Cases of Hospice and Palliative Care ir with End-Stage Liver Disease	Patients Youngmin Park, NHIS Ilsan Hospital

### Room D [B1]

11:10-12:30	$*$ KCDC-KASL Joint Symposium $^{\scriptscriptstyle (*K)}$ Youngmee Jee (Korea National Institution of the test of	ute of Health), Moon Seok Choi (Sungkyunkwan Univ.)
11:10-11:30	Recent Hepatitis C Outbreaks and Political Direction for Hepatitis Co	ontrol in Korea Hyungmin Lee, KCDC
11:30-11:50	Understanding of Recent Research Trends and Future Direction of Hepatitis C Virus	Sangmin Kang, National Cancer Center
11:50-12:10	Identification of Novel Host Factors Involved in Transcriptional Regulation of Hepatitis B Virus Life Cycle	Yong Kwang Park, Korea National Institute of Health
12:10-12:30	Policy Task Report of the KCDC: Development and Primary Investiga In-Depth Survey of Risk Factors in Hepatitis A Endemic Area	ation of Soon Sun Kim, Ajou Univ.

 $^{\ast}$  KCDC: Korea Centers for Disease Control and Prevention

### Room E [2F]

13:10-15:10	KLTS Coordinator Session [*K]	Hea Seon Ha (Asan Medical Center),	Seung Heui Hong (Samsung Medical Center)
13:10-13:50	Liver Transplantation in Alcoholic Liver	Disease	Jun Yong Park, Yonsei Univ.
13:50-14:30	Counselling, Education, and Monitoring for Patients with Alcoholic Liver Disease before Liver Transplantation		Hyung Sook Kim, Seoul St. Mary's Hospital
14:30 <b>-</b> 15:10	Counselling, Education, and Monitoring Alcoholic Liver Disease after Liver Tran	for Patients with splantation	Kyoung Ock Jeon, Severance Hospital

K : Session in Korean

### EAST TOWER

### Room A [2F]

08:30-09:50	KLTS Symposium 1. Transplantation Related Registries: Present and Future Curie Ahn (Seoul National Univ.), Myoung Soo Kim (Yonsei Univ.)	
08:30-08:55	A2ALL, SRTR John Lake, Univ. of Minnesoto	
08:55-09:20	Israel Penn International Transplant Tumor Registry	E. Steve Woodle, Univ. of Cincinnati
09:20-09:45	European Liver Transplant Registry (ELTR): Achievements and Evolution within a 30-Year History	René Adam, Paul Brousse Hospital
09:45 <b>-</b> 09:50	Discussion	
11:10-12:10	KLTS Symposium 2. Various Approaches to Overcome Portal Vein Thrombosis (with videos) [*K] Kyung-Suk Suh (Seoul National Univ.), Donglak Choi (Daegu Catholic Univ.)	
11:10-11:22	Bidirectional Thrombectomy for Extensive Portal Venous Thrombosis in Kiving Donor Liver Transplantation	wang-Woong Lee, Seoul National Univ.
11:22-11:34	4 Portal Inflow Reconstruction from Varix Dong-Sik Kim, Korec	
11:34-11:46	Reno-Portal Anastomosis	Bong-Wan Kim, Ajou Univ.
11:46-11:58	11:58 Jump Graft from Superior Mesenteric Vein Deok-Bog Moon, Univ	
11:58-12:10	0 Panel Discussion: Optimal Indications for Each Procedure and Precautions	
12:10-12:25	KLTS General Meeting [*K]	
12:25-13:10		
14:40-15:30	KAHBPS-KLTS Joint Symposium (Debate with Panel Discussion) : Primary vs. Salvage Liver Transplantation in Patients with Borderline Liver Function <sup>(*K)</sup> Jae-Won Joh (Sungkyunkwan Univ.), Shin Hwang (Univ. of Ulsan)	
14:40-14:55	Primary vs. Salvage Liver Transplantation in Patients with Borderline Liver Funct	ion Jae Geun Lee, Yonsei Univ.
14:55-15:10	Favoring Salvage Liver Transplantation with Borderline Liver Function	Je Ho Ryu, Pusan National Univ.
15:10-15:30	Panel Discussion with Cases Young Seok Han (Kyungpook National Univ.), Gyu-seong Choi (Sungkyunkwan Univ.), Jae C Je Ho Ryu (Pusan National Univ.)	Geun Lee (Yonsei Univ.),

### Room BC [2F]

08:30-09:50	KLCA Symposium 1. Very Early Stage Hepatocellular Carcinoma (HCC): H Seung Kew Yoon (The Catholic Univ	low to Detect a /. of Korea), Jaes	and Diagnose? seok Hwang (Keimyung Univ.)
08:30-08:50	Detect or Not to Detect Very Early Stage HCC: The Western Perspective		Ju Dong Yang, Mayo Clinic
08:50-09:10	HCC Surveillance in Non-Transplant Setting: An Eastern Perspective		So Yeon Kim, Univ. of Ulsan
09:10-09:30	Noninvasive Diagnosis of Very Early Stage HCC: Focused on Subcentimeter	Nodules	Mi-Suk Park, Yonsei Univ.
09:30-09:50	New Biomarkers to Detect Very Early Stage HCC	Youngs	soo Kim, Seoul National Univ.
11:20-12:10	KLCA General Meeting [*K]		
11:20-11:35	0202 Liver Cancer Day Lecture: Alcohol-Associated HCC and Korean Surveillance Policy	Jeong Won Jang	g, The Catholic Univ. of Korea
12:10-13:10	Luncheon Symposium 6 [Bayer]		

K : Session in Korean

14:40-15:30	Clinical Practice Guidelines (CPG) for HCC [Revised by KLCA-NCC]	<sup>[*K]</sup> Joong-Won Park (National Cancer Center)
16:30-17:50	KLCA Symposium 2. Systemic Treatment for Advanced HCC Joong-Won Park (National	Cancer Center), Ho Yeong Lim (Sungkyunkwan Univ.)
16:30-16:50	Predictive Genomics and Proteomics in HCC: In the Era of Targeted	Therapy Ju-Seog Lee, MD Anderson Cancer Center
16:50-17:10	First Line Treatment for Liver Cancer	Stephen Lam Chan, The Chinese Univ. of Hong Kong
17:10-17:30	Second Line Treatment	Thomas Yau, The Univ. of Hong Kong
17:30-17:50	When to Switch Locoregional Therapy to Systemic Therapy?	Hwi Young Kim, Ewha Womans Univ.

### Room ABC [2F]

13:10-14:30	KAHBPS-KLTS-KLCA Joint Symposium. New Treatment Modalities for Ea Yun Hwan Kir	arly Stage HCC m (Korea Univ.), Hee Jung Wang (Ajou Univ.)
13:10-13:30	Local Ablations: Microwave Ablation and Cryoablation	Min Woo Lee, Sungkyunkwan Univ.
13:30-13:50	New Treatment Modalities for Early Stage HCC: SBRT, Proton Beam	Hee Chul Park, Sungkyunkwan Univ.
13:50-14:10	Laparoscopic Liver Resection for HCC	Jai Young Cho, Seoul National Univ.
14:10-14:30	Liver Transplantation for HCC: What Is New	John Lake, Univ. of Minnesota

# Program at a Glance

### DAY 3 Saturday, June 16, 2018 ■ WEST TOWER ■ EAST TOWER ROOM AB (B1) ROOM C (B1) ROOM B (2F) ROOM C (2F) ROOM DE (2F) 08:00-Κ K Κ Abdominal USG Training Course Educational for Certified Common Concerns 09:00-Program of KAHBPS between Hepatologists Trainer Symposium 3 Free Paper 10 Symposium 1 Abdominal (08:30-09:50) and Surgeons (08:00-10:00) (08:30-09:50) **USG** Practice Liver Cancer (08:30-09:50) (08:30-10:10) (08:30-09:50) 10:00-Coffee Break (09:50-10:10) Κ Plenary Session 2 (10:10-11:10) Abdominal USG 11:00 **Training Course** for Certified Κ Trainer KLTS-KASL Joint KASL-KLCA KAHBPS (10:10-12:10) Symposium 2 Joint Symposium Symposium (11:10-12:10) (11:10-12:10) (11:10-12:10) 12:00-LN SYM 9 LN SYM 10 LN SYM 7 LN SYM 8 [Gilead] [MSD] [Green Cross Cell] [Daewoong] (12:10-13:10) (12:10-13:10) (12:10-13:10) (12:10-13:10) 13:00-**KAHBPS** Special Special Lecture Lecture (13:10-13:40) (13:10-13:40) 14:00-KAHBPS Symposium 4 Free Paper 11 Free Paper 12 Free Paper 13 Symposium 3 (13:40-15:00) НСŃ Liver Cancer Liver Cancer (13:40-15:00) (13:50-15:00) (13:50-15:00) (13:50-15:00) 15:00-Free Paper 14 Free Paper 15 Poster Round Cirrhosis НСV East Tower 2F [G1-G9] (15:00-16:00) (15:00-16:00) (15:00-16:00) 16:00-K \* Hands-On Course [Guest Room, East Tower] The Liver Week 2018 Debrief Session <sup>[\*K]</sup> (16:00-17:00) 17:00 Closing & Award Ceremony (17:00-17:30) 18:00

## WEST TOWER

### Room AB [B1]

08:30-09:50	Symposium 3. Recent Updates in Cirrhosis and Sarco	penia Kwang-Hyub Han (Yonsei Univ.), Soon Ho Um (Korea Univ.)
08:30-08:50	Sarcopenia: Definition and Measurement	Do Seon Song, The Catholic Univ. of Korea
08:50-09:10	Sarcopenia: Ammonia Metabolism and Hepatic Enceph	alopathy Ankur Jindal, Institute of Liver and Biliary Sciences
09:10-09:30	Sarcopenia: Prognostic Impact on Cirrhosis	Sang Gyune Kim, Soonchunhyang Univ.
09:30-09:50	Management of Malnutrition in Cirrhosis	Tae Hee Lee, Konyang Univ.
09:50-10:10	Coffee Break	
10:10-11:10	Plenary Session 2 Dae-Ghon Kim (Cho	nbuk National Univ.), Seung Kew Yoon (The Catholic Univ. of Korea), In-Seok Choi (Konyang Univ.)
11:10-12:10	KLTS-KASL Joint Symposium (Voting). Liver Transpla Myoung S	antation for Alcoholic Liver Disease <sup>(*K)</sup> oo Kim (Yonsei Univ.), Jong Young Choi (The Catholic Univ. of Korea)
11:10-11:25	Severe Alcoholic Hepatitis, How to Manage?	Dong Hyun Sinn, Sungkyunkwan Univ.
11:25-11:40	How Should We Do It? Optimal Management of Severe A Hepatologist's View	Alcoholic Hepatitis: Won Kim, Seoul National Univ.
11:40-11:55	Optimal Treatment for Severe Alcoholic Hepatitis: Transplant Surgeon's Perspective	Young Kyoung You, The Catholic Univ. of Korea
11:55-12:10	Panel Discussion: How I Do It KLT	5: Yang Won Nah (Univ. of Ulsan), KASL: Jun Yong Park (Yonsei Univ.)
12:10-13:10	Luncheon Symposium 7 [Gilead]	
13:10-13:40	Special Lecture	Kwan Soo Byun (Korea Univ.)
13:10-13:40	Mechanisms of Hepatic Triglyceride Accumulation in Non-Alcoholic Fatty Liver Disease	David E. Cohen, Weill Cornell Medicine
13:40-15:00	Symposium 4. Recent Updates in Chronic Hepatitis B Cł	ang Min Kim (National Cancer Center), Jong Eun Yeon (Korea Univ.)
13:40-14:00	Unmet Needs in Chronic Hepatitis B Management	Grace Lai-Hung Wong, The Chinese Univ. of Hong Kong
14:00-14:20	Navigating New Indications of Antiviral Treatment	Young-Suk Lim, Univ. of Ulsan
14:20-14:40	New Biomarkers of Chronic Hepatitis B	Man-Fung Yuen, The Univ. of Hong Kong
14:40-15:00	Therapeutic Challenge Towards Hepatitis B Virus Cure	Jin-Wook Kim, Seoul National Univ.
15:00-16:00	Poster Round	EAST TOWER, G1-G9 [2F]
16:00-17:00	The Liver Week 2018 Debrief Session <sup>[*K]</sup> Sang Hoon Ahn (Yon:	sei Univ.), Dong-Sik Kim (Korea Univ.), Young-Suk Lim (Univ. of Ulsan)
16:00-16:15	Best of KASL Presentations	Jun Young Park, Yonsei Univ.
16:15-16:30	Best of KAHBPS Presentations	Sae Byeol Choi, Korea Univ. / Jong Man Kim, Sungkyunkwan Univ.
16:30-16:45	Best of KLCA Presentations	Jae-Jun Shim, Kyung Hee Univ.
16:45-17:00	Best of KLTS Presentations	Jae Geun Lee, Yonsei Univ.
17:00-17:30	Closing & Awarding Ceremony	

### **WEST TOWER**

### Room C [B1]

08:30-09:50	KAHBPS Symposium 1. Obstructive Jaundice: How Does It Affect Outcomes in Hepatic and Non-He Hyung Chul Kim (Soonchunhyang Univ.),	e <b>patic Surgeries?</b> Sang-Geol Kim (Kyungpook National Univ.)
08:30-08:50	The Impact of Hyperbilirubinemia on the Progression of Hepatic Dysfunction: Comprehensive Experimental Review	Say-June Kim, The Catholic Univ. of Korea
08:50 <b>-</b> 09:10	Impact of Obstructive Jaundice on Outcomes after Major Hepatic Resection	Gi Hong Choi, Yonsei Univ.
09:10-09:30	Impact of Obstructive Jaundice on Outcomes after Non-Hepatic Surgery	Wooil Kwon, Seoul National Univ.
09:30-09:50	Optimal Method to Minimize Postoperative Complications in Patients with Obstructive Jaundice	Masato Nagino, Nagoya Univ.
09:50-10:10	Coffee Break	
11:10-12:10	KAHBPS Symposium 2. Controversies in Surgical Management of Intraher Dong Wook Choi (Sungkyunkwan Uni	patic Cholangiocarcinoma iv.), Sang-Jae Park (National Cancer Center)
11:10-11:25	Quest for Tumor Origin of Cholangiocarcinoma	Baek-hui Kim, Korea Univ.
11:25-11:40	Is There an Optimal Extent of Liver Resection in Patients with Masakaz Intrahepatic Cholangiocarcinoma?	zu Yamamoto, Tokyo Women's Medical Univ.
11:40-11:55	Lymph Node Dissection: To-Do or Not-to-Do?	Chang Moo Kang, Yonsei Univ.
11:55-12:10	Panel Discussion Chi-Young Jeong (Gyeongsang National Univ.), Sae Byeol Choi (Korea Univ.)	
12:10-13:10	Luncheon Symposium 8 [MSD]	
13:10 <b>-</b> 13:40	KAHBPS Special Lecture	Dong-Sup Yoon (Yonsei Univ.)
13:10-13:40	Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy (A Registry: What Have We Learned?	ALPPS) Hauke Lang, Univ. of Mainz
13:40-15:00	KAHBPS Symposium 3. Resectability Revisited: Current Changes and Chal Hee Chul Yu (Chonbuk	lenges National Univ.), Kyung Sik Kim (Yonsei Univ.)
13:40-14:00	Resectability Revisited: Current Changes and Challenges for Hepatocellular (	Carcinoma Hee Jung Wang, Ajou Univ.
14:00-14:20	Colorectal Cancer Liver Mets: Multiple Bilateral Lesions	Hauke Lang, Univ. of Mainz
14:20-14:40	Klatskin Tumor: Combined Vascular Invasion	Masato Nagino, Nagoya Univ.
14:40-15:00	The Impact of Neoadjuvant Chemotherapy for Borderline Resectable Pancreatic Cancer	Manabu Kawai, Wakayama Medical Univ.
		Room D [B1
08:30-09:50	Common Concerns between Hepatologists and Surgeons [*K] Dae-Ghon Kim (Chonbuk Natior	nal Univ.), Koo Jeong Kang (Keimyung Univ.)
08:30-08:50	Evaluation of Remnant Liver Function before Hepatic Resection	Bong-Wan Kim, Ajou Univ.
08:50 <b>-</b> 09:10	Laparoscopic Liver Resection for Hepatocellular Carcinoma: Progress and Current Limitation	Yangseok Koh, Chonnam National Univ.
09:10-09:30	Surgical Approach of Liver Tumors in Caudate Lobe: How Much Location Can Change Surgical Plan?	Young Seok Han, Kyungpook National Univ.
09:30-09:50	Salvage Liver Transplantation: Pros and Cons in LDLT Settings	Dona-Hwan Juna, Univ. of Ulsan

### EAST TOWER

### Room BC [2F]

11:10-12:10	KASL-KLCA Joint Symposium. How to Manage Hepatitis C Virus-Relate Hepatocellular Carcinoma Patients? Shuichiro Shiina (Juntendo	ed 1 Univ.), Seung Woon Paik (Sungkyunkwan Univ.)
11:10-11:25	Direct-Acting Antivirals and Risk of Hepatocellular Carcinoma Recurrenc What Are the Facts?	e: Hyung Joon Kim, Chung-Ang Univ.
11:25-11:40	Hepatocellular Carcinoma Risk after Direct-Acting Antivirals Treatment: Who Is at Risk?	Jung Hyun Kwon, The Catholic Univ. of Korea
11:40-11:55	Direct-Acting Antivirals Response in Hepatocellular Carcinoma: Does the Presence of Hepatocellular Carcinoma Matters?	Ming-Lung Yu, Kaohsiung Medical Univ.
11:55-12:10	Hepatitis C Virus Treatment Awaiting Liver Transplantation: When Is the Right Time?	Kwang-Woong Lee, Seoul National Univ.
12:10-13:10	Luncheon Symposium 10 [Daewoong]	

### Room A [2F]

08:00-10:00	Abdominal Ultrasonography Training Course for Certified Trainer [Session Sung Won Cho (Ajou	) <sup>(+K)</sup> Univ.), Soon Koo Baik (Yonsei Univ. Wonju)
08:00-08:10	Course Introduction	Hyung Joon Yim, Korea Univ.
08:10-08:35	Setting-Up of Ultrasonography Examination Facilities	Soung Won Jeong, Soonchunhyang Univ.
08:35-09:00	Standard Report System for Ultrasonography Results	Hana Park, CHA Univ.
09:00-09:25	Advances in Ultrasound Diagnosis for Chronic Liver Diseases	Hitoshi Maruyama, Chiba Univ.
09:25-09:50	Assessment of Liver Fibrosis Based on Ultrasonography	Soo Young Park, Kyungpook National Univ.
09:50-10:00	Q & A	
10:00-10:10	Coffee Break	
10:10-12:10	Abdominal Ultrasonography Training Course for Certified Trainer [Session Hong Soo Kim (Soonchunhyang Univ.),	II) <sup>[*K]</sup> Won Young Tak (Kyungpook National Univ.)
10:10-10:35	Ultrasonography Education Plan of Korean Association of Internal Medicine	Joong Sik Eom, Gachon Univ.
10:35-11:00	Current State of Ultrasound Training Programs in Japan	Shinji Okaniwa, lida Municipal Hospital
11:00-11:25	Experience and Current Status of Ultrasonography Education Program for Re	sidents Jaeyoun Cheong, Ajou Univ.
11:25-11:50	Role of Artificial Intelligence for Ultrasonography Practice and Training in Fut	ure Jeong Won Ryu, Healcerion
11:50-12:10	Current Changes of National Health Insurance System Policy for Reimbursement of Ultrasonography	Hyung Joon Kim, Chung-Ang Univ.
12:10-13:10	Luncheon Symposium 9 [Green Cross Cell]	

### Room C [2F]

08:30-09:50	Educational Program of Abdominal Ultrasonography Practice [*K] Young Soo Moon (Inje Uni	v.), Young Seok Kim (Soonchunhyang Univ.)
08:30 <b>-</b> 08:55	Optimal Scanning of Abdominal Ultrasonography and Troubles Shootings	Moon Young Kim, Yonsei Univ. Wonju
08:55 <b>-</b> 09:20	Differential Diagnosis of Liver Mass Detected by Ultrasonography	Beom Kyung Kim, Yonsei Univ.
09:20 <b>-</b> 09:45	Tips for Sonographic Diagnosis in Pancreatobiliary Diseases	Shinji Okaniwa, lida Municipal Hospital
09:45-09:50	Q & A	

### Plenary Session 1

Plen	ary Session 2
PS 1-4	Transarterial Chemoembolization plus External Beam Radiotherapy Improves Survival of Patients with Hepatocellular Carcinoma Showing Macroscopic Vascular Invasion Compared with Sorafenib: A Randomized Trial Sang Min Yoon, Baek-Yeol Ryoo, So Jung Lee, Jong Hoon Kim, Ji Hoon Shin, Jihyun An, Han Chu Lee, Young-Suk Lim
PS 1-3	Necessity for the Elimination of Total Necrosis from Hepatocellular Carcinoma Staging after Liver Transplantation
PS 1-2	Efficacy of Sorafenib Monotherapy versus Transarterial Chemoembolization (TACE)-Sorafenib Sequential Therapy in Patients with Extrahepatic Metastasis - An Interim Analysis of Randomized Controlled Trial
PS 1-1	Entecavir Plus Pegylated Interferon Alfa-2a and Sequential HBV Vaccination Increases the Chance of HBsAg-Seroclearance: A Results from Randomized Controlled E+VIP Trial 2 Jeong-Hoon Lee, Sungwon Chung, Min Suk Kim, Sung Woong Kim, Jun Sik Yoon, Young Chang, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

- PS 2-3 DNA Vaccine Encoding HCV Nonstructural Proteins Enhances Virus-Specific Cellular Immune Responses in Patients with Chronic Hepatitis C ···· 7 Ji Won Han, Pil Soo Sung, Seon-Hui Hong, Hyojin Lee, Moonsup Jeong, Su-Hyung Park, Jian Yan, Amir Khan, Joel N. Maslow, David B. Weiner, Jeong Heo, Sang Hoon Ahn, Eui-Cheol Shin
- PS 2-4 Feasibility of Total Laparoscopic Living Donor Right Hepatectomy Compared with Open Surgery: Comprehensive Review of 100 Laparoscopic Cases 7 *Jinsoo Rhu, Gyu Seong Choi, Jong Man Kim, Jae-Won Joh, Choon Hyuck David Kwon*

### Free Paper Session

1. HBV

O-001	Prediction of Histologic Immune-Tolerant Phase Chronic Hepatitis B from HBeAg-Positive with Low ALT Level Paitents
O-002	Adverse Outcomes of HBeAg-Negative Chronic Hepatitis B Patients with High Viral Load and No Significant ALT Elevation
O-003	Cost-Effectiveness of Anti-Viral Treatment in Patients with Immune-Tolerant Phase Chronic Hepatitis B
O-004	Cost-Effectiveness Antiviral Therapy Indication for the Prevention of Hepatitis B Virus Related Hepatocellular Carcinoma
O-005	A Multicenter Randomized Trial Investigating the Antiviral Efficacy of Tenofovir Switch Therapy for Lamivudine-Resistant Chronic Hepatitis B Patients with Complete Virological Response to Lamivudine plus Adefovir Therapy: Interim Analysis of 96 Weeks Foll
O-006	Tenofovir-Based Combination Therapy or Monotherapy for Multi-Drug Resistant Chronic Hepatitis B; Five Year Follow-Up Data of Multicenter Prospective Cohort Study (Final Results) 12 Sang Jun Suh, Hyung Joon Yim, Young Kul Jung, Seong Gyu Hwang, Hana Park, Yeon Seok Seo, Soon Ho Um, Sae Hwan Lee, Young Seok Kim, Jae Young Jang, In Hee Kim, Hyoung Su Kim, Ji Hoon Kim, Young Sun Lee, Eileen L. Yoon, Myeong Jun Song, Jun Yong Park
O-007	Entecavir Improves Liver Function and Fibrosis in Hepatitis B Virus-Associated Cirrhosis: A 6 Years-Multicenter Study
O-008	A Single Substitution Mutation in Viral Polymerase of Hepatitis B Virus Confers Antiviral Resistance to Tenofovir Disoproxil Fumarate 13 Seungtaek Kim, Do Young Kim, Hye Jung Park, Hye Won Lee, Bora Jin, Kwang-Hyub Han, Sang Hoon Ahn
O-009	Projection of Health Outcomes Using Tenofovir Alafenamide (TAF) for the Management of Chronic Hepatitis B (CHB) in Korea

O-010	An Observational Study about Long-Term Renal Outcome in Chronic Hepatitis B Patients Treated with Tenofovir Disoproxil Fumarate in Korea Tae Seop Lim, Hye Won Lee, Mi Young Jeon, Beom Kyung Kim, Seung Up Kim, Jun Yong Park, Do Young Kim, Kwang-Hyub Han, Sang Hoon Ahn
O-011	Renal Safety of Entecavir and Tenofovir in Patients with Treatment-NaïVe Chronic Hepatitis B Virus Infection in Real Life Setting: A Multicenter, Retrospective Cohort Study
O-012	Prospective, Randomized Safety Assessment of Long-Term Therapy With Entecavir or Other Nucleos(t)ide Analogues in Korean Patients with Chronic HBV Infection
2. Ci	rrhosis
O-013	Multicenter Validation of the Baveno VI Criteria for Screening High-Risk Varices in Patients with Compensated Advanced Chronic Liver Disease 16
	Han Ah Lee, Seung Up Kim, Hyung Joon Yim, Yeon Seok Seo, Young-Sun Lee, Sang Jun Suh, Ki Tae Suk, Soung Won Jeong, Young Kul Jung, Moon Young Kim, Ji Hoon Kim, Sang Gyune Kim, The Korean Transient Elastography Study Group
O-014	Screening of Esophageal Varices: Performance of Baveno Criteria with Shear-Wave Elastography in Patients with Compensated Advanced Chronic Liver Disease 17
O-015	What Are the Risk Factors and Rescue Treatments for Endoscopic Variceal Ligation Failure?
O-016	Significant Increase of Portal Pressure in Cirrhotic Patients with Gastric Varices after Plug-Assisted Retrograde Transvenous Obliteration (PARTO) and Its Clinical Significances: Single Tertiary Center Experience 18 Jae Woo Park, Jeong-Ju Yoo, Sang Gyune Kim, Soung Won Jeong, Jae Young Jang, Sae Hwan Lee, Hong Soo Kim, Boo Sung Kim, Jae Myung Lee, Jong Joon Shim, Young Don Kim, Gab Jin Cheon, Baek Gyu Jun, Young Seok Kim
O-017	Validation of Korean Stroop Test in the Screening of Minimal Hepatic Encephalopathy
O-018	The Role of Spleen Volume in Predicting Portal Hypertension in Patients with Cirrhosis
O-019	Prediction of Acute Kidney Injury and Mortality in Patients with Decompensated Cirrhosis with Serum Cystatin C and Urine N-Acetyl-β-D-Glucosaminidase 19 Tae Hyung Kim, Yeon Seok Seo, Yoo Ra Lee, Han Ah Lee, Sun Young Yim, Young Sun Lee, Sang Jun Suh, Young Kul Jung, Ji Hoon Kim, Hyunggin An, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um
O-020	The Role of Kidney Biomarkers in Cirrhotic Patients with Acute Kidney Injury: Interim-Analysis of Multicenter, Prospective Cohort Study. 20 Jeong-Ju Yoo, Jung Hyun Kwon, Young Seok Kim, Soon Woo Nam, Ji Won Park, Hee Yeon Kim, Chang Wook Kim, Seung Kak Shin, Young Eun Chon, Eun-Sun Jang, Sook-Hyang Jeong, Jin Woo Lee, Do Seon Song, Jin Mo Yang, Sung Won Lee, Hae Lim Lee, Young Kul Jung, Hyung Joon Yim, Sang Gyune Kim, Ju Hyun Kim
O-021	The Prevalence and Clinical Course of Adrenal Insufficiency in Patients with Cirrhosis
O-022	The Cut-Off Value of Transient Elastography to Hepatic Venous Pressure Gradient for Alcoholic and Viral Cirrhosis in Korean Patients … 21 Se Ri Ryu, Seong Hee Kang, Jeong-Ju Yoo, Soung Won Jeong, Moon Young Kim, Sang Gyune Kim, Jae Young Jang, Young Seok Kim, Soon Koo Baik, Yong Jae Kim, Su Yeon Park
O-023	Influence of Previous Acute Decompensation and Organ Failure on the Long-Term Prognosis in Cirrhotic Patients with Decompensation 21 Do Seon Song, Tae Yeob Kim, Eileen L. Yoon, Jin Mo Yang, Hee Yeon Kim, Chang Wook Kim, Young Kul Jung, Hyung Joon Yim, Soung Won Jeong, Sang Gyune Kim, Jae Young Jang, Moon Young Kim, Dong Hyun Sinn, Ki Tae Suk, Dong Joon Kim, Korean Acute-on-Chronic Liver Failure (KACLIF) Study Group
O-024	Fibrotic Burden Assessed Using FIB-4 Is Significantly Associated with the Risk of All-Cause Mortality in Patients with Newly Diagnosed Rheumatoid Arthritis Seung Up Kim, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Yong-Beom Park, Sang-Won Lee
3. N.	AFLD
0.025	The Impact of Provinus Asute Decomponentian on Long terms Programs Ascerding to the Soverity of Alcoholic Henetitis in Circhetic

O-026	Usefulness of Lactate-Free Asian Pacific Association for the Study of Liver Acute-On-Chronic Liver Failure (ACLF) Research Consortium (AARC)–ACLF Score for Predicting Short-Term Mortality in Patients with Alcoholic Liver Disease
	Wasim Jafri, S S Tan, Hasmik Ghazinian, Deepak n Amarapurkar, Šombat Treeprasertsuk, Ĝ H Lee, S G Lim, Jinhua Hu, L A Lesmana, Cosmas Rinaldi Lesmana, Akash Shukla, Samir Shah, Chetan Kalal, Manoj Sahu, Z Abbas, J D Sollano, Gian Carpio, Fazal Karim, G K Lau, P N Rao, Diana A Payawal, A Kadir, M F Yuen, V G Mohan Prasad, Osamu Yokosuka, Ananta Prasad, Priyanka Jain, Irene Paulson, Shiv K Sarin, AARC working Party
O-027	A Randomized, Double-Blind, Placebo-Controlled Study of a Multispecies Probiotic Mixture in Non-Alcoholic Fatty Liver Disease
O-028	Non-Invasive Evaluation of Liver Fibrosis, Steatosis, and Nonalcoholic Steatohepatitis in Biopsy-Proven NAFLD Patients
O-029	Growth Differentiation Factor 15 Predicts Advanced Fibrosis in Biopsy-Proven Non-Alcoholic Fatty Liver Disease
O-030	Validation of Low Alanine Aminotransferase Cutoff for Predicting Hepatocellular Carcinoma and Decompensated Hepatic Events
O-031	Prevalence of NAFLD in Asia: A Systematic Review and Meta-Analysis of 195 Studies and 1,753,168 Subjects from 13 Countries 26 Jie Li, Biyao Zou, Hideki Fujii, Yee Hui Yeo, Fanpu Ji, Dong Hyun Lee, Yuemin Feng, Xiaoyu Xie, Wanhua Ren, Qiang Zhu, Mindie H. Nguyen
O-032	The Change of Skeletal Muscle Mass Is Associated with Hepatic Steatosis in Non-Alcoholic Fatty Liver Disease
O-033	Liver Fibrosis Is Associated with Risk for Colorectal Adenoma in Patients with Non-Alcoholic Fatty Liver Disease 27 Min Cheol Kim, Jung Gil Park, Byung Ik Jang, Heon Ju Lee
O-034	Improvement of Nonalcoholic Fatty Liver Disease Reduces the Risk of Incidence of Type 2 Diabetes Mellitus
O-035	Noninvasive Prediction of the Presence and Severity of Nonalcoholic Fatty Liver Disease in Korean Patients with Chronic Kidney Disease: A Validation Study
O-036	Sarcopenia Is Associated with Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease
4. Liv	ver Cancer
O-037	Late Presentation of Hepatitis B among Patients with Newly Diagnosed Hepatocellular Carcinoma: A National Cohort Study
O-038	A MoRAL Score Utilizing Serum Tumor Markers Provides Refined Prognostication of Patients with Hepatocellular Carcinoma after Curative Resection: Data from 662 Consecutive Patients
O-039	A Phase 1 Study Using Autologous Natural Killer Cells in Patients with HAIC-Hepatocellular Carcinoma
O-040	Adjuvant Cytokine-Induced Killer Cell Immunotherapy for Hepatocellular Carcinoma: A Real-World Experience from Two Large-Volume Centers in Korea
	Jun Sik Yoon, Byeong Geun Song, Jeong-Hoon Lee, Hyo Young Lee, Sun Woong Kim, Young Chang, Eun Ju Cho, Su Jong Yu, Dong Hyun Sinn, Yoon Jun Kim, Joon Hyeok Lee, Jung-Hwan Yoon
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	Treatment 32	)
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O-044	Association of Preemptive Anti-HBV Therapy with Improved Long-Term Survival in Patients with Hepatocellular Carcinoma Undergoing Transarterial Therapy
	Jeong Won Jang, Sun Hong Yoo, Seawon Hwang, Pil Soo Sung, Sung Won Lee, Jung Hyun Kwon, Soon Woo Nam, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon
O-045	Differential Effect of Hepatitis B Viral Suppression on Hepatocellular Carcinoma Development According to the Phase of Initial Antiviral Treatment: A Multicenter Study
	Young Chang, Jeong-Hoon Lee, Sung Won Chung, Minseok Albert Kim, Sun Woong Kim, Hyo Young Lee, Junsik Yoon, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon
O-046	Impact of Antiviral Therapy on Risk Prediction Models for Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis B … 34 Hye Yeon Chon, Tae Seop Lim, Mi Young Jeon, Hye Won Lee, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Seung Up Kim
O-047	Improved Bone and Renal Safety at 1Year after Switching from TDF to TAF: In Chronic HepatitisB(CHB) Patients from East Asia 35 Young-Suk Lim, Hyung Joon Kim, Ki Tae Yoon, Won Young Tak, Jae-Seok Hwang, Sang Hoon Ahn, Kwan Soo Byun, Seung Woon Paik, Sook-Hyang Jeong, Yoon Jun Kim, So Young Kwon, John F Flaherty, Vithika Suri Shuyuan Mo, Anuj Gaggar, Ting-Tsung Chang, H. Edward Gane, Henry LY Chan, Wan Long Chuang
O-048	Safety and Efficacy at 1-Year after Switching from TDF to TAF in CHB Patients with Risk Factors for TDF Use
O-049	Improvement of Bone Mineral Density and Markers of Proximal Renal Tubular Function in Chronic Hepatitis B Patients Switched from Tenofovir Disoproxil Furmarate to Tenofovir Alafenamide····································
O-050	Fibrates Significantly Increase the Biochemical Response and Reduce the Risk of Cirrhosis Development in UDCA-Refractory Primary Biliary Cholangitis Patients
	Sung Won Chung, Jeong-Hoon Lee, Minseok Albert Kim, Sun Woong Kim, Young Chang, Hyo Young Lee, Joon Sik Yoon, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon
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O-051	Immune Tolerant Phase of Perinatal HBV Infection: Are HBV-Specific T Cells Really "Tolerant"?
O-052	Higher Asialoglyco Protein Receptor Expression on Placental Cells Is Associated with Hepatitis B Virus Vertical Transmission from Mother to Baby
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DAY 2: June 15, 2018, 10:10-11:10

# **Plenary Session 1**

Chairs : Soon II Kim (Yonsei Univ.) Joong-Won Park (National Cancer Center) Jung-Hwan Yoon (Seoul National Univ.)

#### PS 1-1

#### Entecavir Plus Pegylated Interferon Alfa-2a and Sequential HBV Vaccination Increases the Chance of HBsAg-Seroclearance: A Results from Randomized Controlled E+VIP Trial

Jeong-Hoon Lee, Sungwon Chung, Min Suk Kim, Sung Woong Kim, Jun Sik Yoon, Young Chang, Yun Bin Lee, Eun Ju Cho, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

**Aims:** Currently, HBsAg-seroclearance is considered as a functional cure in chronic hepatitis B patients, although it is rarely achievable with oral nucleos(t)ide analogs (NAs) treatment alone. We conducted a randomized controlled trial to evaluate the efficacy on HBsAg-seroclearance and safety of pegylated interferon alfa-2a (Peg-IFN) plus sequential hepatitis B virus (HBV) vaccination in addition to NA treatment.

**Methods:** A total of 111 patients who achieved serum HBV DNA < 20 IU/mL and quantitated HBsAg (qHBsAg) < 3,000 IU/ mL with entecavir (ETV) treatment were enrolled and randomly assigned to the treatment group (ETV + PegIFN [subcutaneous injection of 180  $\mu$ g every week over 48 weeks] + sequential HBV vaccination [intramuscular injection of recombinant HBV vaccine containing 20  $\mu$ g of HBsAg, at weeks 48, 52 and 56], N=37), the control group (ETV only, N=37), or the explorative group (ETV + Peg-IFN + concurrent HBV vaccination [at weeks 0, 4, and 8], N=37). The primary endpoint was HBsAg-seroclear-ance at week 100 and secondary endpoints included change in qHBsAg titer and safety



**Results:** There was no difference in baseline characteristics including qHBsAg, HBV DNA, HBeAg-positivity, and biochemical markers (e.g., ALT, AST, albumin) among three groups. In intention-to-treat analysis, the treatment group showed significantly higher chance of HBsAg-seroclearance at week 100 (16.2% vs 0%, P=0.025 by Fisher's exact test). However, the explorative group (5.4%) failed to reach significant difference (P=0.49). The changes in median qHBsAg titer from baseline to week 100 was –67.7% in the treatment group and –36.3% in the control group, respectively. Maximal decrease in qHBsAg of

each patients are plotted in Figure 1. Adverse events were significantly more frequent in the treatment group (81.1%) than the control group (2.7%) (P<0.0001). However, the frequency of serious adverse events did not differ significantly among groups (2.7% in both treatment and control group, P=1.00).

**Conclusions:** Entecavir plus an additional PegIFN treatment followed by sequential HBV vaccination with intensified schedule significantly increases the chance of HBsAg-seroclearance compared to entecavir alone. ClinicalTrials.gov number: NCT02097004.

Keywords: HBsAg-seroclearance, Interferone, Vaccine, Entecavir

#### PS 1-2

#### Efficacy of Sorafenib Monotherapy versus Transarterial Chemoembolization (TACE)-Sorafenib Sequential Therapy in Patients with Extrahepatic Metastasis - An Interim Analysis of Randomized Controlled Trial

Hyung Joon Yim<sup>1</sup>, Sang Jun Suh<sup>1</sup>, Young Kul Jung<sup>1</sup>, Sung-Bum Cho<sup>2</sup>, Woo Jin Chung<sup>3</sup>, Young Seok Kim<sup>4</sup>, Si-Hyun Bae<sup>5</sup>, Jun Young Park<sup>6</sup>

<sup>1</sup>Department of Internal Medicine, Korea University College of Medicine, Seoul, <sup>2</sup>Department of Internal Medicine, Chonnam National University Medical School, Gwangju, <sup>3</sup>Department of Internal Medicine, Keimyung University College of Medicine, Daegu, <sup>4</sup>Department of Internal Medicine, Soonchunghyang University College of Medicine, Bucheon, <sup>5</sup>Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, <sup>6</sup>Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

**Aims:** Sorafenib is the standard therapy for hepatocellular carcinoma (HCC) with extrahepatic metastasis (EHM). However, transarterial chemothembolization (TACE) which is a standard therapy for intermediate stage may be beneficial for controlling intrahepatic tumour, thereby providing chance of improving survival in HCC patients with EHM. We aimed to compare the efficacy between the sorafenib monotherapy and TACEsorafenib sequential therapy in HCC patients with EHM.

Methods: This study is a prospective randomized controlled study conducted at 6 tertiary hospitals in South Korea. HCC patients with EHM were enrolled and randomized into sorafenib monotherapy or TACE-sorafenib sequential therapy group. Patients with main portal vein invasion, Child-Pugh class B or C, and history of TACE or previous systemic therapy were excluded. The sorafenib monotherapy group received sorafenib immediately after randomization while the TACE-sorafenib group received 2~4 times of TACE before starting sorafenib. Response evaluation was performed every 2 months, and overall survival (OS), time to progression (TTP), and progression free survival (PFS) were compared. We initially planned 130 patients for the present study, and the results of interim analysis are presented. Results: A total of 65 patients were enrolled currently: 33 patients into the monotherapy and 32 into the sequential therapy group. Baseline characteristics of the patients such as gender, age, aetiology of liver disease, Child-Pugh score, HCC stage,

and tumour burden were not significantly different between two groups. Median OS were 6.4 (0.4-30.6) months and median TTP were 3.5 (0.9-25.7) months in all patients. The probability of survival rates were plotted by Kaplan-Meier curve and compared by log-rank test. Median OS were not different in both groups: monotherapy 4.3 (0.4-30.6) months and sequential therapy 7.4 (1.8-25.7) months (P=0.364). However, median TTP were longer in sequential therapy group: monotherapy 2.6 (0.9-9.3) months and sequential therapy 4.6 (1.0-25.7) months (P=0.003), and the median PFS were also better in the sequential therapy group: monotherapy 2.6 (0.4-9.3) months and sequential therapy 4.6 (1.0-25.7) months (P=0.015). The disease control rate were better in sequential therapy group: monotherapy 40.7% and sequential therapy 71.0% (P=0.020). **Conclusions:** The TACE-sorafenib sequential therapy would be a better strategy than sorafenib monotherapy for the treatment of HCC patients with EHM, especially, in controlling tumour progression.

**Keywords:** Hepatocellular carcinoma, Sorafenib, Transarterial chemothembolization, Metastasis

#### PS 1-3

#### Necessity for the Elimination of Total Necrosis from Hepatocellular Carcinoma Staging after Liver Transplantation

Deok Gie Kim, Yoon Bin Jung, Jae Geun Lee, Dong Jin Joo, Soon 11 Kim, and Myoung Soo Kim

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

**Aims:** Bridging therapy for unresectable hepatocellular carcinoma (HCC) is an effective treatment in the patients waiting liver transplantation. Herein, we evaluated whether the degree of TN affect the staging for HCC after liver transplantation.

**Methods:** We conducted a retrospective study of 391 consecutive HCC patients underwent liver transplantation between September 2005 and December 2016. Pathologic staging was made after counting out tumor masses with TN. The group comparison for 10 year HCC recurrence free survival (RFS) was conducted between the patients downstaged or non-downstaged by adjustment with TN.

**Results:** Among patients, 252 received one or more number of bridging therapies such as transarterial chemoemolization or radiofrequency ablation. Patients within UCSF criteria showed significantly better RFS over 10 years (P<0.001). There was significant difference between groups changing over UCSF criteria after adjusting TN (P<0.001) although only Within UCSF to complete TN group showed significantly higher RFS in inter-group analysis. For AJCC TNM staging, 92 (23.5%) patients were downstaged by TN. Group comparison demonstrated that down staged Stage I and II group had similar RFS with non-downstaged Stage I group (P=0.919) but had higher RFS than non-downstaged Stage II and IIIA group (P=0.048). Downstaged T0 group showed higher RFS than non-downstaged Stage II and IIIA group (P=0.005) but similar RFS with other two groups (P=0.418 and 0.438 respectively). For UNOS T staging, 85 (21.7%) patients were downstaged by TN. In the group comparison, only down staged T0 group showed significantly higher RFS than other groups.



**Conclusions:** In this study, TNM stage I and II adjusted by TN showed better RFS than higher original stage of HCCs but showed similar RFS with patients with lower stage. We conclude HCC with total necrosis dose not need to be considered in the TNM staging.

**Keywords:** Hepatocellular carcinoma, Liver transplantation, Total necrosis, Staging

#### PS 1-4

Transarterial Chemoembolization plus External Beam Radiotherapy Improves Survival of Patients with Hepatocellular Carcinoma Showing Macroscopic Vascular Invasion Compared with Sorafenib: A Randomized Trial

Sang Min Yoon<sup>1</sup>, Baek-Yeol Ryoo<sup>2</sup>, So Jung Lee<sup>3</sup>, Jong Hoon Kim<sup>1</sup>, Ji Hoon Shin<sup>3</sup>, Jihyun An<sup>4</sup>, Han Chu Lee<sup>4</sup>, Young-Suk Lim<sup>4</sup>

Departments of <sup>1</sup>Radiation Oncology, <sup>2</sup>Oncology, <sup>3</sup>Radiology, and <sup>4</sup>Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

**Aims:** Patients with hepatocellular carcinoma (HCC) showing macroscopic vascular invasion (MVI) bear an extremely poor prognosis. Sorafenib is the sole treatment option for advanced stage HCC with MVI with unsatisfactory response rate and survival benefit. Combined transarterial chemoembolization (TACE) plus external beam radiotherapy (RT) has shown promising results in these patients by observational studies. Here, we report the efficacy and safety of TACE plus RT compared to sorafenib in patients with advanced HCC and MVI.

**Methods:** This study was a randomized, open-label trial at an academic tertiary care center. Between July 2013 and October 2016, 90 treatment-naive patients with liver-confined HCC showing MVI were randomly assigned to receive sorafenib (400 mg twice-daily; n = 45; sorafenib group) or TACE (every

6 weeks) plus RT (within 3 weeks after the first TACE; n = 45; TACE+RT group). Primary endpoint was 12-week the progression-free survival (PFS) rate by intention-to-treat analysis. Radiologic response was assessed by independent review according to Response Evaluation Criteria in Solid Tumors (version 1.1). Crossover of treatment was permitted after confirming disease progression.

**Results:** Patients were 33 to 82 years of age, and 85.6% were male. All patients had portal vein invasion of HCC and Child-Pugh class A liver function. The median maximal tumor diameter was 9.7 cm. Most (78.9%) patients had multiple lesions. At week 12, the PFS rate was significantly higher in the TACE+RT group than the sorafenib group (86.7% vs. 34.3%; *P*<0.001). The TACE+RT group showed significantly higher radiologic

response rate (33.3% vs. 2.2% at 24 weeks; P<0.001), significantly longer median time to disease progression (31 weeks vs. 11.7 weeks; P<0.001), and significantly longer overall survival (55 weeks vs. 43 weeks; P=0.04), compared with the sorafenib group. No patients in the TACE+RT group discontinued treatment due to hepatic decompensation.

**Conclusions:** In patients with advanced HCC showing MVI, first-line treatment with TACE+RT was well-tolerated and provided improved progression-free survival, objective response rate, time to disease progression, and overall survival, compared with sorafenib.

**Keywords:** Hepatocellular carcinoma, Vascular invasion, Sorafenib, Transarterial chemoembolization, Radiotherapy



DAY 3: June 16, 2018, 10:10-11:10

# Plenary Session 2

Chairs : Dae-Ghon Kim (Chonbuk National Univ.) Seung Kew Yoon (The Catholic Univ. of Korea) In-Seok Choi (Konyang Univ.)

#### A Prospective, Open-Label, Dose-Escalation, Single-Center, Phase 1 Study for gc1102, a Recombinant Human Immunoglobulin for Chronic Hepatitis B Patients

Hye Won Lee<sup>1,4</sup>, Jun Yong Park<sup>1,4</sup>, Taegon Hong<sup>3,5</sup>, Min Soo Park<sup>23,5</sup>, Sang Hoon Ahn<sup>1,4,5</sup>

<sup>1</sup>Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, <sup>2</sup>Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea, <sup>3</sup>Department of Clinical Pharmacology, Yonsei University College of Medicine, Seoul Korea, <sup>4</sup>Yonsei Liver Center, Severance Hospital, Seoul, Korea, <sup>5</sup>Clinical Trials Center, Severance Hospital, Seoul, Korea, <sup>6</sup>Brain Korea 21 Project for Medical Science, Seoul, Korea

**Aims:** Existing treatment with antiviral drugs eliminates hepatitis B virus (HBV) DNA but not hepatitis B surface antigen (HBsAg). GC1102 is a recombinant human hepatitis B immunoglobulin and expected to boost therapeutic effects by improving the sustained virological response through reduction of the blood HBsAg level. This study aimed to evaluate the safety and efficacy of GC1102 with single and multiple intravenous administrations in chronic hepatitis B (CHB) patients.

**Methods:** This study was designed as a prospective, open-label, sequential group dose-escalation, and single-center study in treatment groups. There were two groups with single administration (Part A, n=24) and multiple (4 times of weekly) administrations (Part B, n=29) of GC1102, which had 80,000 IU, 120,000 IU, 180,000 IU, and 240,000 IU, to CHB patients who had  $\leq$  1,000 IU/mL serum HBsAg. The period of treatment and observation for each subject was 4 weeks for Part A and 7 weeks for Part B.

**Results:** According to the result of analysis on safety and tolerability, no dose limiting toxicity has occurred at all doses so it is considered favorable. No adverse drug reaction was observed up to the 120,000 IU group of both Part A and B. A few adverse events (flushing, nausea, and dizziness) were observed in the 240,000 IU group and all are mild and transient. HBsAg loss occurred in 12.5% (1/8) in the 80,000 IU group and 22.2% (2/9) in the 240,000 IU group of Part B. And HBsAg titer was dramatically declined after each administration and increased value at 28 days after except for 3 subjects who experienced HBsAg loss.

**Conclusions:** The tolerability and safety of GC1102 are considered favorable in CHB patients. Concomitant administration of GC1102 and antivirals is expected to have durable efficacy in patients with HBsAg titer  $\leq$ 1,000 IU/mL and to increase a functional curative chance in CHB patients.

Keywords: Immunoglobulin, GC1102, Prospective, Hepatitis B

#### Sorafenib with versus without Concurrent Conventional Transarterial Chemoembolization (cTACE) in Patients with Advanced Hepatocellular Carcinoma (HCC): Results from a Multicenter, Open-Label, Randomized, Controlled Phase III STAH Trial

Joong-Won Park<sup>1</sup>, Yoon Jun Kim<sup>2</sup>, Do Young Kim<sup>3</sup>, Si Hyun Bae<sup>4</sup>, Seung Woon Paik<sup>5</sup>, Youn-Jae Lee<sup>6</sup>, Donghyeon Lee<sup>7</sup>, Han Chu Lee<sup>8</sup>, Sang Young Han<sup>9</sup>, Jae Youn Cheong<sup>10</sup>, Oh Sang Kwon<sup>11</sup>, Jong Eun Yeon<sup>12</sup>, Bo Hyun Kim<sup>1</sup>, Jae-Seok Hwang<sup>13</sup>

<sup>1</sup>National Cancer Center, Korea; <sup>2</sup>Seoul National University Hospital; <sup>3</sup>Severance Hospital; <sup>4</sup>The Catholic University of Korea, Seoul St. Mary's Hospital; <sup>5</sup>Samsung Medical Center; <sup>6</sup>Inje University Busan Paik Hospital; <sup>7</sup>SNU Boramae Medical Center; <sup>8</sup>Asan Medical Center; <sup>9</sup>Dong-A University Hospital; <sup>10</sup>Ajou University Hospital; <sup>11</sup>Gachon University Gil Medical Center; <sup>12</sup>Korea University Guro Hospital; <sup>13</sup>Keimyung University Dongsan Medical Center

**Aims:** Sorafenib is the standard first-line therapy for patients with advanced HCC. Conventional TACE (cTACE) is an effective treatment for unresectable HCC. A previous phase II study revealed that sorafenib combined with concurrent cTACE (SOR+T) tended to improve outcomes. Herein, we present the results from an investigator-initiated phase III trial that evaluated the effects of SOR+T in patients with advanced HCC.

**Methods:** Patients were randomly assigned (1:1) into one of two arms, to receive sorafenib with cTACE (Arm C) or without cTACE (Arm S) according to modified International Union Against Cancer tumor stage, the extent of vascular invasion, Child-Pugh score and serum alpha-fetoprotein level. All eligible patients received 800 mg sorafenib within 3 days (Arm S and C) and cTACE within 7-21 days after randomization, and repeating cTACE on demand (Arm C). The study continued until progression or unacceptable toxicities were observed. The primary endpoint was overall survival (OS), and secondary endpoints included time to progression (TTP), progression-free survival (PFS), tumor response rate (TRR), and safety profile.

Results: Between January 2013 and December 2015, 339 patients were enrolled from 13 hospitals in South Korea, and the last patients completed the trial on June 2017. Patients' baseline characteristics were well balanced. For Arm C and S, respectively, median OS was 12.8 vs. 10.8 months (hazard ratio [HR], 0.91; 90% confidence interval [CI] 0.69-1.21; P=0.290); median TTP was 5.3 vs. 3.5 months (HR, 0.67; 90% CI, 0.53-0.85; P=0.003); median PFS was 5.2 vs. 3.6 months (HR, 0.73; 90% CI, 0.59-0.91; P=0.01); TRR was 60.6% vs. 47.3% (P=0.005). For Arm C and S, respectively, serious adverse events (AE) were 33.3% vs. 19.8% (P=0.006), and grade <sup>3</sup> 3 AE were increased alanine aminotransferase (20.3% vs. 3.6%), hyperbilirubinemia (11.8% vs. 3.0%), ascites (11.8% vs. 4.2%), thrombocytopenia (7.2% vs. 1.2%), anorexia (7.2% vs. 1.2%), hyponatremia (5.2% vs. 0%) (P<0.05); hand-foot skin reaction (10.5% vs. 11.4%), encephalopathy (5.2% vs. 1.2%), and diarrhea (5.2% vs. 4.2%). Subgroup analysis showed a survival

benefit in patients (46.4%) of Arm C who received  $\geq$ 2 cTACE sessions when compared to patients in Arm S (18.6 vs. 10.8 m; HR, 0.58; 95% CI, 0.40-0.82; *P*=0.006).

**Conclusions:** SOR+T therapy did not improve OS versus sorafenib alone in patients with advanced HCC. However, SOR+T therapy significantly improved TTP, PFS, and TRR, and a survival benefit was observed in the patients who received SOR+T  $\geq$  2cTACE sessions.

Keywords: Hepatocellular carcinoma, Sorafenib, TACE,

#### PS 2-3

# DNA Vaccine Encoding HCV Nonstructural Proteins Enhances Virus-Specific Cellular Immune Responses in Patients with Chronic Hepatitis C

Ji Won Han<sup>1</sup>, Pil Soo Sung<sup>1,2</sup>, Seon-Hui Hong<sup>1</sup>, Hyojin Lee<sup>3</sup>, Moonsup Jeong<sup>3</sup>, Su-Hyung Park<sup>1</sup>, Jian Yan<sup>4</sup>, Amir Khan<sup>4</sup>, Joel N. Maslow<sup>3</sup>, David B. Weiner<sup>5</sup>, Jeong Heo<sup>6</sup>, Sang Hoon Ahn<sup>7</sup>, Eui-Cheol Shin<sup>1\*</sup>

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**Aims:** Although direct-acting antivirals (DAA) are successfully used for the treatment of chronic hepatitis C, there are DAA-resistant cases. Furthermore, DAA-treated patients do not develop protective immunity against HCV re-infection. To complement DAA therapy, we developed a DNA vaccine (VGX-6150) containing three plasmids encoding HCV genotype 1 NS3, NS4 and NS5A consensus immunogens and plasmid encoding IL-28B as a molecular adjuvant. In the present study, we performed a phase I clinical trial of VGX-6150 in patients with chronic hepatitis C (n=18) who had failed interferon (IFN)-based treatment.

**Methods:** VGX-6150 was administered 4 times in 4-week intervals with *in vivo* electroporation to three groups of patients (n=6 for 1, 3, and 6 mg/dose groups, respectively) followed by a 6 mg boost 24 weeks later. Significant side effects were not reported. Cellular immune responses of peripheral blood mononuclear cells (PBMCs) were evaluated by IFN-g ELISpot assays using overlapping peptides spanning NS3~NS5A and staining with HCV-specific HLA class I pentamers.



**Results:** The IFN-g spot number specific to NS3~NS5A was increased in 3 and 6 mg/dose groups after the initial vaccination and in all three groups after the boosting vaccination. However, the frequency of HCV-specific HLA class I pentamer<sup>+</sup> CD8<sup>+</sup> T-cells was not increased by the vaccination. Moreover, the frequency of PD-1<sup>+</sup> cells in the gate of HLA class I pentamer<sup>+</sup> CD8<sup>+</sup> T-cells was not changed by the vaccination. Interestingly, the frequency of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T-cells (Treg) was significantly decreased after the vaccination, consistent with a previous report regarding the effect of an IL-28B-encoding plasmid adjuvant.

**Conclusions:** In the present study, we demonstrate that VGX-6150 enhances HCV antigen-specific T-cell responses without significant side effects. The inclusion of IL-28B as an immune adjuvant was associated with a decrease in Treg cells that may have provided greater immune activation in chronic HCV infection.

Keywords: HCV, DNA vaccine, IL-28B, Regulatory T cell

#### PS 2-4

Feasibility of Total Laparoscopic Living Donor Right Hepatectomy Compared with Open Surgery: Comprehensive Review of 100 Laparoscopic Cases

Jinsoo Rhu, Gyu Seong Choi, Jong Man Kim, Jae-Won Joh, Choon Hyuck David Kwon

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Aims:** We designed this study to analyze the feasibility of laparoscopic living donor hepatectomy compared to open living donor hepatectomy.

**Methods:** Donors who underwent living donor right hemihepatectomy or extended right hemihepatectomy by laparoscopy or open surgery from May 2013 to October 2017 were included in the study. Comparisons between laparoscopic surgery and open surgery were performed using Student's t-test, Mann-Whitney test, chi-square test, Fisher's exact test, and linear-by-linear association.

**Results:** During the study period 305 patients underwent living donor right hemihepatectomy or extended right hemihepatectomy. Of these, 100 underwent laparoscopic surgery and 205 underwent open surgery. The laparoscopy group ( $30.9\pm11.2$  years) had significantly younger age than the open group ( $34.5\pm12.3$  years, P=0.014). The laparoscopy group mostly had type 1 (95.0%) bile duct and 81% had single bile duct in liver grafts, compared with 59.5% type 1 bile duct and 59.5% with single bile duct in the open group. The laparoscopy group had significantly longer operation time ( $378.2 \pm 93.5$  minutes vs. 329.1  $\pm$  68.0 minutes, P<0.001) and warm ischemic time (median 271 minutes vs. 151 minutes, P<0.001) compared to the open group. However, estimated blood loss was smaller in the laparoscopy group ( $298.3 \pm 162.9$  mL vs.  $344.3 \pm 149.9$  mL, P=0.015). There was no difference in complication rate (lap-

aroscopy group 22.0% vs. open group 15.6%, P=0.170) and the severity of complications classified by Clavien-Dindo system did not differ significantly between the groups (P=0.094).

**Conclusions:** When living donors are selected cautiously, laparoscopic living donor hepatectomy can be performed safely with similar outcome to open surgery. However, the procedure should be performed by a surgeon experienced in both liver transplantation and minimally invasive surgery.

**Keywords:** Liver transplantation, Donor hepatectomy, Laparoscopic donor hepatectomy

### The Liver Week 2018

# **Free Paper Session**

0-001~0-012	HBV
0-013~0-024	Cirrhosis
0-025~0-036	NAFLD
0-037~0-042	Liver Cancer
0-043~0-050	HBV
0-051~0-058	Basic
0-059~0-066	Surgery-Biliary
0-067~0-073	Liver Transplantation
0-074~0-080	Surgery-Liver
0-081~0-090	Liver Cancer
0-091~0-097	HCV
0-098~0-104	Liver Cancer
0-105~0-111	Liver Cancer
0-112~0-117	Cirrhosis
0-118~0-123	HCV

1. HBV

#### O-001

#### Prediction of Histologic Immune-Tolerant Phase Chronic Hepatitis B from HBeAg-Positive with Low ALT Level Paitents

Jeong-Ju Yoo<sup>1</sup>, Sang Gyune Kim<sup>1\*</sup>, Young Seok Kim<sup>1</sup>, Soung Won Jeong<sup>2</sup>, Jae Young Jang<sup>2</sup>, Sae Hwan Lee<sup>3</sup>, Hong Soo Kim<sup>3</sup>, Baek Gyu Jun<sup>4</sup>, Young Don Kim<sup>4</sup>, Gab Jin Cheon<sup>4</sup>

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**Aims:** In general, the immune-tolerant (IT) phase is defined as HBeAg-positive patients with high HBV DNA levels and low alanine aminotransferase (ALT) levels. However, there are no clinical markers to accurately predict the true IT phase other than biopsy, and the long-term prognosis of these patients is unclear. In this study, we aimed to find the clinical factors that may help predict the true IT phase on histologic examination and investigate the long-term prognosis of these patients.

**Methods:** This retrospective study included consecutive 276 patients who underwent liver biopsy with HBeAg-positive and high HBV DNA levels, ALT level less than 80 IU/mL and no evidence of clinically cirrhosis at three tertiary hospitals in Korea from 1994 to 2017. It was defined as a true IT phase when there is less than mild inflammation (≦grade1) and mild fibrosis (≦F1) by histopathological examination and the incidence of viral breakthrough (VB), liver cirrhosis (LC) and hepatocellular carcinoma (HCC) were investigated.

Results: Mean age of the patients was 42.5 ± 12.4 years and median ALT was 42 IU/mL [interguartile range (IQR) 31-56]. All of the patients had high HBV DNA, median DNA level was 1.8 x  $10^8$  copies (IQR 1.6 x  $10^7$ - 8.5 x  $10^8$ ). Of the 276 patients who were clinically suspected of IT phase, only 85 patients (35.8%) were in true IT phase. Other biochemical factors including ALT did not predict the true IT phase. Of note, liver stiffness was the only predictor of the true IT phase after adjusting age, FIB-4 score and APRI (adjusted odds ratio 1.35, 95% confidence interval 1.10-1.65, P=0.005). During observation period (median 103 months, IQR 51-145), VB occurred in 204 patients (73.9%), progressed to liver cirrhosis in 43 (15.6%), HCC in 17 (6.2%). In groups with ALT levels more than 2 times the upper limit of normal ( $\geq$ 50 U/ for female,  $\geq$ 70 UL/L for male which was from recent AASLD guideline), the incidence of VB was significantly higher (P=0.006) than lower ALT groups. However, the incidence of LC or HCC was not significantly different between the two groups.

**Conclusions:** For the prediction of the histologic IT phase, the liver stiffness value may be helpful in addition to the current standard of ALT. Also, it is necessary to lower the current prescription standards for antiviral agents, ALT 80.

Keywords: Immune-tolerant, Biopsy, Liver stiffness

#### O-002

June 15, 2018

#### Adverse Outcomes of HBeAg-Negative Chronic Hepatitis B Patients with High Viral Load and No Significant ALT Elevation

Gwang Hyeon Choi<sup>1</sup>, Gi-Ae Kim<sup>1</sup>, Jihyun An<sup>1</sup>, Jonggi Choi<sup>1</sup>, Seungbong Han<sup>2</sup>, Young-Suk Lim<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Korea; and <sup>2</sup>Department of Applied Statistics, Gachon University, Korea

**Aims:** Some HBeAg-negative chronic hepatitis B (CHB) patients have HBV DNA levels >2,000 IU/mL accompanied by persistent-ly normal alanine aminotransferase (ALT). These patients have been regarded to have low risk of progression to cirrhosis or hepatocellular carcinoma (HCC). However, the clinical outcomes of these patients are not well known.

**Methods:** A total of 1,737 consecutive HBeAg-negative adult CHB patients with HBV DNA levels >2,000 IU/mL, but without evidence of cirrhosis, were identified at Asan Medical Center, a tertiary referral hospital in Seoul, Korea, between January 2000 and December 2013, and served as the study population. 'HBeAg-negative hepatitis' was defined as high HBV DNA levels ( $\geq$ 2,000 IU/mL) and high ALT levels  $\geq$  80 IU/mL (n=525); and 'Pre-active hepatitis' was defined as high HBV DNA levels ( $\geq$ 2,000 IU/mL) and normal to mildly elevated ALT levels <2 X upper limit of normal for at least 6 months (n=1212). Normal ALT was defined by AALSD criteria (females, <19 IU/mL; males, <30 IU/mL). The clinical outcomes of the untreated Pre-active hepatitis patients were compared with those of HBeAg-negative hepatitis patients treated with nucleos(t)ide analogs.

**Results:** Pre-active hepatitis group was significantly lower HBV DNA levels (median 4.6 versus 6.5  $\log_{10}$  IU/mL, *P*<0.001), lower ALT levels (median 29 versus 125 IU/mL, *P*<0.001), and higher proportion of males (63.4% versus 58.8%, *P*=0.01) than HBeAg-negative hepatitis group. Both groups had a similar age (mean 47 versus 47). During median followed-up of 7.4 years, 163 (9.4%) developed HCC, 84 (4.8%) died, and 16 (0.9%) received transplantation. Among By univariate analyses, the risks of of HCC (HR, 1.59; 95% CI, 1.08–2.34; *P*=0.02) and death/ transplantation (HR, 2.33; 95% CI, 1.29–4.23; *P*=0.01) compared with HBeAg-negative hepatitis group.

**Conclusions:** Untreated HBeAg-negative CHB patients with high viral load and normal ALT (Pre-active hepatitis) had significantly higher risks of HCC and death/transplantation than treated HBeAg-negative hepatitis patients. Unnecessary deaths could be prevented through earlier antiviral intervention in the pre-active hepatitis patients.

**Keywords:** Hepatitis B, High viral load, Hepatocellular carcinoma, Death

#### O-003

### Cost-Effectiveness of Anti-Viral Treatment in Patients with Immune-Tolerant Phase Chronic Hepatitis B

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**Aims:** Currently, antiviral therapy for chronic hepatitis B (CHB) patients in immune tolerant (IT) phase is generally not recommended. There has been a need for studies assessing benefits of antiviral therapy in IT-phase. A recent study showed that untreated IT-phase patients had higher risk of hepatocellular carcinoma (HCC) than treated immune active (IA) phase patients. We aimed to evaluate the cost-effectiveness of starting antiviral treatment from IT-phase (IT-Tx) compared to delaying the treatment to IA-phase (IA-Tx).

**Methods:** We designed a Markov model to compare expected costs and quality-adjusted life-years (QALYs) between IT-Tx group and IA-Tx group from healthcare system and societal perspectives. Transition probabilities and costs were obtained from a cohort of 4,965 HBeAg-positive, treatment-naive CHB patients at Asan Medical Center. Literature review was conducted for other parameters. Cost and effectiveness were discounted at a 5% annual rate, and incremental cost-effectiveness ratio (ICER) was calculated for 10-year horizon and evaluated with various HCC risks.



#### Figure. ICER change with various HCC risk

When an intervention showed superior efficacy and less costing and consequently the ICER had a negative value, it is referred to as a 'dominant' strategy. In case of dominant strategy, usually ICER was not estimated. But in the current work, to compare the difference according to an addition of the costs of lost productivity ICERs were calculated even though below zero.

Results: The cost-effectiveness analysis showed that IT-Tx group

had #6,996,562 incremental costs and additional 0.294 QALY per patient compared to IA-Tx group with 10-year cumulative HCC risk of 10% (base-case). ICER was #23,819,529/QALY, which was borderline high of the cost-effectiveness threshold (#20,000,000/QALY) in Korea. As HCC risk increased, IT-Tx became acceptable in cost-effectiveness. When the HCC risk increased over 11.8%, ICER went below the threshold. The analysis including the cost of lost productivity showed that IT-Tx was dominant with HCC risk greater than 4.6% (ICER<0).

**Conclusions:** To start antiviral therapy for CHB patients in ITphase was borderline high cost-effective from healthcare system perspective dealing with the only medical costs, however, it was a dominant strategy in view of societal perspective covering also the costs for lost productivity.

**Keywords:** Cost-effectiveness, Immune-tolerant, Immune-active, Hepatocellular carcinoma, Lost productivity

#### O-004

#### Cost-Effectiveness Antiviral Therapy Indication for the Prevention of Hepatitis B Virus Related Hepatocellular Carcinoma

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**Aims:** Antiviral therapy for chronic hepatitis B virus (HBV) infection can reduce the risk of hepatocellular carcinoma (HCC). We tested different scenario of antiviral treatment indication in the prevention of HCC using large retrospective cohort of patients with chronic HBV infection.

Methods: We used multi-center, retrospective cohort that included a total of 3,624 patients (age 48.0 ± 11.9 years, male = 57.3%, cirrhosis = 15.9%) who were monitored without antiviral treatment. We obtained 5-years cumulative incidence rate of HCC according to the treatment criteria. Using observed 5-years HCC incidence rate, estimated 5-years cumulative incidence rate of HCC was calculated assuming that patients under certain criteria would have received immediate antiviral treatment that would have reduced HCC incidence. We tested current antiviral treatment indication by HIRA in Korea [cirrhosis with elevated HBV DNA levels ( $\geq$  2,000 IU/ml) and any alanine aminotransferase (ALT) levels, HBeAg positive patients with elevated HBV DNA levels (≥ 20,000 IU/ml) and elevated ALT levels ( $\geq 2$  UNL), HBeAg negative patients with elevated HBV DNA levels ( $\geq$  2,000 IU/ml) and elevated ALT levels ( $\geq$ 2 UNL)]. We tested several expanded criteria, such as including cirrhosis patients with low-viremia, chronic hepatitis patients with mildly elevated ALT levels (> UNL) or any patients with detectable HBV

#### DNA levels.

Results: There were 161 patients who developed HCC while monitoring without antiviral therapy. Under current antiviral indication, 66.4% of the patients developed HCC within 5 years outside antiviral treatment indication. The number needed to treat (NNT) to prevent one HCC was 21.7 at current indication, assuming hazard reduction of 50% by antiviral therapy. When antiviral treatment indication included cirrhotic patients with detectable HBV DNA levels, 49.5% of the patients developed HCC within 5 years outside antiviral treatment indication, NNT decreased to 19.2, and net total cost (additional cost from AVT + total cost saved from preventing HCC) was decreased. When antiviral treatment indication included chronic hepatitis patients with mildly elevated ALT levels, 51.4% of the patients developed HCC within 5 years outside antiviral treatment indication, NNT increased to 24.4, and net total cost (additional cost from AVT + total cost saved from preventing HCC) was increased.

**Conclusions:** Expansion of antiviral therapy indication requires additional cost for antiviral therapy. However, it can save cost from HCC by preventing HCC. In our scenario, expanding antiviral treatment and treating cirrhotic patients with low level viremia resulted in decreasing NNT, decreasing number of patients who would develop HCC outside treatment criteria, and decreasing total net cost.

Keywords: Hepatitis B, Antiviral therapy, Cost effectiveness,

#### O-005

A Multicenter Randomized Trial Investigating the Antiviral Efficacy of Tenofovir Switch Therapy for Lamivudine-Resistant Chronic Hepatitis B Patients with Complete Virological Response to Lamivudine plus Adefovir Therapy: Interim Analysis of 96 Weeks Foll

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**Aims:** The aim of the study was to investigate the efficacy of tenofovir (TDF) monotherapy in lamivudine (LAM)-resistant chronic hepatitis B (CHB) patients who achieved a complete virological response to LAM plus adefovir (ADV).

**Methods:** This is an investigator initiated prospective, open label, randomized controlled, non-inferiority trial. LAM-resistant CHB patients with undetectable hepatitis B virus (HBV) DNA on LAM plus ADV therapy were 1:1 randomized to LAM plus ADV or switching to TDF monotherapy. Serum biochemistry and HBV DNA were checked every 12 weeks for 96 weeks. The primary endpoint was the proportion of patients with sustained undetectable HBV DNA at week 48.

Results: A total of 76 CHB patients including 26 compensated cirrhosis were enrolled in this study. Thirty-eight patients were randomized to TDF and 37 patients to LAM plus ADV arm. Baseline characteristics showed no significant differences between two groups. HBeAg was positive in three (7.9%) patients among LAM/ADV group and 7 (18.4%) patients among TDF group. Four patients (2 in LAM/ADV group and 2 in TDF group) dropped out of the study before the 48-week follow-up. HBsAg loss was achieved in two patients (one in LAM/ADV group, one in TDF group). Two patients achieved HBsAg seroconversion in LAM/ADV group (2/38, 5.3%). HBeAg loss rate at week 48 was 33.3% (1/3) in LAM/ADV group and 42.9 % (3/7) in TDF group. The proportion of patients with sustained complete virological response at week 48 was not significantly different between two groups by per protocol analysis (100% vs 100%) as well as intention-to-treat analysis (94.7% in LAM/ADV group vs 97.2% in TDF group). Among 26 patients who had been followed up for 96 weeks, sustained virological response was maintained in both groups.

**Conclusions:** Switching to TDF monotherapy is effective and safe in LAM-resistant CHB patients with undetectable HBV DNA to LAM plus ADV combination therapy.

**Keywords:** Chronic hepatitis B, Lamivudine resistance, Tenofovir, Switching

#### O-006

#### Tenofovir-Based Combination Therapy or Monotherapy for Multi-Drug Resistant Chronic Hepatitis B; Five Year Follow-Up Data of Multicenter Prospective Cohort Study (Final Results)

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**Background/Aims:** Recommendation of management of multidrug resistant (MDR) chronic hepatitis B (CHB) is still not uniform. Although current guidelines recommend tenofovir plus entecavir (ETV) or tenofovir monotherapy for MDR CHB, real-life data comparing combinations based TDF versus (vs.) TDF monotherapy are sparse. Herein, we report a multicenter

cohort study for the evaluation of TDF-based therapy for MDR CHB.

**Methods:** The inclusion criteria were CHB patients with resistance to more than 2 nucleos(t)ide analogues and hepatitis B virus (HBV) DNA level over 200 IU/mL. Patients with decompensated cirrhosis or hepatocellular carcinoma were excluded. Primary end point was cumulative virologic response defined by undetectable HBV DNA (<20 IU/mL) until month 60.

Results: A total of 256 patients were enrolled and 236 patients were included for analysis. Mean age of patients were 49 years and 77.5 % were male. Mean baseline HBV DNA level was 4.2±1.6 log IU/mL. Genotypic resistance to L-nucleoside analogues (L-NA)+adefovir (ADV) (79 patients), L-NA+ETV (106 patients), L-NA+ADV+ETV (51 patients) were confirmed at enrollment. Initial treatments for MDR CHB were TDF+ETV 1 mg (171, 72.5 %), TDF+ETV 0.5 mg (7, 3.0 %), TDF+L-NA (6, 3.0 %), and TDF monotherapy (52, 22.0%). Virologic response rates of the whole cohort at year 1, year 2, year 3, year 4, and year 5 were 77.2%, 86.9 %, 89.9 %, 90.1 %, and 92.5 %, respectively. At year 5, virologic response rate was not significantly different between the TDF monotherapy group and TDF-based combination group (87.5 % vs. 93.0 %, respectively, P=0.493 by Fisher's exact test). The cumulative virologic response rate of TDF monotherapy was not significantly different at year 3 (92.3 % vs. 94.0%, respectively, P=0.893) and at year 5 (96.2 % vs. 97.8 %, respectively, P=0.910), and was not inferior to combination therapies considering that 95% confidence interval (-9.2% ~ 5.8% at year 3; -6.5% ~ 3.2% at year 5) did not include the 10% of non-inferiority margin.

**Conclusions:** TDF based therapy was effective for the treatment of MDR CHB for during 5 years of follow-up. The efficacy of TDF monotherapy was not inferior to the TDF based combination therapy.

**Keywords:** Chronic hepatitis B, Multidrug resistant, Management, Tenofovir

#### **O-007**

#### Entecavir Improves Liver Function and Fibrosis in Hepatitis B Virus-Associated Cirrhosis: A 6 Years-Multicenter Study

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**Aims:** Previously we reported that entecavir (ETV) improves liver function and non-invasive fibrosis markers in patients with HBV-associated cirrhosis after 2 years of treatment (Shin et al. JGH, 2016). This study extended observational period (6 years) and aimed to verify same objects after 6 years of ETV treat-

#### ment.

**Methods:** Among 370 patients who were enrolled in 2 yearsstudy of ETV, a total 283 naïve patients with HBV associated-cirrhosis was treated by ETV for at least 6 years in 4 tertiary institutions. For the evaluation of liver function or fibrosis, laboratory findings, model for end stage liver disease (MELD) score, Child-Pugh (CP) class, AST platelet ratio index (APRI), FIB-4 index, fibrosis index (FI), and liver stiffness measurement (LSM) value were compared between the baseline and 6 years after ETV treatment.

Results: The final 205 patients (mean age of 50±9 years; 64.2% male; 50.2% HBeAg-positive) were enrolled. The baseline ALT and HBV DNA levels were 139±205 IU/L and 6.9±1.2 log<sub>10</sub> copies/mL, respectively. The ALT normalization and the undetectable HBV DNA rate after 6 years of ETV treatment were 87.3% and 99.0%, respectively. Changes in total bilirubin (1.9±2.7 to 1.1±0.6 mg/dL, P<0.001), albumin (3.7±0.6 to 4.2±0.4 g/dL, P<0.001), platelet count (105±44 to 124±53ĺ10<sup>3</sup>/ mm<sup>3</sup>, P<0.001), and MELD score (8.5±4.6 to 5.9±4.6, P<0.001) were observed. The change of distribution in CP class (A:74.1%, B:21.0%, C:4.9% at baseline to A:96.1%, B:3.4%, C:0.5% at 6 years after ETV treatment) was observed. The changes in APRI score, FIB-4 index, and FI were from 3.7±5.4 to 0.8±0.7 (P<0.001), from 6.4±6.3 to 3.5±2.7 (P<0.001), and from 3.2±0.9 to 2.6±0.9 (P<0.001), respectively. The change in LSM value (n=55) was from 26.5±17.7 to 12.4±8.0 kPa (P<0.001). Conclusions: Long-term treatment with ETV improves liver function and fibrosis in patients with HBV-associated cirrhosis.

Keywords: Liver cirrhosis, Liver function, Liver fibrosis, Entecavir

#### **O-008**

#### A Single Substitution Mutation in Viral Polymerase of Hepatitis B Virus Confers Antiviral Resistance to Tenofovir Disoproxil Fumarate

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**Aims:** Tenofovir disoproxil fumarate (TDF) is currently one of the best options in the treatment of patients with chronic hepatitis B (CHB). The efficacy and safety is well known and the occurrence of antiviral resistance mutation has been rarely reported regarding this treatment. In this study, we aimed to identify and characterize antiviral resistance mutations against TDF from a patient with CHB.

**Methods:** Sera from the CHB patient who experienced viral breakthrough during TDF treatment were collected and viral DNA was isolated. The viral polymerase sequence was determined by clonal sequencing method. In order to assess the effect of the mutations on viral replication, they were introduced

in the genotype C hepatitis B virus (HBV) replicon DNA either as a single substitution or as multiple substitutions and investigated after transfection into the HepG2 cells.

Results: Sequencing of HBV polymerase identified five uncommon mutations. Of these, rtL180H was observed in all the clones that were sequenced and the other mutations (rtD134E, rtN139K, rtV142A, rtA181T) were observed in four out of eleven clones simultaneously. The effect of these mutations on viral replication and in vitro drug susceptibility was assessed after introducing only one mutation (rtL180H) or five of them together (rtL180H, rtD134E, rtN139K, rtV142A, rtA181T). Although the replication capacity was substantially reduced after introducing the mutations, either single substitution or multiple substitutions, the replication of the mutant HBV replicons was less susceptible to TDF treatment compared to that of the wild-type genotype C HBV replicon. A similar in vitro susceptibility was observed in lamivudine+TDF treatment as well. Finally, a critical rtL180H mutation was tested in genotype D HBV replicon and this mutation alone was sufficient to confer resistance to TDF treatment.

**Conclusions:** Novel antiviral resistance mutations against TDF were identified and analyzed regarding viral replication and *in vitro* drug susceptibility. The results from this investigation suggest a more effective measure of control is necessary to inhibit HBV replication and ultimately cure HBV infection.

Keywords: Hepatitis B virus, Antiviral resistance, Tenofovir

#### O-009

#### Projection of Health Outcomes Using Tenofovir Alafenamide (TAF) for the Management of Chronic Hepatitis B (CHB) in Korea

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**Aims:** An estimated 1.5 million in Korea have CHB. KASL guidelines recommend tenofovir disoproxil fumarate (TDF) or entecavir (ETV) as preferred therapy. The 2017 EASL guidelines recommend that CHB-patients with declining renal function/osteoporosis should be considered for switch to TAF or ETV with TAF preferred in lamivudine-experienced patients.

**Methods:** We estimated the health-outcomes of 1,000 Korean CHB patients comparing TAF to ETV or TDF over lifetime using Discretely-Integrated-Condition-Event-Simulation (DICE). Model inputs were drawn from published randomized-controlled trials, peer-reviewed Korean literature, real-world-database analyses, and clinical-expert opinion. Based on results of two pivotal-trials, the model applied similar HBV suppression/resistance rates between TAF and TDF, but improved ALT normalization and bone/renal safety. From literature, the model assumed that 20% of treatment-experienced (TE) patients were lamivu-

dine-exposed and had higher viral resistance rates to ETV. Two treatment pathways were modeled: (1) 1<sup>st</sup> line treatment-naïve (TN) monotherapy and (2) TN and TE sequential-therapy wherein treatments could be switched based on viremia/resistance.

**Results:** Over lifetime, TN-patients on TAF are projected to have better liver-outcomes with fewer compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma events and experienced higher quality-adjusted-life-years (QALYs) compared to ETV or TDF (Table 1). Patients started on TAF also had less chronic kidney disease stage 3 (CKDIII) events compared to both ETV and TDF. Under sequential-therapy, TAF as 1<sup>st</sup> line is projected to have better liver-outcomes and higher QALYs compared to 1<sup>st</sup> line ETV and TDF. TAF as 1<sup>st</sup> line resulted in less CKDIII and fracture events compared to 1<sup>st</sup> line ETV and TDF (Table 1).

Table 1. Number of Events over Lifetime per 1,000 Patients

Treatment	CC	DC	HCC	Fracture	CKD	LY's	QALYs		
Sequence					III	(discounted)	(discounted)		
Treatment-Naïve 1st Line Monotherapy									
TAF	296	70	110	276	101	16.12	10.60		
TDF	297	70	110	291	134	16.07	10.55		
ETV	316	76	137	272	128	15.89	10.41		
Treatment-Naïve and Treatment-Experienced Switch Sequence Therapy									
TAF→ETV	292	62	105	324	195	15.84	10.43		
$\rightarrow$									
ETV+TAF									
TDF→ETV	294	59	111	337	292	15.72	10.34		
$\rightarrow$									
ETV+TDF									
ETV→TAF	315	69	125	328	292	15.68	10.29		
$\rightarrow$									
ETV+TAF									
ETV→TDF	316	70	125	328	292	15.68	10.29		
$\rightarrow$									
ETV+TDF									

CC – Compensated Cirrhosis; DC – Decompensated Cirrhosis; HCC – hepatocellular careinoma; CKDIII – Chronic Kidney Disease Stage 3; LY – Life Years; QALY – Quality Adjusted Life Years; ETV - Entecavir; TAF - Tenofovir Alafenamide; TDF - Tenofovir Disoproxil Fumarate

**Conclusions:** TAF as monotherapy or 1<sup>st</sup> line in sequential-therapy is projected to have fewer hepatic-complications and renal/bone events when compared to TDF and ETV over a lifetime, driven by its favorable resistance and safety profile. This data suggests that switching aging patients to TAF may result in advantageous clinical and safety outcomes.

**Keywords:** HBV, Tenofovir, Entecavir, Health outcomes, Discretely-Integrated-Condition-Event-Simulation (DICE)

#### O-010

#### An Observational Study about Long-Term Renal Outcome in Chronic Hepatitis B Patients Treated with Tenofovir Disoproxil Fumarate in Korea

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**Aims:** Tenofovir disoproxil fumarate (TDF) is known to be an effective and safe antiviral agent for chronic hepatitis B (CHB). However, its long-term effects on renal function have been controversial. This study aimed to analyze the real-world long-term

**Methods:** We analyzed a cohort of consecutive treatment-naïve patients with CHB who were treated with TDF between May 2012 and December 2015 at Severance Hospital, Seoul, Republic of Korea. Patients receiving TDF > 12 months were recruited. Patients with a history of hepatocellular carcinoma at the enrollment were excluded. Estimated glomerular filtration rate(eGFR) was calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

**Results:** A total of 640 patients were analyzed. The mean age was 48.3 years old, and 59.5% were male. The proportions of hypertension and diabetes mellitus (DM) were 11.6% and 14.2%, respectively, and that of liver cirrhosis was 20.8%. During the 5 year follow up, using linear mixed model, serum creatinine increased from 0.77  $\pm$  0.01 mg/dL to 0.85  $\pm$  0.02 mg/dL (P < 0.001), and eGFR decreased from 102.6  $\pm$  0.6 mL/min/1.73m<sup>2</sup> to 93.4  $\pm$  1.4 mL/min/1.73m<sup>2</sup> (P<0.001). In subgroup analysis, eGFR was statistically more decreased in patients with age > 60 than  $\leq$  60 (P=0.027), and in patients with using diuretics than without using diuretics (P=0.008). In multivariate analysis, the independent risk factors for eGFR decrease more than 20% were baseline eGFR less than 60mL/min/1.73m<sup>2</sup> (P=0.049) and use of diuretics (P<0.001).

**Conclusions:** Renal function was more decreased in patients with age > 60 and in group using diuretics, and baseline eGFR < 60 mL/min/ $1.73m^2$  and use of diuretics were independent risk factors of eGFR decline more than 20% on TDF therapy.

**Keywords:** Chronic hepatitis B, Tenofovir disoproxim fumarate, Renal function

#### O-011

#### Renal Safety of Entecavir and Tenofovir in Patients with Treatment-NaïVe Chronic Hepatitis B Virus Infection in Real Life Setting: A Multicenter, Retrospective Cohort Study

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**Aims:** Real life data for renal safety of entecarvir (ETV) and tenofovir (TDF) in patients with chronic hepatitis B (CHB) is still lacking. We investigated the renal toxicity of ETV and TDF in patients with CHB in real life practice setting.

**Methods:** We retrospectively collected data from 1,349 treatment-naïve CHB patients who started oral antiviral treatment with ETV or TDF for at least 1 year from January 2012 to December 2015 at 9 academic hospitals in Korea. Patients with baseline estimated glomerular filtration rates (eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) below 60 mL/min were excluded.

Results: A total of 1,127 patients were enrolled (442 patients (39.2%) who were treated with ETV and 685 patients (60.8%) who were treated with TDF) for over a year. Of these patients, 776 patients (ETV, n=339 (43.7%); TDF, n=437 (56.3%)) were followed for 2 years. The mean age of the patients was 47.2 years with males predominant (n=696, 61.8%). Four hundred forty two patients (39.2%) were diagnosed with cirrhosis. Baseline creatinine (Cr) levels (ETV 0.82 mg/dL and TDF 0.81 mg/ dL, P=0.342) was similar whereas eGFR (ETV 97.9 mL/min/1.73 m<sup>2</sup> and TDF 100.8 mL/min/1.73 m<sup>2</sup>, P=0.002) was a significant difference in both groups. There was no difference in the mean changes in eGFR from baseline between TDF group and ETV group after 1 year of treatment (ETV -3.06% and TDF -4.21%, P=0.121). However, the mean changes in eGFR from baseline of the TDF group declined significantly after 2 year of treatment compared with ETV group (ETV -2.27% and TDF -4.42%, P=0.034). On multivariate analysis, baseline eGFR (odds ratio [OR] 1.025, 95% confidence interval [CI] 1.003-1.048; P=0.028), the use of TDF (vs ETV) (OR 1.936, 95% CI 1.101-3.403; P=0.022), age (OR 1.039, 95% CI 1.008-1.071; P=0.014), diabetes mellitus (DM) (OR 2.030, 95% CI 1.019-4.043; P=0.044), the use of diuretics (OR 3.839, 95% CI 1.798-8.195; P=0.001) and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (OR 3.257, 95% CI 1.277-8.305; P=0.013) were independently associated with a decrease in eGFR >20% from baseline after 2 year of treatment.

**Conclusions:** In real life setting, renal function at 2 years after treatment was significantly lower in the TDF group than in the ETV group. Also, close monitoring of renal function is needed in patients with old age, DM, or the use of diuretics or NSAIDs. **Keywords:** Hepatitis B, Antivirals, Kidney, Safety

#### O-012

Prospective, Randomized Safety Assessment of Long-Term Therapy With Entecavir or Other Nucleos(t)ide Analogues in Korean Patients with Chronic HBV Infection

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**Aims:** REALM was a prospective, randomized, open-label, observational study, conducted to assess rates of long-term clinical outcomes in patients with CHB who were treated with entecavir (ETV) or other standard-of-care HBV nucleos(t)ide analogues (nuc). Korean sub-analysis was conducted to investigate any significant differences on clinical outcomes and safety profiles in Korean subjects.

Methods: Treatment-naive or -experienced Korean patients with CHB were randomly assigned (1:1) to monotherapy with ETV (0.5 mg or 1.0 mg once daily per product label) or a non-ETV nuc (specific agent investigator-selected) and followed for  $\leq$ 10 years. Clinical outcome events (COEs) were reported by investigators, reviewed and adjudicated by an Events Adjudication Committee (EAC). Primary endpoints were rates of adjudicated COEs including 1) malignant neoplasms (composite of non-hepatocellular carcinoma [HCC] and HCC); 2) liver-related HBV disease progression (composite of non-HCC HBV disease progression, HCC, and liver-related death); and 3) all-cause death. Secondary endpoints were adjudicated COE rates of non-HCC malignant neoplasms, HCC, and liver-related death. An exploratory endpoint was the adjudicated COE rate of non-HCC HBV disease progression. Treatment-related serious adverse events (SAEs) were also assessed.

**Results:** Patients were randomized and treated to receive ETV (n=1243) or non-ETV (n=1239). Overall, at baseline, 63% were HBeAg+ and 37% had cirrhosis.. Mean time on study was 91 (ETV) and 86 (non-ETV) months. There were no statistically significant differences in COE rates between treatment groups (Table). Results were consistent in baseline subgroups. Treatment-related SAEs that were not protocol-defined COEs were reported in 2 (0.2%) ETV and 26 (2.1%) non-ETV patients, with spectra as expected.

Table. Analysis of EAC-Reviewed and Adjudicated COEs

ETV N=1243	Non-ETV N=1239	HR (95% CI)*
136 (10.9)	133 (10.7)	0.97 (0.762, 1.229)
60 (4.8)	61 (4.9)	0.91 (0.638, 1.303)
127 (10.2)	135 (10.9)	0.89 (0.701, 1.139)
37 (3.0)	28 (2.3)	1.24 (0.756, 2.019)
100 (8.0)	108 (8.7)	0.88 (0.667, 1.149)
18 (1.4)	13 (1.0)	1.29 (0.633, 2.639)
37 (3.0)	41 (3.3)	0.86 (0.550, 1.339)
	ETV N=1243 136 (10.9) 60 (4.8) 127 (10.2) 37 (3.0) 100 (8.0) 18 (1.4) 37 (3.0)	ETV N=1243         Non-ETV N=1239           136 (10.9)         133 (10.7)           60 (4.8)         61 (4.9)           127 (10.2)         135 (10.9)           37 (3.0)         28 (2.3)           100 (8.0)         100 (8.7)           18 (1.4)         13 (10)           37 (3.0)         41 (3.3)

**Conclusions:** This large, long-term study found no statistically significant differences in COE rates between Korean patients randomized to ETV vs non-ETV nuc monotherapy, and the results of Korean sub-analysis were consistent with the results from entire REALM study subjects. SAEs were uncommon al-

though higher in the non-ETV group.

**Keywords:** Chronic hepatitis B, Entecavir, Long-term clinical outcomes, Korean patients

#### 2. Cirrhosis

#### O-013

Multicenter Validation of the Baveno VI Criteria for Screening High-Risk Varices in Patients with Compensated Advanced Chronic Liver Disease

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**Aims:** The Baveno VI consensus recommended that screening endoscopy can be safely avoided in patients with a liver stiffness (LS) <20 kPa and platelet count >150x10<sup>9</sup>/L. Also, the Expanded Baveno VI criteria was proposed to spare more endoscopies. We aimed to validate and revise these criteria with other non-invasive markers in ruling out high-risk varices.

**Methods:** Patients with compensated advanced chronic liver disease (cACLD), which is defined as LS  $\geq 10$  kPa, and who had endoscopy within 6 months of the transient elastography in 8 centers were included. Patients with hepatocellular carcinoma and those with Child-Pugh score >6 was excluded. Varices needing treatment (VNT) were defined as  $\geq$ F2 varices or varices with red color sign.

**Results:** A total of 1218 patients with cACLD were included. Age was  $56.0\pm11.5$  years and 778 patients (63.9%) were men. Chronic hepatitis B was the most frequent underlying liver disease (479 patients, 39.3%), followed by alcoholic liver disease (359 patients, 29.5%). VNT were noted in 249 patients (20.4%). With Baveno VI criteria, VNT loss rate was only 1.9%, while sparing endoscopy rate was only 25.7%. With the Expanded Baveno VI criteria, 43.5% of endoscopies were avoided, but VNT loss rate was 5.8%. We explored various other parameters and cutoff values in ruling out VNT. Platelet >110x10<sup>9</sup>/L and LS <20 kPa spared 39.1% of endoscopy with 4.4% of low VNT loss rate. When the LS-spleen diameter to platelet ratio score (LSPS) was applied, LSPS <14.5 could spare more endoscopies (44.2%) with low VNT loss rate (4.5%). **Conclusions:** Combination of platelet >110x10<sup>9</sup>/L and LS <20 kPa has VNT loss rate less than 5%, and high endoscopic sparing rate in patients with cACLD. This study also showed LSPS <14.5 as a better strategy with increased number of spared endoscopies while maintaining excellent VNT loss rate.

**Keywords:** Liver stiffness, Advanced chronic liver disease, Esophageal varices, Baveno VI

#### O-014

#### Screening of Esophageal Varices: Performance of Baveno Criteria with Shear-Wave Elastography in Patients with Compensated Advanced Chronic Liver Disease

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**Aims:** Baveno VI and extended Baveno VI criteria have been proposed to avoid screening endoscopies. However, this approach has not been validated in the diagnostic performance of shear wave elastography (SWE). In this study, we aimed to validate these criteria in patients with SWE, also considering potential differences in predictable value with transient elastograpy (TE) and SWE.

**Methods:** We evaluated in 526 patients with compensated advanced chronic liver disease (cACLD) was defined by liver stiffness (LS) measurement  $\geq$ 10kPa, Child-Pugh class A and no prior liver decompensation. LS was obtained by TE (FibroScan, Echosense) or 2D-SWE (APLIO 500, Toshiba). Baveno VI (LS<20 and PLT>150,000) and extended Baveno VI (LSM<25 and PLT>110,000) criteria were tested.

**Results:** Any grade EV were found in 22.2% of the patients with cACLD, while VNT in 18.6%. Two hundred sixty-two patients had LSM by TE, 305 patients by 2D-SWE. In the subgroup of 262 patients with TE, Baveno VI and Baveno VI extended criteria spared 21.6% and 37.1% of endoscopy, missing 7.1% and 12.5% of VNT, respectively. We identified as the best thresholds for rule-out presence of EV, LSM<23.3 kPa and high risk EV, LSM<25.2 kPa for TE. In the subgroup of 305 patients with 2D-SWE, Baveno VI and Baveno VI extended criteria spared 38.7% and 60.0% of endoscopy, missing 5.9% and 9.8% of VNT, reflecting better diagnostic performance than TE. In this subgroup for SWE, we identified as the best thresholds for rule-out presence of EV, LSM<16.5 kPa and high risk EV, LSM<17.2 kPa. For predicting EV, AUROC of SWE was higher than that of TE (0.791 vs. 0.744).

**Conclusions:** The Baveno VI and Baveno VI extended criteria with 2D-SWE spare more endoscopies than with TE with a minimal risk of missing VNT in patients with cACLD.

**Keywords:** Compensated advanced chronic liver disease, Esophageal varix, Baveno criteria, Shear-wave elastography

#### O-015

### What Are the Risk Factors and Rescue Treatments for Endoscopic Variceal Ligation Failure?

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**Aims:** The success rate of endoscopic variceal ligation (EVL) is reported to be 85%-94%. However, there have been limited data about the risk factors for failed EVL, and the rescue treatments have not been established well. Therefore, this study aimed to elucidate the risk factors for and rescue treatments of failed EVL.

**Methods:** The data of 454 patients who underwent emergency EVL at Chonnam National University Hospital from April 2004 to October 2017 were analyzed retrospectively. The enrolled patients were divided into two groups: the EVL success (n=407) and EVL failure groups (n=47).



**Results:** Forty-seven patients (10.4%) experienced EVL failure. In multivariate analysis, male, initial hypovolemic shock, active bleeding on endoscopy, and history of EVL were independent risk factors for EVL failure. The most common cause of EVL failure was an unsuctioned varix due to previous EVL-induced scars (51.1%), followed by insufficient ligation of the stigmata due to nearby EVL-induced scars (34.0%), and inability to ligate the varix due to poor intraoperative visual field (12.8%). Endoscopic variceal obturation using N-butyl-2-cyanoacrylate (48.9%) was the most commonly used rescue treatment method, followed by insertion of a Sangstaken Blakemore tube (14.9%) and a EVL retrial (12.8%). These on-site rescue treatments successfully achieved hemostasis in 90.7% of patients with failed EVL.



**Conclusions:** Risk stratification of EVL failure should be conducted before performing EVL, and active rescue treatments should be undertaken in case of EVL failure.

**Keywords:** Esophageal varices, Gastric varices, Treatment failure, Salvage therapy

#### O-016

Significant Increase of Portal Pressure in Cirrhotic Patients with Gastric Varices after Plug-Assisted Retrograde Transvenous Obliteration (PARTO) and Its Clinical Significances: Single Tertiary Center Experience

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**Aims:** Plug-assisted retrograde transvenous obliteration (PARTO) is the most currently used procedure in patients with gastric varices with portosystemic shunt. Portal pressure and the rate of complications associated with it are expected to rise after PARTO, but it has not yet identified. The study aims: to see how much hepatic venous pressure gradient (HVPG) will be changed after PARTO, and to see if esophageal varix (EV), ascites, hepatic encephalopathy (HE) and liver function will worsen or improve in follow-up period.

**Methods:** During March 2012 to Feburary 2018, 73 patients who had PARTO were analyzed. We reviewed their HVPG, liver function and episode of cirrhotic complications before and 1

and 6 month after PARTO.

Results: Among the patients, CTP score decreased at 1 and 6 month {After 1 month, from 7 (6-8) to 6 (5-7), P<0.001 / After 6 month, from 7 (6-8) to 6 (5-7), P<0.001}. And also, MELD score {After 1 month, from 11 (7.25-14.75) to 9 (8-12), P=0.005 / After 6 month, from 11 (7.25-14.75) to 9 (8-11.75), P=0.036}. There was an improvement in HE grade after 1 month (-0.03±0.036, P=0.025) and no deterioration after 6 month (-0.06±0.035, P=0.083). HVPG was measured before and after PARTO in 27 patients and elevated from 11.92±0.7 (before) to 14.96±1.038 (after) (P=0.001). The difference before and after PARTO showed no correlation with changes in liver function (MELD score, P=0.12), ascites (P=0.352), HE grade (P=0.14), and EV grade (P=0.564). Also, it did not correlate with changes in beta-blocker (BB) (P=0.474) and diuretics requirements (P=0.284), which could affect the patient's clinical index.

**Conclusions:** Artificially blocking the portosystemic shunt evidently leads to an increase in HVPG. However, no significant changes in liver function or cirrhotic complications were observed during the follow-up period of 6 months. Long-term observation is needed in the future.

Keywords: PARTO, HVPG, Liver cirrhosis, Gastric varix

#### O-017

### Validation of Korean Stroop Test in the Screening of Minimal Hepatic Encephalopathy

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**Aims:** Minimal hepatic encephalopathy (mHE) has poor prognosis but hardly drawn attention when patients have no symptoms. We aimed to validate Korean stroop test in the screening of mHE.

**Methods:** Chronic hepatitis B related liver cirrhosis (LC) patients without history of overt hepatic encephalopathy were recruited prospectively from 13 centers for two years. All participants completed Portosystemic encephalopathy syndrome test (PHES) and Korean stroop test. Korean stroop test is consisted of 2 Onstates (color, word) and 2 Off-states (inhibition, switching). Correct response rates and response times were measured. Four types of "OnTime+OffTime" have been analyzed (color+inhibition, color+switching, word+inhibition, and word+switching). mHE was diagnosed when PHES scores less than -4. Healthy controls (HC) were also recruited (n=376).

**Results:** Among 223 LC patients, 67.3% was male. Mean age was 53 years. Prevalence of mHE was 20.6%. Response times for each states showed negative correlation with PHES scores (P<0.001). Also color+inhibition, color+switching, word+inhibition, and word+switching showed negative correlation with PHES scores, -0.361, -0.310, -0.442, and -0.336, respective-ly(all P<0.001). The highest AUC in the discrimination of mHE among various "OnTime+OffTime" was word+inhibition (AUC 0.75, 95% C.I 0.67-0.84, P<0.001). Mean values of word+inhibition were significantly different among the three groups, which were 54.6±13.2sec, 63.4±18.2sec, and 83.4±27.8sec in HC, LC without mHE, and LC with mHE, respectively (all P<0.001). Among various factors, time for word+inhibition was the only significant factor (OR 1.04, 95% C.I 1.02-1.06, P<0.001) in multivariate analysis for diagnosis of mHE.

**Conclusions:** Korean stroop test is simple and valid method for screening of mHE.

**Keywords:** Minimal hepatic encephalopathy, Screening, Stroop test, Paper-pencil test

#### O-018

#### The Role of Spleen Volume in Predicting Portal Hypertension in Patients with Cirrhosis

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**Aims:** It is already well known that the size of the spleen increases as liver cirrhosis aggravates. However, there is few studies for establishing the correlation between portal hypertension and spleen volume (SV). In this study, we aimed to see the relationship between the splenic volume and hepatic venous

wedge pressure (HVPG) and to find what determine the portal pressure.

**Methods:** From May 2007 to February 2018, 337 cirrhotic patients who measured SV and HVPG simultaneously were included. SV was measured based on the ellipsoid volume calculation formula by measuring length, height, and width. Other clinical and biochemical factors which may contribute to increase portal pressure were also collected.

**Results:** Mean HVPG was 14.2  $\pm$  5.3 and Child-pugh class A, B, and C patients were 34%, 40%, and 16%, respectively. A significant positive correlation was noted between splenic volume and HVPG levels (r=0.127, *P*=0.019). Below 16mmHg of HVPG, the stronger correlation was noted between them (r=0.202, *P*=0.003) but this relation was not observed above 16mmHg of HVPG. We divided HVPG into various stages of portal hypertension(HVPG < 5, 5 ≤ HVPG < 10, 10 ≤ HVPG < 16, HVPG ≥ 16). The average spleen volume of each group tended to increase with increasing HVPG value. Mean splenic volume for each group was 320.74cm<sup>3</sup>. 464.78 cm<sup>3</sup>, 501.06 cm<sup>3</sup>, 525.94 cm<sup>3</sup> respectively. But there was no significant difference in the mean spleen volume between the groups., HVPG was correlated with presence of ascites (*P*=0.038) as well as SV (*P*=0.043) after adjusted by MELD, Na, albumin, platelet count.

**Conclusions:** The spleen volume tended to increase with increasing HVPG and this association was stronger when HVPG was below 16 mmHg. More studies with larger numbers are needed to predict the portal pressure non-invasively.

Keywords: Spleen, Portal hypertension, HVPG, Spleen volume

#### O-019

#### Prediction of Acute Kidney Injury and Mortality in Patients with Decompensated Cirrhosis with Serum Cystatin C and Urine N-Acetyl-β-D-Glucosaminidase

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**Aims:** Acute kidney injury (AKI) is a common complication in cirrhotic patients, and also associated with increased mortality and development of complications including variceal bleeding, spontaneous bacterial peritonitis and encephalopathy. Currently, there are limitations to use serum creatinine to distinguish patients at high risk for AKI in patients with cirrhosis. We tried to elicit the association between levels of renal biomarkers including serum cystatin C and urine N-acetyl-β-D-glucosaminidase (NAG) and the prognosis of patients with decompensated cirrhosis.

**Methods:** In 84 hospitalized patients with decompensated cirrhosis and without AKI at baseline, we identified serum creatinine, cystatin C, urine NAG levels and outcomes including AKI development and mortality. **Results:** During a median follow-up of 6.1 months, 17 patients experienced AKI and 21 patients died. In the AUC analysis for predicting the development of AKI within 6 months, those of serum Cr and cystatin C levels and urine NAG level were 0.562, 0.802, and 0.833, respectively. On multivariate Cox-regression analysis, AKI significantly occurred more frequently with higher serum cystatin C (HR, 21.168; *P*=0.010) and urine NAG levels (HR, 1.023; *P*<0.001). Patients significantly survived longer with lower serum cystatin C (HR, 0.273; *P*=0.003), urine NAG levels (HR, 0.983; *P*=0.001), and Child-Pugh scores (HR, 0.627; *P*=0.001). Patients with the serum cystatin C <sup>3</sup> 1.0 mg/L and urine NAG <sup>3</sup> 31 U/g urinary Cr (*n*=12) showed more AKI development (*P*<0.001) and higher mortality (*P*<0.001) than other patients on Kaplan-Meier plots.

**Conclusions:** Serum cystatin C and urine NAG levels are strong predictors for AKI development and mortality in patients with decompensated cirrhosis. In addition, the use of urine NAG in conjunction with cystatin C may provide a more accurate prediction.

**Keywords:** Acute kidney injury, Cystatin C, N-acetyl-β-D-glucosaminidase, Cirrhosis

#### O-020

#### The Role of Kidney Biomarkers in Cirrhotic Patients with Acute Kidney Injury: Interim-Analysis of Multicenter, Prospective Cohort Study

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**Aims:** Current AKI criteria using serum creatinine (Cr) has some limitations to predict reversibility of renal function and discriminate renal parenchymal injury in cirrhotic patients. The aim of this study is to evaluate whether urine biomarkers [cystatin C, N-acetyl-β-D-Glucosaminidase (NAG)] can predict survival and response to terlipressin in cirrhotic patients with AKI.

**Methods:** One hundred eleven cirrhotic patients who developed AKI were prospectively enrolled from 11 tertiary medical centers in Korea during 2016 to 2018. AKI was defined as increase in serum Cr (SCr) of 0.3mg/dL or 50% increase of baseline in SCr with a final value above 1.5 mg/dL. Among them, the patients with SCr  $\geq$  2.5 mg/dL were diagnosed as hepatorenal syndrome (HRS) and treated with terlipressin. Urine samples were collected for the measurement of urine cystatin C and urine NAG at the diagnosis of AKI and/or HRS.

**Results:** Of 111 patients, 29 patients had HRS. The mean MELD score was  $23.92 \pm 8.90$ , and mean SCr was  $2.20 \pm 0.79$  mg/dL. The baseline urine NAG (AKI stage I,  $16.37 \pm 16.48$  mg/dL; stage II,  $27.84 \pm 36.70$  mg/dL; stage III,  $55.69 \pm 62.93$  mg/dL, P=0.007) and urine cystatin C (AKI stage I,  $0.50 \pm 0.78$  mg/dL; stage II,  $0.67 \pm 2.29$  mg/dL; stage III,  $1.07 \pm 2.16$ , P=0.558) increased as the baseline AKI stage increased. During median 2.6 months observational period, all-cause mortality was 39.4%. In patients with liver transplantation or death, urine NAG level tended to be higher than in survival group, but not statistically significant ( $30.56 \pm 40.81$  mg/dL vs.  $20.80 \pm 29.22$  mg/dL, P=0.101). However, this urine biomarkers were not yet different depending on the improvement of renal function and survival.

**Conclusions:** In the interim-analysis of our study, urine NAG and urine cystatin C are strongly associated with severity of AKI in patients with liver cirrhosis and may be helpful to predict transplant-free survival in these patients.

**Keywords:** Acute kidney injury, Hepatorenal syndrome, Cystatin C, N-acetyl-β-glucosaminidase

#### O-021

### The Prevalence and Clinical Course of Adrenal Insufficiency in Patients with Cirrhosis

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**Aims:** Adrenal insufficiency (AI) is found in patients with cirrhosis, as well as in those with critically illness, particularly those with sepsis. However, we often overlook frequent adrenal dysfunction in patients with cirrhosis. Thus, we aimed to evaluate the prevalence in patients at various stages of cirrhosis, and the correlation between AI and long-term clinical courses.

**Methods:** A total of 275 patients with liver cirrhosis were enrolled between 2011 and 2017. A rapid ACTH stimulation test with 250 ug of corticotrophin was performed to detect Al. Al was defined as an increase in serum cortisol of <6 ug/dL in patients with a basal total cortisol of <20 ug/dL.

**Results:** The mean ( $\pm$  S.D) age of the study population (188 men and 87 women) was 59.1 ( $\pm$  13.1) years and the patients with adrenal insufficiency were 156 (56.7%). The proportion of shock event, fever, and use of inotropics were 31.8%, 30.3% and 23.5%, respectively. Among patients diagnosed AI, 49 pa-

tients (31.4%) were treated with hormone therapy. Compared to those with and without AI, serum bilirubin and prothrombin time were significantly higher in patients with AI than in those without (all P<0.05), whereas, age, whole blood cell count, aspartate aminotransferase, alanine aminotransferase, creatinine, and C-reactive protein level were significantly higher in patients without AI than in those with (all P<0.05). The mean survival period and 3-year survival rates were 45.3 (±3.4) months and 51.7%.

**Conclusions:** Al is frequent in patients with cirrhosis. As compared with those with and without adrenal dysfunction, patients with Al have greater impairment of renal function, critically illness, higher probability of sepsis and hepatorenal syndrome, and higher short-term mortality.

**Keywords:** Liver cirrhosis, Adrenal insufficiency, Hepatoadrenal syndrome, Prevalence

#### O-022

# The Cut-Off Value of Transient Elastography to Hepatic Venous Pressure Gradient for Alcoholic and Viral Cirrhosis in Korean Patients

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**Aims:** To investigate correlation between hepatic venous pressure gradient (HVPG) and transient elastography (TE) in patients with cirrhosis and to identify a cut-off value of TE to HVPG in clinically significant portal hypertension (CSPH, HVPG  $\geq$ 10mmHg) and severe portal hypertension (SPH, HVPG >12mmHg) according to the cause of cirrhosis.

**Methods:** Between January 2008 and March 2017, 553 patients who underwent HVPG and TE were consecutively enrolled at the three Korean tertiary medical centers. HVPG and TE were performed within 1 month interval. Patients were classified with the cause of liver cirrhosis, and the cut-off value of TE was analyzed for patients with alcoholic and viral origin of cirrhosis.

**Results:** The mean age was 53.3±9.8 years, and the majority (81.6%) were male. A significant positive correlation was noted between liver stiffness and HVPG levels (r=0.544, *P*<0.001). The area under receiver operating characteristic curves for TE to diagnose CSPH and SPH were 0.829 (95%CI: 0.790-0.868) and 0.80.2 (95%CI: 0.765-0.840). Among all cause of liver cirrhosis, the most common etiology was 1)alcohol 335(60.6%) followed by 2)chronic hepatitis B(CHB) 128(23.1%), 3)CHB with alcohol 45(8.1%), 4)cryptogenic 22(4%), 5)chronic hepa-

titis C(CHC) 18(3.3%), and 6)CHC with alcohol 5(0.9%). HVPG and TE values were evaluated for total patients, patients with alcoholic(1), and viral [(2)+(5)] cirrhosis. In total patients, a cut-off values of TE of 27.6 and 32.5kPa were obtained by using Youden index to best predict CSPH and SPH, respectively. In al-coholic cirrhosis, a cut-off values of TE were 32.2 kPa and 36.6 kPa, for CSPH and SPH, respectively. In viral cirrhosis, a cut-off values of TE was 18.0 kPa for both CSPH and SPH(Table 1).

		Cut-off value	Sensitivity	Specificity	PPV	NPV
HVPG ≥10	All	≥27.55	71.9	21.6	91.9	45.0
	Viral	≥18	76.9	69.0	88.2	57.3
	Alcohol	≥32.2	68.3	49.0	92.8	39.8
HVPG ≥12	All	≥32.45	98.4	77.6	85.2	56.7
	Viral	≥18	84.0	61.5	77.0	72.5
	Alcohol	≥36.55	66.8	49.2	87.6	53.1

**Conclusions:** In the alcoholic cirrhosis, cut off value of TE was higher than that of viral cirrhosis. Therefore, it is necessary to interpret the TE value depending on the cause of liver cirrhosis. **Keywords:** Transient elastography, Hepatic venous pressure gradient, Liver cirrhosis, Alcohol

#### O-023

#### Influence of Previous Acute Decompensation and Organ Failure on the Long-Term Prognosis in Cirrhotic Patients with Decompensation

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**Aims:** To investigate long-term mortality depending on the experience and time of previous acute decompensation (AD) and severity of organ failure (OF) in cirrhotic patients with AD

**Methods:** A total of 1252 cirrhotic patients with AD, defined by acute development of overt ascites, hepatic encephalopathy, gastrointestinal bleeding and infection, were prospectively followed up. OF was defined according to the chronic liver failure-sequential organ failure assessment (CLIF-SOFA). The severity of OF was divided into high CLIF-SOFA ( $\geq$ 7) and low CLIF-SOFA (<7). We then classified 3 groups according to the
experience and time of previous AD as follows: G1, no previous AD; G2, AD one or more years before, G3, AD within a year.

Results: During follow-up duration (14.9±10.6 months), the presence of previous AD negatively affected long-term survival in low CLIF-SOFA (82.6% vs 73.0%, P<0.001) and high CLIF-SOFA (54.6% vs 40.4%, P=0.041). Also, in 1009 patients who survived for more than 3 months following AD (ie "longterm survivors"), the presence of previous AD showed similar pattern (low CLIF-SOFA, 85.1% vs 75.1%, P<0.001; high CLIF-SOFA, 80.5% vs 64.0%, P=0.004). In total, G3 patients showed a significantly lower survival rates than G1 and G2 patients, although no significant difference was seen between G1 and G2 patients in low CLIF-SOFA (82.6%, 79.0%, and 65.9%, P<0.001) and high CLIF-SOFA (54.6%, 50.7%, and 33.0%, P=0.003). However, in terms of long-term survivors with high CLIF-SOFA, G2 and G3 patients showed a significantly lower survival rates than G1 (80.5% vs 67.3% and 60.0%, P=0.021 vs P=0.004, respectively) as shown in the figure.



**Conclusions:** Long-term prognosis was related to the severity of OF and the time of previous AD. Especially, for long-term survivors, previous AD was associated with high mortality regardless of the point of experience. This supports the need to decide on proper treatment policy.

Keywords: Cirrhosis, Decompensation, Organ failure, Survival

#### O-024

#### Fibrotic Burden Assessed Using FIB-4 Is Significantly Associated with the Risk of All-Cause Mortality in Patients with Newly Diagnosed Rheumatoid Arthritis

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**Aims:** Co-morbidities as well as conventional risk factors influence the prognosis of rheumatoid arthritis (RA) patients. We investigated whether liver fibrotic burden is associated with all-cause mortality in RA patients.

**Methods:** A total of 2,812 patients with newly diagnosed RA between October 2000 and September 2016 were retrospectively selected. Liver fibrosis was assessed using Fibrosis-4 (FIB-4) index [age (years)x AST level (IU/L)/ platelet count (10<sup>9</sup>/L)/  $\sqrt{ALT}$  (IU/L)].

**Results:** The mean age of the study population was 51.5 years (482 men and 2,330 women). The mean erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and FIB-4 was 43.5 mm/hr, 9.0 mg/L, and 1.0, respectively. Methotrexate was used in 2,524 (89.9%) patients and biological or targeted synthetic disease modifying ant-rheumatic drug (DMARD) was used in 310 (11.0%) patients. During the follow-up period (mean 93.7 months), 89 (3.2%) patients were dead. Patients with mortality had significantly higher age (mean 64.4 vs. 51.1 years), proportion of male gender (31.5 vs. 16.7%), hypertension (40.4 vs. 18.5%), and diabetes (25.9 vs. 7.7%), ESR (mean 57.1 vs. 43.0 mm/hr), CRP (mean 16.9 vs. 8.7 mg/L), and FIB-4 (mean 1.5 vs. 1.0) (all P<0.05). On multivariate analysis, higher FIB-4 was independently associated with a higher risk of all-cause mortality (hazard ratio=1.130, P=0.004), together with male gender, hypertension, diabetes, ESR, and intensity of glucocorticoid exposure, whereas the use of methotrexate was independently protective (all P<0.05).

**Conclusions:** Beside of conventional risk factors, fibrotic burden assessed using FIB-4 might be useful for risk stratification of newly diagnosed RA patients.

Keywords: FIB-4, Liver fibrosis, Rheumatoid arthritis, Mortality

### 3. NAFLD

#### O-025

#### The Impact of Previous Acute Decompensation on Longterm Prognosis According to the Severity of Alcoholic Hepatitis in Cirrhotic Patients

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**Aims:** To investigate long-term mortality according to the severity of alcoholic hepatitis and the presence or absence of previous acute decompensation (AD) in alcoholic cirrhotic patients with acute deterioration

Methods: A total of 894 alcoholic cirrhotic patients (male 747,

mean age 53.1 years) with acute deterioration were prospectively followed up. Severe alcoholic hepatitis (SAH) was defined by a modified discriminant function  $\geq$ 32. Enrolled patients were divided into 3 groups according to the presence and severity of AH; group1, alcoholic cirrhosis without AH; group2, alcoholic cirrhosis with non-SAH; group3, alcoholic cirrhosis with SAH. AD was defined as: acute development of overt ascites, hepatic encephalopathy, gastrointestinal bleeding, and infection.

**Results:** During follow-up duration  $(14.3\pm10.7 \text{ months})$ , longterm mortality were higher in patients with group 3 than those in group 1 and 2, but there was no significant difference between group 1 and 2 (group 1, 160/596; group 2, 27/141; group 3, 76/157, *P*<0.001). Also, in 671 patients who survived for more than 3 months following acute deterioration (longterm survivors), long-term survival curve between groups showed a similar pattern (*P*=0.004). Interestingly, in group 1, the presence of previous AD negatively affected long-term survival in total and long-term survivors (*P*<0.001 and *P*=0.004, respectively). However, in group 3, previous AD negatively affected long-term survival in long-term survivors (*P*=0.009), but not in total patients (figure 1). Especially in long-term survivors of group 3, previous AD showed hazard ratio of 2.47 (95% confidence interval, 1.16-5.28, *P*=0.019).





**Conclusions:** Compared with the long-term prognosis of patients with acute deterioration except for AH, that of SAH was poor, but that of non-SAH was similar. However, in patients with acute deterioration except for AH and SAH patients overcoming acute deterioration, the presence of previous AD had a great impact on long-term prognosis. These findings will help to determine the therapeutic plan.

**Keywords:** Alcoholic hepatitis, Liver cirrhosis, Acute decompensation, Mortality

### O-026

Usefulness of Lactate-Free Asian Pacific Association for the Study of Liver Acute-On-Chronic Liver Failure (ACLF) Research Consortium (AARC)–ACLF Score for Predicting Short-Term Mortality in Patients with Alcoholic Liver Disease

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**Aims:** Asian Pacific Association for the Study of Liver (APASL) acute-on-chronic liver failure (ACLF) Research Consortium (AARC) proposed new prognostic scoring system of ACLF including lactate. However, lactate is not routinely checked in clinical practice of patient with ACLF in Korea. Therefore, we aimed to investigate the predictive accuracy of lactate-free AARC-ACLF score for predicting short-term mortality in patients with alcoholic liver disease.

**Methods:** A total of 749 ALD patients who had liver failure (bilirubin≥5mg/dL and INR≥1.5) in AARC database were investigated. Diagnostic performances for short-term mortality were compared according to the area under receiver operating characteristic (AUROC) curve. Predictive accuracy of lactate-free AARC-ACLF score were compared with other prognostic scores in 143 ALD patients with liver failure and 60 ALD patients with ACLF according to AARC definition in Korean ACLF cohort.

**Results:** Among 749 patients, 30-day and 90-day mortality were 40.3% and 51.5%. There were no significant differences in AUROC for predicting 30-day and 90-day mortality between AARC-ACLF score and lactate-free AARC-ACLF score (30-day

mortality: 0.752 vs. 0.751, *P*=0.918, 90-day mortality: 0.728 vs. 0.736, *P*=0.346). In Korean ACLF cohort, the AUROCs of lactate-free AARC-ACLF score for predicting 28-day and 90-day mortality were 0.861 and 0.846 in ALD with liver failure, and 0.884 and 0.874 in ALD patients with ACLF according to AARC definition, respectively. In Korean ALD patients with liver failure and ACLF according to AARC definition, diagnostic performance of lactate-free AARC-ACLF score for predicting 28-day and 90-day mortality was comparable to those of Model for End-stage Liver Disease (MELD), MELD-Na, Chronic Liver Failure-Sequential Organ Failure Assessment score.

**Conclusions:** Lactate-free AARC-ACLF score is as excellent as AARC-ACLF score in predicting short-term mortality in ALD patients with liver failure of AARC database and Korean ACLF cohort.

**Keywords:** Alcoholic liver disease, Acute-on-Chronic liver failure, AARC-ACLF score, Lactate

### O-027

#### A Randomized, Double-Blind, Placebo-Controlled Study of a Multispecies Probiotic Mixture in Non-Alcoholic Fatty Liver Disease

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**Aims:** Intestinal microbiota is known to be closely associated with the incidence of obesity and nonalcoholic fatty liver disease (NAFLD). This study aimed to investigate effects of probiotics treatment on visceral fat area (VFA) and intrahepatic fat (IHF) fraction in NAFLD.

**Methods:** Sixty-eight obese NAFLD patients (>5% fat fraction using MRI-derived proton density fat fraction (PDFF)) divided into the probiotics and the placebo group for twelve weeks. The probiotics mixture consists of six kinds of probiotics. VFA and IHF measured by MRI-PDFF. Body fat and muscle composition was evaluated by multi-frequency bioimpedence analysis. Liver stiffness was measured by transient elastography.

**Results:** Body weight and total body fat amount were more reduced in probiotics group compare to placebo group. IHF fraction ( $16.3\pm15.0\dot{a}14.1\pm7.7$ , *P*=0.032) reduced after 12 weeks probiotics treatment compare to baseline, but not in placebo group. Reduction rate of IHF (mean difference: -2.61%, *P*=0.012) was also more in probiotics group compare to placebo. Triglyceride level reduced after 12 weeks probiotics treatment compare to baseline. Probiotics group showed also more decrease triglyceride concentration (mean difference; -34.0 mg/dl, *P*=0.0033). Deep sequencing of the fecal microbiome revealed that the amount of *Agathobaculum*, *Dorea* (OTU 527923), *Blautia*, *Ruminoccous*, and *Dorea* (OTU 195044, OUT

470168) were increased in patients who were improved fatty liver.

**Conclusions:** The 12-week treatment of probiotics resulted in a significant reduction of IHF and BMI in obese NAFLD patients. **Keywords:** Probiotics, Non alcoholic fatty liver

# O-028

#### Non-Invasive Evaluation of Liver Fibrosis, Steatosis, and Nonalcoholic Steatohepatitis in Biopsy-Proven NAFLD Patients

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is becoming a major cause of chronic liver disease worldwide. In this broad spectrum disease, the development of a non-invasive method is urgently needed to identify more severe form of disease including nonalcoholic steatosis and advanced fibrosis. In this study, we compared hepatic fibrosis and steatosis using MR imaging and transient elastography (TE) and tried to find non-invasive diagnostic marker for NASH and advanced fibrosis.

**Methods:** This is a multicenter prospective study of patients with biopsy-proven NAFLD. The patients were underwent laboratory test, liver biopsy, MRI and TE 6 months before enrollment. MRI examination included mDIXON, MR spectroscopy (MRS), and MR elastography (MRE). TE measured liver stiffness and controlled attenuation parameter (CAP).

Results: Ninety-four patients with biopsy-proven NAFLD patients were enrolled from October 2016 to March 2018. Mean age and BMI were 51.29  $\pm$  13.38 years and 29.12  $\pm$  5.64 kg/ m<sup>2</sup>, respectively. Female was dominant (58, 61.7%) and other co-morbidities were diabetes (n=37, 39.4%), hypertension (n=39, 41.5%) and dyslipidemia (n=28, 29.8%). For diagnosis of advanced fibrosis (stage 3-4), the AUROC of MRE tended to be superior (0.844; 95% CI, 0.748-0.915) comparing with TE (0.787; 95% CI, 0.683-0.870) (P=0.272). For diagnosis of severe steatosis (stage 2-3), CAP (0.706; 95% CI, 0.595-0.802) showed lower AUROC compared with mDIXON (0.832; 95% CI, 0.733-0.905; P=0.027) and MRS (0.842; 95% CI, 0.744-0.913; P=0.029), respectively. Age, BMI, DM, dyslipidemia, AST, platelet are associated with NASH in univariate. In multivariate analysis AST, PLT, and MRE were significant factor for diagnosis of NASH.

Conclusions: MRI (mDIXON, MRS and MRE) tended to identify

more severe steatosis and fibrosis compared to TE in patients with biopsy-proven NAFLD. AST, PLT, and MRE were significant factor for diagnosis of NASH. Non-invasive modalities using AST, platelet, and MRI could be potential tools for diagnosis of NASH.

Keywords: NAFLD, NASH, MRI, Elastography

### O-029

Growth Differentiation Factor 15 Predicts Advanced Fibrosis in Biopsy-Proven Non-Alcoholic Fatty Liver Disease

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**Aims:** We explored whether growth differentiation factor 15 (GDF15) affects the histological severity of non-alcoholic fatty liver disease (NAFLD) independent of insulin resistance.

**Methods:** In a biopsy-proven NAFLD cohort, we measured serum GDF15 levels using enzyme-linked immunosorbent assays.

Results: Among 190 subjects (mean age, 53 ± 14 years; men, 52.1%), 72 (men, 65.3%) and 78 (men, 44.9%) were diagnosed with biopsy-proven non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) respectively. GDF15 levels were significantly higher in NASH patients than in controls (P=.010) or NAFL patients (P=.001). Subjects with advanced fibrosis (≥F3) also showed higher GDF15 levels compared to the others (F0-2; P<.001). Among NAFLD patients, the highest quartile of GDF15 levels was significantly associated with a risk of advanced fibrosis even after adjustment for age, gender, body mass index, smoking status, hypertension, diabetes, aspartate aminotransferase, platelet, albumin, insulin resistance and low skeletal muscle mass (odds ratio, 4.27; 95% confidence interval, 1.04-17.63), but not with NASH risk. GDF15 levels showed a significant positive correlation with liver stiffness (Spearman's p, .525; P<.001). Palmitate treatment increased the GDF15 mRNA expression level significantly in Kupffer cells, but not in hepatocytes. In LX-2 cells, GDF15 treatment resulted in enhanced expression of  $\alpha$ -smooth muscle actin and collagen I, as well as phosphorylation of SMAD2 and

#### SMAD3.

**Conclusions:** Our findings suggest that GDF15 may serve as a novel biomarker of advanced fibrosis in NAFLD, thereby indicating the need for urgent anti-fibrotic pharmacotherapy.

**Keywords:** Fibrosis, Growth differentiation factor 15, Sarcopenia, SMAD

#### O-030

#### Validation of Low Alanine Aminotransferase Cutoff for Predicting Hepatocellular Carcinoma and Decompensated Hepatic Events

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**Aims:** Recently several guidelines have suggested true healthy normal ALT are lower than commonly used cutoff value (<40 U/L). There is lack of longitudinal data whether such low ALT cutoff can predict liver related morbidity. Here we investigated the predictive power of low ALT cutoff values on liver-related morbidity.

**Methods:** The National Health Insurance Service-National Health Screening Cohort database was used obtaining a random sample of 10% drawn from the 5.15 million qualified NHIS persons aged between 40 and 79 out of general health screening examinees. Conventional and low ALT cutoff values ability to predict overall mortality, were compared using Kaplan-Meier, Cox Regression Model, and the Likelihood test.

**Results:** Total 338,216 subjects those who didn't have previous liver disease among 426,013 health screening examinees. Age was 52.2± 9.46 years and mean 9.83 years (9~10 years) were followed up. During follow-up, there were 360 liver- related deaths, 28,363 hepatic cancers and 1048 incidences of decompensated liver events. Higher ALT levels led to a significant increase in liver-related mortality. Low ALT cutoff (<30 U/L in male and <19 U/L in female) predict the risks of liver-related mortality, hepatocellular carcinoma and decompensated liver events after adjusting confounding factors using the Cox model. Optimal ALT cutoff point for liver-related mortality was 31.5 U/L in men, and 24.3 U/L in women, respectively. When these low cutoff criteria were added to the prediction model using likelihood ratio test, the prediction model's ability to detect liver-related mortality, hepatocellular carcinoma, and decompensated liver events significantly increased.

**Conclusions:** Low cutoff values of ALT are effective in the prediction of liver-related mortality, hepatocellular carcinoma, and decompensated liver events.

Keywords: ALT, Mortality, HCC, Decompensated LC

# O-031

#### Prevalence of NAFLD in Asia: A Systematic Review and Meta-Analysis of 195 Studies and 1,753,168 Subjects from 13 Countries

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**Aims:** NAFLD is generally correlated with the obesity epidemic. Asia is a heterogeneous region with varying socioeconomic levels and obesity prevalence; therefore, our goal was to estimate the prevalence of NAFLD in Asia through a meta-analytic approach.

**Methods:** PubMed and EMBASE databases were searched from 1989 to 2017 for relevant studies reporting NAFLD prevalence in Asia. All studies were reviewed by three independent investigators. We used random-effects models to provide point estimates with 95% confidence interval (CI) of prevalence. Publication bias was assessed by Egger weighted regression Methods.

Table 1 NAFLD Prevalence in Asia Stratified by Country

Country	No. of Studies	No. of Patients	Pooled Prevalence (%)	95% CI (%)	I <sup>2</sup> (%)
Mainland, China	76	698,603	0.31	0.29-0.33	99.73%
South Korea	48	848,508	0.31	0.29-0.33	99.80%
Japan	19	57,208	0.24	0.21-0.28	99.08%
Taiwan, China	12	91,676	0.35	0.27-0.43	99.86%
Iran	10	30,291	0.36	0.31-0.41	98.67%
India	8	3938	0.28	0.21-0.35	96.50%
Hong Kong, China	б	5978	0.34	0.24-0.43	98.39%
Sri Lanka	5	8816	0.35	0.22-0.49	99.44%
Malaysia	3	2167	0.24	0.10-0.37	NA
Israel	2	539	0.31	0.27-0.35	NA
Pakistan	2	2732	0.15	0.13-0.16	NA
Bangladesh	1	110	0.44	0.34-0.53	NA
Saudi Arabia	1	1312	0.17	0.15-0.19	NA
Philippine	1	1102	0.12	0.10-0.14	NA
Singapore	1	188	0.40	0.33-0.48	NA
Overall*	195	1,753,168	0.31	0.29-0.32	99.72%

\*with the Egger's test p-value of <0.001 for all.

**Results:** From the 2700 titles and abstracts reviewed, 195 papers from 13 countries met the inclusion criteria and included

1,753,168 subjects. The overall pooled prevalence for NAFLD in Asia was 31% (95% CI: 29-32). Individual country prevalence was shown in Table 1. In countries with more than 3 studies, the lowest prevalence was seen in Japan (24%, 95% CI: 21-28) and the highest in Iran (36%, 95%CI 31-41). Notably, pooled prevalence from studies with sample <1,000 subjects was much higher (34%, 95% CI: 31-38, 45 studies, n=23,857) than estimate from larger studies (≥1,000 subjects) (30%, 95% CI: 28-31, 150 studies, n=172,9311). By sub-regions within Asia (Table 2), there was significant regional differences (P<0.01) with the highest NAFLD prevalence seen in West Asia (33%, 95% CI: 28-39, 13 studies, n=32,142) and the lowest in Southeast Asia (24%, 95% CI: 15-33, 5 studies, n=3457). By country income levels, NAFLD prevalence was 30% (95% CI: 29-32, 89 studies, n=1,005,409) for high-income countries and 31% (95% CI: 29-33, 106 studies, n=747,759) for middle-income countries (P<0.63).

Table 2 NAFLD Prevalence in Asia Stratified by sub-regions within Asia

Sub-Regions within Asia	No. of Studies	No. of Patients	Pooled Prevalence (%)	95% CI (%)	I <sup>2</sup> (%)
East Asia	161	1,701,973	0.31	0.29-0.32	99.75%
China[ <u>Mainland, Taiwan</u> , Hong Kong], South Korea, Japan					
South Asia	16	15,596	0.30	0.22-0.37	99.13%
India, Sri Lanka, Pakistan, Bangladesh					
West Asia	13	32,142	0.33	0.28-0.39	98.92%
Iran, Israel, Saudi Arabia					
Southeast Asia	5	3,457	0.24	0.15-0.33	97.65%
Malaysia, Philippine, Singapore					

**Conclusions:** Overall NAFLD prevalence in Asia is 31% similar to Western countries and by country-income levels within Asia but varies by some sub-regions or Asia with the highest prevalence in West Asia (33%).

Keywords: NAFLD, Prevalence, Asia, Meta-analysis

#### O-032

#### The Change of Skeletal Muscle Mass Is Associated with Hepatic Steatosis in Non-Alcoholic Fatty Liver Disease

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**Aims:** We aimed to investigate the association between the change of muscle mass and change of fibrosis and steatosis in NAFLD patients.

**Methods:** We analyzed 2,893 NAFLD subjects who had health check-up more than twice in St. Vincent's Hospital between November 2009 and December 2017. NAFLD was diagnosed by ultrasound, and appendicular muscle mass (ASM) was assessed by Inbody 720, and Sarcopenia index was calculated as ASM divided by weight (SI%) and ASM divided by body mass index (SI-BMI). Non-invasive markers were used to evaluate the

severity of hepatic fibrosis and steatosis; NAFLD fibrosis score (NFS), Fibrosis-4 (Fib-4) score, and Forn's index for fibrosis, and hepatic steatosis index (HSI) and fatty liver index (FLI) for steatosis.

Results: The mean age was 47.3±10.4 years, and 1956 subjects (67.6%) were male. Diabetes, hypertension, metabolic syndrome were more prevalent in sarcopenic subjects (P<0.01), and non-invasive fibrosis and steatosis markers were higher in sarcopenic subjects (P<0.01). The mean interval between two health check-up was 39.8±21.9 months. There was no significant association between the change of NFS, Fib-4, and Forn's index and the change of SI% and SI-BMI (all P>0.1). However, the changes of HIS and FLI were significantly associated with the change of SI% and SI-BMI (all P<0.01). Multivariate logistic analysis demonstrated the independent association between the change of skeletal muscle mass and the changes of non-invasive steatosis markers after adjusting for other confounding factors (all P<0.001). However, the changes of non-invasive fibrosis markers did not show an independent association with the change of appendicular muscle mass after adjusting for other confounders (all P>0.1)

**Conclusions:** The change of muscle mass is strongly associated with the change of hepatic steatosis, but not the change of fibrosis.

**Keywords:** Sarcopenia, Nonalcoholic fatty liver disease, Fibrosis, Steatosis

#### O-033

#### Liver Fibrosis Is Associated with Risk for Colorectal Adenoma in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) is associated with risks for developing colorectal adenoma, which is related to various metabolic factors. However, studies on the risks of developing colorectal adenoma according to the severity of NAFLD are still limited. This study aimed to evaluate the association between advanced fibrosis in NAFLD and the risk for colorectal adenoma.

**Methods:** We retrospectively analyzed the data of 6,332 adults who underwent abdominal ultrasound and first-time colonoscopy on the same day in a health screening program at Yeungnam University Hospital from September 2009 to June 2017. NAFLD was diagnosed using abdominal ultrasound. We evaluated the presence of advanced fibrosis in NAFLD using various non-invasive score, which also analyzed the detection rate of colorectal adenoma according to the presence of advanced fibrosis in the subjects with NAFLD.

**Results:** The subjects with NAFLD had a higher prevalence of colorectal adenoma, advanced adenoma, and multiple adenomas. In the multivariate analysis adjusting for demographic and

metabolic factors, NAFLD was an independent risk factor for colorectal adenoma (adjusted odds ratio [OR], 1.15; 95% confidence interval [CI], 1.02-1.30), advanced adenoma (adjusted OR, 1.50; 95% CI, 1.12-2.01), and multiple adenomas (adjusted OR, 1.32; 95% CI, 1.01-1.73). When NAFLD was further stratified on the basis of the stage of fibrosis using the non-invasive score models, the subjects with NAFLD and advanced fibrosis had a significantly higher risk for colorectal adenoma, advanced adenoma, and multiple adenomas than those with NAFLD without advanced fibrosis.

**Conclusions:** NAFLD with advanced fibrosis is an independent risk factor for colorectal adenoma compared with NAFLD without advanced fibrosis.

Keywords: Liver fibrosis, Non-alcoholic fatty liver disease, Colorectal adenoma

#### O-034

#### Improvement of Nonalcoholic Fatty Liver Disease Reduces the Risk of Incidence of Type 2 Diabetes Mellitus

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**Aims:** There is little evidence about the effect on risk of diabetes mellitus (DM) development according to change in nonalcoholic fatty liver disease (NAFLD) status over time. We attempted to analyze the DM risk according to change in NAFLD status.

**Methods:** A total of 10,141 individuals for whom routine healthcare assessment was performed were reviewed, and 2,816 subjects were included. NAFLD was assessed using abdominal ultrasonography and fatty liver index. The included subjects were categorized into four groups according to changes in NAFLD status over time: persistent NAFLD, resolved NAFLD, incident NAFLD, and never NAFLD groups.

**Results:** Subjects were categorized according to change in NA-FLD status as follows: 702 subjects into the persistent NAFLD group, 157 subjects into the resolved NAFLD group, 505 subjects into the incident NAFLD group, and 1,452 subjects into the never NAFLD group. Multivariate Cox regression analysis revealed that in addition to old age, higher fasting plasma glucose, and higher alanine aminotransferase level, incident NA-FLD (hazard ratio = 1.94, 95% confidence interval = 1.08–3.49, P=0.027) and persistent NAFLD (hazard ratio = 3.76, 95% confidence interval = 2.16–6.55, P<0.001) were independent risk factors for predicting DM development, whereas the risk of resolved NAFLD was not significantly different from that of never NAFLD. fatty liver index could reproduce the result acquired by ultrasonography.

**Conclusions:** This study demonstrated that future DM risk could be influenced by changes in NAFLD status over time. Resolution of NAFLD could reduce the risk of future DM develop-

ment, while the development of new NAFLD could increase the risk of DM development.

**Keywords:** Non-alcoholic fatty liver disease, Diabetes mellitus, Ultrasonography, Fatty liver index

### O-035

#### Noninvasive Prediction of the Presence and Severity of Nonalcoholic Fatty Liver Disease in Korean Patients with Chronic Kidney Disease: A Validation Study

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**Aims:** Data on the clinical characteristics of nonalcoholic fatty liver disease (NAFLD) in patients with chronic kidney disease (CKD) are scarce. We aimed to investigate clinical features and risk factors of NAFLD using noninvasive serum markers in patients with CKD, and attempted temporal validation.

**Methods:** In this in-hospital retrospective cohort study, a total of 819 consecutive patients with CKD were enrolled between January 2011 and December 2016. Diagnostic performance of serum markers was evaluated in terms of the prediction of the presence of NAFLD on ultrasound, and disease severity was assessed using noninvasive fibrosis markers in the training cohort (2011-2014, n=567). Performance of noninvasive prediction for NAFLD was further assessed in the validation cohort (2015-2016, n=252).

Results: In the training cohort, NAFLD was observed in 89 patients (15.7%). Mean body mass index (BMI) was 24.6 kg/m<sup>2</sup>, and median eGFR was 28.0 ml/min. Patients were categorized according to their eGFR as follows: G3a (45-59 ml/min), 102 (18.0%); G3b (30-44 ml/min), 165 (29.1%), G4 (15-29 ml/ min), 139 (24.5%); G5 (<15 ml/min), 161 (28.4%). Predictors for the presence of NAFLD from multivariate logistic regression analysis included higher values of BMI (odds ratio (OR), 3.247; 95% confidence interval (CI), 1.849-5.703), hemoglobin (OR, 1.247; 95% CI, 1.084–1.434), serum ALT (OR, 1.644; 95% CI, 1.034-2.616), eGFR (OR, 3.538; 95% CI, 1.801-6.948), and triglycerides and glucose (TyG) index (OR, 4.903; 95% CI, 3.046–7.893).(all P<0.05) A prediction model for the presence of NAFLD was derived based on these variable; (-21.0935 + 0.2204 \* hemoglobin + 1.590 \* TyG + 0.4974 \* Log (ALT) + 1.263 \* eGFR category (3.1=1; 3.2, 4, 5 =0) + 1.1779 \* BMI category (1 if BMI≥25; 0 if BMI<25). Using the cut-off value of 0.146, AUC for the prediction of NAFLD was 0.850 (95% CI, 0.803-0.897). In patients with NAFLD, the only predictor of higher BARD score (>2) was TyG index (OR, 3.289 (95% CI,

1.229 – 8.801); *P*=0.018). In the validation cohort, NAFLD was observed in 51 patients (20.2%). mean BMI was 25.4 kg/m<sup>2</sup>, and median eGFR was 36.0 ml/min. Patients were categorized according to their eGFR as follows: G3a, 70 (27.8%); G3b, 89 (35.3%), G4, 62 (24.6%); G5, 31 (12.3%). Using the same prediction model and the cut-off value, AUC=0.842. For all CKD patients with NAFLD (n=140), significant risk factors for disease severity included higher ALT (OR, 4.620; 95% CI, 2.117-10.084; *P*=0.001) and bilirubin (OR, 2.801; 95% CI, 1.040-7.538; *P*=0.042) for APRI, and higher bilirubin (OR, 2.747; 95% CI, 1.189-6.347; *P*=0.018) for FIB-4, respectively.

**Conclusions:** Prevalence of NAFLD in patients with CKD was comparable to that of general population, which increased over time in our temporal validation. Our model using BMI, renal function, TyG, ALT and hemoglobin accurately predicted the presence of NAFLD, which requires further validation.

**Keywords:** Chronic kidney disease, Nonalcoholic fatty liver disease, Noninvasive markers, Prediction model

# O-036

# Sarcopenia Is Associated with Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** Sarcopenia has been known to increase risk of non-alcoholic fatty liver diseases (NAFLD). However, there are limited studies in relationship between sarcopenia and advanced fibrosis in large population. We aimed to investigate association between sarcopenia and advanced liver fibrosis in patients with NAFLD.

**Methods:** A total of 53704 subjects were enrolled the study to be analyzed in single healthcare center. Fatty liver and appendicular skeletal muscle mass (ASM) was diagnosed by ultrasound and bio-impedance analysis, respectively. Sarcopenia was defined as two criteria using an ASM/body weight (sarcopenia<sub>-Wt</sub>, %) and ASM/body mass index (BMI) (sarcopenia<sub>-BMI</sub>), respectively. The stage of liver fibrosis is assessed by non-invasive scoring model including NAFLD fibrosis score (NFS) and Fibrosis-4 (FIB-4) index, which was determined as the both low and high cut-off value (COV).

**Results:** Of 10711 patients with NAFLD, 1389 (13.0%) were diagnosed with sarcopenia. The scarcopenic patients were older (47.7 vs. 49.1 years, P=0.001), had lower BMI (24.4 vs. 20.4 kg/m2, P=0.000) and waist circumference (82.1 vs. 72.6 cm, P=0.000) compared to non-sarcopenic patients. Regardless of the classified sarcopenia based on body weight or BMI, presence of sarcopenia was independent risk factor for advanced liver fibrosis, which is assessed by low cut-off value for FIB-4 index (Adjusted for metabolic and lipid profiles and sex, ORs = 1.27 to 2.01, all Ps < 0.05). In addition, regardless of the classified sarcopenia based on body weight or BMI, presence of

sarcopenia was also independent risk factor for advanced liver fibrosis, which is assessed by both COVs of NFS (Adjusted for obesity and hypertension, lipid profile, and sex, ORs = 1.65 to 2.68, P<0.01 in low COV group, ORs = 2.03 to 3.12, P=0.002 in high-COV group, respectively).

**Conclusions:** Sarcopenia is an independent risk factor for advanced liver fibrosis in patients with NAFLD.

**Keywords:** Sarcopenia, Non-alcoholic fatty liver disease, Liver fibrosis, Body mass index

# 4. Liver Cancer

#### O-037

#### Late Presentation of Hepatitis B among Patients with Newly Diagnosed Hepatocellular Carcinoma: A National Cohort Study

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**Aims:** As effective and well tolerated treatments for hepatitis B are available, early identification of patients with hepatitis B could effectively decrease burden from hepatitis B. Recently, a consensus definition of late presentation of chronic viral hepatitis for medical care has been suggested, to help quantify the proportion of patients missing timely diagnosis and treatment. Yet, clinical implications at the population level are largely unexplored.

**Methods:** We used person-level longitudinal National Health Insurance Service-National Sample Cohort registration and claims: data collected between January 1, 2002 and December 31, 2013. From this cohort, we identified newly-diagnosed hepatitis B related hepatocellular carcinoma (HCC) patients, and classified patients into 'late presentation of hepatitis B', who were diagnosed with HCC without a prior clinic visit for hepatitis B, "regular" or "irregular" visit, who were diagnosed with HCC who had regular or irregular pattern of outpatient clinic visits for hepatitis B before HCC diagnosis.

**Results:** Over the years, the proportion of patients with late presentation decreased from 50.8% in 2003 to 23.1% in 2013. In multivariable analysis compared with patients in the regular visits group, patients with late presentation were more likely to be younger and to be in lower income percentiles. After adjusting for age, sex, year of HCC diagnosis, income percentile,

and initial treatment, the hazard ratios (95% confidence intervals) for all-cause mortality comparing the late presentation and irregular visits groups to the regular visits group were 1.76 (1.42–2.18) and 1.31 (1.06–1.61), respectively.

**Conclusions:** In this nationally representative population-based study, timely diagnosis and treatment was suboptimal at the population level up to recent years. More precise and intensive strategies to minimize late presentation for hepatitis B is needed, with a special attention to younger people and lower income levels.

**Keywords:** Hepatitis B, Hepatocellular carcinoma, Late presentation, Mortality

#### O-038

#### A MoRAL Score Utilizing Serum Tumor Markers Provides Refined Prognostication of Patients with Hepatocellular Carcinoma after Curative Resection: Data from 662 Consecutive Patients

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**Aims:** We recently developed and validated a MoRAL score (=11 x  $\sqrt{PIVKA + 2 \times \sqrt{AFP}}$ ) that can predict the risk of hepatocellular carcinoma (HCC) recurrence after living-donor liver transplantation (LDLT) regardless of tumor size and number, which may reflect tumor cell biology. Patients with a low MoRAL score ( $\leq$  314.8) showed excellent treatment outcomes after LDLT, even though they are beyond the Milan criteria. We investigated whether a MoRAL score is a predictor of HCC recurrence and mortality after curative hepatic resection.

**Methods:** A total of 662 consecutive patients who underwent curative resection for HCC of BCLC stage 0–B between 2006 and 2013 at a single tertiary referral center were included. Primary and secondary endpoints were recurrence-free survival (RFS) and overall survival (OS), respectively.

**Results:** During a median observation period of 68.8 months, 326 (49.2%) patients experienced tumor recurrence and 59 (8.9%) died. In multivariable analysis, high MoRAL score (>314.8) was an independent risk factor of both recurrence (adjusted hazard ratio [aHR]=1.61, 95% confidence interval [CI]=1.22-2.12, *P*=0.001) and death (aHR=2.62, 95% CI=1.49–4.59, *P*=0.001). The presence of cirrhosis was an other independent prognostic factor for RFS (aHR=1.76, 95% CI=1.38–2.24, *P*<0.001) and OS (aHR=1.82, 95% CI=1.06–3.14, *P*=0.031). When patients were stratified into four groups as low-MoRAL/no-cirrhosis, low-MoRAL/cirrhosis, high-MoRAL/ no-cirrhosis, or high-MoRAL/cirrhosis; the RFS (Figure 1A) and OS (Figure 1B) significantly differed among strata (all *P*<0.001).

Median RFSs of the high-MoRAL/LC, the low-MoRAL/LC, and the high-MoRAL/no-LC groups were 20.4, 41.8, and 53.2 months, respectively; while the low-MoRAL/no-LC group did not reach median RFS. A MoRAL score showed significant association to hypermetabolism on positron emission tomography (P<0.001, chi-squared test for trend) and cytokeratin 19-positivity in tumor tissue (P=0.003, Pearson chi-square), which reflect aggressive tumor cell biology.



**Conclusions:** A MoRAL score was an independent predictor of tumor recurrence and mortality after curative resection of HCC regardless of tumor size and number and reflects tumor biology. Combination of MoRAL score and the presence of cirrhosis might be utilized as an accurate prediction model.

**Keywords:** Hepatocellular carcinoma, MoRAL score, Recurrence-free survival, Overall survival

#### O-039

# A Phase 1 Study Using Autologous Natural Killer Cells in Patients with HAIC-Hepatocellular Carcinoma

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**Aims:** Natural killer (NK) cell-based immunotherapy has recently been tried with advances of understanding the role of immune defense against hepatocellular carcinoma (HCC). To improve NK cells therapy, we focused to increasing delivery of NK cells and synergic effect combined with hepatic arterial infusion chemotherapy (HAIC).

**Methods:** We did a prospective, open label, phase 1 trial of the safety and efficacy of autologous NK cells through hepatic arterial infusion as sequential therapy after HAIC in advanced HCC patients. Between March 2016 and July 2017, 11 patients were included who showed favorable response more than stable disease (SD) after 2 sessions of HAIC in advanced HCC patients with child A. A total 4 sessions of HAIC were performed the protocols of infusion of cisplatin (25/m<sup>2</sup>) and 5-fluorouracil (750/m<sup>2</sup>) for 4 days every 3-4 weeks interval. The peripheral blood mononuclear cells of patients by leukapheresis were ob-

tained after 3<sup>rd</sup> HAIC and NK cells were expanded for 2 weeks under Current Good Manufacturing Practices (cGMP). Patients received planned dosage of NK cells through chemoport into hepatic artery for 5 days after 4<sup>th</sup> HAIC (3 patients; 2.5x10<sup>8</sup>, 3 patients; 5x10<sup>8</sup>, 5 patients; injection of 10x10<sup>8</sup> NK cells). The primary end point was safety of NK cell injection; secondary endpoint included objective response rate (modified Response Evaluation Criteria In Solid Tumors), time to progression, duration of response and immunologic efficacy.



Figure 1. Protocol of hepatic arterial infusion chemotherapy and Vax-NK cell therapy



Figure 2. Characteristics of autologous Vax-NK cells



Figure 3. NK cell activity analysis in peripheral blood after NK cell infusion through hepatic artery

**Results:** Any adverse events of NK cells injection were none according to dosage. An objective response was observed in 7 patients (63.6%) included three complete responses and four partial responses. Stable disease was observed in 2 patients and progressive disease was in 2 patients and thus disease control rate was 81.8%. The mean duration of time to progression was 9.7±5.3 month and duration of response without chemotherapy was 6.1±5.2 month. The newly metastatic lesion was occurred in 3 patents (27.2%; lymph node 1 patients, Lung 2 patients). Two patients were died by tumor progression and others were still alive. The increasing immunologic response was observed in 5 patients (55 %) to evaluate cytotoxicity and NK cell proportion of peripheral mononuclear cells after NK cell

#### injection.

**Conclusions:** The HAIC and NK cells immunotherapy is safe and effective treatment in the advance HCC patient with favorable liver function. The additional studies are urgently required to establish the new novel treatment.

**Keywords:** Natural Killer Cell, Hepatic arterial infusion chemotherapy, Hepatocellular carcinoma, Immunotherapy

#### O-040

Adjuvant Cytokine-Induced Killer Cell Immunotherapy for Hepatocellular Carcinoma: A Real-World Experience from Two Large-Volume Centers in Korea

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**Aims:** Several randomized controlled trials have shown that adjuvant immunotherapy with autologous cytokine-induced killer (CIK) cells prolongs recurrence-free survival (RFS) after curative treatment for hepatocellular carcinoma (HCC). We investigated the efficacy of adjuvant immunotherapy with activated CIK cells in real-world clinical practice.

**Methods:** A total of 370 patients with stage I or II HCC who underwent curative surgical resection or radiofrequency ablation at Seoul National University Hospital or Samsung Seoul Medical Center were included in this study. Among them, 71 patients received CIK cell immunotherapy after curative treatment and 299 patients did not. Propensity score matching with a 1:1 ratio was conducted to avoid possible bias and 64 pairs of matched patients were generated. The primary endpoint was RFS and secondary endpoints included overall survival.

Results: After a propensity score matching, there was no statistical difference in variables including treatment modalities, HCC stage, presence of cirrhosis, alpha-fetoprotein level between the two groups. The median follow-up duration was 16.0 months (interguartile range, 7.8 – 27.0). The immunotherapy group did not reach median RFS and the control group showed 33.5 months of median RFS (P=0.001 by log-rank test). CIK cell adjuvant therapy reduced the risk of tumor recurrence or death by 65% (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.18-0.68, P=0.002, Figure 1). No patient (0%) in the immunotherapy group and 5 patients (7.8%) in the control group died during the study period. However, the difference in OS between two groups failed to reach statistical significance (P=0.060 by Firth's method, Figure 2). Multivariable Cox regression analysis showed that immunotherapy was an independent predictor for HCC recurrence (adjusted HR, 0.16; 95% CI, 0.04-0.65; P=0.010).

**Conclusions:** The adjuvant immunotherapy with autologous CIK cells prolongs RFS in patients with HCC after curative therapy in a real-world setting.



<sup>&</sup>lt;Figure 2>

**Keywords:** Hepatocellular carcionma, Immunotherapy, Cytokine-induced killer cell, Recurrence

#### O-041

#### Hepatic Safety and Biomarker Assessments in Sorafenib-Experienced Patients with Advanced Hepatocellular Carcinoma Treated with Nivolumab in the CheckMate-040 Study

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**Aims:** Nivolumab (NIVO) is a fully human anti–PD-1 IgG4 mAb that demonstrated durable responses, manageable safety, and long-term survival in pts with advanced HCC (aHCC) in CheckMate-040 (EI-Khoueiry AB et al. *Lancet* 2017). Here we present updated hepatic safety and biomarker analyses in sorafenib-experienced (sor-exp) pts in CheckMate-040.

**Methods:** Sor-exp pts with or without chronic viral hepatitis received NIVO 3 mg/kg Q2W. Primary endpoint was objective response rate (ORR) reported by blinded independent central review using RECIST v1.1. Secondary endpoints included overall survival (OS), disease control rate (DCR), and safety. Exploratory analyses of on-treatment HCV and HBV viral kinetics and alpha-fetoprotein (AFP) levels were performed.

**Results:** Median duration of follow-up was 14.9 mo. Baseline Child-Pugh scores of 5 or 6 and extrahepatic metastases were observed in 99% and 71% of pts, respectively. The ORR with NIVO was 14%; the DCR was 56%; median OS was 15.6 mo. Any-grade and grade 3–4 hepatic treatment-related AEs (TRAEs) occurred in 12 (8%) and 5 (3%) pts, respectively; 100% of grade 3–4 hepatic TRAEs resolved. Frequencies of grade 3–4 treatment-related ALT/AST elevations were 2%–3%. No drug-related deaths due to hepatic AEs occurred, and no new safety signals were observed. AFP levels at baseline were not associated with response; however, AFP levels in responders appeared to decrease on treatment. Updated data will be presented.

**Conclusions:** NIVO demonstrated long-term survival and objective responses across etiologies and manageable overall and hepatic safety profile in aHCC. Responses occurred irrespective of baseline AFP levels, and AFP declines were associated with response.

**Keywords:** Hepatocellular carcinoma, Nivolumab, Immune checkpoing inhibition, PD-1 inhibitor

# O-042

Development and Validation of Nomograms to Provide Individualized Predictions of Survival Benefits from Surgery in Patients with Intermediate/Advanced Hepatocellular Carcinoma

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**Aims:** According to the BCLC treatment guidelines, surgery does not be recommended for intermediate/advanced hepatocellular carcinoma (HCC). In real world, however, liver resections are often performed in patients with intermediate/ advanced but resectable HCC, especially in the East.

**Methods:** We retrospectively evaluated multicentric data of 1,325 patients newly diagnosed with intermediate/advanced HCC who underwent curative resection. We randomly divided the subjects into development (n = 875) and validation (n = 450) samples. Multivariate Cox proportional hazards models were developed and separately validated on the basis of patients' clinicopathological variables assessed for associations with 1-year recurrence and 3-year mortality. The discriminatory accuracy of these models was compared with conventional tools by analyzing receiver operating characteristic (ROC) curves.

**Results:** He statistical nomograms built based on performance status, Child-Pugh grade, portal hypertension, preoperative alpha-fetoprotein level, tumor rupture, largest tumor diameter, tumor number, macrovascular and microvascular invasion, and satellites had good calibration and discriminatory abilities, with c-indices of 0.70 (1-year recurrence) and 0.68 (3-year survival), respectively. These models showed satisfactory goodness-of-fit and discrimination abilities in the validation cohort (c-index, 0.68 for 1-year recurrence and 0.69 for 3-year survival). The areas under the ROC curve using these nomograms exceeded those of traditional staging systems, indicating superior discriminatory capability (c-indices, 0.60-0.63 and 0.56-0.62, respectively).

**Conclusions:** Our proposed online nomograms, which present graphically postoperative prognostic models for recurrence and survival in patients with intermediate/advanced but resectable HCC, offer valuable guidance to surgeons and hepatologists for individually predicting survival benefits from surgery and planning recurrence surveillance and adjuvant therapy.

5. HBV

# O-043

### Alcohol, Smoking and Overweight as Risk Factors of Hepatocellular Carcinoma in Chronic Hepatitis B Patients on Effective Antiviral Treatment

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Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine **Aims:** Heavy alcohol consumption, smoking and obesity have come to be epidemiologically recognized as causes of hepatocellular carcinoma (HCC). It is uncertain whether these risk factors would increase the risk of HCC in patients with chronic hepatitis B (CHB). The aim of this study is to identify prognostic effects of such habitual or metabolic risk factors on HCC occurrence in CHB patients under effective antiviral treatment.

**Methods:** This study from an endemic area retrospectively included 2,892 CHB patients aged  $\geq$ 40 years who started primary or rescue antiviral therapy with entecavir or tenofovir between 2007 and 2015, and continued the therapy for at least 6 months (mean age, 52±8 years; 1,778 males; 426 with a history of heavy alcohol consumption (> 280 g/wk for males and > 140 g/wk for females), 887 with smoking history, 1,717 with high body mass index (> 23 kg/m<sup>2</sup>), 686 with cirrhosis; 1373 with HBeAg-positive CHB; and 2468 with Child-Pugh class A). No patients had a previous history of HCC or decompensated liver function. We measured incidence rates of HCC according to the non-hepatic factors such as alcohol, smoking and overweight, and examined their individual and combined effects on HCC development.

Results: A total of 324 HCC cases were newly identified during a median follow-up of 4.8 years (13,542 person-years). The overall HCC incidence rate was 2.39 (2.15-2.66) per 100 person-years of observation. The annual risk of developing HCC was significantly higher in sets with heavy alcohol consumption (4.17% vs. 2.42%); smoking history (4.36% vs. 2.20%) and overweight (2.78% vs. 1.86%; Ps<0.05). Multivariate Cox analysis revealed that heavy drinking, ever-smoker, overweight, male gender, older age, previous antiviral treatment, lower HBV DNA, ALT, platelet count and albumin in blood were significantly associated with HCC development (hazard ratios 1.39, 1.61, 1.53, 1.75, 1.06, 0.57, 0.94, 0.997, 0.992, and 0.73, respectively; Ps<0.05). There was no difference in the stage of HCC initially detected across patients with the following 3 risk factors: alcohol-drinking, smoking, and overweight (P=NS). The cumulative incidence of HCC at 5 and 10 years was 11.0% and 21.4%, respectively for the entire patients, and 8.7% vs. 10.7% vs. 16.0%; and 15.3% vs. 22.6% vs 32.9%, respectively for patients without the 3 risk factors (n=792), patients with one of them (n=1037), patients with two or three of them (n=402; Ps<0.05).

**Conclusions:** Our data showed that alcohol-drinking, smoking and overweight were independently and more strongly when combined associated with a significant risk for HCC in antivirals-treated CHB patients. Educating patients to quit drinking and smoking and to reduce their weight may help to prevent HCC and further improve survival in such patients.

Keywords: Acohol, Smoking, Obesity, Hepatitis B

#### O-044

# Association of Preemptive Anti-HBV Therapy with Improved Long-Term Survival in Patients with Hepatocellular Carcinoma Undergoing Transarterial Therapy

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**Aims:** The effect of preemptive antiviral therapy (AVT) on survival in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) remains unknown. The study aimed to determine whether preemptive AVT can allow improved long-term survival in patients undergoing transartieral therapy.

**Methods:** A total of 2546 newly diagnosed HBV-related HCC patients treated with transarterial therapy as initial therapy between 2000 and 2016 were screened for the analysis of two groups based on preemptive use of antivirals. Patients who had co-existing other diseases, previous AVT, and other treatment options within 2 years of transarterial therapy were excluded. Treatment effects were analyzed using propensity score (PS) matching (1:1) separately for the entire cohort and each subgroup. The primary endpoint was overall survival. For patients initiating antivirals, analyses were done on an intention-to-treat basis.

Results: Overall, 1547 patients met the inclusion criteria and 1286 were PS-matched for the two groups. Mean follow-up duration was  $32.0 \pm 36.6$  months. In the entire unmatched cohort, patients receiving preemptive AVT survived significantly longer than those not, with the 10-year survival rates of 26.8% vs. 9.6%, respectively (P<0.001). Among AVT-untreated patients, high baseline HBV viremia and HBV reactivation during treatment were significantly associated with shorter survival, but these effects were not observed when analyzed together with AVT-treated patients. Regarding the types of antivirals, survival was significantly longer in patients receiving high-potency than low-potency antivirals. In the PS-matched cohort, the preemptive-AVT group survived significantly longer than the non-preemptive group. Preemptive AVT remained an independent factor for survival. Multivariable stratified analysis further verified the association of preemptive AVT with decreased risk of mortality in all patient subgroups. Sensitivity analyses also confirmed the estimated treatment effect in each matched subgroup stratified by tumor stage and baseline viremia status.

**Conclusions:** Preemptive AVT is associated with significantly improved long-term survival among patients undergoing transarterial therapy. High-potency antivirals are best indicated for this approach.

Keywords: Hepatitis B virus, Antiviral agents, Liver cancer, Survival

# O-045

Differential Effect of Hepatitis B Viral Suppression on Hepatocellular Carcinoma Development According to the Phase of Initial Antiviral Treatment: A Multicenter Study

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**Aims:** Although antiviral therapy for chronic hepatitis B virus (HBV) infection reduces risk of hepatocellular carcinoma (HCC), the risk is reportedly higher in the antiviral-induced viral suppression than inactive carriers. In this study, we aimed to compare the effect of the phases when the antiviral treatment started on the HCC development

**Methods:** This retrospective study included chronic hepatitis B patients with suppressed HBV DNA (<2,000 IU/mL) and normal alanine aminotransferase levels and without evidence of cirrhosis from eight referral hospitals in Korea. Study subjects were categorized into four groups: patients underwent antiviral treatment from immune-tolerant phase (IT group), HBeAg-positive hepatitis phase (HBeAg+ group), or HBeAg-negative hepatitis phase (HBeAg- group); or inactive carriers without any antiviral treatment (IC group). Primary endpoint was an HCC development. Kaplan-Meier survival analysis and Cox proportional hazard model were used for statistical analysis.



**Results:** A total of 887 patients were included: 63 in IT group, 151 in HBeAg+ group, 365 in HBeAg- group, and 308 in IC group. In univariate analyses, there was no significant difference in the risk of HCC development between IT group and IC group (hazard ratio [HR]=0.85, 95% confidence interval [CI]=0.10–7.15, *P*=0.98). However, both HBeAg+ (HR=4.01, 95% CI=1.57–10.28, *P*=0.001) and HBeAg- (HR=3.04, 95% CI=1.29–7.07, *P*=0.007) groups showed significantly higher risk of HCC occurrence. The 5-year risk of HCC occurrence

was 5.6% in IT group, 10.9% in HBeAg+ group, 8.3% in HBeAg- group, and 1.9% in IC group (Figure 1). In multivariate analyses, IT group consistently showed similar risk of HCC development compared to IC group (adjusted HR [aHR]=0.85, 95% CI=0.10–7.15, P=0.88). Both HBeAg+ (aHR=2.91, 95% CI=1.13–7.42, P=0.03) and HBeAg- (aHR=2.48, 95% CI=1.05–5.85, P=0.04) groups showed significantly higher risk of HCC development than IC group.

**Conclusions:** Even if HBV DNA suppression has equally achieved, the risk of HCC development varies depending on the phase of initial antiviral therapy. Early antiviral therapy from immune-tolerant phase is associated with low risk of HCC similar to that of natural inactive carriers which is significantly lower than the risk of patients treated from immune-active phases.

**Keywords:** Immune tolerant phase, Antiviral therapy, Hepatocellular carcinoma

### O-046

#### Impact of Antiviral Therapy on Risk Prediction Models for Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis B

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**Aims:** Risk prediction models for hepatocellular carcinoma (HCC) development have been proposed. However, the influence of antiviral therapy (AVT) on these models in patients with chronic hepatitis B (CHB) is unknown.

**Methods:** We investigated the dynamics of risk prediction models during AVT and the association between on-treatment values from these models and the risk of HCC development.

Results: Between 2005 and 2017, 6,098 patients with CHB (1,758 non-cirrhotic, 4,340 cirrhotic) in whom AVT was initiated with entecavir (n=3,818) or tenofovir (n=2,280) were recruited. The mean age of the study population was 49.1 years and 61.4% (n=3,742) of the patients were male. The mean CU-HCC value was 12.7 at baseline in the entire study population; it was significantly lower (mean, 8.6) after 1-year of AVT (P<0.001) and was maintained throughout 5-years of AVT (mean, 8.2-8.4; P>0.05). The proportion of high-risk patients (CU-HCC score  $\geq$  20) was 28.9% at baseline, which significantly decreased after 1-year of AVT (4.8%; P<0.001) and was then maintained through 5-years of AVT (2.6-3.5%; P>0.05). The CU-HCC score after 1-year of AVT independently predicted the risk of HCC development (hazard ratio=1.037), together with age, male gender, liver cirrhosis, and platelet count (all P<0.05). Similar findings were obtained when the REACH-B criteria were used for non-cirrhotic patients.

**Conclusions:** CU-HCC and REACH-B scores were significantly lower after 1-year of AVT and were maintained thereafter. CU-HCC and REACH-B scores after 1-year of AVT independently predicted the risk of HCC development in patients with CHB in whom AVT was initiated.

**Keywords:** Hepatocellular carcinoma, Chronic hepatitis B, Antiviral therapy, Risk prediction model

#### O-047

#### Improved Bone and Renal Safety at 1Year after Switching from TDF to TAF: In Chronic HepatitisB(CHB) Patients from East Asia

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**Aims:** TAF has shown similar efficacy to TDF with less bone and renal effects in 2 large multinational Phase 3 studies after 96weeks(2 years) of double-blind (DB) treatment. Here we evaluated efficacy and safety, including bone and renal parameters, in the subset of patients from East Asia(EA) who completed 2years of DB treatment with TAF 25mg or TDF 300mg once daily and were switched to open label(OL) TAF 25mg once daily for 1year.

**Methods:** In 2 identically-designed studies, 1298 CHB patients who were HBeAgnegative (Study 108; N=425) or HBeAgpositive(Study 110; N=873) were randomized and treated. At Week96, 540(42%; TAF 360; TDF 180) patients including 240(18%; TAF 156; TDF 84) EA patients, had completed 2years of DB TAF or TDF treatment and been switched to OL TAF. Safety including bone(serial DXA scans of spine and hip) and renal(CrCl by Cockcroft-Gault [eGFR<sub>CG</sub>]) parameters, viral suppression and biochemical response were assessed at Year 3.

**Results:** In EA patients on DB TDF switched to OL TAF(TDF<sup>®</sup>-TAF), eGFR<sub>CG</sub> improved at Year 3 vs. Year 2 (median [Q1, Q3] change = +3.0 [-3.0, +8.4] ml/min); and was stable in those continuing TAF(TAF<sup>®</sup>TAF)(figure). BMD also improved at Year 3 vs. Year 2 in TDF<sup>®</sup>TAF patients (mean[SD]% change: spine = +2.2%[3.48]; hi*P*=+0.7%[2.44]) while BMD changes were stable for TAF<sup>®</sup>TAF patients (figure). High rates of virologic control (HBV DNA<29IU/mL) were maintained in those on treatment at Year3 vs Year2(TDF<sup>®</sup>TAF 96% and 95% and TAF<sup>®</sup>TAF 90% and 93%); ALT normalization (AASLD criteria) increased in TDF<sup>®</sup>TAF patients and was similar to TAF<sup>®</sup>TAF patients at 1 year following switch(46% vs 42%; M=F).



**Conclusions:** EA patients switched to TAF after 2 years of TDF had improved bone and renal safety; virologic control was maintained and ALT normalization increased. The results in EA patients are comparable to those seen in the overall population. **Keywords:** CHB, TDF, TAF, Switch

#### O-048

# Safety and Efficacy at 1-Year after Switching from TDF to TAF in CHB Patients with Risk Factors for TDF Use

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**Aims:** Tenofovir alafenamide (TAF), a new prodrug of tenofovir (TFV), is now a preferred treatment in the 2017 EASL HBV Guidelines, and may be particularly useful in patients with risk factors for TDF associated renal and bone effects. We assessed the 1 year safety and efficacy in CHB patients with TDF risk factors who were switched from TDF to TAF.

**Methods:** In two identically-designed Phase 3 studies, HBeAg(+) and HBeAg(-)patients were randomized 2:1 to TAF 25 mg or TDF 300 mg and treated in a double- blind fashion for 96 weeks; all patients received open-label (OL) TAF for an additional 48 weeks (through Week 144). Renal and bone safety parameters, and antiviral efficacy (HBV DNA <29 IU/mL) and ALT normalization were assessed in the subset of switch patients with baseline risk factors for TDF use: Age >60 years, osteoporosis of hip or spine, <sup>3</sup>Stage 2 CKD (GFRCG <90 mL/ min), albuminurina (UACR >30 mg/g), hypophosphatemia (PO4 <2.5 mg/dL), or presence of comorbidities (e.g. HTN, DM).

**Results:** Of 1298 patients randomized and treated in the 2 studies, 540(42%) switched to open- label TAF at Week 96 (TAF®TAF 360; TDF®TAF 180), of which 284(53%) patients had at least 1 TDF risk factor at baseline; 123(23%) patients had <sup>3</sup>2 risk factors. Baseline demographics and disease characteristics were similar between treatment groups. At Week 144, significant improvements in renal (sCr, eGFRCG) parameters, hip and spine BMD were observed and summarized in the table. Antiviral efficacy was maintained at Week 144 in both groups and in TDF patients who switched to TAF, increased rates of ALT normalization were seen.

Table. Renal and bone safety results at Week 144 in CHB patients with TDF risk factors

Change from Open-label (Week 96) baseline:	TDF→TAF (N=101)	P value <sup>a</sup>	
Renalparameters			
Serum creatinine, mean (SD) change (mg/dL)	-0.018 (0.064)	0.008	
eGFR <sub>CG</sub> , median (Q1, Q3) change (mL/min)	+3.0 (-1.8, 7.8)	< 0.001	
≥1 stage improvement in CKD stage from Week 96 (OL baseline) to Week 144, n/N (%)	9/51 (18)	$ND^b$	
≥1 stage worsening in CKD stage from Week 96 (OL baseline) to Week 144, n/N (%)	4/95 (4)	ND	
Boneparameters			
Hip BMD, mean (SD) % change	+0.97 (2.88)	0.002	
Spine BMD, mean (SD) % change	+2.18 (3.36)	< 0.001	

\*P values from T test; <sup>b</sup>ND is testing not done

**Conclusions:** In CHB patients with risk factors for potential TDF toxicity, switching from TDF to TAF resulted in improved bone and renal safety parameters while efficacy was maintained in this subgroup at one year.

**Keywords:** TAF, Switching from TDF, Risk factors for TDF use, CHB

### O-049

Improvement of Bone Mineral Density and Markers of Proximal Renal Tubular Function in Chronic Hepatitis B Patients Switched from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide

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Aims: Tenofovir alafenamide (TAF) is a novel prodrug that re-

duces tenofovir plasma levels by 90% compared to tenofovir disoproxil fumarate (TDF), resulting in decreased bone mineral density (BMD) loss and renal toxicity. We aimed to study changes in BMD and markers of renal function of chronic hepatitis B (CHB) patients previously treated with TDF who were switched to TAF.

**Methods:** This was a prospective single-arm open-label study of 75 CHB patients treated with TDF 300 mg daily who were switched to TAF 25 mg daily and followed for 24 weeks. All patients had been treated with TDF for at least 12 months and had HBV DNA < 21 IU/mL at the time of switch. BMD and markers of renal function were taken on the day of switch and repeated after 12 and 24 weeks of TAF treatment.

Table	1.	(n=75)
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Mean ± standard deviation or Median (range)	Week 0	Week 12	Week 24
Age (years)	56±11		
Sex	65% Male		
Race	97% Asian		
BMI	$24.2 \pm 3.1$		
Duration of TDF (months)	62.0 ± 29.7		
Calculated GFR Cockcroft-Gault (mL/min)	95.9±29.1	96.6±29.9	93.7 ± 26.9 <sup>†</sup>
Serum Phosphorus (mg/dL)	$3.2 \pm 0.4$	3.3 ± 0.4 **	$3.1 \pm 0.4 *^{11}$
Urine Phosphorus (mg/dL)	53.0 ± 30.5	57.6 ± 32.7	55.7 ± 34.8
Fractional Excretion of Phosphate	11.9 (4.5-41.7)	14.0 (3.5-38.6)	14.0 (3.1-30.4)*
Phosphate Threshold for Renal Tubu- lar Reabsorption (mg/dL)	2.8±0.5	$2.9\pm0.4$	2.6±0.4** <sup>++</sup>
Abnormal (< 2.8 mg/dL)	36 (48)	36 (48)	49 (65)* <sup>†</sup>
Serum Uric Acid (mg/dL)	5.2 ±1.0	5.5±1.1**	5.5 ± 1.0 **
Urine Uric Acid (mg/dL)	45.8±23.0	50.3 ± 27.2	47.9±21.8
Fractional Excretion of Uric Acid	6.9 (0.6-29.0)	6.7 (0.3-29.0)	7.5 (1.6-17.0)
Urine Albumin	4.5 (0.8-154.0)	4.2 (0.4-52.7)	4.6 (1.0-218.1)
Urine Albumin/Cr Ratio	0.04 (0.01-1.9)	0.04 (0.01-0.6)	0.04 (0.02-2.5)
Urine Beta-2-Microglobulin	141 (10-92271)	116 (13-3269) **	89 (0-3991) **
Urine Beta-2-Microglobulin/Cr Ratio	1.5 (0.1-770.6)	1.0 (0.1-138.5) **	1.1 (0-52.6) **
Urine Retinol-Binding Protein	197 (38.7-52200)	156 (17-2400) **	143 (18.2-1380) **
Urine Retinol-Binding Protein/Cr Ratio	1.7 (0.7-656.6)	1.3 (0.4-101.7) **	1.4 (0.4-20.0) **
Hip T-Score	-1.2 ± 1.1	-0.9 ± 1.0 **	-0.8 ± 1.0 **
Hip BMD	$0.79\pm0.18$	0.87±0.16**	0.87±0.18**
% change from week 0	0	12.9 ± 22.7 **	12.8 ± 21.7 **
Spine T-Score	$-1.4 \pm 1.6$	-1.2 ± 1.6 **	-1.2 ± 1.6 **
Spine BMD	$0.92 \pm 0.18$	0.95±0.18**	0.95±0.17**
% change from week 0	0	2.4 ± 5.8 **	3.1±5.0**

\*P<0.05, \*\*P<0.01 compared to week 0.

<sup>+</sup>P<0.05, <sup>++</sup>P<0.01 compared to week 12.

Paired student's t-test or Wilcoxon signed rank test comparing week 0 and week 12 values, week 0 and week 24 values, and week 12 and week 24 values.

**Results:** BMD significantly increased after switch from TDF to TAF from baseline to week 12 and remained stable at week 24. Mean percent changes from baseline to week 12 in hip and spine BMDs significantly increased (+ 12.9% and +2.4%, respectively). There were significantly more patients with gains in hip (86%) or spine (76%) BMD than patients who experienced loss (11% and 25%, respectively). No significant change in BMD was seen between week 12 and 24. There was no significant difference in eGFR<sub>CG</sub> from baseline to week 24. Significant improvement was observed in urinary beta-2 micro-

globulin/creatinine ratio between baseline and week 12 that remained through week 24 (median change from baseline to week 12 and 24; 1.5, 1.0 and 1.1 mcg/g respectively; P<0.01). Similar changes were observed with retinol binding protein/creatinine ratio at from baseline to week 12 and 24 (median change from baseline to week 12 and 24; 1.7, 1.3 and 1.4 mcg/g respectively; P<0.01). There was significant increase in fractional excretion of phosphate from baseline to week 24 (11.9 to 14.0; P<0.05). Phosphate threshold for renal tubular reabsorption decreased from baseline to week 12 (2.8 to 2.6 mg/dL).

**Conclusions:** Switching from long-term TDF to TAF among CHB patients was associated with significant improvement in BMD and some markers of proximal renal tubular function. There was no improvement in urinary phosphate handling after the switch which suggests TDF has a direct effect on bone metabolism that is reversible. Longer term and larger studies are needed to confirm these findings.

Keywords: Tenofovir, Renal dysfunction, Bone

# O-050

Fibrates Significantly Increase the Biochemical Response and Reduce the Risk of Cirrhosis Development in UD-CA-Refractory Primary Biliary Cholangitis Patients

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**Aims:** Ursodeoxycholic acid (UDCA) is the only treatment which can modify the clinical course of primary biliary cholangitis (PBC) and there have been few treatment options for UDCA-refractory PBC. Several studies reported that fibrates effectively reduce serum alkaline phosphatase (ALP) levels in UDCA-refractory PBC, but their long-term effects remain unclear. The aim of this study was to evaluate the effect of fibrates on clinical outcomes in UDCA-refractory PBC.

**Methods:** This retrospective study involved consecutive patients whose ALP had not been normalized with UDCA treatment for >1 year at a tertiary referral center. The primary outcome was the rate of ALP (± gamma-glutamyltransferase [GGT]) normalization and secondary outcomes included the development of liver cirrhosis, hepatocellular carcinoma, death, and liver transplantation. Baseline characteristics were adjusted or balanced using inverse probability weighting analysis (IPW) and the Cox hazards model.

**Results:** A total of 66 UDCA-refractory PBC patients were included: 45 patients who were treated with 13–15 mg/kg of UDCA (the UDCA group) and 21 patients who received UDCA + additional fibrate (fenofibrate 160 mg/day or bezafibrate 200 mg/day; the fibrate/UDCA group). The baseline serum levels of aspartate aminotransferase (53.8 $\pm$ 33.5 vs 38.8 $\pm$ 17.1 IU/L, *P*=0.02) and albumin (4.0 $\pm$ 0.5 vs 4.2 $\pm$ 0.2 g/dL, *P*=0.006) significantly differed between

two groups. The rates of both ALP normalization (hazard ratio [HR]=7.82, 95% confidence interval [CI]=3.65-16.77, *P*<0.001 by log-rank test) and ALP/GGT normalization (HR=5.50, 95% CI=2.34-12.95, *P*<0.001) were significantly higher in the fibrate/UDCA group. At week 48, ALP was normalized in 86.3% of the fibrate/UDCA group and 17.9% of the UDCA group. Of the 36 patients who had no baseline cirrhosis (11 in the fibrate/UDCA group and 25 in the fibrate/UDCA group), none in the fibrate/UDCA group and 9 patients (36.0%) in the UDCA group developed cirrhosis (HR=0.16, 95% CI=0.001–1.35, *P*=0.09) during study period. However, when baseline characteristics were balanced by IPW, the fibrate/UDCA group demonstrated a significantly lower risk of cirrhosis development (*P*=0.02). Neither the risk of hepatocellular carcinoma development (*P*=0.69) nor death or liver transplantation (*P*=0.16) differed significantly.

#### Figure 1. Kaplan-Meier estimates of ALP normalization



Figure 2. Kaplan-Meier estimates of ALP and GGT normalization



**Conclusions:** In PBC patients who failed to achieve ALP normalization despite the appropriate dose of UDCA, additional fibrate treatment is associated with a higher probability of ALP normalization and a lower risk of cirrhosis.

Keywords: Primary biliary cholangitis, Fenofibrate, Bezafibrate

6. Basic

#### O-051

# Immune Tolerant Phase of Perinatal HBV Infection: Are HBV-Specific T Cells Really "Tolerant"?

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**Aims:** Perinatal hepatitis B virus (HBV) infection results in chronic infection in more than 90% of exposed individuals. In most infected children and young adults, liver inflammation is minimal despite high rates of HBV replication; this phase has been traditionally known as the 'immune-tolerant' phase. In this study, we aimed to characterize HBV-specific T cell response in the patients with immune-tolerant chronic hepatitis B (CHB) in Korea.

**Methods:** We formed CHB cohort with 15 immune tolerant (IT), 16 immune clearance (IC), and 13 patients with antiviral treatment (AT). After isolation of peripheral blood mononuclear cells (PBMCs), we performed Enzyme-Linked ImmunoSpot (ELISPOT) assay directly *ex vivo*, and intracellular cytokine staining (ICCS) after *in vitro* short-term peptide stimulation, using mixture of HLA-A2 restricted epitopes of HBV proteins. Moreover, we performed pentamer staining assay to identify HCV-specific CD8+T cells and examined the expression of PD-1 and CD127 in pentamer-positive cells.



**Results:** Ex vivo ELISPOT and cytokine secretion assay showed that HBV-specific T cell function was relatively weak in IT patients compared with patients on antiviral treatment. However, we detected HBV-specific CD8 T cells (using HBV core pentamer) in PBMCs of CHB patients with IT, as well as in IA and AT

patients. PD-1+ and CD127 low population among pentamer+ CD8 T cells was smaller in IT phase, and PD-1 expression of pentamer+ cells is similar with that of total CD8 T cells in IT phase. Interestingly, short-term culture of PBMC also showed that some IT patients can have HBV-specific CD8+ T cells with the ability to produce IFN-y.

**Conclusions:** This is the first report on HBV-specific T cell response of CHB patients in considered immune tolerant phase in Korea. Our data show that HBV-specific T cells are present in IT phases, and appropriate stimulation can enhance the effector function of the cells.

Keywords: Hepatitis B virus, T cell, Immune tolerance,

#### O-052

#### Higher Asialoglyco Protein Receptor Expression on Placental Cells Is Associated with Hepatitis B Virus Vertical Transmission from Mother to Baby

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**Aims:** Vertical transmission of Hepatitis B virus (HBV) from infected mother to the newborn is the major cause of HBV chronicity. Asialoglycoprotein receptor (ASGPR) expression on hepatocytes has been associated with HBV entry and endocytosis. However, there is a big lacuna regarding expression of ASGPR expression on placental cells and its role in HBV vertical transmission.

**Methods:** 34 HBsAg+ve and 13 healthy pregnant mothers were enrolled along with their newborns. QHBsAg, HBV DNA and liver-function-test were performed among the groups. HBsAg+ve women were grouped into transmitting and non-transmitting mothers on the basis of newborns HBsAg and HBVDNA. Expression of ASGPR and HBsAg were analyzed in placental tissue using Immunohistochemistry and immunofluorescence staining. Peripheral and cord blood-mononuclear cell together with dendritic cells (mDCs and pDCs) were analyzed for the expression of DC-ASGPR, using flow cytometry and QPCR in all subjects.

**Results:** The incidence of HBV vertical transmission to the newborn was 18% among the HBsAg positive pregnant females. HBV transmitting mothers showed increased expression of ASGPR in trophoblasts of placenta. Immunofluorescence microscopy revealed co-localization of HBsAg and ASGPR in placenta as well as in DCs of HBV transmitting mothers. HBV transmitting mothers and their HBsAg+ve newborns showed increased mRNA levels of DC-ASGPR in PBMCS. However, flow-cytometry revealed no significant difference in the expression of ASGPR on PBMCs or CBMCs cells between the 2 groups. The HBV transmitting mothers and their HBsAg+ve newborns also showed an increased expression of DC-ASGPR on both myeloid

and plasmocytoid dendritic cells compared to HBV non-transmitting mothers and their HBsAg negative newborns.

**Conclusions:** The present work highlights for the first time a role of ASGPR in the intrauterine mother to baby HBV transmission. Blocking of ASGPR appears to be novel therapeutic strategy for prevention of HBV mother to baby vertical transmission. **Keywords:** Heaptitis B, Vertical transmission, Placental immunity, Viral infection

#### O-053

#### MicroRNA 17-92 Induces Methylation of Hepatitis B Virus DNA in Human Hepatoma Cells

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**Aims:** Small RNAs mediate transcriptional control of gene expression by histone modification and DNA methylation in plants, but its role is relatively not well-established in mammalian cells. We have previously shown that exogenous small RNAs induce methylation of hepatitis B virus (HBV) genome in hepatoma cell lines. Interestingly, the short hairpin RNA which induces HBV DNA methylation has sequence similarity with human microRNA miR-17-92 cluster, which also targets HBV by our previous study. The aim of this study was to examine if endogenous miR-17-92 induces methylation of HBV genome.

**Methods:** HepAD38 cells, a cell line which permits HBV replication under the control of tetracycline-responsive promoter were used for *in vitro* HBV replication model. MicroRNA expression plasmids containing precursor sequences of the miR-17-92 cluster were transfected to HepAD38 cells. Methylation of HBV covalently closed circular DNA was assessed by methylation-specific PCR and bisulfite sequencing. HBV relaxed circular DNA was quantified by real-time qPCR and Southern blotting. The association of Argonaute and DNA methyltransferase 3A (DNMA 3A) with HBV cccDNA was assessed by chromatin immunoprecipitation (ChIP). Presence of nuclear Argonaute-miR complex was assessed by ribonucleoprotein immunoprecipitation (RNP-IP). HBV RNA was quantified by real-time qPCR and Northern blotting.

**Results:** Over-expression of miR-17-92 increased degree of methylation of HBV genome. Methylation of HBV genome was associated with down-regulation of HBV expression. We found that both AGO1 and AGO2 were present in the nucleus. However, AGO1 did not bind HBV cccDNA whereas AGO2 was associated with HBV cccDNA. Intranuclear AGO2 was loaded with miR-17/20, especially when the corresponding miRs were over-expressed.

**Conclusions:** MicroRNA 17-92 induces methylation of hepatitis B virus DNA in human hepatoma cells leading to suppression of HBV replication.

Keywords: Hepatitis B virus, Methylation, MicroRNA,

#### O-054

#### Reprogramming of Human Hepatocytes into Bi-Potent Hepatic Progenitor Cells Using Cocktail of Small Molecules and Growth Factor

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**Aims:** Cell-based regenerative medicine can provide valuable options for end-stage patients with liver disease by solving and considering the lack of donor shortage through gene and/or stem cell therapy. Despite much progress in isolation and prolonged growth of bipotent progenitor cells with regenerative capacity from terminally differentiated mouse hepatocytes, expansion of the adult human hepatocytes remains a major challenge.

**Methods:** We report using two small molecules and growth factors to successfully produce patient-specific hepatic progenitor cells from healthy and diseased human hepatocytes.

**Results:** After three days of treatment small molecule in the presence of growth factor, a key driver of hepatic progenitor cell activity, triggered expansion of small polygonal cells, which co-expressed known hepatic progenitor cells and lineage specific marker genes. These chemically derived human hepatic progenitor cells (hCdHs) could self-renew for at least 10 passages while retaining phenotype, normal karyotype and potential to differentiate into functional hepatocytes and biliary epithelial cells *in vitro*. A next-generation sequencing confirmed a high degree of molecular similarity between hCdHs and human hepatoblasts. Upon intrasplenic transplantation into immunocompromised mice with a diseased liver, hCdHs effectively repopulated and restored.



**Conclusions:** In conclusion, hCdHs provide a safe novel tool that permits expansion and genetic manipulation of patient-specific hepatic progenitor cells to study regeneration and repair of diseased liver.

**Keywords:** Liver stem cell, Hepatic progenitor, Small molecule, Reprogramming

# O-055

#### The Value of Exosomal microRNA 122 in Liver Disease as Biomarker of Fibrosis: Preliminary Study

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**Aims:** The microRNA (miR) from exosome has more specific biologic markers for various diseases than miR extracted from serum. We investigated the correlation between exosomal miR expression and clinical data including histology in patients with liver disease.

**Methods:** We performed liver biopsy for 21 patients with various liver diseases. Results of liver biopsy were classified as steatosis, lobular inflammation, portal inflammation, and fibrosis. We graded the fibrosis as advanced and non-advanced fibrosis. For exosomal miR expression analysis, 8cc of blood sample was drawn and exosome was extracted by exoRNeasy Serum/Plasma Maxi and Midi Kits (Qiagen, Germany). Real time polymerase chain reaction was done by Applied Biosystems Step One Plus. Then, complementary deoxyriboneucleic acid (cDNA) was synthesized by synthesizing reagent and expression of exosomal miR was checked by TaqMan Universal Master Mix and TaqMan Assay. Finally, we calculated exosomal miR-122, miR-155, and miR-194-5p expression and compared between exosomal miR expression and clinical data including histologic grade in patients with liver disease.

**Results:** Twenty-one patients were diagnosed with nonalcoholic steatohepatitis (n=9), toxic hepatitis (n=4), viral hepatitis (n=4), alcoholic liver disease (n=2) primary biliary cirrhosis (n=1) and granulomatous hepatitis (n=1). miR-122 was overexpressed in patients with advanced fibrosis compared to non-advanced fibrosis (P=0.062). miR-155 and mir-194-5p expression did not differ significantly between fibrosis grades (P=0.697 and 0.640, respectively). Furthermore, miR-122 was significantly different in elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) group compared to normal (P=0.007 and 0.049, respectively).

**Conclusions:** The expression of miR-122 was increased in patients with advanced fibrosis compared with non-advanced fibrosis. Also, the expression of miR-122 was significantly different between the patients with normal and abnormal liver function. Therefore, expression of exosomal miRNA can be a factor governing diagnosis and treatment of liver disease. **Keywords:** Exosome, MicroRNA, Liver disease,

# O-056

### Human Chorionic-Plate-Derived Mesenchymal Stem Cells Restore Hepatic Lipid Metabolism in a Rat Model of Bile Duct Ligation

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**Aims:** In cholestatic liver diseases, impaired bile excretion disrupts lipid homoeostasis. We investigated changes of lipid metabolism, including mitochondrial  $\beta$ -oxidation, in a rat model of bile duct ligation (BDL) in which chorionic-plate-derived mesenchymal stem cells (CP-MSCs) were transplanted.

**Methods:** Male 7-week-old Sprague-Dawley rats were used. One week after BDL, rats in the transplanted group were injected with CP-MSCs ( $2 \times 10^6$  cells, 8–10 passages) intravenously via tail vein, whereas rats in the nontransplanted group were injected with culture medium. Liver tissues and blood samples for further analysis were collected 1, 2, 3, and 5 weeks post-transplantation in the transplanted group and 1, 2, 3, and 5 weeks post-BDL in the nontransplanted group.

**Results:** The concentration of serum cholesterol, which was elevated after BDL, was significantly decreased following transplantation of CP-MSCs. The expression levels of genes involved in intracellular lipid uptake, including long-chain fatty acyl-CoA synthetases and fatty acid transport proteins, were decreased in rats after BDL, however, were not significantly changed by subsequent CP-MSC transplantation. Carnitine palmitoyltransferase 1A (CPT1A), a rate-limiting enzyme in mitochondrial  $\beta$ -oxidation, was upregulated after BDL and then was downregulated after CP-MSC transplantation. CPT1A expression was changed via microRNA-33-a posttranscriptional regulator of CPT1Ain a peroxisome proliferator-activated receptor  $\alpha$ -independent manner. Cellular adenosine triphosphate production-an indicator of mitochondrial function-was reduced after BDL and was restored by CP-MSC transplantation. Expression levels of heme oxygenases also were significantly affected following BDL and CP-MSC transplantation.

**Conclusions:** Lipid metabolism is altered in response to chronic cholestatic liver injury and can be restored by CP-MSC transplan-

tation. Our study findings support the therapeutic potential of CP-MSCs in cholestatic liver diseases and help understanding fundamental mechanism by which CP-MSCs affect energy metabolism. **Keywords:** Cholestasis, Bile duct ligation, CP-MSCs, Lipid metabolism, Fatty acid oxidation, CPT1A, MicroRNA-33

### O-057

Novel Necroptosis Pathway in Hepatic Fibrosis: MLKL Activated Hepatic Stellate Cell via CXCL1/2 and Adhesion Molecules

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**Aims:** Necroptosis is an emerging new cell death pathway. We evaluated the role of necroptosis in stellate cell activation and its potential for target in hepatic fibrosis.

**Methods:** Wild type, mixed lineage kinase domain like pseudokinase (MLKL) knock-out (KO), and receptor-interacting protein 3 (RIP3) KO mice were evaluated for the degree of fibrosis in common bile duct (CBD) and thioacetamide induced fibrosis models. Hepatic stellate cell activation was evaluated after necroptosis conditions. MLKL inhibitor (necrosulfonamide) treated activated LX-2 cells were investigated for the stellate cells reversion using wound healing assay,  $\alpha$ -SMA, collagen1 $\alpha$ , and vimentin expressions.

**Results:** Expression of MLKL immunohistochemical stain increased according to the degree of fibrosis in patients with NAFLD. MLKL expression also increased in CBD ligation induced cirrhotic animal model. Both the MLKL-KO and RIP3KO CBD ligated mice had significantly reduced hepatic fibrosis and fibrosis markers including  $\alpha$ -SMA, collagen1 $\alpha$ , and TIMP-1 compared to CBD ligated wild type mice. Necroptotic stimulation with TNF $\alpha$  and zVAD treatment on stellate cells caused morphological change, increased  $\alpha$ -SMA, and cell migration. MLKL inhibitor (necrosulfonamide) reduced stellate cells activation markers including  $\alpha$ -SMA, vimentin, and collagen1 $\alpha$ . Necrosulfonamide reduced ICAM-1 and VCAM-1 expressions in stellate cell.

**Conclusions:** Necroptosis pathway activated stellate cells, and MLKL inhibitor can reduce stellate cell activation through reducing CXCL1/2 and adhesion molecules.

Keywords: Hepatic fibrosis, Necroptosis

#### O-058

# Effects of Probiotics for the Treatment of Non-Alcoholic Fatty Liver Disease in Mice Model

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, comprises a spectrum of diseases ranging from simple steatosis to non-alcoholic steato-hepatitis, fibrosis, and cirrhosis. Currently, there are no Food and Drug Administration–approved therapies for NAFLD. The aim of this study is to find beneficial probiotics and assess the improvement in NAFLD animal model.

**Methods:** Six-week male C57BL/6J mice were used in this study. Mice were randomly assigned to normal diet, Western-diet, and 9 Western diet+probiotics groups (n=10/group). Used probiotics strains are Lactobacillus acidophilus, L. plantarum, L. casei, L. paracasei, L. fermentum, L. helveticus, L. bulgaricus, Bifidobacterium bifidum, Pediococcus pentosaceus *KID7*). Each probiotics were administered to mice in the drinking water at concentration of 1 X 10<sup>9</sup> colony forming units(C-FU)/g/day for 8 weeks. Liver/body weight ratio, liver enzyme (ALT, AST), cholesterol, and histologic findings (hepatitis and steatosis score)) were analyzed.

**Results:** In the analysis of liver/body weight ratio, L. acidophilus (5.5±0.4, P<0.001), L. bulgaricus (5.1±0.5, P<0.001), P. pentosaceus KID7 (5.5±0.5, P=0.009), L. paracasei (5.7±0.4, P=0.032), and L. helveticus (5.2±0.4, P<0.001) groups showed significant improvement compared with that of Western group (6.2±0.6). All strains except B. bifidum were effective in improvement of liver enzyme (AST or ALT, P<0.05). All strains except B. bifidum and L. casei significantly reduced the level of cholesterol (P < 0.05). In comparison of histology (hepatitis score/steatosis score), L. helveticus (1.3±0.5/1.7±0.7, P<0.001), L. fermentum (1.8±0.4/2.7±0.5, P=0.042), L. paracasei (1.6±0.5/2.1±0.9, P=0.035), P. pentosaceus KID7 (1.3±0.5/1.4±0.5, P<0.001), B. bifidum (1.6±0.5/2.5±0.8, P=0.037), L. bulgaricus (0.7±0.7/0.7±0.7, P<0.001), L. casei (1.8±0.4/2.1±0.6, P<0.001), L. plantarum (1.8±0.6/2.3±0.7, P=0.003), and L. acidophilus (1.6±0.7/1.8±0.6, P<0.001) groups reveled significant improvement compared with that of Western group (3.1±0.3/2.0±0.0).

**Conclusion:** Our selected probiotics have beneficial effects on weight reduction, dyslipidemia, and liver inflammation and steatosis. Therefore, probiotics might be effective in the treatment of NALD by regulating the gut-liver axis.

**Keywords:** Nonalcoholic fatty liver disease, Probiotics, Treatment, Mouse

# 7. Surgery-Biliary

#### O-059

Prognostic Factors for Hilar Cholangiocarcinoma after Surgical Resection: A Retrospective Study of Survival Outcome

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**Aims:** Hilar cholangiocarcinoma is known a tumor that have a poor prognosis despite surgical resection. Many patients are diagnosed at advanced stages of disease, especially Bismuth type IV that have worst prognosis traditionally. We retrospectively analyzed survival outcomes of hilarcholangiocarcinoma after surgical resection.

**Methods:** We retrospectively reviewed the 107 patients who were received surgical resection for hilar cholangiocarcinoma at our hospital between 1998 and 2017. The clinical factors associated with survival were analyzed using univariate and multivariate tests.

**Results:** Among 107 cases, 5-year overall survival was 34.4% and 5-year disease free survival was 28.0% after surgical resection. There were no significant difference of survival according to Bismuth and gross type. The multivariate analysis showed that CA19-9 elevation, present of PV invasion and advanced AJCC stages were independently poor prognostic factors for the disease free and overall survival. In Bismuth type I and II, types of surgery were 6 (46.2%) major hepatectomy and 7 (53.8%) bile duct resection(BDR). Among the 7 patients who underwent BDR, R1 resection was 5 (71.4%). Although R1 resection was done frequently in Bismuth type IV, 5-year overall survival was not significantly different between R0 (n=4, 66.7%) and R1 (n=15, 33.3%, *P*=0.740) resection.

**Conclusions:** Among 107 cases, 5-year overall survival was 34.4% and 5-year disease free survival was 28.0% after surgical resection. There were no significant difference of survival according to Bismuth and gross type. The multivariate analysis showed that CA19-9 elevation, present of PV invasion and advanced AJCC stages were independently poor prognostic factors for the disease free and overall survival. In Bismuth type I and II, types of surgery were 6 (46.2%) major hepatectomy and 7 (53.8%) bile duct resection(BDR). Among the 7 patients who underwent BDR, R1 resection was 5 (71.4%). Although R1 resection was done frequently in Bismuth type IV, 5-year overall survival was not significantly different between R0 (n=4, 66.7%) and R1 (n=15, 33.3%, *P*=0.740) resection.

# O-060

# ERBB Signaling Pathway Targeted Therapy Is Available in Gallbladder Cancer Patients

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**Aims:** To profile the somatic mutation spectrum in gallbladder cancers(GBCs), to determine the oncogenic effects of the ERBB3 and ERBB2 mutations, and to find whether targeted therapy focus on ERBB signaling pathway is available for these kind of GBC patients.

**Methods:** We performed a combination of exome sequencing and ultra-deep sequencing of cancer-related genes on 57 tumor-normal pairs. The mutation pattern is defined by a dominant prevalence of C>T mutations at TCN sites.Three patients with staged IV GBCs and ERBB signaling pathway mutated who were not benefit from traditional chemo-radio therapy, were treated with ERBB signaling pathway targeted therapy.

**Results:** Genes with a significant frequency of non-silent mutations include TP53 (47.1%), KRAS (7.8%) and ERBB3 (11.8%). Moreover, ErbB signaling (including EGFR, ERBB2, ERBB3, ERBB4 and their downstream genes), which have not been described previously in GBC, is the most extensively mutated pathway, affecting 36.8% (21/57) of the GBC samples. Multivariate analyses further show that the mutations have a worse outcome. Over-expression of each ERBB mutant resulted in a significant increase in proliferation in at least one cell line.The tumor maker expression including CA-199 and CA-125 had a different level of decline.The primary or metastasis tumor size also revealed a trend of decrease. And the average survival time have exceeded more than 12months.

**Conclusions:** Our findings provide insight into the somatic mutational landscape in GBC and highlight the key role of the ErbB signaling pathway in GBC pathogenesis. And our results suggest that patients harboring mutations in the ErbB pathway might benefit from targeted therapies.

### O-061

Robotic Single-Site Plus One Port Complete Excision of Type I Choledochal Cyst with Hepaticojejunostomy and Extracorporeal Roux-En-Y Bilioenteric Reconstruction in First Experiment

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**Aims:** For the type I choledochal cysts, complete surgical excision and Roux-en-Y bilioenteric reconstruction is treatment of choice. In adults, most of the patients with choledochal cyst are female. These patients are interest in cosmetic result, so they want minimally invasive surgery. Here, we introduce a robotic single incision plus one port surgical technique for a choledochal cyst excision (RSSp1EC).

**Methods:** A 52 year old female patient diagnosed by choledochal cyst, type I. And she underwent RSSp1EC with hepaticojejunostomy and extracorporeal jejunojejunostomy on December 18, 2017. We were using robotic single site surgical system (the da Vinci Xi<sup>®</sup> Surgical System (Intuitive Surgical<sup>®</sup>, Sunnyvale, CA)) with one additional robotic 8mm port. Single-site Port was placed at the umbilicus and one additional port was placed right side of umbilicus at the axillary line. We used the 3rd robot arm, EndoWrist<sup>®</sup> needle driver and EndoWrist<sup>®</sup> scissor which include da Vinci monopolar cautery instruments through the additional port.

**Results:** Total operation time was 360 min. The estimated blood loss was below the 30 ml. Pathologic examination was accorded in choledochal cyst without evidence of malignancy. The patient was discharged on postoperative days of 6 in good condition.

**Conclusions:** RSSp1EC technique is feasible and safety method. And considering its cosmetic results, RSSp1EC technique will be another good way to treat choledochal cyst.

#### O-062

#### Effect of Sarcopenic Obesity on Postoperative Pancreatic Fistula after Pancreaticoduodenectomy in Patients with Pancreas Head Cancer

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**Aims:** Preoperative nutritional status may reflect outcomes after pancreatoduodenectomy(PD) in patients with pancreas head cancer(PHC). Recently, several studies have reported that preoperative sarcopenic obesity(SO), which is a high visceral adipose tissue-to-skeletal muscle ratio, could worsen postoperative complications in patients with various periampullary diseases. The purpose of this study is to evaluate the effect of preoperative SO on POPF following PD.

**Methods:** Preoperative SO was assessed in 548 patients undergoing PD for PDAC at Samsung Medical Center between 2007 and 2016. The visceral adipose tissue-to-skeletal muscle ratio was calculated from cross-sectional visceral fat and muscle area on preoperative CT imaging at the third lumbar vertebra level and normalized for height by an automatic calculation program. Overall survival(OS) and the rate of POPF with ISGPF grade B or C among postoperative complications were extracted from prospectively maintained databases.

**Results:** Preoperative SO was present in 202(36.9%) of the patients. After multivariate analysis, the presence of SO was the only independent risk factor for developing POPF(HR:2.561, 95%CI:1.179-5.564, *P*=0.018). Age over 63 years(HR:1.465, 95%CI:1.154-1.859, *P*=0.002), poorly differentiated carcinoma(HR:2.175, 95%CI:1.709-2.769, *P*<0.001), nodal metastasis(HR:2.127, 95%CI:1.604-2.819, *P*<0.001), portal vein invasion(HR:1.488, 95%CI:1.143-1.936, *P*=0.003), and absence of adjuvant treatment(HR:2.454, 95%CI:1.933-3.116, *P*<0.001) were identified as independent risk factors for OS, but preoperative SO was not significantly associated with decreased OS.

**Conclusions:** Preoperative SO is the only predictive factor for CR-POPF after PD in patients with PHC. Preoperative SO measures may stratify patients into risk categories for developing POPF. For evaluation of the effect of SO on survival after PD, more observational studies will be needed.

#### O-063

#### Single Port Laparoscopic Distal Pancreatectomy

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**Aims:** Laparoscopic distal pancreatectomy has become the standard treatment of choice for pancreatic tail cystic and solid tumors when technically feasible. Technological advances have led to the development of single-port laparoscopic surgery, a safe alternative procedure. We present our experiences with single-port laparoscopic distal pancreatectomy.

**Methods:** We retrospectively reviewed clinical records and compared clinical outcomes in 49 patients diagnosed with a pancreatic tail mass between 2007 and 2013 who received either conventional laparoscopic (n = 28) or single-port laparoscopic distal pancreatectomy (n = 21).

**Results:** The mean surgery time in the single-port group (270.6  $\pm$  53.0 minutes) was significantly longer than in the conventional group (186.9  $\pm$  86.6 minutes) (*P*=.007). The mean duration of postoperative hospital stays in the single-port group (13.3  $\pm$  11.3 days) was longer than in the conventional group (8.3  $\pm$  4.7 days), but the difference was not significant (*P*=.068). The spleen was preserved more in the conventional group (60.7%) than in the single-port group (42.9%), but the differences and significant differences in intraoperative blood loss, tumor size, conversion rate, or postoperative complications (including pancreatic fistula) between the two groups.

**Conclusions:** Blood loss, postoperative hospital stays and postoperative complications of single-port laparoscopic distal pancreatectomy are similar to those of conventional laparoscopic distal pancreatectomy. Single-port laparoscopic distal pancreatectomy can be performed safely and effectively in patients with pancreas tail cystic and solid neoplasms, but is associated with a longer surgery time.

#### O-064

# The Single Center Experience of One Thousand Cases of Robotic Pancreatectomy

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**Aims:** Operation plan for pancreatic tumor used to be divided in four main type, pancreaticoduodenectomy (PD), central pancreatectomy, distal pancreatectomy (DP) and pancreatic enucleation. To evaluate the value of da Vinci robotic surgery system in pancreatectomy.

**Methods:** The clinical data of a consecutive of 1000patients who underwent robotic-assisted pancreatectomy from Novem-

ber, 2011 to September 2017 were retrospectively reviewed. All the operations were performed by the same team, which mainly approach in Da Vinci robotic system Si. The demographic characteristics, intraoperative blood loss, operative duration, post-operative hospital stay, blood transfusion details, and conversion rate were all analyzed.

**Results:** A total of 1000 patients were included in this study, with an average age of 54.0, and 486 cases of them were male. The average operative time was 3.5 hours (2-7 h), the estimated blood loss was 100ml (20-1200 ml), and the postoperative hospital stay was 9.3 days in average. Overall complication morbidity was 7.9% (79/1000) and 6.7%(67/1000) cases suffered from grade B-C Pancreatic fistula, with the conversion rate of 3.2% and 30-Day mortality rate of 0.42%.

**Conclusions:** Robotic pancreatectomy could be successfully performed with the assistance of da Vinci surgery system, the operative duration, post-operative hospital stay and intraoperative blood loss were satisfying, with very patients died in 30 days and very operations converted.

#### O-065

# How Aggressive Are Solid Pseudopapillary Tumors of the Pancreas: A Meta-Analysis

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**Aims:** Solid Pseudopapillary Tumors of the pancreas are rare pancreatic tumors considered to be benign although 10-15% of SPTs have been reported to be aggressive causing recurrence and/or metastasis. Due to its rarity, there have only been a few cases reported regarding the clinical course of patients with aggressive SPTs. The goal of this study is to describe the clinical course of patients diagnosed with aggressive SPTs.

**Methods:** A pubmed search was done in search of articles describing the clinical course of patients diagnosed with SPT that recurred or metastasized. Patient information, including age, gender, tumor size, operation, recurrence, and death were extracted from the articles. Survival and recurrence curves were plotted and factors associated with survival and recurrences were analyzed.

**Results:** Patients with aggressive SPTs can survive for up to 152.67 months (5-year survival of 71.1%). Recurrence was noted to occur at 45 months after initial diagnosis, with a rate of 69.5%. Age, gender, tumor size, tumor location, combined resection (en bloc resections, and/or metastasectomies), type of recurrence, stage IV on diagnosis were not significant factors in predicting survival. However, tumors described as unresectable (*P*<0.001), and tumors that metastasize/recur within 3 years (*P*=0.002) had a statistically significant impact on survival. An unresectable tumor (*P*=0.008) was also statistically associated with earlier recurrence.

**Conclusions:** Solid pseudopapillary tumors of the pancreas carry a favorable course. Despite having aggressive properties,

patients can still survive for more than 10 years as long as the tumor can be resected completely.

### O-066

# The Impact of Neoadjuvant Chemotherapy Associated with Intraoperative Radiation Therapy (IORT) in Pancreatic Cancer

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**Aims:** To analyze the impact of multimodal treatment strategy with neoadjuvant chemotherapy and intraoperative radiation therapy (IORT), on overall median survival in patients with pancreatic cancer.

**Methods:** We analyzed 128 patients, from 1995 to 2016, who underwent multimodal treatment with and without neoadjuvant chemotherapy, surgery and intraoperative radiation therapy (IORT). The patients were stratified in two groups based in multimodality therapy. The data analyses were carried out using the chi-squared test, and the median survival was estimated according to the Kaplan-Meier method.

**Results:** The mean age was 65 years, 71 men (55%) and 58 women (45%), the mean follow-up was 32.5 months with a median of 15.5 months. 19.5% received complete treatment and 41 patients were also treated with IORT, 23 patients (56.1%) were treated as part of the multimodal treatment versus 18 (43.9%), P=<0.001). The overall survival was 57.90 +/-12.59 months for the neoadjuvant treatment group compared to 39.05 +/- 6.76 months in the control group without neoadjuvant treatment, (P=0, 05). IORT vs Not IORT was 62.05 +/-13.34 months VS 38.65 +/- 6.58 months, P=0.027 respectively. **Conclusions:** Neoadjuvant and local therapy with intraoperative radiation therapy (IORT) are feasible strategies and associated with a longer overall median survival.

8. Liver Transplantation

# O-067

## Validation of the Alpha-Fetoprotein Model for Hepatocellular Carcinoma Recurrence after Transplantation in an Asian Population

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Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea **Aims:** This study was designed to validate the alpha-fetoprotein model for predicting recurrence after liver transplantation in Korean hepatocellular carcinoma patients.

**Methods:** Patients who underwent liver transplantation for hepatocellular carcinoma at Samsung Medical Center between 2007 and 2015 were included. Recurrence, overall survival, and disease-specific survival of patients divided by both the Milan criteria and the alpha-fetoprotein model were compared using Kaplan-Meier log-rank test. The predictability of the alpha-fetoprotein model compared to the Milan criteria was tested by means of net reclassification improvement analysis applied to patients with a follow-up of at least 2 years.

**Results:** A total of 400 patients were included in the study. Patients within Milan criteria had 5-year recurrence, and overall survival rates of 20.9% and 76.3% respectively, compared to corresponding rates of 50.3% and 55.7%, respectively, for patients who were beyond Milan criteria. Alpha-fetoprotein model low risk patients had 5-year recurrence and overall survival rates of 21.1% and 76.2%, respectively, compared to corresponding rates of 57.7% and 52.2%, respectively, in high risk patients (*P*<0.001, all). Although overall net reclassification improvements were statistically nonsignificant for recurrence (NRI=1.7%, Z=0.30, *P*=0.7624), and overall survival (NRI=9.0%, Z=1.60, *P*=0.1098), they were significantly better for predicting no recurrence (NRI=6.6%, Z=3.16, *P*=0.0016) and no death. (NRI=7.7%, Z=3.65, *P*=0.0003)

**Conclusions:** The alpha-fetoprotein model seems to be a promising tool for liver transplantation candidacy, but further investigation is needed.

**Keywords:** Alpha-feto protein, Liver transplantation, Milan criteria, Hepatocellular carcinoma

#### O-068

#### The Learning Curve in Pure Laparoscopic Donor Right Hepatectomy: Cumulative Sum Analysis

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**Aims:** Due to increased experience and knowledge in laparoscopic surgery in the era of minimally invasive surgery, laparoscopic donor hepatectomy is also being performed at some experienced centers. However, more evidence of feasibility, safety, and especially the learning curve is needed for wide introduction of this technique. Therefore, in the current study, we aimed to determine the learning curve for this procedure with single surgeon experience of 100 consecutive cases using Cumulative Sum (CUSUM) method.

**Methods:** Between November 2015 and October 2017, 150 donors underwent pure laparoscopic hepatectomy at our cen-

ter. Of these, 100 donors underwent right or extended right hepatectomy by a single surgeon.

**Results:** According to the CUSUM analysis, the graph showed steep decrease in the curve and the learning curve was accomplished after about 60 cases of pure laparoscopic donor right hepatectomy. When we performed the risk-adjusted CUSUM to take into account the expected risk of surgical failure associated with each specific case, 65-70 cases were the learning curve.

**Conclusions:** Our experience indicates that, when performed by an experienced adult living donor liver transplant surgeon, performance of about 65-70 PLDRHs is needed to standardize the procedure.

**Keywords:** Laparoscopy, Donor hepatectomy, Transplantation, Right hepatectomy

#### O-069

#### Clinical Features and Surveillance of Very Late Hepatocellular Carcinoma Recurrence after Liver Transplantation

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**Aims:** This study aimed to assess patterns of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) and to establish long-term surveillance protocols for late HCC recurrence. **Methods:** The 232 LT recipients experiencing subsequent HCC recurrence were categorized as Group 1, early recurrence (within 1 year of LT; n=117); Group 2, late recurrence (occurring in years 2–5; n=93); and Group 3, very late recurrence (after year 5; n=22).



**Results:** Recurrence was detected by only elevated tumor marker levels in 11.1%, 30.1%, and 45.5% of patients in Groups 1, 2, and 3, respectively (*P*<0.001). The proportion of intrahepatic and extrahepatic metastases was similar in all three groups. Common sites of extrahepatic metastasis were the lung and bone; these were also similar across the three groups. Overall post-recurrence patient survival rates were 60.2% at 1 year, 28.2% at 3 years, 20.5% at 5 years, and 7.0% at 10 years. Median post-recurrence survival periods were 10.2, 23.8, and 37.0 months in Groups 1, 2, and 3, respectively.

**Conclusions:** While the pattern of HCC recurrence was similar regardless of time of recurrence, post-recurrence survival was

significantly longer in patients with later recurrence. Long-term surveillance for HCC recurrence beyond 5 years post-LT is recommended.

**Keywords:** Hepatocellular carcinoma, Recurrence, Liver transplantation, Survival

# **O-070**

#### Renal Safety of Entecavir and Tenofovir with Hepatitis B Immunoglobulin in Liver Transplant Patients

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**Aims:** Combination of potent nucleos(t)ide analougues (NAs) and hepatitis B immunoglobulin is recommended after liver transplantation for the prevention of hepatitis B virus (HBV) recurrence. Despite its proven efficacy, renal safety of NAs in liver transplant recipients has not been well defined. We aimed to assess the impact of entecavir and tenofovir on glomerular and tubular function.

**Methods:** We analyzed 201 liver transplant patients treated with entecavir (n=122) or tenofovir (n=79) with hepatitis B immunoglobulin between 2012 and 2016. Serum creatinine, phosphorus, and uric acid were measured, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Proximal tubular dysfunction was defined as the combination of hypophosphatemia (< 2 mg/dL) and hypouricemia (< 2 mg/dL).



**Results:** Mean eGFR at start of NAs after liver transplant was 100.8 for entecavir, 102.7 mL/min/1.73 m<sup>2</sup> for tenofovir group (P=0.554). Mean eGFR at the last on-treatment visit was 80.0 for entecavir and 82.5 mL/min/1.73 m<sup>2</sup> for tenofovir group (P=0.491). During the 28 months of median follow-up, 30 patients experienced decrease of eGFR < 30 mL/min/1.73 m<sup>2</sup> (20 [16.4%] of entecavir and 10 [12.7%] of tenofovir group, P=0.468). Serum phosphorus and uric acid in both groups were statistically not significant at start of NAs. A total of 37 patients developed renal tubular dysfunction (11 [9.0%] of entecavir and 26 [32.9%] of tenofovir group, P<0.001). Tenofovir (HR, 5.24; 95% CI, 2.25-12.19; P<0.001), decrease of eGFR < 30

mL/min/1.73 m<sup>2</sup> (HR, 4.44; 95% CI, 1.67-11.85; P=0.003), and use of mTOR inhibitor (HR, 2.31; 95% CI, 1.04-5.11; P=0.04) were independent risk factors for proximal tubular dysfunction. **Conclusions:** The effect of tenofovir on glomerular function was comparable to that of entecavir in liver transplant patients. However, tenofovir increased the risk of proximal tubular dysfunction. Longitudinal studies are needed to assess the long-term outcomes.

**Keywords:** Liver transplantation, Hepatitis B virus, Renal function, Antiviral agents

# O-071

# A New Approach to Overcoming Biliary Complications after Laparoscopic Living Donor Liver Transplantation

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**Aims:** Biliary strictures and bile leaks are one of the major causes of morbidity after liver transplantation. Biliary reconstruction of multiple ducts in grafts is challenging in living donor liver transplantation (LDLT). We introduce our new approach of dunking duct reconstruction of the bile duct for reducing bile duct complications in LDLT.

**Methods:** Twenty consecutive LDLT with laparoscopic living donor graft from February to September 2017 were analyzed through a comparison of 10 conventional duct-to-duct reconstructions (DDR) and 10 dunking hepaticocholedocostomy (DHC) in bile duct anastomoses.

**Results:** At a mean follow-up of 5.4 months, median graft duct number for DDR is one and for DHC is two. Overall, 3 patients developed leakage (15%) and 4 patients suffered stricture (20%). For biliary anastomosis with DDR, the incidence of stricture and leakage was significantly higher (40%, 20%) than DHC (0%, 10%).

**Conclusions:** In conclusion, DHC in graft with multiple ducts as well as in graft with single bile ducts has excellent results with regard to minimizing biliary complications. Therefore, DHC can be recommended as the preferred method for the presence of multiple ducts in the graft in LDLT.

Keywords: Stricture, Leakage, Complication,

# O-072

### A Comparison of Models for Tumor Recurrence After Liver Transplantation for the Patients with Hepatocellular Carcinoma: A Long-Term Multicenter Follow-Up Study

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**Aims:** We recently have developed a model to predict tumor recurrence after liver transplantation (MoRAL) using two objective biomarkers and reported that hepatocellular carcinoma (HCC) patients with a low-MoRAL score ( $\leq$ 314.8) have excellent treatment outcomes after living-donor liver transplantation (LDLT). We investigated long-term prognosis of LDLT recipients by the MoRAL score with extended follow-up data and compared the prognostication power between the MoRAL score with other models.

**Methods:** This study included a total of 564 patients who underwent LDLT in three large-volume hospitals in Korea. The primary endpoint was time-to-recurrence and secondary endpoint was overall survival (OS). The discrimination function was evaluated with Harrell concordance (c)-index and area under the ROC curve (AUC) and the calibration function with Hosmer-Lemeshow goodness-of-fit test.

Results: The median follow-up duration was 39.2 months (range, 0.1–179.5). The MoRAL score showed the best performance in predicting the risk of tumor recurrence after LT with c-index of 0.77 and AUC of 0.78; compared to the Milan criteria (c-index=0.64, AUC=0.65) and the model of Weill Cornell Medical College group (WCM) (c-index=0.69, AUC=0.69). The MoRAL score represented better calibration function than the model of WCM with Hosmer-Lemeshow test P-value of 0.152 versus 0.068. In the beyond-MC subcohort (n=205), the predictive power of the MoRAL score for recurrence was increased even more with c-index of 0.80 whereas that of the model of WCM was 0.70 (P<0.01). In addition, AUC of total, 1yr, 3yr, and 5yr-recurrence were consistently and significantly higher by the MoRAL score with 0.84 to 0.88 compared to by the model of WCM with 0.72 to 0.74 (all P<0.05). The performance of the MoRAL score on predicting OS for the beyond-MC subcohort was better than that of the model of WCM (c-index 0.70 vs. 0.63, P=0.05). The 5-year cumulative risk of tumor recurrence and death were 29.0% and 21.5% in the low-MoRAL/ beyond-MC group and 17.4% and 21.3% in the low-MoRAL/ within-MC group, respectively.

**Conclusions:** The MoRAL score provides the most refined prognostication in predicting HCC recurrence after LDLT.

**Keywords:** MoRAL, Hepatocellular carcinoma, Liver transplantation, Tumor recurrence

# O-073

# Clinical Analysis of Emergency Liver Transplantation in Patients with High MELD Score

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**Aims:** In general, patients with a high model for end-stage liver disease (MELD) score have a poor prognosis before and after liver transplantation. The current allocation system is based on the MELD score in emergency liver transplantation. Therefore, the mortality rate after liver transplantation in high MELD patients is an important consideration in future liver allocation system. This study was performed to identify poor prognostic factors and mortality rates in patients with high MELD score.

**Methods:** From September 2001 to December 2017, living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) were performed in 851 and 157 patients in our center, respectively. The 81 patients with MELD score of 35 or more were analyzed. We divided 81 patients into postoperative survival group (POS) and postoperative mortality (POM) group. To assess the risks associated with high MELD score, we evaluated various preoperative and operative factors.

**Results:** Of the 81 patients, LDLT was performed in 49 (60.5%) patients and DDLT in 32 (39.5%) patients. Overall survival rates at 1, 3, and 5 years in 81 patients were 72.8%, 67.8%, and 67.8%, respectively. The POS group was 63 (77.8%) and the POM group was 18 (22.2%). In univariate analysis, the mean age of the POM group was higher (*P*=0.028), the mean MELD score was higher (*P*=0.045), the proportion of intubated patients was higher (*P*=0.042). There were more patients with mental status above stupor (*P*=0.014). In multivariate analysis, age [*P*=0.006, Exp(B) = 1.118], intubation status [*P*=0.042, Exp(B) = 6.073], and culture positive [*P*=0.036, Exp(B) = 5.218] were significant.

**Conclusions:** In patients with high MELD score, the 3-year and 5-year survival rates are not significantly deteriorated unless initial post-operative mortality is achieved. And the prognosis was poor in patients with old age, preoperative intubation or positive culture.

Keywords: Liver transplantation, High MELD

# 9. Surgery-Liver

#### O-074

#### Comparative Study of Laparosocpic Liver Resection and Open Liver Resection in Patients over 70 Years of Age

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**Aims:** Laparoscopic liver resection(LLR) tends to be preferred by young patients because of its cosmetic effect. The aim of this study was to compare the results of laparoscopic liver resection and open liver resection(OLR) to evaluate the safety and efficacy of laparoscopic liver resection in patients over 70 years of age.

**Methods:** All consecutive cases of LLR between November 2007 and May 2017 and 1:1 case matched OLR during same period were enrolled in this retrospective cohort study. All surgical procedures were performed by one surgeon(KH Kim). The LLR and OLR groups were compared in terms of demographics, clinical perioperative outcomes.

**Results:** A total of 61 cases of LLR were performed in patients over 70 years of age during the study period, including 36 cases of HCC, 5 cases of intrahepatic cholangiocarcinoma, 5 cases of liver metastasis of colorectal cancer, 7 cases of IHD stone, 3 cases of biliary cystadenoma, 2 cases of biliary IPMN, 2 cases of hemangioma, and 1 case of liver cyst. The ratio of anatomical resection to non-anatomical resection was 47:14. LLR group (n=61) had a significantly shorter postoperative hospital stay than the OLR group (n=61) (9.1 ± 2.3 vs 12.3 ± 2.1 days, P<0.001) and less estimated blood loss than OLR group (153.4 ± 67.5 vs 260.4 ± 89.2mL, P<0.001).

**Conclusions:** LLR is a well considered operation in patients over 70 years of age who have no abnormality in pulmonary and cardiac function. The authors suggest that LLR could be a reasonable operative option for selected old aged patients.

#### O-075

#### Novel Classification for Right Posterior Portal Vein (RPPV) Evaluated by SYNAPSE VINCENT

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**Aims:** There was no consensus on right posterior section (RPS) graft was a routine option for adult living donor liver transplantation (LDLT). The main reason for it was that the vascular pedicles of the RPS graft which was the second order branches

were complicated. And there was no deep and detailed description of the patterns of the  $2^{nd}$ ,  $3^{rd}$  portal branch in RPS. The present study is an attempt to describe the patterns of the  $2^{nd}$ ,  $3^{rd}$  portal branch in RPPV.

**Methods:** Between November 2008 and January 2017, a total of 106 preoperative liver multidetector-row computed tomography (MDCT) images were obtained from the donor and the 3D images were reconstructed by SYNAPSE VINCENT medical imaging system. The patterns of the 2<sup>nd</sup>, 3<sup>rd</sup> portal branch of the RPPV were investigated using SYNAPSE VINCENT medical imaging system.

**Results:** We classified the RPPV into four types. Type A: the RPPV have a common trunk (more than 5mm) with two main 3<sup>rd</sup> order branch (36 cases, 34%); Type B: there was no common trunk with two main 2<sup>nd</sup> order branch (16 cases, 15%); Type C: there was one major common trunk with multiple 3<sup>rd</sup> order branch (48 cases, 45.3%); Type D: the right posterior section have sliding branches to/from anterior portal vein (6 cases, 5.7%). The median length of the type A portal trunk was 12.35mm (range 5.0mm-28.7mm). In the present study, there were 16 cases of right posterior sector (RPS) graft which were selected by volumetry-Based criteria. There was only one RPS graft has multiple portal veins opening.

**Conclusions:** The Couinaud segment was not always supplied with one inflow portal pedicle. In the present study, there were 52 cases (Type A and B, 49%) which one segment has only one inflow portal pedicle. Others, 54 cases which one segment have two or more 3rd inflow portal pedicle. RPPV type C and D could not apply with anatomic segmentectomy, only the systematic resection is possible.

#### O-076

#### Risk Factors for Surgical Site Infections after Liver Resection (A Multivariate Analysis of 6,132 Patients)

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**Aims:** Surgical site infection (SSI) is a common postoperative complication and associated with an increased morbidity, hospital stay, and overall cost. The aim of the present study was to identify risk factors for SSIs after hepatic resection based on a large single-center cohort.

**Methods:** A retrospective study was conducted of 6,132 patients who underwent liver resection without concomitant biliary reconstruction or gastrointestinal procedures between 2014 and 2016 at the largest hepatic center in China. The occurrences of SSI, classified as incisional SSI and organ/space SSI within 30 days after operation were investigated. Patient- and surgical-related risk variables were collected using standardized data collection form. A likelihood ratio forward regression model was used to assess the independent association of risk factors with SSI.

**Results:** SSI developed in 587 patients (9.6%), including superficial/deep incisional SSI in 357 patients (5.8%), and organ/space SSI in 304 patients (5.0%). Multivariate logistic regression analysis showed that obesity, diabetes mellitus, ASA score  $\geq$  2, liver cirrhosis, re-hepatectomy, hepatoliathiasis, and intraoperative blood transfusion were independent risk factors of overall SSI. However, incisional and organ/space SSI differed from each other with respect to risk factors. Among a variety of risk factors, hepatolithiasis, liver cirrhosis, and intraoperative blood transfusion were consistently associated with both incisional and organ/space SSI.

**Conclusions:** SSI is a common complication after liver resection, and more caution should be taken in patients with hepatolithiasis or liver cirrhosis. Prevention strategies focusing on factors associated with SSI is necessary in order to reduce SSI after liver resection.

#### O-077

#### Outcomes after the Liver Resection of Colorectal Cancer Liver Metastases: A Single Center Experience

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**Aims:** Colorectal cancer (CRC) is associated with frequent distant metastases. Traditional surgical option for colorectal liver metastasis (CRLM) was a staged operation. And with advances of surgical techniques, devices, perioperative management and chemotherapeutic agents, CRLMs are now believed to be curable by operation. We analyze the differences of perioperative and oncologic outcome between simultaneous and staged operation.

**Methods:** Four hundred fifty six patients who underwent hepatic resection for known CRLM between January 2001 and December 2014 were retrieved from a retrospective database at our institution. Simultaneous resection was defined as co-operation between colorectal resection and liver resection. And staged operation was defined as colon resection was performed first and additional chemotherapy was followed.

**Results:** There were no statistically significant differences except ASA, preoperative chemotherapy state, number of metastatic tumor, liver resection margin (P=0.034, P=0.001, P=0.001, and P=0.017, respectively). Only major liver resection showed statistically significant difference in multivariate analysis for postoperative complication (P=0.018). In the multivariate analysis for disease-free survival and overall survival, there was a statistically significant increased risk of recurrence and poor prognosis in patients who had primary colorectal cancer histologic grade with poorly differentiated or mucinous adenocarcinoma, over 3 numbers of liver metastases, surgical margin of < 0.1 cm.

**Conclusions:** This study showed that simultaneous resections present similar major complication rates and oncologic outcomes compared with staged resection for synchronous CRLM. Simultaneous resection for synchronous CRLM appears to be feasible and safe.

#### O-078

# Efficacy of Platelet-Rich Fibrin on Bile Duct Anastomosis in a Rat

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**Aims:** Promoting the healing process and increasing the regenerative capacity of the biliary system might play a crucial role in preventing biliary complications following hepatopancreaticobiliary operations and liver transplantation. Aim of the study is to evaluate the effect of platelet-rich-fibrin (PRF) concentrate on the bile duct anastomosis healing process in rats.

**Methods:** Thirty male Sprague Dawley (SD) rats were used for the study. The animals were allocated into three groups: Group I Control Group (n=10): Anastomosis to the common bile duct (CBD) with a stent. Group II PRF Group (n=10): Anastomosis to the CBD with a stent and covered with PRF. Group III Sham Group (n=10): Preparation of the common bile duct, no anastomosis. The animals were followed up for 1 month, then sacrificed. Study parameters were adhesions around the anastomosis, bridging the bile duct tissue thickness over the stent and histopathologic examination of the bridging bile duct tissue.

**Results:** CBD anastomosis using a stent caused severe adhesion around the anastomosis, bridging bile duct tissues were weak and histopathologically, healing was incomplete in most of the control animals. However, PRF application significantly reduced the adhesions, increased the quality of the bridging bile duct tissues and caused complete healing histologically.

**Conclusions:** PRF is a safe, autologous, easily prepared membrane. The present study findings shows that PRF prevents local complications, and increases the healing capacity of the bile duct after CBD anastomosis. Therefore, it might be a new treatment option for preventing bile duct complications in liver transplantation patients.

#### O-079

#### Comprehensive Evaluation of Liver Resection Procedures: Surgical Mind Development through Cognitive Task Analysis

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**Aims:** Liver resection is a complex procedure for trainee surgeons. Cognitive task analysis facilitates understanding and decomposing tasks that require a great proportion of mental activity from experts.

**Methods:** Using cognitive task analysis and video-based coaching to compare liver resection by open and laparoscopic approaches, we decomposed the task of liver resection into exposure (visual field building), adequate tension made at the working plane (which may change three-dimensionally during the resection process), and target processing (intervention strategy) that can bridge the gap from the basic surgical principle.

**Results:** The key steps of highly-specialized techniques, including hanging maneuvers and looping of extra-hepatic hepatic veins, will be shown on video by open and laparoscopic approaches.

**Conclusions:** Familiarization with laparoscopic anatomical orientation may help surgeons already skilled at open liver resection transit to perform laparoscopic liver resection smoothly. Facilities at hand (such as patient tolerability, advanced instruments, and trained teams of personnel) can influence surgical decision making. Application of the rationale and realizing the interplay between the surgical principles and the other paramedical factors may help surgeons in training to understand the mental abstractions of experienced surgeons, to choose the most appropriate surgical strategy effectively at will, and to minimize the gap.

#### O-080

#### Laparoscopic Right Hepatectomy without Hanging Maneuver and CUSA

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**Aims:** CUSA and Hanging maneuver were routinely used in laparoscopic right hepatectomy in many centers. LigaSure has been reported as a safe and effective approach for parenchymal transection in open hepatectomy; however, its roles in laparoscopic right hepatectomy (LRH) have not been evaluated. The aim of present study is to evaluate the safety and feasibility of LigaSure in LRH.

**Methods:** A prospectively collected single-center database containing all laparoscopic liver resections performed by single surgeon at the Samsung Medical Center between March 2016 and December 2017. He used LigaSure and Bipolar during LRH without Hanging maneuver and CUSA.

**Results:** Thirty-four patients underwent LRH, but conversion to the open procedure occurred in two patients (5.9%). All pa-

tients had non-cirrhotic or cirrhotic liver with Child-Pugh class A. Median age was 55 years and 26 patients (81.3%) had hepatocellular carcinoma. Other disease included liver metastasis (n=2), living donor (n=2), focal nodular hyperplasia (n=1), cavernous hemangioma (n=1) excluded conversion cases (n=2). Median number of Pringle maneuver was 2 times during procedure. Median operating time was 256 minutes and median blood loss 225 mL. None was transfused red blood cells. Four patients experienced the complications such as ascites (n=2), bleeding (n=1), and delirium (n=1). Median hospitalization was 7 days and none developed to death at the last visit.

**Conclusions:** The method using LigaSure and Bipolar without Hanging Maneuver and CUSA demonstrates a simplicity, safety, and effectiveness for LRH in patients.

Keywords: Minimal invasive surgery, Complications, Outcomes

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#### O-081

Clinical Characteristics of Long Term Survivors Following Sorafenib Treatment for Unresectable Hepatocellular Carcinoma: Korean National Multi-Center Retrospective Cohort Study

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**Aims:** Sorafenib is the standard systemic therapy for treatment of advanced stage hepatocellular carcinoma (HCC), and progressive HCC after locoregional therapy. The efficacy and safety of the drug in clinical practice have been addressed by several real world studies. However, little data are available regarding clinical factors of good responders following sorafenib treatment. This study aimed to evaluate prognostic factors of long term survivors.

**Methods:** This multi-center retrospective cohort study included 1,605 unresectable HCC patients who received sorafenib treatment between 2007 and 2014 in 9 tertiary centers in Korea. The patients were classified into long-term survivor group (survival longer than 2 years, n=246) or control group (n=1,359). The primary endpoint was prognostic factors on survival for overall patients. Secondary endpoints included time-to-progression and other safety profiles.

**Results:** The patients were predominantly male (83.8%), chronic hepatitis B (77.3%), and Barcelona Clinic of Liver Cancer stage C (78.3%). The median overall survival was 9.0 months. After treatment, 12 patients (0.7%) achieved complete response, and 146 patients (9.1%) achieved partial response by mRECIST criteria. The prognostic factors predicting long-term survival were metformin use (hazard ratio [HR]=2.44; *P*=0.004), hand foot skin reaction (HR=1.77; *P*=0.001), and concomittent treatment with chemoembolization or radiotherapy (HR =2.59; *P*<0.001). Prognostic factors against long-term survival were child pugh score B (HR=0.375; *P*<0.001), presence of extrahepatic metastasis (HR=0.625; *P*=0.002), main portal vein invasion (HR=0.625; *P*=0.002), and elevated AFP (>1,000 ng/mL; HR=0.393; *P*<0.001).

**Conclusions:** This large multi-center retrospective study showed that the objective response was 9.8%, and the proportion of long-term survivors was 15.3% in Korean patients. The prognostic factors predicting long-term survival after sorafenib treatment were hand foot skin reaction, metformin use, concomittent treatment, good liver function, absence of extrahepatic metastasis, low degree of portal vein thrombosis, and low AFP.

**Keywords:** Hepatocellular carcinoma, Sorafenib, Long-term survival, Prognosis

# O-082

New Prediction Model of Convolutional Neural Network for Hepatocellular Carcinoma in Patients of Hepatitis B Virus-Related Cirrhosis on Potent Antiviral Therapy with Comparison of Preexisting Models

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**Aims:** Although there are several prediction models for hepatocellular carcinoma (HCC) development in chronic hepatitis B virus (HBV) infection including various proportion of liver cirrhosis, they are not based on the entirely cirrhotic patients on antiviral therapy. This study aimed to develop a new model of convolutional neural network (CNN) using deep learning technique for the prediction of HCC among HBV-related cirrhosis on the potent antivirals.

**Methods:** The subjects were 424 patients with HBV-related cirrhosis on entecavir therapy and followed for median 62.0 months at a single tertiary hospital in Korea. Four existing models (PAGE-B, CU-HCC, HCC-RESCUE and ADRESS-HCC) were applied to our subjects and, compared for the accuracy of each model at 5 years using Harrell's c-index. A New model using CNN was developed, and accuracy of the new model was calculated.

Results: During the follow-up period, HCC developed in 86 out of 424 patients (20.3%) with 5 year cumulative incidence of 22%. In discrimination assessment, PAGE-B (c-index= 0.612), HCC-RESCUE (c-index=0.613), and ADRESS-HCC (c-index=0.606) showed a better discriminatory power compared to CU-HCC (c-index=0.563). The predicted 5 year cumulative HCC incidence among PAGE-B, CU-HCC, and HCC-RESCUE using the reported cutoff of each model were 16.0%, 21.1%, and 41.2%, respectively. However, application of the PAGE-B, CU-HCC, and HCC-RESCUE for our cohort showed a predicted 5 year HCC incidence of 23.6%, 17.2%, and 21.7%, respectively, suggesting an underestimation in PAGE-B, but overestimation in CU-HCC, and HCC-RESCUE. Accuracy of new model using CNN was 79.7 %, which seems to be a better performance. Conclusions: Our new model of CNN may present better prediction than the preexisting 4 models for HBV-related cirrhosis on potent antivirals. Further validation study is warranted.

**Keywords:** Risk model, Liver cirrhosis, Liver cancer, Convolutional neural network

#### O-083

The Current Surveillance Strategy Does Not Improve the Detection Rate of Small Hepatocellular Carcinoma: A Single-Center Experience in South Korea

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**Aims:** Abdominal ultrasonography (US) and alpha-fetoprotein (AFP) testing are components of the nationwide liver cancer surveillance program in South Korea. However, whether this surveillance strategy improves the detection rate of single and small (< 2 cm) hepatocellular carcinoma (HCC) in high-risk groups is unclear.

**Methods:** We investigated the detection process and the clinical features of small HCC in a single healthcare center in South Korea from 2006 to 2015. Surveillance comprised US and AFP screening every 6 to 12 months; computed tomography (CT) was performed in place of US at the discretion of the clinician.

**Results:** During the study period, 916 patients were newly diagnosed with HCC, of whom 91 (9.9%) had a small HCC. The proportion of small HCC was 9.5% from 2006 to 2010 and

10.4% from 2011 to 2015 (P=0.677). The proportion of small HCC did not increase significantly during the 10-year period (Figure, P for trend = 0.297). The majority of patients with small HCC were detected by surveillance (N=57, 62.6%), followed by screening (N=14, 15.4%), and incidentally (N=20, 22.0%). Between 2006 to 2010 and 2011 to 2015, 65.2% and 60.0%, respectively, of small HCCs were detected by surveillance (P for trend=0.609). CT scan detected the largest proportion of small HCCs (45.1%), followed by US (40.7%), AFP elevation (12.1%), and magnetic resonance imaging (MRI) (2.2%). The overall 1-, 3-, and 5-year survival rates of treated patients were 96.0%, 84.6%, and 79.8%, respectively. Transarterial chemoembolization (TACE) was the most commonly performed initial treatment (N=46, 50.5%), due to an unfavorable tumor location or decreased liver function. Surgical resection and ablation were performed in 11 (12.1%) and 26 (28.6%) patients, respectively. However, there was no significant difference in the overall survival rate between patients who underwent surgical resection and those subjected to surgical ablation (P=0.295 by log-rank test).



**Conclusions:** Surveillance plays a major role in early detection of HCC. However, the current surveillance strategy is inadequate for the detection of small HCC in cirrhotic patients; more effective and practical surveillance strategies are needed.

**Keywords:** Early Detection of Cancer, Diagnosis, Epidemiology, Hepatocellular carcinoma, Mass Screening

# O-084

#### Metformin-Associated Chemopreventive Effects on Recurrence after Hepatic Resection of Hepatocellular Carcinoma: From *in vitro* to a Clinical Study

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**Aims:** We investigated metformin-induced cytotoxic effects *in vitro* and assessed the chemopreventive effects of metformin in

patients undergoing hepatic resection (HR) for hepatocellular carcinoma (HCC).

**Methods:** This study consisted of two independent parts: a laboratory research and a clinical study to assess the antitumor effects of metformin. The laboratory research assessed whether exposure to metformin has any cytotoxic effect on liver tumor cell lines. In the clinical study, the rate of tumor recurrence and overall patient survival after HR of HCC were investigated to assess whether long-term exposure to metformin has any chemopreventive effects.



**Results:** *In vitro* study using HCC cell lines revealed noticeable cytotoxic effects of metformin, which were largely weaker than those of sorafenib. In the clinical study, no statistical differences were found in tumor recurrence or overall survival between metformin and control groups. In contrast, there was a non-significant difference in tumor recurrence between metformin and propensity score-matched control groups, but there was significant difference in overall patient survival. Metformin administration was an independent risk factor for patient survival.



**Conclusions:** In conclusion, our *in vitro* laboratory study demonstrated presence of cytotoxic effects of metformin. Metformin administration was associated with reduced tumor recurrence and helped induce significant improvements in overall patient survival in patients who underwent HR for HCC.

**Keywords:** Metformin, Chemoprevention, Hepatocellular carcinoma, Recurrence

#### O-085

# A Nationwide Analysis of Conditional Survival Estimates for Korean Patients with Hepatocellular Carcinoma

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**Aims:** Conditional survival estimates (CSE) can provide more useful prognostic information on survival for a period of time after diagnosis and helps counseling patients with cancer on their individual prognosis of mortality. This study aimed to analyze survival rate over time and estimate conditional survival (CS) for Korean HCC patients using a national population-based registry.

**Methods:** Patients with HCC, registered in the population-based Korean cancer registry database, were retrospectively reviewed. Cumulative overall survival (OS) was calculated by using Kaplan-Meier method, and conditional 1-year survival at "X" year or month after diagnosis were calculated as  $CS_1$ =  $OS_{(X+1)}/OS_{(X)}$ . Cumulative CS calculations were performed with secondary subgroup analyses by BCLC stages, and then patients of stage 0, A, and B underwent subgroup analysis by initial treatment Methods.

**Results:** 3,509 patients diagnosed as HCC from January 2008 to December 2010, and 2,408 from January 2011 to December 2012 in Korea were separately reviewed. In 2008-2010, the actual OS at 1, 2, 3, 4, 5, and 6 years were 68.8%, 57.1%, 48.5%, 42.7%, 37.7%, and 33.4%. 1-year CS of 1, 2, 3, 4, and 5-year-survivors were 83.1%, 84.8%, 88.0%, 88.4%, and 88.5%. Patients demonstrated increase in CSE over time and showed same tendency in almost of all treatment Methods. In 2011-2012, OS at 1, 2, 3, and 4 years were 72.5%, 60.7%, 52.2%, and 46.5%. Overall 1-year CS of 6, 12, 18, 24, 30, and 36 months were 81.4%, 83.7%, 85.0%, 86.9%, 96.9%, and 89.1%. The CSE was also showed tendency to rise over time in subgroup analysis.

#### Table 1. Actual survival rates and CSE of HCC patients

(A) Survival rates and CSE of HCC patients diagnosed in 2008-2010 (Cohort A)

	Patients Survival						
Variables	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	
All patients (n=3509)	68.8%	57.1%	48.5%	42.7%	37.7%	33.4%	
1 yr CSE	83.1%	84.8%	88.0%	88.4%	88.5%		
2 yr CSE	70.5%	74.6%	77.8%	78.3%			
3 yr CSE	62.0%	66.0%	68.9%				
4 yr CSE	54.8%	58.4%					
5 vr CSE	48 5%						

(B) Survival rates an	d CSE of HCC patients	diagnosed in 2011-2	2012 (Cohort B)
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Mariahlar		Patients Survival						
variables	6 mo	1 yr	18 mo	2 yr	30 mo	3 yr	42 mo	4 yr
All patients (n=2408)	81.3%	72.5%	66.2%	60.7%	56.3%	52.2%	48.9%	46.5%
1 yr CSE	81.4%	83.7%	85.0%	86.0%	86.9%	89.1%		
2 yr CSE	69.2%	72.0%	73.9%	76.6%				



diagnosed in 2011-2012 (n. number; mo, month conditional survival estimate; YR, year conditional survival estimate)

**Conclusions:** Overall CSE improved with each additional year after diagnosis in both groups. CS may provide a more accurate prognosis and hopeful message to patients who are surviving with or after treatment. Further prospective nationwide research would be required.

**Keywords:** Conditional survival estimates, Hepatocellular carcinoma, Survival trends, Period analysis

#### O-086

#### Targeting the Crosstalk between Cytokine-Induced Killer Cells and Myeloid Derived Suppressor Cells in HCC

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**Aims:** Cytokine-induced killer (CIK) cell-based immunotherapy is effective as adjuvant therapy in early stage hepatocellular carcinoma (HCC), but lacks efficacy in advanced HCC. We investigated immune suppressor mechanisms and focused on CIKs and myeloid-derived suppressor cells (MDSCs).

**Methods:** MDSCs were quantified by flow cytometry, PCR, and immunohistochemistry. Cytokines were detected by cytokine array. LDH cytotoxicity assay was performed in the presence or absence of MDSCs to study CIK function against HCC cells *in vitro*. An FDA approved PDE5 inhibitor, tadalafil, was used to target MDSCs *in vitro* and *in vivo*. Two different murine HCC cell lines were tested as subcutaneous and orthotopic tumor models in C57BL/6 and BALB/c mice. Anti-tumor effects of human CIK and MDSC were tested *in vitro*.

**Results:** Adoptive cell transfer of CIK cells into tumor bearing mice induced inflammatory mediators (e.g., CX3CL1, IL-13) in the tumor microenvironment and an increase of tumor infiltrating MDSCs leading to impaired anti-tumor activity in two different HCC tumor models. MDSCs efficiently suppressed the cytotoxic activity of CIK cells *in vitro*. In contrast, treatment with a PDE5 inhibitor reversed MDSC suppressor function via ARG1 and iNOS blockade and systemic treatment with a PDE5 inhibitor prevented MDSC accumulation in the tumor microenvironment upon CIK cell therapy and increased its anti-tumor

efficacy. Similar results were seen when human CIK cells were tested *in vitro* in the presence of CD14<sup>+</sup>HLA-DR<sup>-/low</sup> MDSCs. Treatment of MDSCs with a PDE5 inhibitor suppressed MDSCs suppressor function and enhanced CIK activity against human HCC cell lines *in vitro*.

**Conclusions:** Our results suggest that targeting MDSCs is an efficient strategy to enhance the antitumor efficacy of CIK cells for the treatment of patients with HCC.

Keywords: CIK, PDE5 inhibitor, HCC, Immunotherapy

# O-087

#### Sarcopenia Measured by Psoas Muscle Index Is an Independent Factor for Overall Survival in Korean Patients with Hepatocellular Carcinoma

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**Aims:** This study investigated the effect of sarcopenia on the survival of hepatocellular carcinoma (HCC) patients who underwent curative or non-curative treatment.

**Methods:** There were 2 sets of subjects (test and validation set) in the same center. The test set included curatively resected 160 HCC patients from 2003 to 2011. The validation set included 257 HCC patients who underwent curative or palliative treatment from 2012 to 2015. The cross-sectional areas of the bilateral psoas muscles at the third lumbar level were normalized for the patient's height, and presented as psoas muscle index (PMI). Sex-specific cut-offs of PMI to define the sarcopenica were ascertained by the maximal chi-square method.

Results: In the test set (n=160, curative resection, median age of 56 years, male 75%), the PMI (mean  $\pm$  SD) was 4.78  $\pm$  1.64 (males) and 2.91  $\pm$  0.93 cm<sup>2</sup>/m<sup>2</sup> (females), showing sarcopenic prevalence of 17.5%. In the validation set subjects (n=257, mostly non-curatively treated, median age of 60 years, male 80.9%), the PMI was 4.46  $\pm$  1.25 (males) and 2.28  $\pm$  0.81 (females), showing the sarcopenic prevalence of 57.2%. The 5-year overall survival rate in the sarcopenic group (52.2%) was significantly lower than in the nonsarcopenic group (76.5%) (P=0.008) in the test set, which was confirmed in the validation set (65.2% vs. 80.3%, respectively, P=0.004). Moreover, sarcopenia was an independent factor for poor survival in both test [(hazard ratio (HR), 2.374, 95% confidence interval (CI), 1.308-4.309, P=0.004) and validation set (HR, 2.035, 95% CI 1.047-3.958, P=0.036). However, recurrence free survival was not different according to the sarcopenia in both test and validation set.

**Conclusions:** Sarcopenia measured by PMI predicts poor survival in Korean HCC patients who underwent curative or non-curative treatment. Therefore, nutritional support and exercise enforcement for HCC patients may improve the survival of HCC patients.

**Keywords:** Sarcopenia, Psoas muscle index, Hepatocellular carcinoma, Prognosis

# O-088

#### Clinical Impact of CD4+CD25+Foxp3+ Regulatory T Cell in Hepatocellular Carcinoma Patients Undergoing Transarterial Chemoembolization

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**Aims:** Regulatory T cell (Treg) play an essential role in regulation of antitumor immunity. Although several studies regarding Treg in hepatocellular carcinoma (HCC) have been reported, knowledge of Treg after transarterial chemoembolization (TACE) is still unrevealed. The aim of this study was to investigate clinical impact of Treg in HCC patients who treated with TACE.

**Methods:** We measured the frequency of peripheral blood Tregs in 23 healthy controls and 27 HCC patients undergoing TACE between 2010 and 2012 at Severance Hospital. The patients were divided into two groups according to tumor response; complete response group and incomplete response group.

Results: The frequency of Treg in HCC patients was significantly higher than in healthy controls (7.52±2.62% vs. 4.99±1.4%, P < 0.001). In a Treg subpopulation, the frequency of Treg (II) was significantly higher in HCC patients than in healthy controls (2.51±1.08% in HCC vs. 0.60±0.28% in healthy controls, P<0.001). In comparison of Tregs numbers at baseline and post-TACE by tumor response, the change of Treg (III) in complete response group from before to after TACE was statistically significant (63.8±42.2/mm<sup>3</sup>→53.2±31.9/mm<sup>3</sup>, *P*=0.050). The complete response group contained more patients with low post-TACE Treg (III) numbers, and the incomplete response group more patients with high post-TACE Treg (III) numbers, with statistical significance (70.9% vs. 29.4% in complete response group; 30.0% vs. 70.0% in incomplete response group, P=0.040). Patients with high post-TACE Treg (III) exhibited a significantly shorter time to progression than those with high post-TACE Treg (III) (3.8 months vs. 11.6 months, P=0.038). On multivariate analysis, hypoalbuminemia (HR 3.324; 95% CI (1.098-10.063), P=0.034) and high post-TACE Treg (III) (HR 3.080; 95% CI (1.091-8.696), P=0.034) were independent significant prognostic factors in terms of progression.

**Conclusions:** High peripheral blood Treg (III) levels at 1 month after TACE were independently prognostic of poor progression-free survival.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Regulatory T cell, Immunologic change

#### O-089

# Caveolin-1 Promotes Hepatocarcinogenesis in Cirrhotic Liver

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**Aims:** Liver cirrhosis is a soil for the development of hepatocellular carcinoma (HCC) and prevention of HCC is urgent. However, biomarkers to predict development of HCC from liver cirrhosis are still lacking. We aimed to discover a biomarker directly from protein analysis and relate it with genomics to validate in a larger cohort.

**Methods:** Forty six patients who had surgical resection for HCC that developed from cirrhotic liver and developed HCC recurrence 3 years after resection were enrolled. HCC that recur less than 3 years was considered as intrahepatic metastasis while those that recur 3 years later was defined as de novo recurrence from liver cirrhosis. Systematic analysis was performed using reverse-phase protein array (RPPA) and microarray data acquired from these patients.

Results: Proteomics analysis performed after selecting 20 proteins from 201 proteins with AUROC >70 in predicting late recurrence were able to categorize patients into high (n=20) and low risk (n=26) HCC groups. Caveolin-1 was the dominant protein for this categorization and 298 genes that significantly differed between these 2 groups were derived. This proteome derived late recurrence (PDLC) gene signature well predicted the development of HCC in cohort 1 (n=216) with background of liver cirrhosis. The robustness of this signature was also validated in predicting de novo HCC recurrence in cohort 2 (n=259). PDLC gene signature remained significant in multivariate analysis when compared with clinical variables (HR 1.904, P=0.01) and showed the lowest AIC among previously reported gene signature (186-BROAD gene signature and hepatic injury and regeneration gene signature). in vitro experiment revealed that immortalized liver cell overexpressed with CAV1 showed significantly increased proliferation and soft agar colony formation than the control (P<0.001 and 0.033). Immunohistochemical staining of tissue microarray analysis also supported our findings with increased HCC development in CAV1 positive tissues (P=0.047).

**Conclusions:** Expression of CAV1, a structural protein of caveolae in the plasma membrane appears to be an important predictor of HCC development from liver cirrhosis and our study has provided new insight in considering CAV1 as a biomarker and target for prevention strategy.

**Keywords:** Caveolin-1, Liver cirrhosis, Hepatocellular carcinoma, Reverse-phase protein microarray

#### O-090

#### Is the Anatomical Resection Necessary for Single Hepatocellular Carcinoma Smaller than 3 cm?

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**Aims:** Liver resection has been accepted as the first-line treatment for single hepatocellular carcinoma (HCC). However, the superiority of anatomical resection (AR) for a small HCC remains controversial. In this study, we investigated the clinical outcomes after AR and non-anatomical resection (NAR) for single HCC smaller than 3 cm and the risk factors for HCC recurrence.

**Methods:** A total of 116 consecutive patients who underwent liver resection for single HCC (<3 cm) between Jan 2006 and Dec 2015 were included in this study. The medical records of these patients were reviewed and analyzed retrospectively.

**Results:** The mean follow up period was 69.9 months. There was no difference between AR and NAR group in patients demographics and pathologic data except tumor location. The 1-, 2-, 3- and 5-year disease-free survival (DFS) rates were 75, 66, 56 and 43 % in AR group and 90, 81, 70, and 51 % in NAR group, respectively (*P*=0.455). There was no significant difference in tumor recurrence and survival between AR and NAR group. Multivariate analysis showed that HBeAg (+) (*P*=0.018, HR=3.09) and presence of satellite nodule (*P*=0.005, HR=6.21) were independent risk factors for early recurrence within 1 year. The overall recurrence was independently related to the presence of satellite nodule (*P*=0.001, HR=4.98) and background liver cirrhosis (*P*=0.032, HR=1.96).

**Conclusions:** The outcomes of NAR are comparable with those of AR in single HCC smaller than 3 cm. The presence of satellite nodule and background liver cirrhosis are the independent risk factors for recurrence.

# 11. HCV

#### O-091

Clinical and Epidemiological Features of Hepatitis C Virus Infection in South Korea from 2007 to 2017: A Prospective, Multicenter Cohort Study

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**Aims:** This study aimed to investigate the clinical and epidemiological features of chronic hepatitis C patients in South Korea from 2007 to 2017.

**Methods:** The Korea hepatitis C virus (HCV) cohort is a prospective, multicenter cohort which enrolled 2,910 adult patients with anti-HCV positivity at 7 tertiary centers. A standardized questionnaire survey on the risk factor for HCV infection, and clinical data collection with patient follow-up were prospectively performed. Among them, clinical profiles of 2,758 patients with HCV RNA viremia were described.

Results: The HCV cohort showed a mean age of 57.3 years with 50.7% men, current or past alcohol intake in 52.8%, obesity in 27.4%, and diabetes mellitus in 18.6%. Past history of transfusion before 1995 was in 14.4%, intravenous drug use (IVDU) in 5.6%, piercing in 33.4%, and tattooing in 37.4%. The diagnostic category consisted of chronic hepatitis (69.5%, n=1918), liver cirrhosis (18.9%, n=522), and hepatocellular carcinoma (HCC) (11.5%, n=318). The mean level of platelet count was 235K, ALT level over upper normal limit (UNL) in 50.1%, and HCV RNA level>600,000 IU/mL in 48.1%. The major HCV genotypes were genotype 1b (48.2%), genotype 2 (46.4%), genotype 3, 4, and 6 in 0.6%, 0.2%, and 0.5%, respectively. Liver biopsy was performed in 227 patients (8.2%), while FibroScan<sup>®</sup> was performed in 289 patients. Antiviral treatment including interferon-based therapy and direct acting antivirals was undergone in 32.8%. Comparison of clinical profiles between the first half period (2007-2011) and second half (2012-2017) will be discussed.

**Conclusions:** The current clinical profile of Korean chronic hepatitis C patients showed a mean age of 57 years with male to female ratio of 1, past history of transfusion and IVDU in less than 25%, genotype 1 and 2 in 95%, liver cirrhosis and HCC in 30%, and one third of the patients underwent antiviral therapy.

**Keywords:** Hepatitis C virus, Epidemiology, Prospective cohort, Multicenter cohort

# O-092

## A Tool to Measure the Impact of Inaction towards Elimination of Hepatitis C: A Case Study in Korea

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**Aims:** Chronic hepatitis C (CHC) and its sequelae present a significant source of economic and societal burden. Introduction of highly effective curative therapies have made elimination of HCV attainable. Our study used a predictive model scalable at national, regional or local level to assess the clinical and economic impact of implementing national screening and treatment policies towards HCV elimination in Korea.

Methods: A Markov disease progression model of HCV infection was developed to analyse the clinical and economic impact of delaying diagnosis and treatment of HCV using modules that quantified the disease burden and medical costs associated with CHC. In this analysis, the model compared the clinical outcomes of the national status quo in Korea of 6,990 treatments and 4,205 newly diagnosed HCV-infected cases annually, starting in 2018 to 1) a scenario that met WHO's diagnosis, incidence, and mortality targets for elimination of HCV by 2030, 2) a scenario of delaying these intervention by one year, and 3) delaying these interventions by two years. Modelled historical incidence of HCV was calibrated to match the reported prevalence of antibodies against HCV (0.80% in 2013). Elimination scenario required 24,000 treatments and 34,000 newly diagnosed cases annually, starting in 2018, to reach the 2030 targets.

**Results:** Compared to base case, elimination would avert 30,607 incident cases of HCV, 14,879 cases of decompensated cirrhosis (DCC), 18,334 cases of hepatocellular carcinoma (HCC), 523 liver transplantations (LTs), and 14,001 liver-related deaths (LRDs) over the 2017–2030 periods. Postponing this elimination intervention by one (or two) years would fail to avert over 4,621 (8,879) new HCV infections, nearly 3,446 (6,760) cases of end-stage liver disease (ESLD), and 1,403 (2,758) LRDs by 2030.

**Conclusions:** Leveraging a tool to quantify the impact of screening and treatment interventions and track their progress towards WHO targets, HCV elimination in Korea would avert a significant portion of incident cases, as well as new cases of end-stage liver disease (ESLD) and LRDs due to HCV. Also, postponing this intervention by just one or two years would fail to avert hepatic complications and new infections, thus bringing considerable burden to patients and society.

Keywords: Hepatitis C, Elimination

#### O-093

SVR Rate (12 Weeks and 1 Year) and Improvement of Fibrosis after Daclatasvir/Asunaprevir Treatment in Genotype 1b HCV-Infected Patients

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**Aims:** The long term data with daclatasvir (DCV)/asunaprevir (ASV) treatment for genotype 1b (GT1b) HCV-infected patients was not reported in Korea. This study investigated the efficacy in virologic response (SVR<sub>12</sub> and SVR<sub>48-60</sub>), improvement of liver function and fibrosis markers after DCV/ASV treatment.

**Methods:** HCV GT1b patients who had not resistant associated substitute (RAS) were enrolled in 5 tertiary Korean hospitals. A total of 287 patients treating with DCV/ASV were observed for SVR<sub>12</sub>. Virologic response was measured at 12 weeks (SVR<sub>12</sub>), and 48-60 weeks (SVR<sub>48-60</sub>) after the end of treatment. In patients with cirrhosis, liver function, aspartate transaminase to platelet ratio index (APRI), FIB-4 index, fibrosis index (FI), and liver stiffness measurement (LSM) were compared between before and after treatment (at SVR<sub>48-60</sub>).

**Results:** SVR<sub>12</sub> was obtained in 97.6% (280/287) patients. Among them, 189 patients were observed for SVR<sub>48-60</sub>. Baseline characteristics (n=189): age (55±11 years), male 91(48%), cirrhosis 57(30.2%), treatment-naïve 135(71.4%), ALT (58±53 IU/L), and HCV RNA (1,738,132±2,279,517 IU/mL) were shown. SVR<sub>48-60</sub> was obtained in 96.8 % (183/189) patients. In cirrhotic patients (n=57), changes of ALT (52±36 to 25±13 IU/L, P<0.001), total bilirubin (1.0±0.8 to 0.9±0.5 mg/dL, P=0.112), albumin (3.9±0.7 to 4.2±0.5 g/dL, P=0.003), and platelet (130±96 to 144±80 10<sup>3</sup>/mm<sup>3</sup>, P=0.132) were observed. The changes of APRI score (2.1±0.3 to 0.8±0.1, P<0.001), FIB-4 index (7.2±0.9 to 3.7±0.4, P<0.001), FI (2.8±0.2 to 2.4±0.2, P=0.021), and LSM (n=16, 19.3±3.1 to 13.0±2.0 kPa, P=0.015) were observed. The characteristics of patients who failed SVR<sub>48~60</sub> (n=6) were such as: age 62(47-78) years, female 5(83%), treatment-naïve 3(50%), cirrhosis 2(33%), ALT 40(14-62) IU/L, HCV RNA 2,599,557(459,017-12,149,394) IU/mL.

**Conclusions:** DCV and ASV treatment for HCV GT1b infected Korean patients without RAS achieved high SVR rates. However, 3% patients who achieved SVR<sub>12</sub> failed in SVR<sub>48-60</sub>. The cirrhotic patients with SVR<sub>48-60</sub> showed improvement of liver function and fibrosis markers.

Keywords: SVR, Daclatasvir, Asunaprevir, HCV 1b

## O-094

#### Ribavirin May Help to Improve Sustained Virological Response of Daclatasvir Plus Asunaprevir for Chronic Hepatitis C 1b Patients

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**Aims:** Daclatasvir is a nonstructural protein 5A inhibitor, and asunaprevir is a nonstructural protein 3 protease inhibitor with activity against genotypes 1, 4, 5, and 6. Despite a 90% sustained virologic response (SVR) rate without baseline NS5A-L31/ Y93H polymorphisms, the SVR rate is slightly lower than that of other DAA agents combination. Therefore, an alternative regimen under the consideration of cost-effectiveness would be important. Whether the addition of ribavirin could improve the SVR rate among this group of patients remains unknown and so we investigated ribavirin effect.

**Methods:** Total 262 CHC patients with genotype 1b were prospectively enrolled in three KUMC hospital. 218 patients of them were treated with daclatasvir plus asunaprevir with (n=30) or without rivabirin (n=188). The other patients were excluded because of other DAA agents or loss during treatment.

**Results:** Mean age was 60 years old and Male was 43.6% (n=95). Gradually RVR, ETR, and SVR was 90.8%, 90.8%, and 84.4% by ITT protocol, respectively. RVR, ETR, and SVR was 96.6%, 94.7%, and 92% by Per protocol. IFN experienced patients was 23.2% (n=46) and SVR was 95.7%, which is similar rate compared with naïve patients 92.1% (P=0.528). Liver cirrhosis patients was 32.3% (n=64) and SVR was 90.6%, which is also similar rate compared with non cirrhotic patients 94% (P=0.555). However, RBV additional therapy patients was 11.6% (n=23) and SVR was 100% which is slightly improved compared with non RBV therapy patients 87.5% (P=0.230). No patients developed significant adverse effects during and after the treatment.

**Conclusions:** In genotype 1b chronic hepatitis C patients without NS5A-Y93H polymorphism, the addition of ribavirin to daclatasvir/asunaprevir may increase the SVR12 rate with minimal side effects, and thus deserves more comprehensive trials in resource-limited areas

Keywords: Daclatasvir, Asunaprevir, Ribavirin, Hepatitis C virus

#### O-095

#### Twelve Weeks of Ledipasvir/Sofosbuvir for Patients with Chronic Hepatitis C Genotype 2 Infection: Integrated Analysis of Three Clinical Studies

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#### Youn<sup>8</sup>, Chen-Yu Wang<sup>8</sup>, Joe Llewellyn<sup>8</sup>, Anu Osinusi<sup>8</sup>, Jenny Svarovskaia<sup>8</sup>, Hongmei Mo<sup>8</sup>, Gerald Crans<sup>8</sup>, Wan-Long Chuang<sup>1</sup>, Pei-Jer Chen<sup>3</sup>, Nobuyuki Enomoto<sup>9</sup>

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**Aims:** HCV genotype (GT) 2 is the second most common genotype in several Asian countries including Taiwan and Korea. Treatment options for GT2 remain limited in these countries. The once-daily fixed-dose combination of ledipasvir/sofosbuvir (LDV/SOF) was evaluated for the treatment of GT 2, in patients with or without compensated cirrhosis, in three phase 2 and 3 studies.

**Methods:** This was a retrospective analysis of subjects treated with LDV/SOF for 12 weeks in the GS-US-337-1655 (Taiwan), GS-US-337-1903 (Japan) and GS-US-1468 (New Zealand) studies. Subjects analyzed in this integrated analysis were either mono-infected with HCV GT2, or co-infected with HCV GT2 and HBV. The data was pooled and safety and efficacy were analyzed.

Results: Overall 200 subjects were treated and analyzed; 88% of subjects were Asian, 46% male, 31% had prior treatment failure, 15% were cirrhotic, 25% were IL28B non-CC, 34% were 65 years or older and 22% (n=43) were co-infected with HBV. The overall SVR rate was 97% (194/200), and was 93% (27/29) among patients with cirrhosis and 97% (59/61) in patients who had failed previous therapy. Of the 197 patients with available testing; NS5A resistance-associated substitutions (RASs) were present in 86% (169/197) at baseline. SVR12 rate was 98% (165/169) in patients with baseline NS5A RASs compared with 100% (28/28) in patients without NS5A RASs. No new RASs emerged in patients with virologic failure. Treatment with LDV/SOF for 12 weeks was well tolerated. Overall the most common adverse events AEs were headache and nasopharyngitis. Few subjects experienced serious AEs, none of which were assessed as treatment related. One patient discontinued treatment due to AE.

**Conclusions:** Treatment with LDV/SOF for 12 weeks is highly effective and well tolerated in patients with GT2 HCV infection, including patients who are treatment experienced and/or have compensated cirrhosis, baseline NS5A RASs and with HBV/HCV coinfection.

Keywords: Genotype 2, Ledipasvir, Sofosbuvir

#### O-096

## Safety and Efficacy of Elbasvir/Grazoprevir in Asian Participants with Hepatitis C Virus Genotypes 1 and 4 Infection

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**Aims:** Clinical experience with direct-acting antiviral treatments for hepatitis C virus (HCV) infection is emerging in the Asia-Pacific region. We conducted an integrated analysis of the safety and efficacy of elbasvir (EBR)/grazoprevir (GZR) in self-identified Asian participants who were enrolled in 11 EBR/GZR phase 2/3 studies. **Methods:** All participants received EBR/GZR 50 mg/100 mg alone for 12 weeks or in combination with ribavirin (RBV) for 16 weeks. The primary endpoint of all studies was sustained virologic response (HCV RNA <15 IU/mL) 12 weeks after end of therapy (SVR12).

Results: A total of 780 Asian participants with HCV GT1 or 4 infection were included (GT1b, n=715; GT1non-b, n=63; GT4, n=2). Most participants were enrolled from Japan (n=366, 46.9%), mainland China (n=146, 18.7%), Taiwan (n=109, 14.0%) and South Korea (n=90, 11.5%). Overall, 12.4% of participants had cirrhosis, and 20.4% were treatment-experienced. SVR12 was achieved by 756/780 (96.9%, 95% CI 95.5-98.0) of all Asian participants, including 748/772 (96.9%, 95% CI 95.4-98.0) who received EBR/GZR for 12 weeks and 8/8 (100%, 95% CI 63.1-100.0) who received EBR/GZR + RBV for 16 weeks. The frequency of safety events among Asian participants was: any adverse event (AE), 58.1% (453/780), drug-related AEs, 23.6% (184/780), serious AEs, 2.6% (20/780), and discontinuation due to an AE, 0.9% (7/780). Fifteen participants (1.9%) had elevated ALT/AST levels that met the criteria for an event of clinical interest (ALT/AST >3× baseline and >100 U/L), 3 of whom discontinued treatment. The efficacy and safety profile of EBR/GZR was comparable to that observed among non-Asians.

**Conclusions:** The combination of EBR/GZR was safe and highly effective in this large population of Asian participants with primarily HCV GT1b infection. Late transaminase elevations were reported in approximately 2% of participants, which is consistent with the safety profile of EBR/GZR in non-Asians.

Keywords: HCV, Elbasvir/grazoprevir, Asian data

#### O-097

#### Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Patients with Chronic HCV Genotype 1-6 Infection

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**Aims:** The direct acting-antivirals (DAA) glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor), coformulated as G/P, are a once-daily, all-oral treatment regimen with high rates of sustained virologic response at 12 weeks post-treatment (SVR12) and a favourable safety profile indicated for use in patients at any stage of chronic kidney disease (CKD). Here we report preliminary data from a Phase 3b study assessing the efficacy and safety of 8, 12, and 16 weeks of G/P treatment in patients with chronic hepatitis C virus (HCV) genotype (GT) 1-6 infection and CKD Stage 3b, 4, or 5, including those on dialysis. This study aims: to provide further evidence supporting G/P's labeled regimen among patients with moderate or severe CKD, including efficacy of an 8-week G/P treatment duration for patients who are treatment naïve and non-cirrhotic.

**Methods:** EXPEDITION-5 (NCT03069365) is an ongoing, Phase 3b, multicenter study evaluating the efficacy and safety of G/P in patients without cirrhosis or with compensated cirrhosis and with CKD. Patients were either treatment-naïve or -experienced with interferon (IFN), pegIFN  $\pm$  ribavirin (RBV), or sofosbuvir (SOF) + RBV  $\pm$  pegIFN. Prior treatment with a DAA other than SOF was not permitted. Patients had an estimated glomerular filtration rate (eGFR)<45mL/min/1.73 m<sup>2</sup> without a history of acute renal failure within 3 months prior to screening. Patients were treated with label (U.S. and E.U.) indicated treatment duration. Efficacy was evaluated by the percent of patients achieving SVR12 (HCV RNA<lower limit of quantification). Safety was assessed in all patients.

**Results:** In total, 101 patients were enrolled with 84, 13, and 4 patients receiving G/P for 8, 12, and 16 weeks, respectively. Demographics for the first 99 patients are as follows: 41 (41%) were female, 72 (73%) were white and 13 (13%) had compensated cirrhosis. At screening, 7 (7%), 17 (17%), and 75 (76%) patients had CKD stage 3b, 4, and 5, respectively; 73 (74%) patients required dialysis. Safety information identified pruritus, occurring in 14%, as the only adverse events (AEs) reported in  $\geq$  5% of patients. Grade  $\geq$ 3 serious and non-serious treatment-emergent AEs were reported in 5% of patients; none of which were related to G/P or led to treatment discontinuation. To date, 81/84 patients treated with G/P for 8 weeks have achieved SVR12 (2 d/c, 1 missing SVR 12). Overall mITT SVR12 rate of 100 %(98/98).

Conclusions: safety data suggest that G/P was safe and

well-tolerated. Data confirms the 8-weeks use of G/P in CKD patient with no virologic failures

**Keywords:** Hepatitis C, Antiviral agent, Treatment outcome, Chronic Kidney Disease

#### 12. Liver Cancer

#### O-098

Transarterial Chemoebolization-Stereotactic Body Radiation Therapy versus Transarterial Chemoebolization for ≤5cm Hepatocellular Carcinoma: Propensity Score Matching

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**Aims:** Patients with liver cirrhosis and hepatocellular carcinoma (HCC) are often ineligible for resection or local ablation therapy due to poor liver function and/or difficult location. The aim of this study is to evaluate therapeutic outcomes of stereotactic body radiotherapy (SBRT) combined with transarterial chemoembolization (TACE) compared with TACE alone for HCC measuring less than 5 cm.

**Methods:** From March 2011 to December 2016, 85 patients underwent SBRT with TACE (SBRT-TACE group) and 114 underwent TACE (TACE group) at 4 tertiary hospitals. Local control rate (LCR), progression-free survival (PFS) and overall survival (OS) were compared after propensity-score matching (1:1 ratio).

**Results:** The SBRT-TACE group showed significantly higher 1- and 3-year LCR than the TACE group (91.1% and 89.9%, respectively vs 69.9% and 44.8%, respectively; *P*<0.001). The SBRT-TACE group showed better 1- and 3-year PFS than the TACE group (56.5% and 32.3%, respectively vs 42.2% and 21.6%, respectively; *P*=0.022). However, 1-, 3- and 5-year OS was not different between the SBRT-TACE and TACE groups (98.8%, 89.1% and 80.7%, respectively vs 99.7%, 83.3% and 71.0%, respectively; *P*=0.206). In multivariate analysis, the overall SBRT added to TACE did not contribute to extend PFS. However, in patients with less than 2 tumors, the combined therapy was effective (HR 0.590, 95% CI 0.392-0.889, *P*=0.012).

Variable	Before propensity matching			After prop match	oensity ing
	SBRT-TACE (n=85)	TACE (n=114)	P-value	TACE (n=85)	P-value
Sex					
Male	65	88	0.905	64	0.858
Female	20	26		21	
Mean age (mean ± SD)	62.64 ± 10.08	63.32 ± 10.10	0.639	62.85 ± 10.65	0.894
Number			0.045		0.816
1 2 3	55 20 10	55 33 26		51 23 11	
Mean tumor size (mean ± SD)	2.23 ± 1.17	2.54 ±1.35	0.095	2.29 ± 1.17	0.753
Mean total tumor size	$3.05\pm1.79$	$3.58 \pm 2.34$	0.074	$2.94 \pm 2.01$	0.691
Child-Pugh score (mean ± SD)	5.52 ± 0.85	5.57 ± 1.18	0.183	5.59 ± 1.06	0.633
Child-Pugh class					
A	71	96	0.897	74	0.516
В	14	18		11	
BCLC stage			0.054		0.476
0	22	32		29	
A	55	58		50	
В	8	24		6	
Etiology Alcohol Hepatitis B virus Hepatitis C virus Others	22 47 11 5	27 65 13 9	0.920	18 51 9 7	0.778
ALT (mean ± SD	27.7 ± 24.3	29.4±18.8	0.674	29.1 ± 18.1	0.666
Total bilirubin (mg/dl) (mean ± SD)	0.94 ± 0.56	0.95 ± 0.65	0.857	0.90+0.63	0.654
Platelet count (x109/L) (mean ± SD)	128 + 63.5	$116\pm53$	0.160	118 ± 53	0.261
Prothrombin time (INR) (mean ± SD)	$1.14 \pm 0.20$	1.17 ± 0.18	0.283	1.15 ± 0.19	0.651

 Table 1. Baseline characteristics before and after propensity score matching

ALT alanine transaminase, INR = International Normalized Ratio

**Table 2.** Prognostic factors for progression-free survival

Variable	ι	Univariate analysis		Multivariate analysis		
Variable	HR	95% CI	P value	HR	95%CI	P value
SBRT-TACE	0.688	0.477-0.992	0.045	0.695	0.480-1.005	0.053
Sex, female	1.009	0.656-1.550	0.968			
Tumor size	1.299	1.107-1.523	< 0.001	1.131	0.897-1.426	0.298
Number of tumor			< 0.001			0.007
1	1.000			1.000		
2	1.553	1.020-2.365	0.040	1.458	0.910-2.337	0.117
3	3.310	1.986-5.517	< 0.001	2.710	1.494-4.915	< 0.001
Child-Pugh class						
А	1.000			1.000		
В	2.029	1.242-3.315	0.005	1.945	1.183-3.197	0.009
Age	1.011	0.994-1.029	0.197			
BCLC stage			< 0.001			0.004
0	1.000			1.000		
А	1.350	0.885-2.058		1.073	0.665-1.733	0.773
В	6.344	3.170-12.697		3.701	1.635-8.379	0.002
AFP (ng/mL)						
<200	1.000					
≥200	1.130	0.635-2.013	0.677			

HR, hazard ratio; CI, confidence interval; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; BCLC, Barcelona clinic liver cancer; AFP, a-fetoprotein

Table 3. Prognostic factors for overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95%CI	P value
SBRT-TACE	0.722	0.378-1.380	0.324			
Sex, female	1.021	0.484-2.154	0.957			
Tumor size	1.174	1.018-1.354	0.028	1.179	0.746-1.863	0.482
Number of tumor			0.056			0.303
1	1.000			1.000		
2	0.593	0.228-1.542	0.284	0.582	0.219-1.548	0.278
3	2.426	1.043-5.644	0.040	1.697	0.652-4.417	0.279
Child-Pugh class						
A	1.000			1.000		
В	2.570	1.241-5.324	0.011	2.570	1.241-5.324	0.011
Age	0.989	0.957-1.022	0.508			
BCLC stage			0.068			0.019
0	1.000			1.000		
А	1.755	0.811-3.797		2.231	0.997-4.994	0.051
В	4.367	1.325-14.395		5.835	1.719-19.801	0.005
AFP (ng/mL)						
<200	1.000					
≥200	0.772	0.237-2.511	0.667			

HR, hazard ratio; CI, confidence interval; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; BCLC, Barcelona clinic liver cancer; AFP, a-fetoprotein

**Table 4.** Prognostic factors for progression-free survival in patients

 with 1 to 2 nodules

Variable	Univariate analysis			M	Iultivariate anay	lsis
	HR	95% CI	P value	HR	95%CI	P value
SBRT-TACE	0.604	0.402-0.907	0.015	0.590	0.392-0.889	0.012
Sex, female	1.057	0.662-1.668	0.817			
Tumor size	1.290	1.141-1.458	0.001	1.132	0.878-1.461	0.339
Child-Pugh class						
A	1.000					
В	1.925	1.100-3.368	0.022	2.136	1.121-3.762	0.009
Age	1.012	0.993-1.032	0.214			
BCLC stage			0.004			0.001
0	1.000			1.000		
A	1.186	0.766-1.837	0.444	1.226	0.790-1.902	0.363
В	5.570	2.363-13.131	< 0.001	6.703	2.817-15.951	< 0.001
AFP (ng/mL)						
<200	1.000					
≥200	1.324	0.737-2.376	0.348			

HR, hazard ratio; CI, confidence interval; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; BCLC, Barcelona clinic liver cancer; AFP, a-fetoprotein



P < 0.001

**Figure 1.** Comparison of the local control rates between SBRT-TACE and TACE groups.



P < 0.022

**Figure 2.** Comparison of progression-free survival rates between SBRT-TACE and TACE groups.



P < 0.206

**Figure 3.** Comparison of overall survival rates between SBRT-TACE and TACE groups.



P < 0.006

**Figure 4.** Comparison of progression-free survival with SBRT-TACE and TACE in subgroup analysis by tumor number ( $n\leq 2$ ).

**Conclusions:** SBRT-TACE is superior to TACE in terms of LCR. Particularly, SBRT-TACE may be an effective alternative in patients with HCC number ( $\leq 2$ ), which is not indicated for resection or local ablation.

**Keywords:** Hepatocellular carcinoma, Stereotactic body radiation therapy, Transarterial chemoembolization, Propensity analysis

#### O-099

Risk Assessment and Suitability of Transarterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma with or without Impaired Hepatic Function

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**Aims:** The decision of initiation or repetition of transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC) still remains challenging, especially in patients with impaired hepatic function. The aims: were (i) to identify prognosticators in patients undergoing TACE, (ii) to develop a risk prediction model, and (iii) to investigate the outcomes according to the scores in patients undergoing TACE with or without impaired hepatic functional reserve.

**Methods:** A total of 597 consecutive patients were enrolled who underwent TACE as their initial treatment for unresectable HCC without macrovascular invasion or extrahepatic spread from two university hospitals in Korea. The entire cohort was randomly divided into two groups with 7:3 ratio to derive and validate a risk prediction model. Tumor- and liver function-related risk factors for overall survival were explored using Cox proportional-hazards model.

Table 1. ASAR (ALBI-size-AFP-response) scoring system

	SCORE		
-	0	1	2
ALBI grade	1	2	3
Maximal tumor diameter (cm)	<3	3 - <5	$\geq 5$
AFP (ng/mL)	<200	≥200	
Tumor response	CR, PR	SD, PD	

Abbreviations: ALBI, albumin-bilirubin grade; AFP, alpha-fetoprotein; CR, complete

response; PR, partial response; SD, stable disease; PD, progressive disease.



**Results:** Median age was 64.0 years, and 474 patients were male (79.4%). Etiologies of underlying liver diseases were mostly viral (HBV, 386 [64.7%]; HCV, n=82 [13.7%]) or alcoholic (n=60, 10.1%). Multiple tumors were found in 379 patients

(63.6%), and median maximal tumor diameter was 3.2 cm (interguartile range [IQR], 2.2–5.2). Median alpha-fetoprotein (AFP) was 16.0 ng/mL (IOR, 6.0–153.0). Child-Pugh classes were A in 479 patients (80.2%) and B in 118 (19.8%), respectively. Hepatoma arterial-embolisation prognostic (HAP) score D and modified HAP score D were in 95 patients (15.9%) and in 43 (7.2%), respectively. Albumin-bilirubin (ALBI) grades were 1 in 204 patients (34.2%), 2 in 363 (60.8%) and 3 in 30 (5.0%), respectively. Multivariable Cox model with stepwise selection identified the following four relevant prognostic factors: ALBI grade (hazards ratio [HR], 2.299; 95% confidence interval[CI], 1.694-3.119; P<0.001); AFP (HR, 1.583; 95% CI, 1.164-2.154; P=0.003); maximal tumor diameter (HR, 1.704; 95% CI, 1.424-2.038; P<0.001); tumor response (HR, 1.915; 95% CI, 1.431-2.563; P<0.001). A scoring system (ASAR) based on these risk factors was developed by assigning points as shown in Table 1. C-index for the prediction of overall survival (OS) was 0.73 (95% CI, 0.70-0.77). The 1-year and 3-year survival rates were 92.1% and 69.7% in patients with ASAR<4, and 52.4% and 23.7% in those with ASAR  $\geq$  4, respectively (*P*<0.001). The 1-year and 3-year survival rates in subgroups according to the hepatic function and ASAR scores were as follows (all P<0.001): i) 93.6% and 73.3% in Child-Pugh class A and ASAR <4; ii) 54.4% and 29.0% in Child-Pugh A and ASAR≥4,; iii) 85.2% and 53.4% in Child-Pugh B and ASAR <4; iv) 46.3% and 6.6% in Child-Pugh B and ASAR  $\geq$ 4. However, no significant differences were observed in Child-Pugh class B patients using HAP score (P=0.523) or modified HAP score (P=0.298).

**Conclusions:** A novel scoring system (ASAR) may be helpful in patient selection undergoing TACE for unresectable HCC, especially those with impaired hepatic function.

**Keywords:** Liver cancer, Outcome, Embolotherapy, Prediction model

#### O-100

Surgical Resection versus Radiofrequency Ablation in Single Small Hepatocellular Carcinoma: Data from Korea Central Cancer Registry for Hepatocellular Carcinoma Database

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**Aims:** This study compared the survival benefits between surgical resection and radiofrequency ablation (RFA) in single small hepatocellular carcinoma (HCC).

**Methods:** Patients registered in the database of Korea central cancer registry for HCC between 2008 and 2014 who received surgical resection or RFA for a single HCC of maximum size

3cm were reviewed. The cumulative overall survival (OS) and retreatment-free survival (RFS) were compared according to the type of treatment.

**Results:** A total of 1426 patients were included, 662 (46.4%) in the resection group and 764 (53.6%) in the RFA group. The 5-year OS rates were 91.8% for resection, and 84.9% for RFA, respectively (P<0.001). The 5-year RFS rates were 77.8% for the resection and 70.5% for RFA, respectively (P=0.002). In patients with maximum tumor size <2cm, there was no significant difference in 5-year OS rates between the two groups (91.8% for resection, and 87.5% for RFA, respectively; P=0.094), while resection was superior to RFA in the 5-year RFS rates (81.0% for resection, and 72.3% for RFA, respectively; P=0.017). Resection was superior in both 5-year OS and RFS rates in those with maximum tumor size ≥2cm and <3cm (91.9% for resection, and 80.2% for RFA, respectively; P<0.001; 76.2% for resection, and 67.2% for RFA, respectively; P=0.007). In the entire cohort, type of treatment (HR 1.457, P=0.032), age (HR 1.031, P<0.001), serum albumin (HR 0.466, P<0.001), and serum creatinine level (HR 1.282, P<0.001) were independently associated with survival. Type of treatment (HR 1.544, P<0.001) and maximum size of tumor (HR 1.353, P=0.002) were independent predictors of RFS.

**Conclusions:** In patients with maximum tumor size <2cm, OS is comparable between resection and RFA groups, while RFS is better in resection group. Surgical resection is superior in both OS and RFS in patients with maximum tumor size  $\geq$ 2cm and <3cm.

**Keywords:** Surgical resection, Radiofrequency ablation, Cancer registry, Hepatocellular carcinoma

#### O-101

#### Down-Regulation of microRNA-100 and Up-Regulation of microRNA-582 Are Associated with Vascular Invasion and Poor Prognosis in Hepatocellular Carcinoma

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**Aims:** Although gross vascular invasion (VI) has prognostic value for patients with hepatocellular carcinoma (HCC) who have undergone hepatic resection, few studies have investigated the relationship between gross VI and the aberrant expression of microRNAs. This study identified microRNAs selectively expressed in HCC with gross VI and investigated their prognostic roles.

**Methods:** Clinical data and microRNA expression profiles for 372 HCC patients were extracted from The Cancer Genome Atlas database. MicroRNAs that were differentially expressed in the patients with gross VI and those without VI were identified and investigated as potential prognostic factors for HCC.

**Results:** MicroRNA-338 and microRNA-582 were upregulated more ( $\log_2 FC$  of 1.34 with FDR = 0.014 and  $\log_2 FC$  of 1.09 with FDR = 0.015, respectively), and microRNA-100 and mi-

croRNA-99a were downregulated to a greater extent in gross VI group ( $\log_2 FC$  of -1.45 with FDR < 0.001 and  $\log_2 FC$  of -1.12 with FDR = 0.009, respectively). Receiver operating characteristic curve analysis showed the discriminatory power of these microRNAs in predicting MVI(figure). Multivariate survival analysis revealed that the types of surgery (HR 1.676, 95% CI 1.205-2.332, P=0.002), advanced TNM stage (HR 1.795, 95% CI 1.266–2.547, P=0.001) and under-expression of microRNA-100 (HR 1.511, 95% CI 1.041-2.194, P=0.029) were independently associated with tumor recurrence, and that the types of surgery, advanced TNM stage, under-expression of microRNA-100 and over-expression of microRNA-582 were independent risk factors for overall survival after hepatic resection for HCC (HR 1.844, 95% CI 1.110-3.065, P=0.018; HR 2.401, 95% CI 1.433-4.024, P<0.001; HR 2.652, 95% CI 1.519-4.629, P<0.001; HR 2.016, 95% CI 1.109-3.663, P=0.021, respectively). PLK1 was considered a target gene of microRNA-100 with strong evidence.



**Conclusions:** Under-expression of microRNA-100 and over-expression of microRNA-582 were associated with gross VI and poor survival of patients after hepatic resection for HCC.

Keywords: Hepatectomy, MicroRNA, Recurrence, Vascular invasion

#### O-102

#### Risk Factors, Patterns, and Outcomes of Late Recurrence after Liver Resection for Patients with Hepatocellular Carcinoma (Analysis of a Multicenter Cohort over 15 Years)

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**Methods:** From a multicenter database from 2001 to 2015, 734 patients who were alive and recurrence-free at 2 years after curative resection of initial HCC were enrolled into this retrospective study. Univariate and multivariate Cox-regression analysis were used to identify independent risk factors of late recurrence. Patterns, treatments and outcomes of late recurrence were investigated and analyzed.

**Results:** During a median follow-up of 78.0 months after surgery, 303 patients (41.3%) developed late recurrence. Multivariate analysis revealed that cirrhosis, macroscopic vascular invasion, satellites, and tumor size > 5cm were independent risk factors of late recurrence. Among them, 273 (90.1%) were sole intrahepatic recurrence, 30 (9.9%) were concurrent intrahepatic and extrahepatic recurrence, and none of them was sole extrahepatic recurrence; 165 (54.4%) patients received curative treatments for recurrent HCC, including re-resection, transplantation and local ablation. Multivariate analysis showed regular postoperative surveillance and receiving curative treatments were two independent protective factors of prolonging survival for those patients with late recurrence.

**Conclusions:** Late recurrence is correlated with cirrhosis and certain tumor-related characteristics of initial HCC. The patterns of late recurrence suggest that postoperative surveillance after 2 years of surgery could be adjusted and more targeted. Regular postoperative surveillance improves the probability to receive curative treatments again, yielding to better outcomes for patients with late recurrence.

#### O-103

#### Predicting Hepatocellular Carcinoma Recurrence beyond Milan Criteria after Liver Resection for Solitary Hepatocellular Carcinoma

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**Aims:** Several hepatectomy patients with hepatocellular carcinoma (HCC) who are initially transplantable (within Milan criteria) developed untransplantable HCC recurrence (beyond Milan criteria) after primary curative liver resection. The aim of this study is to identify the risk factors of untransplantable HCC recurrence after primary curative resection of solitary HCC and solitary HCC within Milan criteria (MC). **Methods:** We retrospectively reviewed 592 patients with recurrent HCC who underwent liver resection due to solitary HCC between 2005 and 2011.

**Results:** All patients were Child-Pugh class A. At primary curative hepatectomy, 411 patients (69.4%) were diagnosed with HCC within MC and 181 patients (30.6%) had HCC beyond MC. The mean time from primary hepatectomy to recurrence was 14 months (range, 1-116 months). At HCC recurrence, 93 patients (15.7%) were diagnosed beyond MC. Multivariate analysis showed that microvascular invasion and tumor grade 3 or 4 were closely associated with high risk of HCC recurrence beyond MC in patients who had hepatectomy for solitary HCC. Of the 411 patients within MC at primary curative hepatectomy, 54 patients (13.9%) developed HCC recurrence beyond MC. Multivariate analysis also showed that microvascular invasion and grade 3 or 4 were closely associated with HCC recurrence beyond MC. Multivariate analysis also showed that microvascular invasion and grade 3 or 4 were closely associated with HCC recurrence beyond MC. Multivariate analysis also showed that microvascular invasion and grade 3 or 4 were closely associated with HCC recurrence beyond MC in these patients.

**Conclusions:** The present study suggests that the presence of unfavorable histologic factors in patients who underwent initial liver resection of transplantable HCC within MC with good liver function predicted the development of recurrent HCC beyond MC. Therefore, the presence of microvascular invasion and grade 3 or 4 led to us to consider liver transplantation before HCC recurrence if there is no recurrence for a certain period after liver resection.

**Keywords:** Milan criteria, Tumor recurrence, Liver transplantation, Hepatocellular carcinoma

#### O-104

Conventional versus Drug-Eluting Beads Transarterial Chemoembolization for Nodular Hepatocellular Carcinoma in a Superselective Fashion Using Cone-Beam CT: Retrospective Analysis of a Five-Year Outcome

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**Aims:** To retrospectively compare clinical outcomes of conventional transarterial chemoembolization (cTACE) and drug-eluting bead (DEB-TACE) in a superselective fashion using conebeam CT (CBCT) for nodular hepatocellular carcinoma (HCC).

**Methods:** From January 2011 to April 2013, 198 consecutive patients with nodular HCC ( $n \le 5$ ) and Child-Pugh class A liver function were initially treated with cTACE (n = 125) or DEB-TACE (n=57) and follow-up for 5 years or until death. Cumulative probabilities of local tumor progression (LTP), intrahepatic distant recurrence (IDR), vascular invasion, and metastasis were investigated. Overall survival (OS) and progression free survival (PFS) were compared using the Kaplan-Meier method with logrank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Adverse events after

TACE were also analyzed.

**Results:** OS was not statistically different between two groups (P=0.301). Median PFS (18 months vs 7 months, respectively; P<0.031) and time to LTP (34 months vs 11 months, respectively; P<0.001) were significantly longer in cTACE group than in the DEB-TACE group. There was no significant difference in IDR, vascular invasion, and metastasis between two groups. In multivariable analysis, DEB-TACE showed a hazard ratio of 1.601 in PFS (P=0.021) and 2.795 in LTP (P<0.001) compared with cTACE. Postembolization syndrome occurred more frequently in cTACE group than in DEB-TACE group (P=0.006).

**Conclusions:** cTACE was superior to DEB-TACE in improving PFS because of better local tumor control in a superselective fashion using CBCT for nodular HCC. DEB-TACE had advantages on postembolization syndrome.

**Keywords:** Hepatocellular carcinoma, Chemoembolization, Drug-eluting bead, Cone-beam CT

13. Liver Cancer

#### O-105

#### Heterogeneous Exhaustion Status of Tumor-Infiltrating CD8 T Cells Determines Distinct Subgroups of Hepatocellular Carcinoma Patients

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**Aims:** T-cell exhaustion, or an impaired capacity to secrete cytokines and proliferate with overexpression of immune checkpoint receptors, occurs during chronic viral infections but has also been observed in tumors, including hepatocellular carcinomas (HCCs). We investigated features of exhaustion in CD8<sup>+</sup> T cells isolated from HCC specimens.

**Methods:** We obtained HCC specimens, along with adjacent non-tumor tissues and blood samples, from 79 patients who underwent surgical resection at Asan Medical Center (in Seoul, Korea) from April 2016 through December 2017. Intrahepatic lymphocytes and tumor-infiltrating T cells were analyzed by flow cytometry. Tumor-infiltrating CD8<sup>+</sup> T cells were sorted by

flow cytometry into populations based on expression level of programmed cell death 1 (PDCD1 or PD1): PD1-high, PD1-intermediate, and PD1-negative. Sorted cells were analyzed by RNAseq. Proliferation and production of interferon gamma (IFNG) and tumor necrosis factor (TNF) by CD8<sup>+</sup> T cells were measured in response to anti-CD3 and antibodies against immune checkpoint receptors including PD1, hepatitis A virus cellular receptor 2 (HAVCR2 or TIM3), lymphocyte activating 3 (LAG3), or isotype control. Tumor-associated antigen-specific CD8<sup>+</sup> T cells were identified using HLA-A\*0201 dextramers.

**Results:** PD1-high, PD1-intermediate, and PD1-negative CD8<sup>+</sup> T cells from HCCs had distinct gene expression profiles. PD1-high cells expressed higher levels of genes that regulate T-cell exhaustion than PD1-intermediate cells. PD1-high cells expressed TIM3 and LAG3, and a low proportion was TCF1<sup>+</sup>, TBET<sup>high</sup>/ eomesodermin<sup>low</sup>, and CD127<sup>+</sup>. PD1-high cells produced the lowest amounts of IFNG and TNF upon anti-CD3 stimulation. Differences in proportions of PD1-high CD8<sup>+</sup> T cells led to the identification of 2 subgroups of HCCs; HCCs with a larger proportion of PD1-high cells were more aggressive than HCCs with a smaller proportion. Incubation of CD8<sup>+</sup> T cells from HCCs with high proportions of PD1-high cells with antibodies against PD1 and TIM3 or LAG3 further restored proliferation and production of IFNG and TNF in response to anti-CD3.

**Conclusions:** We found HCC specimens to contain CD8<sup>+</sup> T cells that express different levels of PD1. HCCs with high proportions of PD1-high CD8<sup>+</sup> T cells express TIM3 and/or LAG3 and produce low levels of IFNG and TNF in response to anti-CD3. Incubation of these cells with antibodies against PD1 and TIM3 or LAG3 further restore proliferation and production of cytokines; HCCs with high proportions of PD1-high CD8<sup>+</sup> T cells might be more susceptible to combined immune checkpoint blockade-based therapies.

**Keywords:** Hepatocellular carcinoma, PD-1, T-cell exhaustion, Immune checkpoint blockade

#### O-106

Tumor-Stroma Crosstalk Enhances REG3A Expressions that Drives the Progression of Hepatocellular Carcinoma

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**Aims:** Crosstalk between tumor cells and their microenvironment plays a crucial role in the progression of hepatocellular carcinoma (HCC). In this study, we investigated the key signal that modulates crosstalk between HCC cells and their microenvironment.

**Methods:** Human HCC cell lines (Huh-7, HepG2, and SNU-761) were cocultured with an activated human hepatic stellate cell line (HSCs; LX-2) under normoxic (20% O2 and 5% CO2,

at 37 °C) conditions. Complementary DNA (cDNA) microarray analysis was performed to find the molecule which is significantly enhanced by crosstalk between HCC cells and stroma. *In vivo* study using a subcutaneous xenograft model by injecting MH134 cells (C3H mice) was performed to confirm the effect of coculturing HCC cells and HSC cells and the inhibitory effect by small interfering RNA (siRNA) transfection. Immunoblot analyses were used to investigate the signaling pathway.

Results: Using cDNA microarray analysis, we found the molecule, REG3A, which was significantly enhanced by coculturing Huh-7 cells and HSC cells (+ 8.2 log) as compared to mono-culturing Huh-7 cells. Coculturing HCC cells (Huh-7, HepG2, and SNU-761) with HSC cells enhanced the mRNA and protein expressions of REG3A as compared to mono-culturing HCC cells. Downregulation of REG3A by siRNA significantly decreased the proliferation of tumor cells in vitro and in vivo, when HCC cells were cocultured with HSCs (both P<0.05). In immunoblot assay, downregulation of REG3A by siRNA decreased the expressions of phosphorylated p42/44 and  $\beta$ -catenin, especially when HCC cells were cocultured with HSCs. Immunofluorescence study also revealed that deoxycholic acid-induced HCC cell apoptosis was inhibited when REG3A was down-regulated in HSCs-cocultured HCC cells. Interestingly, crosstalk-induced REG3A up-regulation was modulated by PDGF-β in p42/44-dependent manner.



**Conclusions:** In conclusion, crosstalk between HCC cells and HSCs cells was modulated by up-regulation of REG3A in p42/44-dependent manner. Moreover, the up-regulation of

REG3A by crosstalk between HCCs and HSCs was mediated by PDGF- $\beta$ . Targeting REG3A might be a novel therapeutic target in the management of human HCCs by inhibiting crosstalk between HCCs and HSCs.

**Keywords:** Hepatocellular carcinoma, REG3A, Crosstalk, RE-G3A

#### O-107

#### A Novel Thermal Accelerant for Augmentation of Microwave Energy during Image-Guided Thermal Ablation of Tumors

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**Aims:** To investigate the properties of a novel thermal accelerant (TA) *in vitro*, and the effects on ablation zone volumes following *in vivo* microwave ablation of porcine liver and skeletal muscle, and to investigate the TA administration on the heat sink effect.

**Methods:** *In vivo* study was performed in the liver using Sus scrofa domesticus swine, with and without TA administration. Treated tissues were explanted and stained with a vital stain (triphenyltetrazolium chloride, TTC) for quantification of ablation zone volumes, which were compared between TA and non-TA conditions. Hematoxylin and Eosin (H&E) staining was also performed for histologic analysis. A generalized, mixed-modeling with a negative binomial distribution was used for all quantitative comparisons. An overall a priori significance level of *P*=0.05 was used.

**Results:** The use of TA significantly increased microwave ablation zone volumes in a dose-dependent manner in both porcine muscle and liver (*P*<0.01), compared with the control. Both the absolute mean ablation zone volume and percentage increase in ablation zone volume were greater in resting skeletal muscle than in liver, likely secondary to differences in organ vascularity. Qualitative mitigations of heat sink effects were observed by TTC and H&E staining.

**Conclusions:** In comparison to the control, the use of TA significantly increased mean ablation zone volumes during the same ablation period. The ablation volume increase was TA dose-dependent, and inversely proportional to the degree of target organ perfusion. The results suggest that the use of TA enables the control of ablation size, direction as well as mitigation of the heat sink effect.

#### O-108

# Protein Disulfide Isomerase Inhibition Synergistically Enhances the Efficacy of Sorafenib for Hepatocellular Carcinoma

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**Aims:** Sorafenib is the only approved targeted drug for hepatocellular carcinoma (HCC), but its effect on patients' survival gain is limited and varies over a wide range depending on patho-genetic conditions. Thus, enhancing the efficacy of sorafenib and finding a reliable predictive biomarker are crucial to achieve efficient control of HCCs.

**Methods:** In this study, we employed a systems approach by combining transcriptome analysis of the mRNA changes in HCC cell lines in response to sorafenib with network analysis to investigate the action and resistance mechanism of sorafenib.

**Results:** Gene list functional enrichment analysis and gene set enrichment analysis (GSEA) revealed that proteotoxic stress and apoptosis modules are activated in the presence of sorafenib. Further analysis of the endoplasmic reticulum (ER) stress network model combined with *in vitro* experiments showed that introducing an additional stress by treating the orally active protein disulfide isomerase (PDI) inhibitor (PACMA 31) can synergistically increase the efficacy of sorafenib *in vitro* and *in vivo*, which was confirmed using a mouse xenograft model. We also found that HCC patients with high PDI expression show resistance to sorafenib and poor clinical outcomes, compared to the low PDI expression group.

**Conclusions:** These results suggest that PDI is a promising therapeutic target for enhancing the efficacy of sorafenib and can also be a biomarker for predicting sorafenib responsiveness. **Keywords:** PDI, Sorafenib, HCC, ER stress

#### O-109

#### Anti-Tumor Effect of Ginsenoside Rh2 and Rg5 in Xenograft Hepatoma Animal Model: Comparison with Sorafenib

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**Aims:** Animal & cell models of hepatoma give a crucial information, not only pathogenesis of liver cancer but also therapeutic effects of various agents. In this study, we investigate therapeutic effects of ginsenoside Rh2 and Rg5 using animal & cell models of hepatoma comparing with sorafenib.

**Methods:** Huh7 & huh7.5.1 cells were harvested from 2-D petri-dish and cultured in 1.5 % soft agarose gels for 10-14 days. After 10-14 days, 3-D hepatic structure was formed and treated with ginsenoside Rh2 (100, 200uM) and Rg5 (10, 50, 100uM) for 72h. Hep3b cells ( $2 \times 10^{5}$ ) in matrigel were suspended in 100 µl of phosphate-buffered saline (PBS) and then injected into the flanks of BALB/C nude mouse at 6 weeks. Sorafenib (10mg/kg), ginsenoside Rh2 (100 uM) and Rg5 (100 uM) was injected to intra-peritoneum twice a week. After 4 weeks, all mice were sacrificed and tumor tissue was collected. The tissue was stained with hematoxylin and eosin and histological evaluation was conducted by blindly pathologist. Area of necrosis and vascular change in tumor tissue was calculated using the lasso tool to encircle the area in ZEN 2011 Imaging Software.

**Results:** Both ginsenoside Rh2 and Rg5 induced cell necrosis in hepatocellular carcinoma (HCC) cell lines, and more necrosis occurred in 2D models. The expression of cleaved PARP protein was increased in both 2D and 3D cells with exposure to ginsenoside Rh2 and Rg5. The hepatocellular carcinoma was confirmed in hepatoma mouse models by H&E stain. Increased necrosis and telangiectasia were observed in mice treated with sorafenib, Rh2, and Rg5 compared to control mouse.

**Conclusions:** Our findings provide insight into the use of xenograft mouse as models of HCC and ginsenoside Rh2 & Rg5 might be a potential treatment candidate of liver cancer.

**Keywords:** Xenograft hepatoma animal model, Ginsenoside Rh2, Ginsenoside Rg5, Sorafenib

#### O-110

#### EpCAM-High Liver Cancer Stem Cells Resist Natural Killer Cell-Mediated Cytotoxicity by Upregulation of Cell Surface CEACAM1

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**Aims:** There are conflicting results on the cytotoxicity of natural killer (NK) cells against cancer stem cells (CSCs). In this study, we investigated whether NK cells exhibit enhanced or decreased cytotoxicity against Epithelial Cell Adhesion Molecule (EpCAM)-expressing liver CSCs and the underlying mechanism of the phenomenon.

**Methods:** EpCAM<sup>high</sup> and EpCAM<sup>low</sup> Huh-7 cells were sorted by flow cytometry. Human NK cells were isolated by magnetic sorting from peripheral blood mononuclear cells of healthy donors. NK cell and hepatoma cells were co-cultured and cytotoxicity assay were performed. Immunohistochemistry and western blot was performed using human HCC tissues obtained from surgical specimens. *In vivo* experiments were performed using Hepa1-6 mouse hepatoma cells and C57/BL6 mice.

Results: Patients with positive EpCAM expression in their tumors showed higher serum  $\alpha$ -fetoprotein levels and histological Ki-67 expression. The frequency of early and massive recurrence was higher in patients with positive EpCAM expression in their tumors. Co-culture experiment demonstrated that EpCAM<sup>high</sup> Huh-7 cells resisted NK cell-mediated cytotoxicity. We have identified that carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) was upregulated on the surface of EpCAM<sup>high</sup> Huh-7 cells. Silencing of CEACAM1 restored cytotoxicity of NK cells against EpCAM<sup>high</sup> Huh-7 cells. Moreover, neutralizing CEACAM1 on NK cell surface also enhanced killing of Huh-7 cells, suggesting that homophilic interaction of CEA-CAM1 is responsible of attenuated NK cell-mediated killing of CEACAM1<sup>high</sup> cells. In vivo mice experiments with Hepa1-6 cells demonstrated that EpCAM<sup>high</sup> Hepa1-6 cells form larger tumors and show higher CEACAM1 expression after NK cell depletion. Finally, we found that CEACAM1 expression positively correlated with EpCAM expression in human liver tissues at both mRNA and protein levels.



**Conclusions:** Overall, our data clearly demonstrate that Ep-CAM<sup>high</sup> liver CSCs resist NK cell-mediated cytotoxicity by upregulation of cell surface CEACAM1 expression. **Keywords:** Cancer stem cell, Natural killer cell, EpCAM,

#### O-111

## Cereblon as a Novel Prognostic Biomarker for Small Hepatocellular Carcinoma

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**Aims:** Cereblon is a substrate receptor of the E3 ubiquitin ligase complex and functions as a metabolic regulator, directly interacting with AMP-activated protein kinase (AMPK)  $\alpha$ 1 and inhibiting AMPK activation. We raise a hypothesis that cereblon is a biomarker for hepatocellular carcinoma (HCC).

**Methods:** We developed CRBN-specific monoclonal primary antibody to detect cereblon at the tissue samples (Korea patent). After immunocytochemical staining and Western blot assay, cereblon was quantitatively measured. We performed two development cohort studies to find out the role of cereblon as a diagnostic and prognostic biomarker for HCC. The cutoff of cereblon expression was set to be 2 folds comparing with that at the surrounding liver tissue.

**Results:** One development cohort included 40 patients who underwent macroscopic curative resection for HCC of 7<sup>th</sup> AJCC stage I or II. The profiles of patients in stage I and II groups were similar each other. There was no significant difference in tumor recurrence (P=0.14) and patient survival (P=0.33) between the stage I and II groups. Higher cereblon expression was observed in 19 (47.5%). High cereblon expression group showed higher recurrence (P=0.017) and lower survival (P=0.025) rates than low cereblon expression group. The hazard ratio of cereblon was estimated to 3.5 (P=0.035). Another development cohort study for response treatment to sorafenib was performed, in which cereblon does not appear to be a reliable response biomarker so far.

**Conclusions:** The post-resection prognostic impact of cereblon was greater than that of microvascular invasion in solitary HCCs. We think that cereblon can be an independent biomarker to predict post-resection prognosis even in patients with early or small HCCs. Further high-volume validation study is necessary to investigate the role of cereblon in HCC.

**Keywords:** Hepatocellular carcinoma, Cereblon, Recurrence, Biomarker



#### O-112

#### Characterization of Cirrhotic Cardiomyopathy Using Cardiac Magnetic Resonance Imaging: A Prospective Study

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Aims: Liver cirrhosis is known to decrease the cardiac performance. However, it is unclear whether this change is related to the change in myocardial muscle itself, or is a secondary functional phenomenon. In this study, we aimed to characterize myocardial tissue using cardiovascular magnetic resonance (CMR) imaging in cirrhotic patients.

**Methods:** Thirty-five patients with cirrhosis who were listed for liver transplantation and 20 normal healthy controls were prospectively enrolled. All included subjects underwent conventional echocardiography, speckle-tracking echocardiography, and CMR imaging with T1 mapping and late gadolinium enhancement. Native T1 and extracellular volume (ECV) were measured for assessing myocardial fibrosis. Echocardiography and CMR imaging were performed at just before and 1 year after liver transplantation.

Results: Both echocardiography and CMR imaging demonstrated hyperdynamic left ventricular (LV) function in cirrhotic patients. There were no significant differences in LV size, LV wall thickness, LV mass index, E/A ratio, and deceleration time between cirrhotic patients and non-cirrhotic healthy controls (all P>0.1). However, cirrhotic patients showed significantly higher values of native T1 (1230.1±79.0 vs 1173.3±34.7, P=0.001) (Table 1 and Figure 1A) and ECV (31.4±4.9 vs 25.4±1.9, P<0.001) (Table 1 and Figure 1B) compared to non-cirrhotic controls. Specifically, ECV had a significant correlation with Child-Pugh class (26.2±3.4 in Child class A or B vs 33.2±4.3 in Child class C; P=0.001). At 1 year after liver transplantation, native T1 (from 1224.0±55.7 to 1155.8±77.0, P=0.010) and ECV (from 30.9±3.6 to 25.2±2.6, P<0.001) values significantly decreased, but there was no difference in other parameters regarding LV function and LV size.

 Table 1. Cardiac magnetic resonance imaging parameters in patients with cirrhosis

	Normal	All (LC)	Child A,	Child C		
	control		Child B		P value†	P value*
	N=20	N=32	N=10	N=22	-	
LVEF	63.4±6.4	67.8±7.0	66.1±6.5	68.6±7.2	0.028	0.362
LVEDV	134.5±19.9	148.1±46.2	153.4±41.7	145.7±49.0	0.155	0.673
LVESV	51.1±15.5	48.6±21.1	52.3±18.2	46.9±22.5	0.653	0.511
Stroke volume	85.2±15.1	99.5±29.3	101.0±28.3	98.8±30.3	0.049	0.845
Cardiac index	3.3±0.7	4.3±1.1	3.8±1.0	4.5±1.1	0.002	0.073
LGE	0 (0%)	1 (3.1%)	0 (0%)	1 (4.5%)	0.555	0.254
Native T1	1173.3±34.7	1230.1±79.0	1216.1±59.5	1236.4±87.0	0.001	0.510
ECV	25.4±1.9	31.3±4.9	27.2±3.4	33.2±4.3	< 0.001	0.001

<sup>T</sup>*P* value between normal and liver cirrhosis groups

\* P value between Child A and B, and Child C groups

LC, liver cirrhosis; LV, left ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LGE, late gadolinium enhancement; ECV, extracellular volume.





**Conclusions:** Decreased cardiac performance in cirrhotic patients may result from myocardial change reflected by the increase in native T1 and ECV values, which was normalized after liver transplantation. Native T1 and ECV values of CMR imaging could be more straightforward diagnostic indices for cirrhotic cardiomyopathy.

**Keywords:** Liver cirrhosis, Cardiac MR, Cirrhotic cardiomyopathy, Liver transplantation

#### O-113

#### Effects of Branched-Chain Amino Acids (BCAAs) on the Progression of Advanced Liver Disease a Korean Nationwide, Multicenter, Prospective, Observational, Cohort Study

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Aims: To evaluate potential benefits of long-term oral branched amino acids (BCAAs) supplements in advanced liver disease Methods: Liver cirrhosis patients with Child-Pugh (CP) score from 8 to 10 were prospectively recruited from 13 medical centers. The patients supplemented with 12.45g of daily BCAAs over 6 months or regular diet were assigned to either BCAA group or control group, respectively. We evaluated the effect of BCAAs therapy on the model for end-stage liver disease (MELD) score, CP score, serum albumin, serum bilirubin, incidence of cirrhosis-related events, and event-free survival over 96 months. Results: A total of 124 patients was enrolled (n=63 in the BCAA group and n=61 in the control group). Baseline characteristics of the patients including age, sex, CP score, and MELD score were not significant different between two groups. The MELD score (P=0.009) and CP score (P=0.011) were significantly improved in the BCAA group compared to the control group over time. However, serum albumin and bilirubin levels in the BCAA group failed to improve over study period. Cumulative event-free survival in the BCAA group was significantly better than that in the control group (HR=0.389, 95% CI 0.221-0.684, P=0.001).



**Conclusions:** Long-term supplements of BCAAs could potentially improve liver function and delay the liver related complications in patients with advanced liver disease.

Keywords: Branched chain amino acids, Liver cirrhosis

#### O-114

#### Association between Sarcopenia and Minimal Hepatic Encephalopathy and Quality of Life in Patients with Liver Cirrhosis

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**Aims:** We aimed to investigate the association between sarcopenia and minimal hepatic encephalopathy and quality of life in cirrhotic patients.

**Methods:** Liver cirrhosis patients associated with chronic hepatitis B were prospectively recruited in 15 hospitals between April 2016 and December 2017. Among these 223 patients, 128 patients who assessed handgrip strength and skeletal muscle mass were analyzed. Minimal hepatic encephalopathy was diagnosed when psychometric hepatic encephalopathy score (PHES) was less than -4. Quality of life was assessed by 36-Item Short Form Health Survey (SF-36). Sarcopenia was defined as lower quintile using handgrip strength and skeletal muscle index (SMI). SMI was calculated by total muscle mass/height<sup>2</sup>.

Results: Mean age was 53.5 years, and 63.3% was male. MHE was 27.3%. Cut-off values of sarcopenia were as follows; 10.2 kg/m<sup>2</sup> in men and 8.15kg/m<sup>2</sup> in women for sarcopenia by SMI, and 27 kg in men and 18 kg in women for sarcopenia by handgrip strength. There were no significant differences in the prevalence of MHE and PHES score value between sarcopenic and non-sarcopenic group (P=0.077 and P=0.152 by SMI, P=0.935 and P=0.888 by handgrip strength). An SF-36 score of the sarcopenic group was significantly lower than that of the non-sarcopenic group (60.2±17.9 vs. 68.1±17.1, P=0.038) by SMI, but not by handgrip strength (62.6±16.8 vs. 67.3±17.7, P=0.260). Among 8 domains constituting SF-36 score, general health score was significantly lower in the sarcopenic group by SMI (P=0.032). Pain score and energy/fatigue scores were significantly lower in the sarcopenic group by handgrip strength (P=0.035 and P=0.020).

**Conclusions:** Sarcopenia by SMI and handgrip strength was not associated with MHE. However, sarcopenia by SMI and hand-grip strength were significantly associated with quality of life.

Keywords: Sarcopenia, Minimal hepatic encephalopathy, Quality of life

#### O-115

Presence of Sarcopenia and Its Rate of Change are Independently Associated with Long-Term Mortality in Patients with Liver Cirrhosis

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**Aims:** Sarcopenia is associated with a poor prognosis in patients with liver cirrhosis. However, it is not known whether the rate of skeletal muscle depletion is also associated with a poor prognosis. We investigated the prognostic impact of the rate of skeletal muscle depletion in patients with liver cirrhosis.

Methods: We enrolled retrospectively all non-critically-ill pa-

tients with liver cirrhosis who underwent both multiple computed tomography scans and hepatic venous pressure gradient (HVPG) measurements.

**Results:** A total of 131 patients with liver cirrhosis were enrolled. The mean age of the patients was 53.7 years and alcoholic liver disease was the most common cause (61.8%). Sixty-four patients (48.9%) were diagnosed with sarcopenia. The median changes in skeletal muscle area per year ( $\Delta$ SMA/y) were -0.89%. During a median follow-up period of 46.2 months (range, 3.4-87.6), 45 patients (34.4%) died. In multivariate analyses, age (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01-1.08; *P*=0.019), Child-Pugh score (HR 1.23, 95% CI 1.05-1.44; *P*=0.012), HVPG (HR 1.08, 95% CI 1.02-1.15; *P*=0.007), presence of sarcopenia (HR 2.27, 95% CI 1.17-4.40; *P*=0.015) and  $\Delta$ SMA/y (HR 0.95, 95% CI 0.91-0.99; *P*=0.010) were independently associated with mortality. Cumulative mortality was significantly higher in patients with  $\Delta$ SMA/y < -1.0% than those with  $\Delta$ SMA/y ≥ -1.0% (log-rank test, *P*=0.033).

**Conclusions:** Both the presence and rate of change of sarcopenia are independently associated with long-term mortality in patients with liver cirrhosis.

Keywords: Liver cirrhosis, Sarcopenia, Nutrition, Prognosis

#### O-116

#### Efficacy of 4-Weeks Taurine Replacement to Improve Muscle Cramp in Patients with Liver Cirrhosis – A Single Arm, Pilot Study

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**Aims:** Painful muscle cramp is commonly developed in liver cirrhosis (LC) patients, resulting in impaired quality of life without effective treatment. This study aimed to evaluate the effect of taurine replacement on muscle cramp in Korean LC patients.

**Methods:** In this single arm pilot study, 10 LC patients who experienced muscle cramps  $\geq$  one time/week were enrolled. Subjects had given oral taurine solution (1,000 mg/50 mL) x3/ day for 4 weeks, discontinued taurine and followed for the subsequent 4 weeks. Pain scale and frequency of muscle cramp were surveyed using a structured questionnaire at week 0, 2, 4, 6, and 8. Kruskal-Wallis and Wilcoxon signed-rank tests were used for statistical analyses.

**Results:** Mean age of enrolled patients was 62 (range 43-80) y.o. and 6 (60%) were males. Etiologies of LC were HBV (n=4), HCV (n=4) and alcohol (n=2), and Child-Pugh class A (n=2) and B (n=8) with 6 patients taking diuretics. Median frequency of muscle cramp was 6 times/week (range 2-21), and 9 (90%) had severe pain ( $\geq$  4 out of 5 scale) at baseline. Muscle cramp score (frequency \* intensity) was significantly decreased during taurine administration period (P=0.04). Seven (70%) subjects showed reduced frequency and intensity of muscle cramp (P=0.047). After stopping taurine therapy, 5 (71.4%) showed a durable response until 4 weeks. After 4-weeks therapy, plasma taurine level increased in 6 (60%) patients, in whom 4 patients improved symptoms at week 4 and 2 (33.3%) recurred after stopping therapy. None had adverse events during the 4-weeks of taurine therapy.

**Conclusions:** Taurine replacement for 4 weeks showed an improvement of symptom in 7 of 10 LC patients with muscle cramp with excellent safety. Further analysis regarding serum levels of taurine, zinc, and magnesium will be discussed in the Liver Week 2018.

Keywords: Liver cirrhosis, Muscle cramp, Taurine

#### O-117

#### High-Volume Plasma Exchange in Patients with Acute Liver Failure: Initial Experience in Single Liver-Transplantation Center

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**Aims:** Acute liver failure is a serious condition which results in multiple organ failure. Recent study suggested that high-volume plasma exchange (HVP) defined as exchange of 8-12 or 15% of ideal body weight with fresh frozen plasma, improves survival in acute liver failure (ALF) patients. Herein, we report initial experience using HVP as a bridge treatment in patients with ALF at our center.

**Methods:** We retrospectively reviewed consecutive 36 patients who were enlisted for a liver transplantation (LT) due to ALF between 2014 and 2017 at Samsung medical center in Korea. HVP was initiated in patients with ALF in May 2015 at our institution. The primary endpoint was comparison of overall survival before and after the implementation of HVP with intention-to-treat analysis.

**Results:** There were 18 cases of ALF before HVP was adopted and 18 cases of ALF afterwards. Mortality was observed in 12 patients (33.3%). Among 18 patients who presented with ALF after implementation of HVP program, 9 patients received HVP (50.0%). The 60-day mortality rate was 88.9% and 59.3% for patients who received HVP and for patients who did not (P=0.111). In intention-to-treat analysis, overall outcome was improved after implementation of HVP (77.8% vs. 55.6% at 60-days), although the difference was statistically marginal (P=0.207). When stratified according to HVP and LT, 60-day survival rate was 100%, 80.0%, 66.7% and 33.3% for those with LT+/HVP+ (n=6), LT+/HVP- (n=15), LT-/HVP+ (n=3), and LT-/HVP-(n=12), respectively (P=0.013).

**Conclusions:** In this real-world, intention-to-treat analysis, outcome was improved after HVP implementation for ALF patients. HVP can be a viable option to improve outcome for patients presenting with ALF.

**Keywords:** Acute liver failure, High-volume plasma exchange, Liver transplantation

#### 15. HCV

#### O-118

#### An Integrated Analysis of the Efficacy of Glecaparevir/ Pibrentasvir by Geographical Region

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**Aims:** The pangenotypic direct-acting antiviral (DAA) regimen glecaprevir (developed by AbbVie and Enanta) coformulated with pibrentasvir (G/P) is approved in the US, EU, and Japan to treat chronic HCV genotype (GT) 1-6 infection. In the US and EU, G/P is indicated for treatment-naïve, HCV genotype (GT) 1–6-infected patients without and with compensated cirrhosis for 8-week and 12-week treatment durations, respectively, and achieved SVR12 rates  $\geq$ 95% across all six major GTs. In clinical studies, G/P exposures were similar across ethnicities; an integrated analysis of the efficacy of G/P by geographical region was conducted to assess the impact of geography and ethnicity on SVR12.

**Methods:** Data were pooled from 9 phase 2 and 3 clinical studies; data from 2 additional phase 3 clinical studies conducted in Japan were pooled separately. Patients had HCV GT1–6 infection with or without compensated cirrhosis and were either HCV treatment-naïve or experienced with interferon (IFN) or pegIFN with or without ribavirin (RBV), sofosbuvir and RBV with or without pegIFN, or NS5A- and/or protease inhibitor-containing regimens. G/P (300 mg/120 mg) was orally dosed once-daily for 8, 12, or 16 weeks. The primary efficacy endpoint in all studies was SVR12. Safety and tolerability were assessed in all patients. Data from all 11 studies will be pooled for presentation.

#### Table 1: Baseline Demographics

Characteristic	G/P./ N=2369./	G/P Japan⊷ N=332⇔
Male, n (%)₽	1318 (56)-	138 (42)
Race, n (%)↔	ø	P
White	1898 (80)+	0+2
Asian	272 (11)+	332 (100)-
Black	149 (6).	00
Hispanic or Latino ethnicity, n/N (%)-	211 (9)-	0.0
Age, median years (range)₀	54 (19-88)₽	65 (21-86) <sub>e</sub>
HCV genotype, n (%) 🦂	ø	ø
<b>1</b> 0	998 (42)	202 (61)
1b.	505 (21)-	198 (60)-
2+	466 (20)₽	118 (36)-
3 <i>₀</i>	643 (27)	12 (4)
4/5/60	182 (8)/32 (1)/48 (2)	00
Baseline HCV RNA, median log10 IU/mL (range)₽	6.2 (0.7-7.8)	6.2 (2.7-7.4)
HCV treatment-naïve, n (%).	1640 (70)-	222 (67)
With compensated cirrhosis, n (%)-	308 (13)-	64 (19)
Any NS3 or NS5A baseline polymorphism, n/N (%).	487/2369 (21)÷	36/219* (16)-
*Data not collected for 113 patients@		

**Results:** In total, 2369 patients were included in the integrated analysis: 964 (41%) were enrolled in North America, 891 (38%) in Europe, and 514 (22%) enrolled and pooled from Taiwan, Korea, Australia, New Zealand, Chile, Israel, and South Africa; 332 additional patients were enrolled in Japan. The SVR12 results by region were 97% (935/964; 95% CI 95.9–98.1), 98% (876/891; 95% CI 97.5–99.1), and 96% (496/514; 95% CI 94.9–98.1) for patients enrolled in North America, Europe, and the other pooled countries, respectively. Patients enrolled in Japan achieved a 98% (325/332; 95% CI 95.7-99.0) SVR12 rate. Less than 1% of all patients had virologic failure. G/P was well-tolerated with a favorable safety profile; treatment discontinuations due to adverse events and cases of drug-induced liver injury were rare (<1%).

**Conclusions:** G/P efficacy, safety and tolerability were consistently favorable regardless of baseline characteristics, suggesting that recently updated HCV treatment guidelines for the use of G/P in clinical practice can be applied to all ethnicities and geographical regions, without need for modification.

**Keywords:** Hepatitis C, Treatment efficacy, Ethnic groups, Antiviral agent

#### O-119

## Survival Benefits of Direct-Acting Antiviral Therapy in Patients with Decompensated Hepatitis C Cirrhosis

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**Aims:** Current direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection leads to sustained virological response

(SVR) in the vast majority of patients, even in those with decompensated cirrhosis. SVR in patients with decompensated cirrhosis has been associated with improvement in liver function; however, the extent to which DAA impacts on mortality remains to be determined. We analyze mortality in patients who participated in clinical trials evaluating sofosbuvir-based regimens in patients with decompensated HCV cirrhosis (GS-US-334-0125, SOLAR and ASTRAL studies), in comparison with mortality predicted by a survival model derived in untreated HCV patients.

**Methods:** Current direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection leads to sustained virological response (SVR) in the vast majority of patients, even in those with decompensated cirrhosis. SVR in patients with decompensated cirrhosis has been associated with improvement in liver function; however, the extent to which DAA impacts on mortality remains to be determined. We analyze mortality in patients who participated in clinical trials evaluating sofosbuvir-based regimens in patients with decompensated HCV cirrhosis (GS-US-334-0125, SOLAR and ASTRAL studies), in comparison with mortality predicted by a survival model derived in untreated HCV patients.

Results: There was a total of 492 patients, whose median age was 58 years, MELD 12, sodium 137mEq/l and albumin 2.9 g/ dl. Ascites and HE were common (79% and 63%, respectively). Altogether, 411/479 (86%) patients achieved SVR12. During the follow up, there were 25 deaths within one year of DAA therapy start, including 15 in the SOLAR and 10 in the ASTRAL data; no deaths occurred in GS-US-334-0125. The number of observed deaths in the clinical trials closely followed the expected/predicted numbers early in the treatment course (Figure). Starting at 100 days after initiation of DAA, however, the observed number of deaths was statistically significantly smaller than expected (SMR=0.54, 95% confidence interval [CI]=0.30-0.98). All subsequent deaths occurred at a lower frequency than expected. The last (25th) death during the study period occurred on day 339, when the SMR had decreased to 0.44 (95% CI=0.30-0.65), which remained unchanged at the end of the analysis (day 365).

**Conclusions:** DAA therapy in patients with decompensated HCV cirrhosis leads to significantly decreased mortality, which may be apparent as early as 100 days after the initiation of therapy with the risk of mortality decreasing to 44% of the expected by the end of the first year.

Keywords: Hepatitis c, Cirrhosis, Direct-acting antiviral therapy

#### O-120

#### Differential Effect of HCV Eradication and Fibrosis Grade on Hepatocellular Carcinoma and All-Cause Mortality

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**Aims:** Whether a sustained virologic response (SVR) improves long-term outcomes in chronic hepatitis C (CHC) patients with earlier-stage fibrosis has not been established. We investigated the differential effect of SVR on the risk of outcomes according to hepatic fibrosis grade.

**Methods:** Fibrosis grade was categorized using FIB-4: <1.45, low-probability of significant fibrosis; 1.45–3.25, intermediate-probability; and  $\geq$ 3.25, high-probability. Primary and secondary endpoints were hepatocellular carcinoma (HCC) occurrence and death, respectively.



Results: Among 1,373 included CHC patients, 744 patients were treated with interferon-based or -free regimens and 622 (83.6%) achieved SVR. The 5-year cumulative incidences of HCC were 12.3%, 12.7%, and 3.4% in the untreated group, the non-SVR group, and the SVR group, respectively (P<.001 by log-rank test) (Figure A). SVR was independently associated with lower risk of HCC (vs. untreated: adjusted hazard ratio [aHR], 0.150; 95% confidence interval [CI], 0.067-0.332; P<.001) and overall death (vs. untreated; aHR, 0.162; 95% CI, 0.056-0.472; P<.001) during the median observation of 3.5 (interguartile range, 1.4–6.6) years. The SVR group had significantly lower risk of HCC than the untreated group among patients with intermediate-probability (n=492: aHR, 0.061; 95% CI, 0.008–0.479; P=.008) and high-probability (n=446: aHR, 0.217; 95% CI, 0.087-0.540; P=.001) of significant fibrosis, but not among patients with low-probability (n=258: adjusted HR, 0.884; 95% CI, 0.044–17.637; P=.94) (Figure B–D). Among 622 patients achieving SVR, 314 patients received IFNbased therapy and 308 received DAA therapy. Type of antiviral agent that induced SVR was not associated with HCC risk (vs. IFN-based therapy; adjusted HR, 2.383; 95% CI, 0.183–30.998; P=.51) and all-cause mortality (vs. IFN-based therapy; adjusted HR, 2.885; 95% CI, 0.372–22.346; P=.31). HRs were maintained after balancing with inverse probability weighting. **Conclusions:** SVR was associated with reduced risk of HCC development and all-cause mortality in patients with CHC. **Keywords:** Direct acting antivirals, Survival, APRI, Liver cancer

#### O-121

#### Response to DAA in HCV Patients with HCC from East Asia: A REAL-C Study with Propensity Score Matching (PSM)

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**Aims:** Reports suggest HCV-HCC patients do not respond as well to the IFN-free DAAs, but background risks and confounders for treatment failures may not have been adequately controlled. Our goal was to compare SVR12 of DAAs in East Asian patients with HCV-HCC to those without HCC using PSM to balance the HCC and non-HCC groups.

Characteristic	HCC (n = 171)	No HCC (n = 171)	P-value
Male	89 (52.1)	81 (47.4)	0.39
Age	69.5 ± 9.4	$68.9 \pm 10.0$	0.60
Body mass index (BMI)	$23.3 \pm 3.2$	$23.1 \pm 3.8$	0.65
Hypertension	38 (53.5)	17 (40.5)	0.18
Hyperlipidemia	6 (4.7)	7 (4.9)	0.96
Coronary artery disease	1 (1.5)	2 (5.1)	0.28
Chronic renal insufficiency	20 (14.8)	14 (9.3)	0.15
Other cancer			0.69
Prostate	1 (1.9)	1 (3.5)	
Colon	1 (1.9)	1 (3.5)	
Gastric	0 (0.0)	1 (3.5)	
Other	2 (3.9)	1 (3.5)	
Cirrhosis	106 (62.0)	103 (60.2)	0.67
Decompensation	8 (8.5)	7 (6.9)	
Hepatitis C virus (HCV) genotype and subtype			0.078
Genotype l	127 (74.2)	123 (71.9)	
Untyped	14 (8.2)	3 (1.8)	
la	3 (1.8)	1 (0.6)	
lb	110 (64.3)	119 (69.6)	
Genotype 2	42 (24.6)	46 (26.9)	
Untyped	13 (7.6)	9 (5.3)	
2a	15 (8.9)	26 (15.2)	
2b	11 (6.4)	11(6.4)	
2a/2c	3 (1.8)	1 (0.6)	
Genotype 6	2 (1.2)	2 (1.2)	
Prior treatment	72 (42.1)	70 (40.9)	0.36
Prior direct acting antiviral (DAA)	5 (2.9)	10 (5.9)	
Prior non-DAA	67 (39.2)	60 (35.1)	
log10 HCV RNA, mean (SD)	$5.6 \pm 1.3$	$5.5 \pm 1.3$	0.55
Platelets, median (range)	115 (79 - 161)	116 (84 - 161)	0.58
Total bilirubin, mean (SD)	$1.1 \pm 0.9$	$1.0 \pm 0.7$	0.20
ALT, median (range)	46 (33 - 65)	47 (29 - 75)	0.55
DAA treatment initiated			0.53
SOF+RBV (sofosbuvir±ribavirin)	33 (19.3)	45 (26.3)	
LDV/SOF (ledipasvir/SOF)	94 (55.0)	87 (50.9)	
3D (paritanteviz/ritonavir, ombitasviz + dasabuviz)	12 (7.0)	13 (7.6)	
2D (paritantevit/ritonavir, ombitasvir)	1 (0.6)	0 (0.0)	
DCV+ASV (daclatasvir±asunaprevir)	19 (11.1)	21 (12.3)	
SOF+DCV	3 (1.8)	1 (0.6)	
EBR/GZR (elbasvir±grazoprevir)	1 (0.6)	1 (0.6)	
Other	8 (4.7)	3 (1.8)	

Table 1: Baseline Demographics of Propensity Score Matched (PSM) Patients (n=342)

**Methods:** Data were from 10 study centers comprising of 30 clinical sites in Hong Kong, Japan, Korea, and Taiwan representing the Real-World Evidence from the Asia Liver Consortium for Chronic Hepatitis C (REAL-C) - a registry of patients treated with IFN-free DAAs in routine practice (n=3702). 1:1 PSM matching on cirrhosis, prior treatment, baseline platelet, age, sex, baseline HCV RNA, treatment regimen, baseline ALT,

HCV genotype, and BMI was used to balance the groups at baseline.

Results: In our cohort, there were 195 patients with HCC at baseline or prior to DAA initiation and 3507 patients who did not have HCC at baseline. Prior to PSM, HCC patients were significantly older, more likely male, more likely to have renal insufficiency, cirrhosis, and decompensation (all P<0.004). After PSM, there were 171 HCC and N=171 non-HCC patients for analysis. As shown in Table 1, there were no significant differences in the baseline characteristics between the matched HCC and non-HCC cohorts. The majority (51-55%) of both groups received LDV/SOF; eight (three HCC, five non-HCC) stopped treatment before completion while ~10-12% had an adverse reaction (most common: anemia [>~5-6%] and fatigue [~3-5%]). There were seven deaths: five in the HCC group (four were liver-related) and two in the non-HCC group (both were non-liver-related). Overall, SVR12 rate was >96% for both groups with no significant differences. (Table 2)

Table 2: Tolerability and Outcom	Table 2: Tolerability and Outcomes for PSM Patients with and without HCC			
	HCC	No HCC	P-value	
Death	5	2	0.11	
Non-liver related	1 (0.6)	2 (1.2)		
Liver-related	4 (2.3)	0 (0.0)		
Adverse events	21 (12.9)	17 (10.1)	0.43	
Headache	0 (0.0)	2 (3.3)	0.14	
Fatigue	3 (4.6)	2 (3.3)	0.71	
Insomnia	3 (4.6)	1 (1.6)	0.35	
Nausea	0 (0.0)	1 (1.6)	0.30	
Arthralgia	1 (1.5)	0 (0.0)	0.33	
Myalgia	0 (0.0)	1 (1.6)	0.30	
Rash	3 (2.5)	2 (1.5)	0.57	
Pruritus	2 (3.0)	0 (0.0)	0.17	
Anemia	7 (6.0)	7 (5.2)	0.78	
Dyspnea	1 (1.5)	0 (0.0)	0.33	
Study discontinuation Non-	3	5	0.59	
compliance Psychological	1 (0.8)	1 (0.7)		
side effects Other	0 (0.0)	1 (0.7)		
	2 (1.5)	3 (2.0)		
SVR-12 rates	96.8	96.3	0.83	
	95% CI: 93-99	95% CI: 92-99		

**Conclusions:** This PSM study compared treatment for HCV patients with/without HCC, finding no difference in treatment tolerability, completion, and cure rates. **Keywords:** HCV, HCC, DAA

#### O-122

#### Hepatocellular Carcinoma Recurrence after Direct-Acting Antiviral Therapy in Patients with Chronic Hepatitis C: A Korean Multi-Center Retrospective Study

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**Aims:** The risk factor of hepatocellular carcinoma (HCC) recurrence following direct-acting antiviral (DAA) therapy remains unclear. The aims: of this study were to estimate the rate of HCC recurrence following DAA therapy in Korean patients with chronic hepatitis C (CHC), and to evaluate the risk factors for HCC recurrence after DAA therapy.

**Methods:** A total of 103 participants with CHC who obtained complete response after HCC treatment were treated with DAA between August 2015 and December 2016 and were followed up until January 2018. HCC treatments were classified as potentially curative included liver resection, radiofrequency ablation, percutaneous ethanol injection, cryoablation and liver transplantation.

Results: Among 103 patients, 82 patients had cirrhosis (79.2%) and 98 patients had Child-Pugh class A (95.1%). HCC stage of the patients was 49.6%, 38.9%, 9.7%, and 2.0% at stage I, II, III, and IV, respectively, according to modified UICC classification. Total duration of HCC treatment was median 2.3 (range, 0.03-143.0) months, and interval from last HCC treatment to start of DAA therapy was median 12.6 (range, 1.5-28.6) months. During the median 15.7 (range, 4.3–29.9) months follow-up, 38 patients (36.9%) experienced tumor recurrence. The median time to recurrence was 22.8 months. The univariate analyses showed that lower platelet count, non-curative HCC treatment, shorter interval from HCC treatment to DAA therapy and longer total HCC treatment duration could be the risk factors for HCC recurrence. In multivariate analysis, shorter interval from HCC treatment to DAA therapy (<12 months) and longer total HCC treatment duration (≥18 months) were found to be the independent risk factors for HCC recurrence (hazard ratio [HR], 2.76; 95% confidence interval [CI], 1.21-6.30; P=0.016 and HR, 1.96; 95% CI, 1.00-3.83; P=0.049, respectively).

**Conclusions:** In CHC patients with HCC, DAA therapy should be cautiously performed after sufficient interval without recurrence after complete treatment response.

**Keywords:** Carcinoma, Hepatocellular, Hepatitis C, Chronic, Direct-acting antiviral agent, Neoplasm recurrence, Risk factors

#### O-123

#### Pretreatment NAFLD Activity Score Significantly Predicts Fibrosis Regression in Hepatitis C Patients Receiving Antiviral Therapy

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**Aims:** Previous studies have reported that antiviral therapy engenders histological improvement and fibrosis regression in patients with hepatitis C. However, the effect of non-alcoholic fatty liver disease (NAFLD) accompanying hepatitis C on histological improvement and fibrosis regression during antiviral therapy remains unclear.

**Methods:** In this prospective cohort study, a total of 55 patients with hepatitis C underwent paired liver biopsy during antiviral therapy. Among them, 44 patients achieved sustained virologic response (SVR) after antiviral therapy. The NAFLD activity score (NAS) assessment and the quantification of a fibrotic surface area (FSA) were done by a single liver pathologist using paired Masson's trichrome-stained liver tissues for each patient. The relative changes of FSA between before and after antiviral treatment was defined as "[(% of FSA after treatment)-(% of FSA before treatment)]/(% of FSA before treatment)".

**Results:** Baseline fibrotic surface area was significantly related to Metavir fibrosis stage in only patients attaining SVR (P<0.05) but not in all patients with hepatitis C. In univariable analysis, age, serum protein level, and the NAS were significant predictors of the quantitative reduction of FSA during antiviral therapy (all P<0.1). In multiple linear regression analysis, serum protein level (P=0.07) and the NAS (P=0.03) were independent predictors of fibrosis regression. In patients with the NAS < 4, the quantitative reduction of FSA was more frequently observed after antiviral treatment rather than in those with the NAS > or = 4 (P=0.02).

**Conclusions:** The underlying severe NAFLD may hinder fibrosis regression in hepatitis C patients after antiviral treatment. Especially, in patients with the NAS < 4, fibrosis regression may be anticipated by antiviral treatment.

Keywords: HCV, NAFLD, NAFLD activity score, Fibrosis

The Liver Week 2018

# Poster Oral Presentation

PO-001~PO-006	Nonalcoholic Fatty Liver Disease / Alcoholic Liver Disease / Toxic Injury
PO-007~PO-010	Basic
PO-011~PO-016	HBV
PO-017~PO-022	HBV
PO-023~PO-028	HBV
PO-029~PO-034	Cirrhosis
PO-035~PO-040	Cirrhosis
PO-041~PO-046	Liver Transplantation
PO-047~PO-052	Biliary and Pancreatic Disease
PO-053~PO-058	HCV
PO-059~PO-064	HCV & Infectious disease
PO-065~PO-070	Cirrhosis
PO-071~PO-076	Liver Cancer, Basic
PO-077~PO-082	Liver Cancer, Clinical
PO-083~PO-088	Liver Cancer, Clinical
PO-089~PO-094	Liver Cancer, Clinical
PO-095~PO-100	Liver Transplantation
PO-101~PO-105	Surgery, Technical Issues

#### [Group 1] June 15, 2018 | 15:30-16:30

Nonalcoholic Fatty Liver Disease Alcoholic Liver Disease/Toxic Injury

#### PO-001

#### NAFLD Is Associated with High Prevalence and High Recurrence Rate in Patients with Breast Cancer

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Aims: Breast cancer is most common cancer in women worldwide. The incidence of breast cancer is correlated with metabolic component including diabetes, hypertension, and obesity. Likewise breast cancer, metabolic components are important risk factors for development of NAFLD. In this study, we analyzed the prevalence of NAFLD in patients with breast cancer and the effect of NAFLD on the prognosis of breast cancer.

Methods: Patients with breast cancer were enrolled from January 2007 to June 2017. Patients who had other chronic liver were excluded. Hepatic steatosis was evaluated by non-enhanced CT scan. We diagnosed NAFLD when the mean attenuation of the liver is lower than 40 HU or 10 HU lower than that of the spleen. 123 healthy controls who took non-enhanced CT scan were also analyzed.



Figure K-M curve for overall survival (A) and recurrence-free survival (B)

Results: Total 1587 patients were enrolled from January 2007 to June 2017. The prevalence of NAFLD in patients with breast cancer was 15.8% (251/1587) and it was significantly higher comparing with healthy control (8.9%, 11/123)(P=0.036). After propensity score matching, the difference of NAFLD prevalence was still significant between control group (8.9%, 11/123) and breast cancer patients (17.9%, 22/123) (P=0.040). In breast cancer patients, overall survival did not showed significant difference between NAFLD group and non-NAFLD group (P=0.304) (Figure A). However, recurrence-free survival was significantly higher in patients without NAFLD comparing with those with NAFLD (P=0.009) (Figure B). Among breast cancer patients received endocrine treatment, NAFLD group showed higher cumulative incidence of significant liver injury comparing with non-NAFLD group (P<0.001).

Conclusions: The prevalence of NAFLD in patients with breast cancer is significantly high compared to healthy control group. Moreover, breast cancer patients with NAFLD showed poor prognosis in terms of recurrence. Therefore, diagnostic evaluation to determine whether or not NAFLD is present would be important in managing patients with breast cancer.

Keywords: NAFLD, Breast cancer, Prevalence, Prognosis

#### **PO-002**

#### Azathioprine Induce Hyperbilirubinemia in Inflammatory Bowel Disease: A Hospital Based Cohort Study

Kwang Il Seo, Won Moon, Seun Ja Park, Moon In Park, Sang Uk Lee, Byung Chul Yun, Byung Hoon Han and Eun Taek Park

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Aims: Intestinal mucosal injury is supposed to cause liver disease. Abnormal liver function tests are frequently observed in inflammatory bowel disease (IBD). Therefore, we investigated the hepatic biochemistry changes in IBD.

Methods: IBD patients who were newly diagnosed and followed up with the results of hepatic biochemistries at the both time points of diagnosis (before IBD treatment) and then 2 year later (after IBD treatment) were enrolled. The biochemical profile including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB), alkaline phosphatase (ALP), Gamma-glutamyltransferase (GGT) were analysed.

Results: One hundred forty-six (77 patients of crohn's diseas and 69 ulcerative colitis) patients were able to confirm the liver function test at second year after first diagnosis. HBsAg positivity was found in 9 (6.2%) patients and anti-HCV antibody in 1 (0.7%). Radiologic diagnosis of fatty liver was found in 15 (10.2%) patients and gallbladder stone in 10 (6.8%). Within first year, 85 (58.2%) patients started azathioprine (AZA) treatment. At diagnosis, 45 (30.8%) patient revealed abnormal hepatic biochemistry. AST was elevated than upper limit of normal (ULN) in 9 (6.2%) patients, ALT in 11 (7.5%), TB in 14 (9.5%), DB in 16 (11%), ALP in 21 (14.6%) and GGT in 15 (10.3%). At 2 year later, 59 (40.4%) patients showed abnormal hepatic biochemistry. TB was elevated significantly compared to baseline (P<0.001) and absolute elevation of TB (>0.5mg/ dL) was related with AZA (P=0.006). In AZA group, hyperbilirubinemia (>1.2mg/dL) was found in 6 (7.1%) patients at initial diagnosis, but 19 (22.4%) patient at 2 year later. In this group, absolute TB elevation was found in 63 (64.1%) patients. Eighteen (21.2%) patients were normal at diagnosis, experienced newly developed hyperbilirubinemia after AZA treatment.

Conclusions: Abnormal liver function tests were observed in nearly one-third of IBD patients at diagnosis. Azathioprine elevated TB level significantly in inflammatory bowel disease. **Keywords:** Azathioprine, Inflammatory bowel disease, Hyperbilirubinemia

#### PO-003

# The Effects of Non-Pharmacological Interventions for Patients with Non-Alcoholic Fatty Liver Disease: A Systematic Review

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**Aims:** Non-pharmacological interventions (NPI) to modify healthy lifestyles and dietary habits are recommended for patients with non-alcoholic fatty liver disease (NAFLD). The purpose of this review was to evaluate the effects of NPI for improving health outcomes in patients with NAFLD.

#### Figure 1. Risk of bias graph



Figure 2. Risk of bias summary



**Methods:** We searched for randomized controlled trials of NPI for NAFLD published from 2008 to 2017, identified from elec-

tronic databases: PubMed; CINAHL; EMBASE; Cochrane Library. Two reviewers independently extract data and assessed risk of bias (ROB) using Cochrane Collaboration's tool. We analyzed data using *p*-value of differences between groups.

**Results:** A total of 94 studies identified, 36 studies assessed for eligibility, and 12 studies were collected for final review. The overall ROB in the included studies was unclear, as a result of performance bias and detection bias. NPI of the studies were categorized into three types: exercise, dietary focused lifestyle modification and dietary supplements. The interventions were delivered to individual or groups. To report for effect of interventions, studies identified primarily focused on liver enzyme and body mass index (BMI). Mixed findings were reported for effect of interventions (exercise, supplements) on ALT/AST and BMI. Lifestyle modification interventions appears to be effective in improving ALT (not AST) and BMI in patient with NAFLD.

**Conclusions:** This review shows that there are insufficient evidences regarding the effects of NPI to improve health outcomes for NAFLD. It may reflect heterogeneity among studies and small sample size. Therefore, well-designed randomized controlled trials using standardized protocol for patients with NAFLD should be conducted in the future.

**Keywords:** Non-alcoholic fatty liver disease, Systematic review, Non-Pharmacological Intervention

#### PO-004

#### The Prognostic Stratification Using Acute-On-Chronic Liver Failure Scoring System for Predicting Short-Term Mortality in Patients with Alcoholic Hepatitis

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**Aims:** To compare the existing various prognostic scoring models and newly proposed scores for acute-on-chronic liver failure (ACLF) and evaluate usefulness of stratification for the prediction of short-term morality in patients with alcoholic hepatitis (AH).

**Methods:** A total of 705 clinical AH patients, enrolled in the APASL-ACLF Research Consortium (AARC) with 90-day follow-up, were analyzed. AARC-ACLF score, Maddrey discrimination function (DF) score, age, bilirubin, international normalized ratio and creatinine score (ABIC), Glasgow Alcoholic Hepatitis Score (GAHS), Child-Turcott-Pugh (CTP) score, model for end-stage liver disease (MELD), and MELD-Sodium (Na) scores were used to compare the performance for predicting 30-day and 90-day mortality. AARC-ACLF scores were categorized into three grades (Gr I: 5-7; II: 8-10; and III: 11-15 points) and survival curves by the Kaplan-Meier method were created and compared using log-rank test.

**Results:** Of 708 patients, 286 (40.4%) and 363 (51.3%) patients died within 30 days and 90 days, respectively. The area under receiver operating characteristics curve (AUC) of AARC-ACLF, DF, ABIC, GAHS, CTP, MELD, and MELD-Na was 0.752 (0.705-0.799), 0.630 (0.575-0.685), 0.658 (0.604-0.711), 0.577 (0.523-0.631), 0.641 (0.589-0.694), 0.705 (0.653-0.756), 0.703 (0.651-0.755), respectively, for 30-day mortality. The AUC of various prognostic scores for the prediction of 90-day mortality is similar. The performance of AARC-ACLF was superior to that of DF, ABIC, GAHS, CTP, while comparable to that of MELD and MELD-Na in predicting short-term mortality. According to AARC-ACLF grades, short-term cumulative survivals was statistically different (30-day, 82.4, 70.4, and 35.3%, *P*<0.001; 90-day, 76.9, 56.0, and 26.4%, *P*<0.001).

**Conclusions:** Compared to the previous AH prognostic scores, AARC-ACLF score and grades are simple and useful for predicting the short-term mortality in patients with AH. Further studies are needed to confirm these implications.

Keywords: Alcoholic hepatitis, AARC-ACLF score, Mortality,

#### PO-005

#### 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

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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 antioxidative 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,  $\alpha$ -amylase, urea, SGPT and SGOT; liver tissue peroxidation and antioxidants alterations; histopathological alterations in liver and pancreas 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, PQQ, Liver, Vitamin C, S. cumini, Lipid peroxidation, Antioxidants

#### Handgrip Strength among Korean Adolescents with Elevated Alanine Aminotransferase and Obesity in 2014-2015

#### Yunkoo Kang, Sowon Park, Seung Kim, and Hong Koh

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**Aims:** Measuring handgrip strength is a useful method to evaluate sarcopenia. This study aimed to define the correlation between handgrip strength and body mass index (BMI), elevated alanine aminotransferase (ALT) and waist circumferences (WC), based on data from the Korea National Health and Nutrition Examination Survey (KNHANES).



**Methods:** Data of 1,057 adolescents (577 boys; 480 girls; age, 10–18 years) who participated in the KNHANES in 2014 and 2015 were obtained. The ALT was classified as ALT<30, 30fALT<40, 40fALT<50, 50fALT<60, 60U/LfALT. BMI was classified as BMI<85<sup>th</sup>, 85<sup>th</sup>fBMI<90<sup>th</sup>, 90<sup>th</sup>fBMI<95<sup>th</sup>, 95<sup>th</sup>fB-MI<97<sup>th</sup>, 97<sup>th</sup>fBMI and WC was classified as WC<90<sup>th</sup>, 90<sup>th</sup>fW-C<95<sup>th</sup>, 95<sup>th</sup>fWC<97<sup>th</sup>, 97<sup>th</sup>fWC percentile for age and sex.

**Results:** Handgrip strength adjusted with body weight (handgrip-to-weight) decreases with higher ALT. (*P*<0.019) The handgrip-to-weight also decreased with higher BMI and WC. (*P*<0.001) Among participants who had all features (elevated ALT, BMI and WC) had much decreases in handgrip-to-weight values than who did not have those features. (*P*<0.001)

**Conclusions:** Handgrip-to-weight ratio were decreased in participants with elevated ALT, BMI and WC. Given that handgrip strength is associated with ALT, BMI and WC in adolescents, it can be a diagnostic modality to easily identify the patients' current state in the clinic.

**Keywords:** Handgrip-to-weight ratio, Knorea National Health and Nutrition Examination Survey, Sarcopenia

#### [Group 2] June 15, 2018 | 15:30-16:10

Basic

#### PO-007

#### Chemical Derived Patient-Specific Hepatic Stem Cells from Various Patients

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**Aims:** Hepatocyte like cells can be derived from many different sources of stem cells including induced pluripotent stem cells, embryonic stem cells or directly converted cells. These Methods: are well developed, however, some problems such as tumor formation, low functionality and differentiation ratio as well as genomic variation are yet to be solved.

**Methods:** We have developed a method using two small molecules and no ectopic gene expression to develop patient-specific hepatic stem cells (hCdH) from primary hepatocytes. Of interest, from 52 patients healthy and diseased patient livers, we were able to generate hCdH.

**Results:** Among the 52 patients, significant differences in fibrosis were observed with 4.17% and 52% in the normal and diseased group respectively. The harvested hepatocytes ratio (number of cells/the liver weight) also differed with a mean of  $5.9\times10^6$  in normal livers and  $1.1\times10^6$  in diseased livers. In normal livers ALP ranged from 66 to 95 U/L whilst there was a sig-

nificant increase in the ALP level of diseased livers ranging from 80 to 174 U/L. Through the evaluation of different platforms such as generation and differentiation ratio, hepatic marker expression and functionality of these hCdHs, we were able to find the most significant difference in the statistical analysis between the generation of CdH in healthy and diseased livers and the level of ALP(alkaline phosphatase). Through FACS analysis we were also able to find the stemness marker NPB24-B3 obtained from embryonic stem cells as a characteristic of CdH and sorted 36.2% of the cells accordingly.

**Conclusions:** Although the CdH characteristics vary, it was possible to generate CdH from all patients. We therefore suggest that the functional state and generation efficiency of CdH are related to patient liver condition. In further studies, we plan to use the CdH marker to sort the cells obtained from the patients to allow for homogeneous population.

**Keywords:** Hepatic stem cells, Small molecules, Various liver patients, Primary hepatocytes

#### PO-008

#### Impact of Probiotics in NAFLD in Mice with Western Diet

Sang jun Yoon, Dae Hee Han, Haripriya Gupta, Na Young Lee, Ki Tae Suk, Dong joon Kim

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is one of the most common and increasing liver diseases worldwide. However, definitive medical treatment has not been established with the exception of lifestyle modification. Probiotics can be used as a promising mediation targeting gut-liver axis in NAFLD. The aim of study was to evaluate the impact of some strains in Western diet induced NAFLD mice model.

**Methods:** We used 6-week aged C57BL/6 mouse and mice were divided into 8 groups (n=10/group; normal diet group, Western diet for 8 weeks group, and 6 Western diet with probiotics administration groups [10<sup>9</sup> CFU/g, for 8 weeks]). Used probiotics strains are *Lactobacillus reuteri*, *L. salivarius*, *L. gasseri*, *Bifidobacterium lactis*, *B. breve*, and *B. longum*. We compared liver/body weight ratio, histology (fatty liver and hepatitis), liver enzymes (AST, ALT, and bilirubin), and cholesterol.

**Results:** In the analysis of liver/body weight ratio, *L. salivarius* (5.73±0.52, *P*=0.028), *B. breve* (5.27±0.47, *P*=0.001), and *B. longum* (4.85±0.57, *P*<0.001) groups showed significant improvement compared with that of Western group (6.33±0.63). In comparison of histology (fatty liver score/hepatitis score), *L. salivarius* (1.9±0.3/1.0±0.0, *P*<0.001), *B. breve* (1.2±0.7/0.9±0.6, *P*<0.001), *L. gasseri* (1.9±0.3/1.0±0.3, *P*<0.001), *B. lactis* (2.1±0.3/1.2±0.4, *P*<0.001), and *B. longum* (1.2±0.4/0.8±0.4, *P*<0.001) groups reveled significant improvement compared with that of Western group (3.0±0.4/1.9±0.3). Especially, *B. breve* and *B. longum* showed liver histology like that of normal control. All strains are effective in improvement

of liver enzyme (ASTT or ALT, P<0.05). In case of *B. longum*, mean cholesterol level was significantly decreased after administration of *B. longum* (0.9±0.5/0.3±0.2, P<0.001)

**Conclusions:** Gut-liver axis plays an important role in the NA-FLD and probiotics effectively reduce inflammation and steatosis of the liver in NAFLD. In addition, *B. longum* can be used in the treatment of dyslipidemia.

**Keywords:** Nonalcoholic fatty liver disease, Probiotics, Improvement, Mouse

#### PO-009

#### Formation of Functional Hepatocyte-Like Cells through Direct Conversion and Transplantation into Various Mice Models

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**Aims:** The incidence of liver disease is increasing worldwide. Liver transplantation is the only way to treat serious liver diseases. However, demand for transplants is increasing, while supply is very scarce. Therefore, many researchers are studying ways to replace liver transplantation. The most representative of these is cell therapy using ESCs and iPSCs. However, these are not available for clinical use because of the disadvantage that it may form teratoma in the body. Therefore we suggest other method that direct conversion technique produce generation of hepatocyte-like cells from fibroblasts with two liver-specific transcription factors.

**Methods:** First generation of hepatocyte-like cells (miHeps) were produced by lentivirus infection for continuously expression in host genome during conversion. Second generation of hepatocyte-like cells (R-iHeps) were produced by mRNA transfection. NSG and Albumin-Treck mice were used for *in vivo* transplantation.

**Results:** Directly converted hepatocyte-like cells can proliferate, split, store, re-seed, and mature with DMSO. And hepatocyte marker genes and protein expressions, albumin, AFP, etc., were increased in both cells, and albumin secretion in the media was much higher than fibroblasts. Also these cells were transplanted into liver injury model, jo2-treated NSG mice and Albumin-Treck mice, to confirm engraftment in liver. After transplant, miHeps and R-Heps can be detected in the liver under the fluorescence microscope.

**Conclusions:** Directly converted hepatocyte-like cells can be useful for liver regeneration instead of ESCs and iPSCs-derived hepatocyte-like cells.

**Keywords:** Direct Conversion, Hepatocyte-like Cells, 3D Printing, Transplantation

#### PO-010

## Characteristics of Bone Marrow Derived Mesenchymal Stem Cells in Patients with Liver Cirrhosis

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**Aims:** Cirrhosis is the end stage of chronic liver disease, which may lead to severe hepatic dysfunction and even life-threatening conditions. The beneficial impact of mesenchymal stem cells (MSCs) transplantation on liver diseases has been confirmed on several studies include our previous clinical trial for autologous bone marrow-derived mesenchymal stem cells (BM MSCs) transplantation to patients with liver cirrhosis, which have shown the ability of MSCs to reduce liver cirrhosis and improve liver function. We aimed to identify secreted factors by undifferentiated BM-MSCs in order to describe related pathways potentially targeted gene by MSC in liver cirrhosis.

**Methods:** Human BM-MSCs from normal and patients who had liver cirrhosis after autologous BM-MSCs transplanted and cultured specific medium condition for mesenchymal stem cells. We evaluated the potential of differentiation to osteoblast and adipocytes, morphological changes and cell proliferation depending on culture period, and immunophenotyping assay with flow cytometer with CD14, CD34, CD45, CD73 and CD105. At passage 4-5 of BM-MSCs were used for cDNA microarrays to identify secreted genes and related pathway that differentially expressed in specific stem cell population in liver cirrhosis and identified by biomathmatical analysis.



**Results:** On immunophenotyping analysis to determine mesenchymal function, CD14, CD34 and CD45 were 0.88%, 0.68% and 0.78%, respectively, however CD73 and CD105 for specific antigen of MSCs were 99.81% and 99.92%. BM MSCs secreted different factors in normal and patients with liver cirrhosis. We found 2968 genomes of 15 maps in KEGG pathway include Metabolic pathways, TGF-beta signaling pathway, Wnt signaling pathway, Cytokine-cytokine receptor interaction, HIF-1 signaling pathway, Ras signaling pathway and Natural killer cell mediated cytotoxicity. Within these pathways, functionally up-regulated genes were 7 genes and down-regulated genes were 9. In particular, we were able to identify potential specific genes might have typical function for regulation of liver cirrhosis and regeneration (FBN2, P4HA1 and STC1), and KIR3DL2, which is gene for regulation of immune system process.

**Conclusions:** Based on our previous clinical trial for autologous BM MSCs transplantation to patients with liver cirrhosis, the results have shown the ability of MSCs to reduce liver cirrhosis and improve liver function. Application of MSCs might target a widespread pattern of biological, cellular compositional and molecular functional event in the liver. MSC secreted genes and proteins can be differ depending on pathways and molecular mechanisms. Genes involved liver cirrhosis are able to release hepatotropic factors from transplanted MSCs, also potentially supporting liver regenerations.

**Keywords:** Bone Marrow, Cirrhosis, Characteristics, Transplantation

[Group 3] June 15, 2018 | 15:30-16:30

HBV

#### PO-011

Two-Center, 24-Months Result of Switching to Tenofovir-Monotherapy in Multi-Drug Experienced Chb Patients

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**Aims:** Chronic hepatitis B(CHB) patients with multi-drug experience are frequently switched to tenofovir-monotherapy, recently in Korea. We aimed to evaluate safety and efficacy of switching to tenofovir-monotherapy from tenofovir-based combination therapy upto 24 months.

**Methods:** This is a retrospective study of multi-drug experienced CHB patients who have switched from tenofovir-based combination therapy to tenofovir-monotherapy after achievement of virologic response(VR, less than 20 IU/mL) in two centers from 2013 to 2018

**Results:** A total of 39 patients were included. Median age was 52 years old. Twenty nine patients were male(74.4%). HBeAg positive patients were 32(82.1%). Thirty three patients(84.6%) had experienced not only nucleoside analogues, but also nu-

cleotide analogues previously. Median duration of VR before switching to monotherapy was 16.3 months and median duration of monotherapy was 32.0 months(range, 3-55). VR at 12 and 24 months were achieved in 36 patients. One patient lost to follow-up after 12 months of monotherapy without non VR. Two patients experienced virologic breakthrough during 24 months of tenofovir-monotherapy. All the 5 patients who experienced non VR easily achieved VR within 3 months with tenofovir-monotherapy, but all of them had experienced adefovir previously. Duration of consolidation with combination therapy after VR were less than 6 months in 4 out 5 patients who showed non-VR during 24 months of tenofovir-monotherapy.

**Conclusions:** Switching to tenofovir-monotherapy in multidrug experienced patients is generally safe and effective upto 24 months. Constant monitoring of virus may be required in patients with previous adefovir-exposure and short duration of consolidation after VR achievement.

Keywords: Chronic hepatitis B, Tenofovir, Entecavir, Resistance

#### PO-012

Medication Nonadherence Increases Hepatocellular Carcinoma, Cirrhotic Complications and Mortality in Chronic Hepatitis B Patients Treated with Entecavir

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**Aims:** Optimal adherence to nucleoside analogue treatment is necessary to achieve undetectable levels of HBV DNA in patients with chronic hepatitis B (CHB), and to prevent cirrhotic complications. However, no large long-term follow-up study has investigated the effect of adherence to entecavir (ETV) treatment on specific liver-related events (LREs), namely, hepatocellular carcinoma (HCC), cirrhotic complications and mortality.

**Methods:** This was a 10-year longitudinal observational study of treatment-naïve patients with CHB who received ETV treatment. The primary outcome was the cumulative probability of LREs. The cumulative level of adherence to medication was categorized as good ( $\geq$ 90%) or poor (<90%).

**Results:** Data from 894 treatment-naïve CHB patients who received ETV were analyzed. Overall mean adherence rates were 89.1%. Patients with poor adherence had a higher risk of virologic breakthrough (VBT) (HR, 22.42; 95% CI, 19.57–52.52; *P*<0.001) than those with good adherence. Multivariate analyses showed a higher risk of liver-related (HR, 14.29; 95% CI, 3.49–58.47; *P*<0.001) or all-cause (HR, 4.96; 95% CI, 2.19–11.27; *P*<0.001) mortality, HCC (HR, 2.86; 95% CI, 1.76–4.64; *P*<0.001) and cirrhotic complications (HR, 2.86; 95% CI, 1.93–4.25; *P*<0.001) with poor adherence. Medication

adherence was further stratified into three groups according to adherence rates of <70%,  $\geq$ 70- <90% and  $\geq$ 90%. The dose-response analyses of adherence rates showed that the risk of LREs increased progressively as medication adherence declined. In particular, the unfavorable effects of nonadherence were more pronounced in patients with cirrhosis.

**Conclusions:** Poor adherence to medication was associated with a higher mortality and greater risk of HCC and cirrhotic complications, particularly among patients with liver cirrhosis. **Keywords:** Hepatitis B virus, Hepatocellular Carcinoma, Antiviral Therapy, Adherence

#### PO-013

#### Efficacy and Safety of Tenofovir with and without Ursodeoxycholic Acid in Chronic Hepatitis B Patients with Elevated ALT: Interim Analysis of Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study

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**Aims:** This study aimed to assess the effect of ursodeoxycholic acid (UDCA) in improving liver inflammation in alanine amino-transferase (ALT) elevated chronic hepatitis B (CHB) patients who commence tenofovir therapy.

**Methods:** Eighty-nine tenofovir-naïve patients with CHB were enrolled from 6 centers. Patients were randomly assigned into 3 groups; tenofovir combined with placebo, tenofovir combined with UDCA 600mg, and tenofovir combined with UDCA 1000mg groups. The primary endpoint is ALT normalization rate at 4 weeks.

**Results:** Out of 89 patients, 8 patients dropped out, 58 patients completed 1-year follow-up, and follow-up of remaining patients is ongoing. The ALT normalization rates at week 4 by central lab criteria were 19%, 11%, and 22% for tenofovir monotherapy, UDCA 600mg combination therapy, UDCA 1000mg combination therapy, respectively (*P*=0.58). ALT normalization rates based on AASLD criteria at week 4 were not statistically different between 3 groups. ALT normalization rates by central lab criteria between 3 groups did not reach statistical significance at week 24 and 48. However, ALT normalization rates by AASLD criteria was higher in UDCA combination group than those in tenofovir monotherapy groups at week 24, 36 and 48 (*P*<0.05). Improvement of liver fibrosis measured by enhanced liver fibrosis score at week 48 was not different

between groups (P=0.66). Inhibitory molecules of T cell such as PD-1, CTLA-4 and FoxP3, superoxide dismutase, malondialdehyde and TNF-alpha were checked longitudinally, however, there were no significant differences among these three groups (P>0.05).

**Conclusions:** Combination treatment of UDCA with tenofovir can improve ALT normalization rate based on AASLD criteria in ALT elevated CHB patients.

**Keywords:** Chronic hepatitis B, Ursodeoxycholic acid, Tenofovir, ALT

#### PO-014

Mortality, Liver Transplantation and Hepatic Complications among Patients with Treatment-Naïve Chronic Hepatitis B with Entecavir vs. Tenofovir

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**Aims:** There have been limited studies directly comparing the long-term clinical outcomes between entecavir (ETV) and tenofovir disoproxil fumarate (TDF). This study was aimed to compare the risk of death, liver transplantation or hepatic complications including hepatocellular carcinoma (HCC) and hepatic decompensation between them in treatment-naïve chronic hepatitis B (CHB).

**Methods:** We performed a retrospective analysis of data from 1325 consecutive adult patients with CHB, treated with ETV (n=721) or TDF (n=604). Among the patients, 708 were analyzed using propensity score matching with a ratio of 1:1.

**Results:** During a mean follow-up of 49.9 (range 12-122) months, virologic response (HBV DNA negativity) was achieved in the majority (89.5%) of patients. Nine patients (0.7%) died or received a liver transplant, 64 (4.8%) developed HCC, and hepatic decompensation occurred in 24 (1.8%). HCC occurred in 58 (9.5%) among the patients with cirrhosis, whereas in 6 (0.8%) among those without cirrhosis (*P*<0.001). The ETV groups did not differ compared with TDF group in terms of the risk of liver-related death or LT (HR 0.96; 95% CI, 0.23-4.07; log-rank *P*=0.340), and hepatic decompensation (HR, 1.64; 95% CI, 0.67-4.00; log-rank *P*=0.276), respectively. In the 708 overall propensity-matched pairs, ETV and TDF also associated with a similar risk of death, liver transplantation and hepatic complications.

**Conclusions:** In a retrospective study of 1325 patients with CHB, ETV and TDF therapy did not have different effects on risk of death, HCC, liver transplantation and hepatic decompensation.

**Keywords:** Hepatitis B virus, Hepatocellular Carcinoma, Hepatic Decompensation, Antiviral Therapy

#### PO-015

Clinical Characteristics and Prevelance of Hepatitis Delta Virus Infection in Patients with Chronic Hepatitis B in Korea

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**Aims:** Hepatitis delta virus (HDV) and hepatitis B virus (HBV) coinfection is associated with more severe liver disease than HBV alone. More knowledge on the epidemiology and clinical impact of HDV-infected individuals is needed in Korea. Despite the development of new antiviral agents of HDV these days, it is not well known characteristics and prevelance of hepatitis delta virus infection in patients with chronic hepatitis B in Korea.

**Methods:** Total 1263 HBV infected patients visiting liver clinic at Korea University Ansan Hospital from January to December 2014 were screened for anti-HDV antibodies using ELISA assays. Comfirmed positive samples were further tested for HDV RNA using a commercial RT-PCR assay. Clinical characteristics and biological data from patients were researched and compared based on anti-HDV antibodies and HCV RNA results

**Results:** Most patients (n=814, 65%) were men and mean age was 49 years old. Anti-HDV anti-bodies were detected in 11 individuals (0.87%), 2 of whom were HDV RNA positive. Anti-HDV antibody positive patients showed similar clinical features, these had liver cirrhosis (45.5% vs. 33.8%, *P*=0.524) and HCC (18.2% vs. 12.9%, *P*=0.643) compared with HDV negative. However, all of 2 patients with HDV-RNA positivity showed significant cirrhosis.

**Conclusions:** HDV infection is rare in patients with chronic hepatitis B in Korea, but is related with liver cirrhosis in HDV RNA positive patients. However, HDV co-infection may not have a clinical importance.

Keywords: Hepatitis B virus, Hepatitis D virus, Prevalence, Korea

#### PO-016

#### The Risk of Hepatocellular Carcinoma within and after the First 5 Years of Entecavir in Patients with Chronic Hepatitis B

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**Aims:** The development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) has decreased with the potent antiviral agents. However, it was uncertain whether the risk of HCC would diminish after the long-term antiviral therapy in Asia, where the CHB is endemic and vertical transmission is common. This study aimed to compare the incidence of HCC within and beyond the first 5 years of entecavir (ETV) in treatment-naïve Korean patients with CHB.

**Methods:** We performed a retrospective observational analysis of data from 894 consecutive, adult patients with CHB undergoing ETV treatment at a tertiary referral hospital in Ulsan, Korea from January 1, 2007 through April 31, 2017. We compared the HCC incidence rates per 100 person-years, within and beyond the first 5 years. Univariate and multivariate analyses for factors predictive of HCC were performed.

**Results:** The incidence rate of HCC in the patients with CHB did not differ statistically when comparing within and beyond the first 5 years of ETV therapy (2.29% vs. 1.66% per person-year, *p* value=0.217). Failure to achieve a maintained virologic response (MVR) were a major independent risk factors for HCC in patients at follow-u*P*<5 years. In contrast, for patients with follow-u*p*  $\geq$ 5 years, achieving MVR did not show a significant association with HCC development.

**Conclusions:** The incidence rate of HCC in patients with CHB did not show a significant decrease through the study period. The risk of HCC in Asian patients with CHB may remain for a longer period.

**Keywords:** Hepatitis B virus, Hepatocellular Carcinoma, Liver Cirrhosis, Antiviral Therapy

[Group 4] June 15, 2018 | 15:30-16:30

HBV

#### PO-017

#### A Long Term Clinical Outcomes of Pegylated Interferon Treatment in Patients with Chronic Hepatitis B: Up to 10 Years Follow-Up

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Aims: Pegylated interferon (PEG-IFN) with a high rate of

off-therapy host immune control is still an attractive strategy although long-term nucleos(t)ides (NAs) can induce complete viral suppression. There remains uncertain about the rate of starting NAs or disease progression after PEG-IFN treatment. We investigated the long-term outcomes of PEG-IFN treatment in patients with CHB up to 10 years.

**Methods:** Fifty-six non-cirrhotic CHB patients who completed 48 weeks PEG-IFN therapy between 2009 and 2014 at Incheon St. Mary's Hospital were consecutively enrolled. The median follow-up period was 5.3 (2 to 10) years. The virologic response (VR) and serologic response (SR) of PEG-IFN was defined as <2000 IU/ml of HBV DNA and HBeAg loss/seroconversion at 24 weeks post-treatment. The progression to cirrhosis and the rate of starting NAs were investigated.

**Results:** The median age was 34.5 (24 to 56) year-old and 38 (67.9%) patients had HBeAg positive. VR was achieved in 17 (30.4%) patients and SR was achieved in 12 (31.6%) of 38 HBeAg positive patients. During follow-up, 26 (46.4%) patients were retreated with NAs in  $3.1\pm1.5$  years post-treatment. Patients without VR had higher NA starting rate than those with VR (76.5% vs. 43.6%, *P*=0.023). An additional SR was observed up to 80.9% (17/21) in HBeAg positive patients without starting NAs. Finally, three patients with VR achieved HBsAg loss in  $4.1\pm2.8$  years post-treatment. However, cirrhosis was developed in three patients 3.5 to 5.2 years after treatment: all of them did not achieve VR and had baseline HBeAg negative. No one developed hepatocellular carcinoma.

**Conclusions:** The present study showed the long-term outcomes of CHB patients with PEG-IFN therapy up to 10 years in Korea. The patients who had showed the favorable response of PEG-IFN therapy might show an off-therapy disease control, although half of all patients with PEG-INF therapy restarted with NAs.

**Keywords:** Chronic hepatitis B, Pegylated interferon, Long-term follow up, Nucleos(t)ide analogues

#### PO-018

Efficacy and Safety of Entecavir and Tenofovir in Chronic Hepatitis B Patients with Chronic Kidney Disease: Multicenter, Retrospective Cohort Study

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**Aims:** We investigate the efficacy and safety of entecavir (ETV) versus tenofovir (TDF) in treatment-naïve chronic hepatitis B (CHB) patients with chronic kidney disease (CKD) in real life setting.

**Methods:** A total of 1,349 naïve CHB patients treated with ETV or TDF at least 1 year in 9 academic hospitals from Jan. 2012 to Dec. 2015 were enrolled. Among them, 44 patients had CKD at enrollment. CKD was defined as glomerular filtration rate <60ml/min/1.73m2. Renal functional decline was defined when serum creatinine level increased by more than 50% from base-line or over than 0.3 mg/dL at 1 year

Results: A total of 44 patients (ETV=30 and TDF 14) were followed up for a median 28 months. There were no significant differences in cumulative biochemical response rate and culmulative HBeAg seroconversion rate between the ETV group and the TDF group at weeks 12, 24, and 48 of treatment. However, there were significant differences in culmulative virologic response rate between the ETV group and the TDF group at weeks 12, 24, and 48 of treatment (14%/31%/55% vs.14%/64%/86%, P =0.022). Renal functional decline occurred in 13 (29.5%) patients. Renal functional decline showed no significant difference between the ETV group and TDF group (33% vs. 21%, P=0.420). In multivariate analysis, serum albumin was an independent factor associated with renal functional decline (odd ratio, 0.28; confidence interval, 0.08-0.95; P=0.041). However, age, sex, BMI, DM, hypertention, baseline HBV-DNA level, HBeAg positivity, cirrhosis, baseline renal function, bilirubin level, platelet count, hemoglobin level, ascites and treatment regimen were not associated with renal functional decline in CHB patient with CKD.

**Conclusions:** TDF had better clinical efficacy than ETV in CHB patient with CKD. This study suggests that close monitoring of renal function are required for CHB patients with CKD and low albuminemia who are receiving antiviral agents.

**Keywords:** Hepatitis B, Chronic kidney disease, Tenofovir, Entecavir

#### PO-019

#### Association between Hepatic Steatosis and the Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

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**Aims:** As nonalcoholic fatty liver disease becomes a worldwide epidemic, hepatic steatosis has been frequently demonstrated in chronic hepatitis B patients without excessive alcohol intake. Whether presence of hepatic steatosis in these patients is associated with higher risk of developing hepatocellular carcinoma (HCC) has not been well established. We investigated the impact of histologically proven hepatic steatosis on the risk of HCC development.

**Methods:** Chronically hepatitis B virus-infected patients without significant alcohol consumption, who underwent liver biopsy from January 2007 to December 2015 in a single centre, were consecutively included. Patients were categorised into two groups according to the presence or absence of hepatic steatosis  $\geq$  5%, and the association of steatosis with subsequent HCC risk was analysed. To adjust for differences in patient characteristics including metabolic features, inverse probability weighting (IPW) using propensity scores was used.

**Results:** Hepatic steatosis was histologically proven in 70 patients (21.8%) among a total of 321 patients. During the median (interquartile range) follow-up of 5.3 (2.9–8.3) years, 17 of 321 patients (5.3%) developed HCC: 9 of 251 patients (3.6%) without steatosis and 8 of 70 patients (11.4%) with steatosis. The 5-year cumulative incidences of HCC were 1.9% and 8.2% among patients without steatosis and with steatosis, respectively (*P*=.004) (Figure *A*). Steatosis was associated with higher risk of HCC development (adjusted hazards ratio [HR], 3.005; 95% confidence interval [CI], 1.122–8.051; *P*=.029). After balancing with IPW, the incidences of HCC were not significantly different between the groups (*P*=.187) (Figure *B*), and the association between steatosis and HCC development was not significant (adjusted HR, 2.292; 95% CI, 0.693–7.587; *P*=.17).



**Conclusions:** Hepatic steatosis was associated with higher risk of developing HCC in patients with chronic hepatitis B. However, the association of steatosis per se with HCC development was not evident after adjustment for metabolic characteristics. **Keywords:** Hepatitis B virus, Fatty liver, NAFLD, Metabolic syndrome, Liver cancer

#### PO-020

#### Increasing Age and Comorbidities in Adult Patients with Chronic Hepatitis B (CHB) from 2007 to 2016 in Korea

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**Aims:** CHB prevalence in Korea ranges from 2-7% and is attributable for ~64-70% of hepatocellular carcinoma (HCC) cases. This study aims: to characterize the distribution and trend in demographics and comorbidity among CHB patients in Korea between 2007 and 2016.

**Methods:** We used the Health Insurance Review & Assessment Service (HIRA) Database to identify patients  $\geq$ 18 years with CHB as identified by ICD-10 codes (B18.1). Demographic and comorbidity data was reported cross-sectionally for 2007, 2011, and 2016. Patients were required to have  $\geq$ 1 inpatient or  $\geq$ 2 outpatient claims: for CHB for each eligible year. Comorbidities were confirmed through both disease code and medication prescriptions.

Results: A total of 253,002 patients met inclusion and exclusion criteria in 2007, with 320,245 in 2011 and 418,099 patients in 2016. Males made up 63% of patients in 2007 and decreased to 60% in 2016 (P<0.0001). The mean age of patients was 47 years (SD 13.3) in 2007 and increased to 52 years (SD 12.5) in 2016 (P<0.0001). The proportion of the population over 65 years of age increased from 10.4% in 2007 to 15.7% in 2016 (P<0.0001). As shown in Figure 1, by 2016, 36% of CHB patients in Korea had hyperlipidemia, 28.8% with hypertension, 14.6% with osteoarthritis, 13.1% with diabetes, 11.9% with osteoporosis/bone fracture, 4.8% with cerebrovascular disease, and 2.3% with chronic kidney disease ; all of which have increased significantly from 2007 (all P<0.001). Furthermore, 2007 prevalence of cirrhosis (23%), decompensated cirrhosis (3.7%) and HCC (5.4%) decreased significantly in 2016 to 22.3%, 2.2%, and 4.6% respectively (P<0.0001).



Figure 1: Proportions of Patients with Chronic Hepatitis B (CHB) and Comorbidities in Korea between 2007 and 2016. (P<0.001 between all years for all comorbidities)

**Conclusions:** Between 2007-2016, the Korean CHB population has significantly aged with more comorbidities, including renal

and metabolic bone disease that may affect CHB management. Careful selection of treatment and monitoring should be considered in these populations. Liver sequalae have also decreased, possibly due to better vaccination and CHB management.

Keywords: CHB, Comorbidities, Increasing age, Korea

#### PO-021

#### No Resistance to Tenofovir Alafenamide Detected through 96 Weeks of Treatment in Patients with Chronic Hepatitis B

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**Aims:** Presented herein are the post Week 48 through Week 96 resistance analyses for Phase 3 studies evaluating tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF).

**Methods:** Patients were randomized 2:1. HBV pol/RT population or deep sequencing was conducted for patients with viremia at Week 96 or at early discontinuation post Week 48. Deep sequencing was conducted for patients with HBV DNA >159 IU/mL and sequence changes at the consensus sequence level are reported. Phenotypic analysis was performed for Virologic breakthrough (VB) patients who were adherent to study drug, patients with conserved site substitutions, or for polymorphic substitutions emergent in >1 patient.

**Results:** TAF and TDF were treated in 866 and 432 patients, respectively. A similar percentage of patients in the arms qualified for sequence analysis. In the TAF arm, 87 (10.5%) patients qualified: 31 had no sequence change from baseline, 15 were unable to sequence (UTS), 32 had polymorphic site substitutions, and 9 had conserved site substitutions. In the TDF arm, 45 (10.9%) patients qualified: 26 had no sequence change, 6 were UTS, 11 had polymorphic site substitutions, and 2 had conserved site substitutions. Each detected conserved site substitution other than rtA181T was observed in one patient. The rtA181T substitution in 2 patients, 1 from each arm, was not associated with increasing plasma HBV DNA levels. At Week 96, a small percentage of patients experienced VB, and VB was

often associated with nonadherence. 27 patients qualified for phenotypic analysis and no patient isolates tested showed a reduction in susceptibility to TAF or tenofovir, respectively.

**Conclusions:** The proportion of patients analyzed and the HBV sequence changes observed were similar between patients in the TAF and TDF arms. Most substitutions occurred at polymorphic positions and no substitutions associated with resistance to TAF were detected through 96 weeks of treatment.

Keywords: TAF, Tenofovif Alafenamide, Resistance, HBV

#### PO-022

Predictors of HBeAg Loss and Seroconversion by Clinical Features and Viral Sequencing after 144 Weeks of Treatment with Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate

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**Aims:** HBeAg seroconversion remains an important endpoint for antiviral therapy. We previously reported on HBeAg loss following 48 weeks of oral antiviral therapy in the ongoing phase 3 study described below. Here we present an updated evaluation of factors associated with HBeAg loss with/without anti-HBe seroconversion following 3 years of antiviral therapy.

**Methods:** The study included adults with HBeAg-positive CHB enrolled in a Phase 3 trial(Study GS-US-320-0110) comparing TAF 25mg QD vs. TDF 300mg QD. At Week144, 340(39%; TAF 226; TDF 114) patients had received 1year of open label TAF 25mg QD after switching from double blind(DB) treatment. The associations between HBeAg loss at Week144 with host, viral, and treatment-related factors, including on-treatment virologic suppression, were determined using logistic regression analyses.

**Results:** Among 873 ipatients, the median age was 36yrs, 82% were Asian, and median baseline (BL) ALT and HBV DNA were 85U/L (IQR 60-138) and 7.9 log10IU/mL (IQR 6.9-8.6), respectively. At Week144, a total of 194patients (22%) experienced HBeAg loss and 142 patients (16%) underwent HBeAg seroconversion (Figure 1). Compared with subjects with persistent HBeAg-positivity, those with HBeAg loss were older

(median age, 35 vs. 40yrs), were infected with non-genotype D HBV (75% vs 86%), had lower median HBsAg levels (4.3 vs 3.8 log10 IU/mL), a higher median BL ALT (83 vs. 101U/L), a higher prevalence of presumed cirrhosis (Fibro Test  $\geq$ 0.75:6.4% vs. 13.2%), and lower median BL serum HBV DNA (8.1 vs. 7.7 log10 IU/mL) (all P $\leq$ 0.005). In multivariate analysis, baseline HBV DNA<8 log10 was an independent predictor of both HBeAg loss(OR: 1.816 [1.174-2.808]; *P*=0.007) and seroconversion (OR: 2.512 [1.684-3.746]; *P*<0.001); treatment with TAF in the DB period was a predictor of seroconversion (OR:1.596 [1.044-2.439]; *P*=0.031) but not loss.

**Conclusions:** Following 144 weeks of treatment, HBeAg loss/ seroconversion rates remains low in subjects treated with TAF or TDF with lower baseline HBV DNA levels associated with higher rates of response.

Keywords: CHB, TAF, HBeAg seroconversion, TDF

#### [Group 5] June 15, 2018 | 15:30-16:30

HBV

#### PO-023

#### Clinical Impact and Durability of Hepatitis B Surface Antigen Seroclearance in Untreated and Nucleos(t)ide Analogue Treated Patients

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**Aims:** The durability of nucleos(t)ide analogue (NA)-induced hepatitis B surface antigen (HBsAg) seroclearance is uncertain compared with HBsAg seroclearance of non-treated patients. We investigated to reaffirm that the quality of HBsAg seroclearance in NA is as good as that occurring spontaneously. Also, the occurrence of hepatocellular carcinoma (HCC) was investigated.

**Methods:** A cohort study was conducted using data from Gangnam Severance Hospital. We identified all subjects with positive HBsAg between January 1, 2001 and March 21, 2018. NA use, liver biochemistries, serial HBsAg and anti-HBs results were retrieved. The primary endpoint was confirmed HBsAg seroclearance, defined least two negative HBsAg test results, with the last HBsAg test being negative in patients with chronic hepatitis B (CHB). The secondary endpoint was to evaluate the incidence of hepatocellular carcinoma (HCC) after HBsAg sero-clearance in untreated and NA-treated patients.

**Results:** A total of 145 CHB patients with HBsAg seroclearance were included for analysis. In patients with spontaneous HBsAg seroclearance (n = 132), 105 patients (79.5%) had confirmed HBsAg seroclearance and 2 patients (1.5%) had HBsAg serore-version. In patients with NA-induced HBsAg seroclearance (n =

13), 10 patients (76.9%) had confirmed HBsAg seroclearance and HBsAg seroreversion was not observed. 1 patient (7.7%) had received consolidation therapy for <6 months, 1 patient (7.7%) had received it for 6–12 months and 11 patients (84.6%) had received it for  $\geq$ 12 months. The incidence rate of HCC in patients with HBsAg seroclearance was 6.21%. At a median (interquartile range) follow-up of 12 years, 5 untreated patients developed HCC. 4 NA-treated patients developed HCC. 6 patients were male aged >50 years (NA-treated patients: 2, untreated patients: 4), and 3 patients were male aged 50 years (NA-treated patients: 2 (age 47, 39), untreated patients: 1 (age 37)). There was no female patient who developed HCC with HBsAg seroclearance. Similar findings were observed in patients with spontaneous and antiviral treatment-induced HBsAg seroclearance.

**Conclusions:** NA-induced HBsAg seroclearance is as durable as spontaneous HBsAg seroclearance. All male patients are still at risk of HCC even if the incidence of HCC is very low.

**Keywords:** Chronic Hepatitis B, Seroclearance, Durability, Hepatocellular Carcinoma

#### PO-024

#### Comparison of Risk for Hepatocellular Carcinoma in Chronic Hepatitis B Patients Treated with Entecavir and Tenofovir

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**Aims:** Entecavir and tenofovir are currently recommended as first-line nucleos(t)ide analogs (NAs) for the treatment of chronic hepatitis B (CHB). NAs also reduce the risk of hepatocellular carcinoma in CHB, but it is not clear if there is difference in reducing the HCC risk between entecavir and tenofovir. This study aimed to compare the incidence of HCC between propensity-score (PS) matched groups on entecavir and tenofovir.

**Methods:** All consecutive patients who started entecavir or tenofovir in our institute as an initial NA therapy were enrolled. Propensity score matching was performed by using age, HBV DNA titer, HBeAg and liver cirrhosis as covariates with caliper = 0.2. The cumulative incidence of HCC was calculated by Cox regression with death as a competing risk.

**Results:** A total of 4959 patients received entecavir or tenofovir as an initial NA therapy. After excluding patients with HCC at presentation and incomplete follow-up, 1606 patients were enrolled for PS matching, which resulted in 840 patients: 356 and 484 for entecavir and tenofovir, respectively. Cox regression with competing-risk analysis showed similar risk for HCC between entecavir and tenoforvir (subdistribution hazard ratio = 0.93, 95% CI = 0.52 – 1.68, *P*=0.813). whereas presence of cirrhosis and low pre-treatment HBV viral loads were independent risk factors for HCC.

**Conclusions:** Entecavir and tenofovir show comparable effect in terms of risk modulation for HCC

**Keywords:** Hepatitis B, Entecavir, Tenofovir, Hepatocellular carcinoma

#### PO-025

#### Baseline Factors Associated with Compensation in Patients with Hepatitis B Virus-Related Decompensated Cirrhosis Commencing Antiviral Therapy

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**Aims:** Decompensation in patients with liver cirrhosis deteriorates the quality of life and reduces the survival sharply. It is well-known that treatment with nucleos(t)ide analogues can restore liver function, resolve the decompensation and reduce mortality in patients with hepatitis B virus (HBV) related cirrhosis. This study aimed to reveal the efficacy of entecavir and tenofovir, which are preferred as initial treatment for chronic hepatitis B, in patients with HBV-related decompensated cirrhosis

Methods: Patients with HBV-related decompensated cirrhosis who received entecavir or tenofovir as the initial antiviral therapy were retrospectively identified. Patients with chronic kidney disease or coexisting malignancy, such as hepatocellular carcinoma, were excluded. The primary outcome was the compensation, defined as reduction of Child-Pugh-Turcotte (CTP) score to five. Results: A total of 251 patients were enrolled. Mean age was 53.6 ± 10.8 years and 147 patients (58.6%) were men. CTP grade C presented in 146 patiens (58.2%). During a median follow-up of 34.3 months, the compensation and death occurred in 153 and 71 patients, respectively. Kaplan-Meier plots showed that type of antiviral agents did not influence significantly on compensation (log-rank test, P=0.088) and survival (P=0.295). In multivariate Cox-regression analysis, the compensation significantly occurred more frequently with lower BMI (odds ratio [OR], 0.955; 95% confidence interval [CI], 0.918-0.993; P=0.021), higher platelet count (OR, 1.006; 95% CI, 1.004-1.011; P<0.001), log value of serum AFP level (OR, 1.905; 95% CI, 1.486-2.443; P<0.001) and absense of ascites (OR, 1.762; 95% CI, 1.234-2.517; P=0.002).

**Conclusions:** The effects on prognosis of HBV-related decompensated cirrhosis were comparable between entecavir and tenofovir. We identified four predictive factors including BMI, platelet count, serum AFP level and ascites for reversibility of decompensation in patients with HBV-related cirrhosis.

Keywords: Entecavir, Tenofovir, Decompensated cirrhosis, Efficacy

#### PO-026

Long-Term Clinical Outcomes of Chronic Hepatitis B Patients Treated with Entecavir or Tenofovir: A Multi-Institutional, Retrospective, Observational and Comparative Study

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**Aims:** Entecavir(ETV) and tenofovir(TDF) are globally named among potent antivirals for the treatment of chronic hepatitis B virus infection. The purpose of this study is to compare long-term clinical outcomes of ETV and TDF in chronic hepatitis B patients in the real-world setting.

**Methods:** We performed a multi-institutional, retrospective, observational, and comparative study of 788 nucleos(t)idenaïve chronic hepatitis B patients who were given ETV 0.5 mg/ day(n=517) or TDF 300 mg/day(n=271) at Dankook University Hospital, Eulji University Hospital, and Chungbuk National University Hospital. We assessed and compared the development of hepatocellular carcinoma(HCC) and overall mortality as well as virologic and biochemical responses.

**Results:** The cumulative incidence rates of HCC tended to be higher in ETV than TDF arm (0.8% vs. 0% at 1-year; 2.3% vs. 1.6% at 2-years; 5.4% vs. 2.5% at 3-years). Overall mortality in ETV arm were 0% at 1-year, 0.5% at 2-years, and 0.6% at 3-years, while those of TDF were 0%, 1.0%, and 1.7% at each year. Cumulative probabilities of complete virologic response and serum ALT normalization were 95% vs. 97% and 97% vs. 96% at 36 months, respectively. Cumulative rates of virologic breakthrough were noted 0.2% vs. 0% at 1-year, 0.9% vs. 0.5% at 2-years, and 1.7% vs. 0.8% at 3-years on ETV vs. TDF arm. Cox proportional hazard model for ETV vs TDF presented as follows: HCC(HR 1:0.47[95% CI 0.16-1.37], *P*=0.167), overall mortality(HR 1:1.13[95% CI 0.21-6.15], *P*=0.890), and virologic breakthrough (HR 1:0.63[95% CI 0.13-3.09], *P*=0.572).

**Conclusions:** Long-term clinical outcomes such as the development of HCC and overall mortality may be different between two ETV and TDF arms, although both antivirals are comparable in antiviral efficacy of nucleos(t)ide-naive patients with chronic hepatitis B. So, the decision on which antiviral agent to select should be given cautiously consideration based on the individual status of liver function.

**Keywords:** Mortality, Hepatocellular carcinoma, Hepatitis B virus, Chronic hepatitis B

#### PO-027

#### Impact of HBeAg Seroclearance on the Risk of HCC Development in HBeAg-Positive Chronic Hepatitis B Patients Treated with Entecavir or Tenofovir

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**Aims:** HBeAg seroclearance is one of surrogate markers by current guidelines to predict the long-term outcomes in patients with chronic hepatitis B (CHB). However, whether HBeAg seroclearance in HBeAg-positive CHB patients under antiviral treatment can reflect the long-term outcomes remains unanswered in the era of high potency antiviral agents.

**Methods:** A historical cohort of 2,829 treatment-naïve HBeAg-positive CHB patients who initiated treatment with entecavir or tenofovir disoproxil fumarate at a tertiary referral hospital in Korea from 2007 through 2016 were included. The risk of HCC was analyzed by multivariable Cox proportional hazards model and time-dependent Cox model.

Results: The mean age was 45.0 years and 1,832 (64.8%) were male. Cirrhosis was present in 1,077 (38.1%) of patients. With the median follow-up of 56.8 months, HBeAg seroclearance was observed in 905 (32.0%) patients. HBeAg seroconversion and virologic response (HBV-DNA <60 IU/mL) were achieved in 694 (24.5%) and 2249 (79.5%) patients, respectively. During 13,526 person-years of follow-up, 238 patients developed HCC, with an annual incidence rate of 1.75/100PYs. The unadjusted cumulative incidence of HCC of patients experiencing HBeAg seroclearance during the first 2-year of antiviral treatment was not significantly different compared with that of patients who persisted HBeAg-positivity (P=0.15), regardless of presence of cirrhosis. By time-dependent Cox model, HBeAg seroclearance during overall treatment period was not a significant factor for predicting HCC development (adjusted hazard ratio: 0.92, 95% confidence interval: 0.58-1.44, P=0.70). In multivariable analysis, older age, male sex, lower ALT level, lower albumin, lower platelet count, and cirrhosis at baseline were independent predictive factors for HCC development.

**Conclusions:** In a large historical cohort of HBeAg-positive CHB patients, HBeAg seroclearance during antiviral treatment was not a significant surrogate marker for predicting HCC. **Keywords:** HBeAg, Seroclearance, Entecavir, Tenofovir

#### PO-028

#### Incidence and Risk Factors of Hepatitis B Virus Reactivation in HBsAg-Negative, Anti-HBc-Positive Kidney Transplant Recipients

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**Aims:** Recently, the emergence and use of potent immunosuppressive drugs has increased interest in the incidence of hepatitis B virus (HBV) reactivation. However, studies on the factors that predict the HBV reactivation in patients with resolved infection undergoing renal transplantation are insufficient. The aim of this study is to investigate the incidence and potential risk factors for HBV reactivation in kidney transplant (KT) patients with resolved HBV infection.

**Methods:** A consecutive 735 patients who received KT between 1995 and 2010 at a single tertiary referral center were included. Patients who were younger than 20 years old, HBsAg-positive, not available with hepatitis B surface antibody (anti-HBs) or hepatitis B core antibody (anti-HBc) data, and who received combined or previous liver transplantation were excluded. A total of 228 patients were analyzed. HBV reactivation was defined as HBsAg seroreversion or detectable viremia.

**Results:** During a median observation period of 128.9 months, five (2.2%) patients experienced HBV reactivation. The median time to reactivation from KT was 54.7 months. We could not find an association between donor HBV profile and HBV reactivation rate in this study. Also, immunosuppressive therapy was similar in patients with and without reactivation. Multivariable cox regression analysis with Firth's penalization showed that graft failure (adjusted hazard ratio [aHR] = 39.9, 95% confidence interval [CI] = 6.6-241.5, *P*<0.001), rejection (aHR=7.9, 95% CI=1.3-47.2, *P*=0.024) and low anti-HBs titer ( $\leq$ 40 mlU/ml, aHR=29.27, 95% CI=3.3-3842.7, *P*<0.001) at baseline were significant predictive factors for HBV reactivation.

**Conclusions:** HBV reactivation rate in KT recipients with resolved infection was low, but not negligible. Monitoring of HBV reactivation may be warranted in patients with low anti-HBs levels, graft rejection or failure.

**Keywords:** HBV reactivation, Kidney transplant, Anti-HBc-positive, Immunosuppressive

[Group 6] June 15, 2018 | 15:30-16:30

#### Cirrhosis

#### PO-029

#### Four Steps for the Surgical Treatment of Hepatic Hydrothorax

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**Aims:** Treatment of refractory hepatic hydrothorax, a complication of liver cirrhosis, is complex. We aimed to validate the usefulness of the "four-step approach," which is a treatment strategy combining 4 therapeutic modalities: 1) pneumoperitoneum to localize diaphragmatic defects, 2) thoracoscopic pleurodesis, 3) postoperative positive-pressure ventilation, and 4) peritoneal drainage for abdominal decompression.

**Methods:** We retrospectively analyzed the medical records of 12 patients with hepatic hydrothorax who underwent surgical treatment using the four-step approach from January 2013 to December 2017. Child C cases were nine of them (75.0%) and the median Model for End-Stage Liver Disease score was 20.5. The diaphragmatic defects localized after forming pneumoperitoneum were treated with primary closure followed by thoracoscopic pleurodesis, postoperative positive-pressure ventilation, and peritoneal drainage.

**Results:** Diaphragmatic defects were localized in all patients except one. The median postoperative positive-pressure ventilation duration was 20.1 hours. Peritoneal drainage was performed for a median duration of 5 days, and the peritoneal drains were removed at a median of 8 postoperative days. The median duration of postoperative hospital stays until discharge/ transfer was 9.5 days. No operative mortalities occurred. None had pleural effusions on plain chest radiographs at the time of discharge. The median duration of follow-up was 4.5 months. Eight deaths (66.7%) occurred during the follow-up period; three (25.0%) within 3 months postoperatively. No deaths were surgically related. One patient (8.3%) required additional drainage of pleural effusion due to treatment failure.



hepatology department

**Conclusions:** The four-step approach is a safe and effective surgical strategy for treating refractory hepatic hydrothorax. **Keywords:** Hydrothorax, Cirrhosis, Surgery,

#### PO-030

## Phase 1/2a Trial of a Bioartificial Liver Support System (LifeLiver) for Acute Liver Failure Patients

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**Aims:** Bioartificial liver (BAL) support offers a potential means of improving survival of acute liver failure (ALF) patients by providing partial liver function until a suitable donor liver is found or the native liver undergoes regeneration. Previous studies have suggested that ALF patients treated using BAL maintain a more stable medical condition, which may positively influence outcome after liver transplant (LT). This clinical trial was conducted to evaluate the safety and efficacy of the LifeLiver BAL system in ALF patients.

**Methods:** Patients with evidence of acute liver failure exhibiting hepatic encephalopathy grade 2 or worse who were listed for deceased donor liver transplant were eligible for enrollment. Hepatocytes were harvested from 3~4 weeks old male pigs weighing 4 to 10 kg, raised in a sterile environment. The isolate hepatocytes were cultured to form spheroids and were then mixed with 1.5% alginate solution and placed in a high content/speed immobilization apparatus and dropped into 100mM calcium solution. The Ca-alginate-immobilized hepatocyte spheroid beads were packed within the bioreactor of the BAL system. BAL treatment was continued for up to 12 hours.

**Results:** Six patients were given BAL treatment and were included in the safety analysis. Adverse events related to BAL treatment included coagulopathy (increased INR), pneumonia, sepsis and disease progression. One patient developed upper gastrointestinal tract bleeding and sepsis following BAL treatment and eventually died while waiting for transplant. No evidence of porcine endogenous retrovirus (PERV) were seen. Five patients completed the study per protocol and were included in the efficacy analysis. Four patients showed apparent decrease in serum ammonia levels and MELD scores during BAL treatment. Hepatic encephalopathy either decreased or remained stable throughout the BAL treatment period in 4 patients.

**Conclusions:** The LifeLiver BAL support system showed safety and efficacy in ALF patients with hepatic encephalopathy. Two patients were successfully bridged to liver transplantation.

**Keywords:** Acute liver failure, Bioartificial liver support, Liver transplant, Artificial liver support

#### PO-031

#### Management of Hydrothorax in Cirrhotic Patients: Is Surgical Management Safe and Efficient?

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**Aims:** Hepatic hydrothorax is a complication of decompensated liver cirrhosis and its management is very difficult and complex. Due to refractoriness of pleural effusion and low reserved liver function which cannot be improved without liver transplantation, there are many limitations managing hydrothorax only with diuretics or thoracentesis. Therefore, we analyzed clinical features and management of hepatic hydrothorax and compared outcomes between different treatment modalities especially surgical management.

**Methods:** From January of 2013 to December of 2017, patients who were diagnosed as hepatic hydrothorax by pleural fluid analysis were enrolled. Patients who has possibility of pleural effusion owing to other etiologies other than liver cirrhosis such as heart failure, acute kidney injury or pneumonia were excluded.

**Results:** 46 patients were enrolled and 33 patients (71.7%) were male and mean age was 60.11. The etiology of liver cirrhosis was alcohol(45.7%), hepatitis B virus (26.1%), hepatitis C virus (8.7%) and non-alcoholic fatty liver (4.3%). 10 patients (21.7%) underwent surgery, 2 patients had liver transplantation, 16 patients (35.6%) were treated with diuretics and pigtail drainage and 18 patients (40.0%) were treated with diuretics only. The mean CPT (Child-Pugh-Tourette) score was 10.2 and mean MELD (Model for end-stage liver disease) score was 18.8. The mean follow-up duration was 310 days and overall mortality was 47.8%. On Cox-regression analysis, CPT score, body weight, body mass index and treatment modalities was related to mortality (P<0.05). Mean survival duration was 252.3 days on surgical management group, 129.9 days on diuretics and pigtail drainage group, 351 days on liver transplantation group and 512.1 days on diuretics only group. There was no statistically significant difference between surgical management group and pigtail drainage group but survival duration was significantly higher in diuretics only group compared to surgical management group and pigtail drainage group with statistic significance. Due to small sample size, liver transplantation group comparison was not possible. Among 10 patients who underwent surgery, 6 patients had aggravation of ascites and 2 patients had recurrence of hepatic hydrothorax after operation. Conclusions: Surgical management of hepatic hydrothorax showed safe and high success rate. Also there was no statistically significant difference in survival duration compared with

pigtail drainage group. However aggravation of ascites was frequently observed and careful monitoring is needed to those who undergo surgery of hepatic hydrothorax.

Keywords: Hydrothorax, Liver cirrhosis, Surgery, Clinical outcome

#### PO-032

#### Impact of Liver Fibrosis on Long-Term Outcome in Ischemic Stroke Patients

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**Aims:** To investigate whether there are differences in long-term all-cause and cardiovascular mortality by the burden of liver fibrosis or steatosis in patients with ischemic stroke or transient ischemic attack (TIA).

**Methods:** Consecutive patients with acute ischemic stroke or TIA, who underwent transient elastography (TE) from January 2014 to December 2014, were considered eligible. The influence of liver fibrosis or steatosis, assessed using TE, on long-term outcomes was investigated using Cox proportional hazard models.

**Results:** Among 395 patients included in this study, there were 37 (9%) patients with significant fibrosis (>8.0 kPa) and 164 (41.5%) patients with fatty liver (>250 dB/m). During the follow-up (median 2.7 years), all-cause and cardiovascular mortality occurred in 28 (7.1%) and 20 (5.1%) patients. On multivariate analyses, significant liver fibrosis was independently associated with increased risk of all-cause (HR 8.14, 95% CI 3.03-21.90, *P*<0.001) and cardiovascular (HR 4.04, 95% CI 1.17-13.98, *P*=0.028) mortality, whereas fatty liver was not (all > p 0.05)

**Conclusions:** This study demonstrated that the burden of liver fibrosis, not steatosis assessed on TE was an independent predictor of all-cause and cardiovascular mortality during long-term follow-up in patient with ischemic stroke.

Keywords: Stroke, Liver fibrosis, Outcomes

#### PO-033

#### Efficacy and Tolerance of Maximally Tolerable Dose of Propranolol in the Prevention of Esophageal Variceal Rebleeding

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Aims: Although the efficacy of propranolol for the prevention

of esophageal variceal (EV) rebleeding has been well documented, there is a paucity of clinical data regarding the tolerance of maximal dose of propranolol. The aim of this study was to assess the tolerance of maximal dose of propranolol in liver cirrhosis patients during treatment for the prevention of esophageal variceal rebleeding.

**Methods:** A total of 90 patients, who were treated with emergent EV ligation for acute EV bleeding and have since then taken propranolol for more than 1 month, were enrolled. We retrospectively investigated the clinical course of propranolol treatment, particularly maximally tolerable dose (MTD) of propranolol in these patients.

**Results:** Fifty-four patients took maximally tolerable dose (MTD) of propranolol (163  $\pm$  72.9 mg/day), and 36 patients took low dose (LD) of propranolol (37.8  $\pm$  6.4 mg/day). During the follow-up period (median duration 58 months, range 2-175 months), rebleeding occurred in 15 (41.7%) and 12 (22.2%), LD and MTD of propranolol, respectively (*P*=0.049), and 13 patients died [11 (30.6%) in the LD of propranolol and 2 (3.7%) in the MTD of propranolol]. Median duration of maximally tolerable doe of propranolol was 27 months (range 1-89 months). Among patients with MTD of propranolol, 18 patients experienced dose reduction, but 12 patients maintained high dose of propranolol ( $\geq$  80mg/day) after dose reduction. The most common cause of dose reduction was bradycardia (50%). A total of 8 patients stopped taking propranolol, 1 patient with LD of propranolol and 7 patients with MTD of propranolol.

**Conclusions:** MTD of propranolol was well tolerated and showed good efficacy for preventing esophageal variceal rebleeding.

Keywords: Esophageal varix, Propranolol, Maximally tolerable dose,

#### PO-034

#### Usefulness of Linear Type Wireless Hand-Held Ultrasound for the Evaluation of Liver Surface Nodularity in Patents with Liver Cirrhosis

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**Aims:** Sonographic liver surface nodularity (LSN) is a useful parameter for diagnosis of liver cirrhosis (LC). Recently, easy-to-use linear type wireless hand-held ultrasound (wireless US) has been introduced. We aimed to assess the performance of wireless US compared to conventional ultrasound system (conventional US) in evaluating the LSN, and to verify the usefulness of LSN measured by wireless US in diagnosing LC.

**Methods:** We enrolled 104 patients who underwent wireless US (SONON 300L, 10 MHz linear transducer, Healcerion), conventional US (Logic E9, 9 MHz linear transducer, GE) and Fibro-
scan for evaluation of liver diseases between March 2017 and January 2018. LSN measurement (LSNM, defined as the length of curve line in liver surface matching the 2-cm linear segment in left lateral segment) was used to objectively evaluate the LSN. Diagnosis of LC was based on clinical criteria, and was compared with fibroscan results.

**Results:** Among 104 patients, 54 (51.9%) patients were diagnosed with LC. The mean liver stiffness measurement (LSM) on fibroscan (28.1±22.3 vs. 6.7±4.8, *P*<0.001) and LSNM on conventional US (2.075±0.459 vs. 2.028±0.119, *P*<0.001) were significantly different between LC and non-LC group. The mean LSNMs (2.051±0.034 vs. 2.052±0.041, *P*=0.13) on between wireless and conventional US by paired t-test were not significantly different. The sensitivity, specificity, positive predictive value, and negative predictive value of high LSNMs ( $\geq$  2.04) on wireless US in diagnosing LC were 88.9%, 90.0%, 90.6%, and 88.2%, respectively. The mean LSMs (25.7±22.8 vs. 9.6±10.6 kPa, *P*<0.001) were significantly different between high LSNMs ( $\geq$  2.04) and low LSNMs (<2.04) group.

**Conclusions:** The ability of liver surface nodularity evaluation with wireless US was not inferior to conventional US. Linear type wireless hand-held ultrasound can be a useful tool to easily identify the liver surface nodularity for diagnosis of LC.

**Keywords:** Wireless Ultrasound, Liver Cirrhosis, Liver surface nodularity, Hand-held

[Group 7] June 15, 2018 | 15:30-16:30

Cirrhosis

#### PO-035

#### Optimal Selection of Sedative Drug during Gastroduodenoscopy in Cirrhotic Patients to Avoid Minimal Encephalopathy: Interim-Analysis of Randomized Controlled Trial

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**Aims:** The indiscriminate use of sedative drug during endoscopy can pose a risk of minimal hepatic encephalopathy (MHE) in patient with liver cirrhosis, . However, it has not been studied yet which drugs are safest and most inviting on these patients. The aim of this study is to evaluate which one among midazolam, propofol, or combination therapy, was the least likely to cause complications including MHE by using Stroop application in cirrhotic patients.

**Methods:** This randomized prospective study included consecutive 32 patients who underwent upper GI endoscopy at tertiary hospitals in Korea. Patients were randomly assigned to one of three groups, midazolam, propofol, or combination group, and underwent Stroop test before endoscopy, and 2 hours after the completion of endoscopy. The vital signs was checked before and after the drug administration and the patient / physician / nurse satisfaction was scored after endoscopy.

**Results:** Mean age of the patients was  $54.0 \pm 9.30$  years and 81.3% were male. Fifteen patients (46.9%) were child-pugh class A, and 17 (53.1%) were child-pugh class B or C. Alcohol was the most common etiology (21, 65.6%). Patients did not show significant changes in Ontime, Offtime on Stroop test before and after drug administration, and there was no significant difference between the three treatment groups. Also, there was no significant vital sign changes after drug use in all groups. However, with respect to subjective indicators, the satisfaction scores of patient and nursing staff was higher in the combined group than in the other two groups, and time to recovery was shorter in propofol than other groups.

**Conclusions:** In patients with cirrhosis, sedative endoscopy using midazolam, propofol, or combination therapy is relatively safe, and was not associated with increased risk of MHE. However, since there is subjective satisfaction or recovery time difference among sedative agents, it should be considered according to each individual patient.

**Keywords:** Stroop, Minimal encephalopathy, Gastroduodenoscopy, Sedation

#### PO-036

#### Sarcopenia Is Independently Associated with Significant Fibrosis Assessed Using Transient Elastography in Patients with Chronic Liver Disease

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**Aims:** Sarcopenia is frequently identified in patients with advanced fibrosis or cirrhosis. We investigated the correlation between sarcopenia and other clinical variables, especially for significant liver fibrosis in patients with chronic liver diseases (CLDs). **Methods:** Patients with CLDs who received transient elastography and bioelectrical impedance analysis between January 1, 2015 and December 31, 2017 were recruited for this retrospective study. Sarcopenia index (SI) was calculated as follows:

SI=total appendicular skeletal muscle mass (ASM, kg)/ body mass index (BMI, kg/m<sup>2</sup>). Sarcopenia was defined when SI was <0.789 for men and <0.521 for women. Significant liver fibrosis and fatty liver was defined as > 7 kPa and controlled attenuation parameter > 250 dB/m, respectively.

**Results:** A total of 2,168 patients were recruited. Of these, 218 (10.1%) patients showed sarcopenia. Age, BMI, diabetes, hypertension, fasting glucose, aspartate aminotransferase, and liver stiffness value were positively correlated with sarcopenia (all *P*<0.05), whereas male gender, viral etiology, obesity (BMI>25 kg/m<sup>2</sup>), total bilirubin, and serum albumin were negatively correlated with sarcopenia (all *P*<0.05). On multivariate analysis, significant liver fibrosis was independently associated with sarcopenia (odds ratio [OR]=1.597, 95% confidence interval [CI], 1.174-2.172, *P*=0.003), together with age, male gender, viral etiology, and fatty liver (all *P*<0.05). Among the subgroups with non-alcoholic fatty liver disease (n=957), sarcopenia was also independently associated with significant liver fibrosis (OR=1.887, 95% CI, 1.261-2.823, *P*<0.001).

**Conclusions:** Sarcopenia is independently associated with significant liver fibrosis in patients with CLDs. Further studies are required whether interventions for improving muscle mass can regress fibrotic burden.

**Keywords:** Sarcopenia, Significant fibrosis, Chronic liver disease, Liver stiffness

#### PO-037

#### The Usefulness of Child-Turcotte-Pugh Class plus Hepatic Venous Pressure Gradient Model in Low and Intermediate MELD Era

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**Aims:** We investigated the usefulness of Child-Turcotte-Pugh (CTP) plus hepatic vein pressure gradient (HVPG) model for stratifying prediction of long-term survival in low and intermediate model for end-stage liver disease (MELD) era.

**Methods:** Of 1,025 patients with liver cirrhosis, we excluded critically ill cases and those with MELD scores  $\ge$  15. The data of 494 patients were subsequently collected between 2008 and 2013. We determined the CTP score as follows: score 1 (CTP class A), score 2 (CTP class B), and score 3 (CTP class C). We

also determined the HVPG score as follows: score 1 (HVPG < 13 mmHg), score 2 (13 mmHg  $\leq$  HVPG < 21 mmHg), and score 3 (HVPG  $\geq$  21). We determined subgroups using the sum of the MELD and HVPG scores as follows: CTP+HVPG score 2 as group 1, CTP+HVPG scores 3 and 4 as group 2, and CTP+HVPG score 5 and 6 as group 3.

**Results:** According to CTP+HVPG score, the cumulative survival rate decreased significantly as the CTP+HVPG score increased, as shown in the Figure 1 (P=0.000). The mortality rates increased significantly according to CTP+HVPG score in patients with in low and intermediate MELD score (Group 2 [hazard ratio, HR=4.97] (P =0.004)), (Group 3 [HR=8.84] (P =0.001)). In the comparison between two groups (group 1 vs. 2, 2 vs. 3, and 1 vs. 3), the cumulative survival rate was significantly different between groups 1 and 2, between groups 2 and 3, and between groups 1 and 3 (P=0.000, 0.021, and 0.000, respectively).



**Conclusions:** In low and intermediate MELD era, the calculation of the combined score using CTP plus HVPG model can help stratify the long-term prognosis. Also, in compensated and decompensated cirrhosis, the combined score has a discrimination value in prediction of long-term survival.

Keywords: Cirrhosis, CTP plus HVPG model, Survival, Prediction

#### PO-038

Role of Plasma Cystatin C and Urine NGAL in Prediction of Acute Kidney Injury and Mortality in Patients with Acutely Decompensated Cirrhosis: A Prospective Cohort Study

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**Aims:** Acute kidney injury (AKI) is the most frequent and devastating complication in cirrhotic patients. Emerging evidences suggest that novel biomarkers could predict AKI earlier than conventional markers and better predict prognosis in these patients. To determine the incidence and prognosis of AKI in acutely decompensated cirrhotic patients and also test whether plasma cystatinc C, urine neutrophil gelatinase associated lipocalin (NGAL) or tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin like growth factor 7 (IGFBP7) could predict the development of AKI and prognosis.

**Methods:** This is a single center prospective observational study conducted between May 2015 and Dec. 2017 with acutely decompensated cirrhotic patients. AKI was defined by KDIGO (Kidney Disease Improving Global Outcomes) criteria and urine and plasma samples were collected at the time of admission. Performances of novel biomarkers as well as various functional, clinical parameters were compared.

**Results:** Of 111 patients, 45 (40.5%) developed AKI during hospitalization and these patients showed significantly higher mortality (25% vs. 46.5%, *P*=0.02). Although initial BUN and serum creatinine were not different, plasma cystatin C and urine NGAL at the time of admission were significantly increased in patients who developed AKI and also death. Plasma cystatin C and urine NGAL were independently associated with the development of AKI after adjusting for clinical variables including age, co-morbidity and Child-Pugh score. [plasma cystatin C, odds ratio (OR) 2.09; 95% confidence interval (CI), 1.01-4.35), urine NGAL, OR 1.04, CI 1.01-1.05]. Although these biomarkers failed to predict mortality independent of clinical variables, urine NGAL significantly improved the accuracy of MELD in predicting mortality.

**Conclusions:** Novel biomarkers including plasma cystatin C or urine NGAL might be useful in earlier diagnosis of AKI and also in predicting mortality in acutely decompensated cirrhotic patients.

Keywords: AKI, Biomarker, Decompensated, Cirrhosis

#### PO-039

#### Relationship between Timing of Endoscopy and Mortality in Cirrhotic Patient with Variceal Bleeding

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**Aims:** The optimal timing of emergency endoscopy in patients with variceal bleeding is remains unclear. Most guidelines recommend performing endoscopic evaluation and treatment within 12 hours after patient's arrival, but there are few related studies. The aim of this study was to examine the association between timing of endoscopy and mortality of esophageal variceal bleeding in cirrhotic patients.

**Methods:** This retrospective study included 274 of consecutive patients admitted to two tertiary hospitals in Korea due to esophageal variceal bleeding. Using descriptive statistics and Kaplan-Meier survival analyses, we analyzed the association between the timing of endoscopy and patients' mortality. We adjusted confounding factors and balanced the baseline characteristics of the subjected patients using Cox proportional hazards model and inverse probability weighting (IPW) method.

Results: A total of 173 patients received endoscopy within 12 hours after admission and 101 patients, after 12 hours. Endoscopy was performed after a median of 7.6 hours (interguartile range [IQR], 2.9–16.5) after admission. The median overall survival (OS) was 8.2 months (IQR, 1.4-25.9) months, and in-hospital mortality was 8.0%. Performing endoscopy within 12 hours was associated with longer OS than performing after 12 hours (33.2 vs. 23.5 months, log-rank P=0.01). Early endoscopy was independently associated with longer OS after adjusting presence of hepatocellular carcinoma, MELD score, and Glasgow-Blatchford score (adjusted hazard ratio [aHR] 1.61, 95% confidence interval [CI]=1.05-2.46, P=0.03). Also, after balancing baseline characteristics using IPW, endoscopy within 12 hours group consistently showed longer OS than endoscopy after 12 hours group (aHR 2.17, 95% CI=1.56-3.03; P=0.03). However, outcomes were not significantly different between the urgent (within 6 hours) and early endoscopy groups.

**Conclusions:** Timing of endoscopy is associated with mortality in patients with esophageal variceal bleeding. It is important to perform emergency endoscopy within 12 hours, especially for high-risk patients.

**Keywords:** Esophageal variceal bleeding, Endoscopy, Mortality, Emergency

#### PO-040

#### Comparison of Liver Volume of Chronic Liver Disease between Viral and Non-Viral Etiology by Using Computed Tomography Volumetry

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**Aims:** To evaluate the correlation between liver fibrosis and liver volume using computed tomography (CT) images in patients with chronic liver disease according to the etiology.

**Methods:** This retrospective study included 121 chronic liver disease patients who underwent a liver biopsy or hepatic resection. On the basis of CT imaging, the total liver volume was calculated with a dedicated professional software. Volume index was calculated as the ratio of expected standard liver volume to CT-measured liver volume. Comparison of liver volume according to the underlying etiology and pathology-proven stage of fibrosis was assessed by t-test.

**Results:** The number of patients in viral group and non-viral group were 37 and 84, respectively. The CT-measured liver volume was smaller in viral group (1191.73 mL vs 1435.14

mL, 95% CI 1106.73-1276.73 mL vs 1327.83-1542.45 mL, P=0.0055). In patients without significant fibrosis (F0 and F1 fibrosis), there were no significant difference between viral and non-viral groups (1263.64 mL vs 1460.05 mL, 95% CI 1095.16-1432.12 mL vs 1293.43-1626.67 mL, P=0.2283). However, liver volumes were significantly smaller in viral group compared to non-viral group when significant fibrosis (F2 or higher) was present (1161.31 mL vs 1413.56 mL, 95% CI 1057.18-1264.43 mL vs 1268.84-1558.28 mL, P=0.0159). This pattern of difference remained significant for the adjusted liver volume, i.e., volume index.

**Conclusions:** Compared to non-viral etiology, CT-measured liver volume and volume index decreased more profoundly in chronic liver disease with viral etiology, especially with significant liver fibrosis group which has F2, F3, F4 fibrosis.

**Keywords:** Liver fibrosis, Computed tomography, Chronic liver disease, Volumetry

[Group 8] June 15, 2018 | 15:30-16:30

#### Liver Transplantation

#### PO-041

Clinical Outcomes of Patients with Injuries of Adjacent Organs by Expanded Polytetrafluoroethylene Grafts Used for Middle Hepatic Vein Reconstruction in Right Lobe Living Donor Liver Transplantation: A Single-Center Real-World Experience

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**Aims:** Congestion of the right liver (RL) anterior section without middle hepatic vein (MHV) may lead to graft dysfunction. Various outflow reconstruction Methods: have been devised to prevent congestion. An expanded polytetrafluoroethylene (ePTFE) graft may be used for anterior section drainage. We recently experienced several cases of injuries of adjacent organs caused by ePTFE grafts. The aim of this study was to explore these rare complications and their clinical outcomes in a single center.

**Methods:** From January 2005 to December 2016, 638 patients underwent RL living donor liver transplantation draining MVH branches with ePTFE grafts. Medical records of recipients who developed ePTFE-related adjacent-organ injuries were retrospectively reviewed.

**Results:** ePTFE-related adjacent-organ injuries developed in 5 patients (0.78%). The mean interval between transplantation and identification of injury was 73.4±38.1 months. All patients presented with dyspepsia. ePTFE graft induced injury of the

gastric antrum or duodenal bulb was observed in 3 patients, one at the small bowel with fistula formation, and another at the common bile duct (CBD). Such injuries were identified by gastroscopy and computed tomography (CT). The patient with gastric antrum perforation did not receive aggressive treatment although the remaining graft penetrated the gastric wall but no leakage. In one patient with duodenal bulb injury, ePTFE graft was removed with gastroscopy. In the remaining 3 patients, surgical exploration and ePTFE graft removal was performed. **Conclusions:** Although the incidence of adjacent-organ injuries by ePTFE graft is rare, close monitoring of ePTFE grafts is necessary since unexpected injuries can occur during long-term

PO-042

follow-up.

### Totally Laparoscopic Living Donor Right Hepatectomy in Bile Duct Anomalies

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**Aims:** Decreased blood loss, less postoperative pain, shorter length of stay in hospital, and excellent cosmetic outcome have well been validated as the advantage of laparoscopic hepatectomy. However, donor safety is the most important issue in living donor hepatectomy. Hence, pure laparoscopic right lobe donor hepatectomy has been applied in donors with favorable hepatic vascular and biliary anatomy.

**Methods:** We present the experiences for totally laparoscopic right hepatectomy in living donors with bile duct anomalies. From May 2016 to November 2017, totally laparoscopic right lobe donor hepatectomy for adult-to-adult living donor liver transplantation was performed in 24 cases. Among them, right hepatic ducts with more than 2 orifices were demonstrated in 11 patients.

**Results:** By Nakamura classification, type 2 anomaly was identified in 5 patients, type 3a in 3 patients, and type 3b in 3 patients, respectively. All donors were recovered without vascular or biliary complication. Biliary complications occurred in four cases of 24 recipients. Anastomosis site stricture of hepatic duct was confirmed in 3 cases (1 case in type 1, 1 case in type 2, and 1 case in type 3b). And bile leakage from anatomosis site was identified in one case (type 3a). All complicated recipients was improved by biliary stents by endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic biliary drainage.

**Conclusions:** Conclusively, totally laparoscopic living donor right hepatectomy is feasible and acceptable in donors with bile duct anomaly. But, to become a routine procedure, further evaluation and long-term results by highly experienced surgeons should be demanded.

#### PO-043

#### The Effect of Tacrolimus Intrapatient Variability on the Transplant Outcomes in Liver Transplantation

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**Aims:** Tacrolimus (TAC) is the mainstay of immunosuppression for liver transplantation. Although more than 20 years has passed since the introduction of TAC, its narrow therapeutic window and high intra-patient variability (IPV) remains a challenge in the management of transplant patients. We aimed to assess the impact of TAC IPV on graft outcomes and acute rejection after liver transplantation.

**Methods:** We analyzed patients underwent adult liver transplantation between 2010 and 2016 and treated with TACbased immunosuppressant. We excluded patients treated with mTOR inhibitors during the follow-up. TAC IPVs were calculated from the TAC concentrations between 1 and 12 months after transplantation. Patients were categorized as low (lowest quintile), normal (three middle quintiles), and high (highest quintile) IPV.

**Results:** A total of 339 patients with a mean TAC concentration of 7.6  $\pm$  1.6 ng/mL were included (68 low IPV, 203 normal IPV, and 68 high IPV groups). Mean TAC concentration was not different among three groups (*P*=0.35). During the 54 months of median follow-up, 43 patients (12.7%) reached the primary end point of graft failure. After adjusting for other risk factors, high IPV remained a significant risk factor for graft failure (HR, 3.89; 95% CI, 1.43-10.61; *P*=0.003). A total of 19 patients (5.6%) experienced biopsy proven acute rejection 1 month after liver transplantation. There was no difference among IPV groups with respect to the incidence of acute rejection (*P*=0.73). **Conclusions:** While acute rejection rates were similar among IPV groups, high TAC IPV is an independent risk factor for graft loss after liver transplantation.



**Keywords:** Liver transplantation, Tacrolimus, Intrapatient variability, Graft survival

#### PO-044

Changes of Standardized Uptake Value in 18F-FDG Positron Emission Tomography after Recurrence of Hepatocellular Carcinoma in Patients with Sirolimus in Living Donor Liver Transplantation

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**Aims:** Sirolimus is known to have both an immunosuppressive effect and also an anticancer effect. The standardized uptake value(SUV) of 18F-FDG positron emission tomography(18F-FDG PET) reflects tumor cell viability in not only hepatocellular carcinoma(HCC)but also in other cancers. We hypothesized that sirolimus could reduce the SUV compared to the calcineurine inhibitor(CNI)group after HCC recurrence in living donor liver transplantation(LDLT).

**Methods:** We retrospectively reviewed 532patients who underwent LDLT for HCC. Among them 92patients(17.3%) experienced recurrence and 47patients underwent 18F-FDG PET before LDLT and after recurrence. We measured the maximum value of SUV in the tumor(SUV-Tmax)before transplantation and compared to the recurrence site of that after recurrence. The repeated-measure-ANOVA was used to compare the patient group who used only CNI and those who used CNI and sirolimus together(S-CNI).

**Results:** A total of 25patients were included in the CNIgroup and 22patients were included in the S-CNIgroup. There was no difference in the age and sex, recurrence site, and time to recurrence(11±9 vs. 10±8, *P*=0.56)However the S-CNI group had more aggressive tumor features such as following; microscopic vascular invasion, beyond Milan, and SUV-Tmax before LDLT(6.13 ± 3.38 vs. 4.02 ± 2.52, *P*=0.019). In the repeated ANOVA analysis, the SUV-Tmax was significantly more decreased in the S-CNI group than the CNI group(F=6.022, *P*=0.018). In patients with early recurrence less than 1year, SUV-Tmax was more decreased in the S-CNI group than the CNI group(F=6.113, *P*=0.02).

**Conclusions:** Sirolimus has an impact on reducing the SUV-Tmax after HCC recurrence based on comparison of the maximum value of the original tumor before LDLT.

#### PO-045

### Risk Factors for Renal Impairment at One-Year after Liver Transplantation

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**Aims:** Renal dysfunction before and after liver transplantation (LT) is common and may progress to chronic kidney disease which significantly affects post-LT mortality. The aims: of the study were to identify serial changes in estimated glomerular filtration rate (eGFR) in the first year after LT and to determine peri-LT risk factors for the development of renal impairment at one year after LT.

**Methods:** A total of 96 consecutive patients who underwent LT at two tertiary centers between 2013 and 2017 were enrolled, and 62 patients who fully followed over one year after LT were finally analyzed. Renal function was measured by eGFR.

Results: Forty-two (67.7%) patients underwent deceased donor LT and 26 (41.9%) patients had hepatocellular carcinoma at baseline. Sixteen patients (25.8%) had episodes of acute kidney injury (AKI) within a month before LT and 12 patients (19.4%) received de-novo renal replacement therapy (RRT) within a month before and after LT. The proportion of patients who had eGFR<60 ml/min/1.73m<sup>2</sup> was 40.3% at baseline and decreased to 27.4% at 1 month after LT. However, it increased gradually to 37.1% at one year after LT. Three patients eventually started maintenance RRT during follow-up period. MELD score >30, eGFR <60 ml/min/1.73m<sup>2</sup> and ascites at baseline, de-novo RRT within a month before and after LT and large blood loss during operation were significantly associated with renal impairment (eGFR<60 ml/min/1.73m) at one year after LT. Among them, eGFR <60 ml/min/1.73m<sup>2</sup> at baseline remained an independent factor on multivariate analysis. DM, HBP and AKI episodes at pre-LT did not affect the development of renal impairment at one year after LT.

**Conclusions:** The mean eGFR of LT recipients was improved shortly after LT, though it gradually decreased with time. Baseline eGFR <60 ml/min/1.73m<sup>2</sup> was the strongest factor for renal impairment at one year after LT. Personalized care considering eGFR in LT recipients may improve post-transplant outcomes.

**Keywords:** Liver transplantation, Chronic kidney disease, Estimated glomerular filtration rate,

#### PO-046

#### Laparoscopy of Hepatocellular Carcinoma Is Helpful in Minimizing Intra-Abdominal Adhesion during Salvage Transplantation

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<sup>1</sup>Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Korea; <sup>2</sup>Hepatobiliary-Pancreatic Surgery, Hospital Beaujon, APHP, Clichy, France **Aims:** This study analyzes the impact of laparoscopic liver resection on intra-abdominal adhesion.

**Methods:** Patients who underwent salvage liver transplantation after liver resection for hepatocellular carcinoma from January 2012 to October 2017 at Samsung Medical Center were included. Information about the severity of intra-abdominal adhesions was collected from a prospectively maintained database. Intra-abdominal adhesions were graded according to Beck et al. (Dis Colon Rectum 2000; 43: 1749-1753) after the agreement of two surgeons who participated in the salvage liver transplantation. Adhesion severity and demographic, operative, and postoperative data were compared between the laparoscopic group and the open group. Multivariate logistic regression was performed to consider potential factors related to severe adhesion during salvage transplantation.

**Results:** Sixty-two patients who underwent salvage liver transplantation after liver resection were included in this study. Among them, 52 patients underwent open surgery, and 10 patients underwent laparoscopy. Adhesion was significantly more severe in the open group than in the laparoscopy group (P=0.029). A multivariate logistic regression model including potential factors related to severe adhesion showed that laparoscopy (OR=0.168. Cl=0.029-0.970, P=0.048) was the only significant factor.

**Conclusions:** Laparoscopic liver resection for hepatocellular carcinoma can minimize intra-abdominal adhesion during salvage liver transplantation.

#### [Group 8] June 15, 2018 | 15:30-16:30

**Biliary and Pancreatic Disease** 

#### PO-047

#### Dual-Incision Laparoscopic Spleen-Preserving Distal Pancreatectomy ; Merits in the Surgical Aspect Compared with Conventional Method

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**Aims:** Herein we evaluate the safety and feasibility of the dual-incision laparoscopic spleen-preserving distal pancreatectomy (DILSPDP) for benign and borderline malignancy in the body or tail of the pancreas comparing with the surgical outcome of conventional LSPDP.

**Methods:** In the right lateral decubitus position of the patient, we performed DILSPDP using a multichannel trocar at the mid-clavicular line in left mid-abdominal quadrant via 3-cm transverse incision with one additional 5-mm trocar at the sub-

xiphoid area, whereas four or five trocars were generally used in the supine position of the patient in case of conventional LSPDP. We retrospectively compared the demographics and operative outcomes between groups using two different types of surgical techniques.

**Results:** In this study, 22 cases of DILSPDP and 26 cases of conventional LSPDP were reviewed. Although there was no difference in terms of demographic features including disease diagnosis, tumor size or location between two groups, the operative time, blood loss and length of hospital stay was significantly lower in DILSPDP group (P=0.004, 0.011, and 0.028, respectively). Moreover, DILSPDP was more successful for complete preservation of splenic vessels than conventional LSPDP (95.5% vs. 65.4%, P=0.013).

**Conclusions:** Authors suppose that DILSPDP could be a safe and feasible technique for benign or borderline malignant tumors in the body or tail of pancreas accompanying with not only the advantages of minimal invasive surgery but also technical ease for LSPDP.

#### PO-048

#### Totally Laparoscopic Pancreaticoduodenectomy Using 3D Flexible Laparoscopic System

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**Aims:** Robotic PD has not yet been expanded due to the needs of the dedicated teams and the excessive costs. 3D flexible laparoscopic system (3D) with depth perception and spatial orientation allows the precise dissection of the dangerous site and facilitate the comfortable reconstruction. We present experiences regarding the efficacy of L-PD using 3D.

**Methods:** Totally L-PD was attempted in 15 patients from June 2016 to June 2017. However, conversion to open PD was required in one patient with tumor invasion to the superior mesenteric vein. Pancreaticojejunostomy was completed with the dunking procedure in 1 patient and with duct-to-mucosa technique in 13 patients.

**Results:** Mean operation time was 500 min. The replaced right hepatic artery originated from superior mesenteric artery of hepatic artery was identified in one patient and preserved well because of the precise dissection under the excellent visual field. The mean size of pancreatic duct and hepatic duct were 3 mm and 10 mm. There was no major intra-operative complications and post-operative mortality. Postoperative complications were detected in 7 patients, including pancreatic fistula (n=5), and delayed gastric emptying (n=2). All pancreatic fistula was grade A and were recovered with conservative treatment.

**Conclusions:** In selected patients, L-PD is a safe and effective procedure with comparable surgical outcomes to open surgery.

Especially, we believe that 3D will play an important role in the expansion of complicated PD surgery and will provide a bridge role for future robot systems.

#### PO-049

### The Value of Infectious Biomarkers for Prediction of Complication after Pancreatic Surgery

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**Aims:** To assess the predictive value of biomarkers for early complication after pancreatic surgery.

**Methods:** 950 cases were recruited from 6 centers in China. Procalcitonin,C-reactive protein and WBC were measured on 1st, 3rd and 5th postoperative day . Chi-square test was for the complication risk factors. One-way ANOVA was for the comparison between the biomarkers in these 4 days. ROC curves was for the complication predictive value.

Results: 1) 502 with and 448 without complication, pancreatic fistula (380, 40%) had the highest morbidity, while the level A B C fistula were 278, 90 and 12. 2) In the non-complication subgroup, the mean baseline, POD1, POD3 and POD 5 of PCT were 0.1, 0.81, 0.93, 0.57ug/L (P=0.118); CRP were 8.39, 70.81, 99.59, 49.49mg/L (P=0.000). In the complication subgroup, the mean baseline, POD1, POD3 and POD 5 of PCT were 0.09, 0.93, 0.77, 0.37(P=0.000), CRP were 9.30, 79.70, 153.01, 85.83. (P=0.000) 3) There were significant differences in the subgroups classified by occurrence of infectious complication, abdominal infection and sepsis in POD3 and POD 5 of PCT, and significant difference by occurrence of complication, pancreatic fistula in POD3 and POD 5 of CRP, WBC and neutrophil%. 5) The AUC of POD3 and POD 5 of PCT were 0.8, 0.7, 0.6 (P=0.000) to predict sepsis, abdominal infection and infectious complication. AUC of POD3 and POD5 of CRP and WBC were 0.7,0.6 (P=0.000) to predict complication and pancreatic fistula. Conclusions: PCT is better to predict infectious complication, abdominal infection and sepsis while CRP, WBC and Neutrophil % are better to predict complication and pancreatic fistula.

#### PO-050

#### Portal Vein Stenting for Symptomatic Portal Vein Occlusion after Pancreaticoduodenectomy

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**Aims:** Portal vein occlusion is the worrisome late complication following pancreaticoduodenectomy that caused variceal bleeding, which must be diagnosed correctly and treated promptly. This study aimed to describe characteristics and evaluate patency of portal vein stent for post pancreaticoduodenectomy.

**Methods:** Eleven consecutive patients (age range 45 to 78; nine men and two women) who underwent portal vein stenting between January 2000 and December 2016, all of them suffer portal vein occlusion after pancreaticoduodenectomy, were retrospectively reviewed. Primary stent patency was plotted using the Kaplan-Meier method.

**Results:** Portal vein occlusion was caused by benign postoperative change (n= 8) and local tumor recurrence (n=3). Symptoms were gastrointestinal bleeding (n=10) and uncontrolled ascites (n=1). Symptoms occurred at 38 moths (2 to 121 months), on average, postoperatively. Technical success, treatment efficacy and clinical success rates were 90.9, 100 and 90.9%, respectively. The primary patency rate of portal stent was 91.9% during the mean follow-up period of 12months. There was no procedure related complication or mortality occurred.

**Conclusions:** Portal vein stenting is a feasible and safe treatment for symptomatic portal vein occlusion after pancreaticoduodenectomy.

#### PO-051

A Prospective, Pilot Study to Evaluate the Safety and Efficacy of the Unity Balloon-Expandable Bioresorbable Biliary Stent System in Subjects with Benign Biliary Strictures

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**Aims:** Significant experience with biodegradable biliary stenting has been reported in the literature. The biodegradable stents are typically made from polymeric materials including Polylactide (PLA) or Polyglycolide, which have been approved by the FDA and CE as drug carriers, sutures, and bone fixtures. We have embarked on a pilot study to assess the safety and feasibility of a novel balloon expandable bioresorbable biliary stent.

**Methods:** This is a prospective, pilot, open-label descriptive safety and feasibility study, conducted at UKM Medical Centre, Kuala Lumpur. Patients with benign biliary strictures were recruited. Patients will be follow-up at interval period of weeks 1 and 2, months 1,3,6,9 and 12. The primary objective was to assess safety of the UNITY stent. The secondary objectives were clinical, technical and procedural success. The novel UNITY-B stent comprised of biodegradable magnesium alloy core with biodegradable polymer coating. It degrades through hydrolysis. **Results:** 6 patients has been recruited from 1 October 2017 until 30 April 2018. Among the indications include; 4 patients with type-2 benign distal common bile duct (CBD) stricture, 1 patient with post-cholecystectomy (Strasberg type E5) stricture,

1 patient with post-operative end-to-end common bile duct anastomotic stricture. At the primary safety endpoint within 30 days of the index procedure, all patients has remained symptom free. Only one patient has reached 6 months follow-up. The secondary objectives were achieved in all 6 patients. Serum bilirubin dropped more than 20% at one week and remained low at 1 month in 5 patients. 1 patient did not show reduction in serum bilirubin but reported improvement in symptoms. 1 patient who has reached 6 month follow-up reported pruritus but has normal serum bilirubin.



**Conclusions:** The UNITY stent has fulfil the safety criteria and has demonstrated good radial force to maintain patency of the stricturoplasty at 1 month. It is easy to be deployed and has the potential to replace the role of covered metal stents. None-theless, this is an interim result of a small cohort of patients. A long term data on safety and efficacy of a larger number of patients is anticipated.

Keywords: Bioresorbable, Biliary, Stent, Benign stricture

#### PO-052

#### The Content of Cytokines in Ductal Bile and Serum with Obstructive Jaundice of Non-Tumor Origin

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**Aims:** Comparative study of local and systemic (serum) TNF- $\alpha$  and IL-6 in dynamics during surgical treatment of patients with obstructive jaundice (OJ).

**Methods:** 9 patients with non-tuberculosis left ventricular etiology were examined. In all patients, the cause of OJ was choledocholithiasis. The level of TNF- $\alpha$  and IL-6 in blood serum was studied in patients before the operation, on the 3rd and 7th day after the operation, and in bile - during the operation (the first dose), on the 3rd and 7th days after decompression of the biliary tract (choledocholithotomy and external drainage of choledochus).

**Results:** In patients with OZH, the content of TNF- $\alpha$  in the blood serum was 66.2 to 112.6 pg / ml (average 88.3 ± 6.5 pg / ml, ie, 2.2 times the norm), in the ductal bile - from 8.2 to 121.8 plg / ml (average 111.2 ± 4.1 pg / ml). In the postoperative period, by the 7th day there was a slight increase in the

concentration of TNF- $\alpha$  in the blood serum. After decompression of the biliary tract on day 3, the content of TNF- $\alpha$  in the ductal bile increased from  $111.2 \pm 4.1 \text{ pg}$  / ml in the first batch to  $120.6 \pm 5.6$  pg / ml. However, on the 7th day, the level of TNF- $\alpha$  in the ductal bile decreased to 113.5 ± 4.5 pg / ml. Before the operation, the concentration of IL-6 in serum averaged  $17.4 \pm 1.9$  pg / ml, i.e. by 4.7% was below the normal value. The proinflammatory cytokine IL-6 content in the first batch of ductal bile averaged 19.46 ± 3.02 pg / ml, i.e. was somewhat larger than in serum. On the 7th day after the operation, the concentration of IL-6 in the blood serum, significantly increasing by 49.7% compared with the baseline, remained 42.7% (P<0.01) higher than in healthy subjects. The concentration of IL-6 in the ductal bile after decompression on days 3 and 7, significantly increasing, was  $28.30 \pm 4.05$  and  $38.82 \pm 2.93$ pkg / ml. The conducted studies showed that, in the course of treatment, all patients had an increase in the content of TNF- $\alpha$ and IL-6 in the ductal bile.

**Conclusions:** In patients with OJ in the postoperative period, changes of the same direction were observed: in the first days an increase and then a decrease in the serum and bile concentrations of TNF- $\alpha$ . Comparative evaluation of the dynamics of IL-6 in serum and bile revealed various changes, which indicates different compensatory mechanisms at the local and systemic level.

Keywords: Cytokines, Obstructive jaundice, IL-6, TNF-α

[Group 1] June 16, 2018 | 15:00-16:00

#### PO-053

#### Long-Term Follow-Up of Patients with Chronic HCV Infection and Compensated or Decompensated Cirrhosis Following Treatment with Sofosbuvir-Based Regimens

HCV

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**Aims:** Early results from registries and cohort studies have demonstrated that patients with cirrhosis who achieve SVR with DAA experience improvements in liver-related morbidity, HCC risk, and mortality. However, follow-up time for these studies is generally short. This analysis from the Gilead Cirrhosis Registry evaluates long-term outcomes in patients with cirrhosis who achieved SVR following treatment with a sofosbuvir-(SOF) based regimen.

**Methods:** Patients with cirrhosis who achieved SVR after receiving a SOF-based regimen were eligible for enrollment. Patients enrolled within 60 weeks of completing a treatment study or transfer from another SVR registry study, or within 2 years of achieving SVR following treatment in a clinical practice setting. Patients return for visits every 24 weeks for 5 years for laboratory, clinical, and radiographic assessments of durability of SVR and clinical progression of liver disease. In this abstract we report the HCC incidence, CTP scores, and SVR durability.

**Results:** As of 5 OCT 2017, 1564 patients have been enrolled in the cirrhosis registry. Mean age (range) is 59 (26-86) years, 68% are male, and 84% of patients had pretreatment CTP scores A. Median (range) of registry follow-up time was 53 (<1-144) weeks. Overall, there were 55 observed events of HCC in 3922 person-years (PYs) of follow-up since the start of DAA treatment (34 cases in 3292 PYs of follow-up for CTP-A patients and 21 in 601 PYs of follow-up for CTP B+C patients). Overall, patients with pretreatment CTP-A cirrhosis maintained CTP-A status while patients with pretreatment CTP B or C cirrhosis showed improvement.

**Conclusions:** In this ongoing registry of patients with cirrhosis who achieved SVR after treatment with a SOF-based regimen, HCC was uncommon and occurred more often in patients with decompensated cirrhosis. The majority of patients maintained or improved their CTP category relative to pretreatment through up to week 96.

Pretreatment	Registry Baseline, n=1476			Registry Week 48, n=966			Registry Week 96, n=315		
CTP Class, n (%)	CTP A	CTP B	СТР С	СТРА	CTP B	СТР С	СТРА	CTP B	СТР С
CTP A, n=1318	1211/125 0 (97)	37/1250 (3)	2/1250 (<1)	768/793 (97)	24/793 (3)	1/793 (<1)	256/260 (99)	4/260 (2)	0/260
СТР В, n=201	127/187 (68)	60/187 (32)	0/187	95/151 (63)	55/151 (36)	1/151 (<1)	32/48 (67)	16/48 (33)	0/48
CTP C, n=26	10/21 (48)	11/21 (52)	0/21	13/19 (68)	6/19 (32)	0/19	6/7 (86)	0/7	1/7 (14)

**Keywords:** Long-term outcomes, Compensated cirrhosis, Decompensated cirrhosis, Sofosbuvir, SVR

#### PO-054

#### Integrated Analysis of Elbasvir/Grazoprevir Clinical Trials in Korean Participants with Hepatitis C Virus Genotype 1b Infection

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**Aims:** All-oral direct-acting antiviral medications have transformed the treatment of hepatitis C virus (HCV) infection; however, local evidence is limited in some regions, including Korea. We conducted an integrated analysis of the efficacy of elbasvir (EBR)/grazoprevir (GZR) in Korean participants with HCV infection enrolled in EBR/GZR phase 3 clinical studies.

**Methods:** Participants with HCV GT1b infection enrolled at Korean study centers who received EBR/GZR 50 mg/100 mg for 12 weeks were included. The primary endpoint of all studies was sustained virologic response (HCV RNA <15 IU/mL) 12 weeks after end of therapy (SVR12) in the full analysis set (all participants who received  $\geq$ 1 dose of study medication).

Results: A total of 74 Korean participants were included. Mean age was 55 years (SD, 11 years), 25 (33.8%) had cirrhosis, and 70 (94.6%) were treatment-naïve. There were no participants with HCV/HIV coinfection. SVR12 was achieved by 73 of 74 (98.6%) participants; and only 1 participant, who withdrew consent, failed to achieve SVR12. Therefore, in the modified full analysis set (excluding participants who discontinued for reasons unrelated to study medication), SVR12 was 100% (73/73). SVR remined high among participants with cirrhosis (25/25, 100%), baseline viral load >2,000,000 IU/mL (34/34 (100%), and age >65 years (16/16, 100%). Baseline NS5A resistance associated substitutions (RASs) were detected in 16 of 73 participants (22%) who had a treatment outcome of SVR or virologic failure; all 16 achieved SVR12. Rates of SVR12 among Korean participants in this analysis (73/74, 98.6%) were similar to those in non-Korean Asian participants with GT1b infection (378/388, 97.4%), and to non-Asian participants with GT1b infection (589/608, 96.9%) enrolled in phase 2/3 EBR/GZR clinical trials.

**Conclusions:** The combination of EBR/GZR was highly effective in Korean participants with HCV GT1b infection, with high rates of SVR12 across all subgroups examined, including those with NS5A RASs.

Keywords: Hepatitis C, Elbasvir, Grazoprevir

#### PO-055

Rapid Virological Response, as a Predictor of Sustained Virologic Response of Sofosbuvir and Ribavirin in Korean Patients with Genotype 2 Chronic Hepatitis C Virus Infection

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**Aims:** The aim of this study is to investigate real-world data with sofosbuvir/ribavirin (SOF/RBV) in Korean patients with genotype 2 hepatitis C virus (HCV) infection and to investigate predicting factor of SVR 12.

**Methods:** 140 patients with genotype 2 chronic HCV infection treated with SOF/RBV were investigated prospectively. 400mg of SOF combined with weight adjusted RBV was administered for 12 weeks in patients without cirrhosis and for 16 weeks with cirrhosis. HCV RNA level was examined in pre-treatment, 4 weeks, end of treatment, and 12 weeks after end of treatment by RT-PCR method (COBAS<sup>®</sup> TaqMan<sup>®</sup> Analyzer, low detection limit,15 IU/mL; non-detection and below 15 IU/mL reported separately). The definition of rapid virological response (RVR) was defined as non-detection of HCV RNA at 4 weeks only.

Results: A total of 136 completed the treatment. 55 was male (40.4%) with a mean age of 61.6 ± 11.1 years. 99 (72.8%) were treatment naïve, 6 (4.4%) had a history of HCC, 23 (16.9%) had diabetes, and 33 (24.3%) had cirrhosis, of which had decompensation in 6. RVR was 77.9% (106/136), end of treatment response was 100% (136/136) and SVR12 was 96.0% (122/127). Of 5 with relapse, 4 were received 12 weeks of treatment and three of them did not reach RVR. Clinical factors associated with SVR12 were RVR status in multivariable analysis (P-value = 0.031). Contributing factors of RVR, cirrhosis, estimates glomerular filtration rate, and pre-treatment HCV RNA level were found to be significant. According to treatment duration, in 16 weeks treatment, SVR12 was not significantly different in RVR (-) and RVR (+) (94.7% vs. 100%, P-value = 0.483). However, in 12 weeks treatment, SVR12 was significantly higher in RVR (+) than RVR (-) (98.7% vs. 83.3%, P-value = 0.003). During treatment, 51/136 (37.5%) showed mild to moderate adverse events (urticaria, anemia, fatigue, insomnia, headache). 26 (19.1%) were reduced RBV dose due to anemia. Conclusions: SOF/RBV treatment in genotype 2 HCV was effective, tolerable and RVR is an important predictor of SVR12. 16 weeks of treatment would be better for patients without RVR.

**Keywords:** Chronic hepatitis C, Genotype 2, Sofosbuvir, Rapid virologic response

#### PO-056

#### The Risk of HBV Reactivation among HBV/HCV Co-Infected Patients Treated with Direct-Acting Antiviral Agents: A Single Center Experience

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**Aims:** As the number of reports of hepatitis B virus (HBV) reactivation increases in patients with HBV/HCV co-infection with direct-acting antiviral (DAA) agents, the US Food and Drug Administration has issued warnings about the potential risk of HBV reactivation in these patients. So far, there are very limited clinical data. We report the experience of DAA treatment in patients with HBV/HCV co-infection and factors affecting HBV reactivation during and after treatment with DAA.

**Methods:** We conducted a retrospective observational study of 62 patients with HBV/HCV co-infection between January 2005 and April 2018 at the Pusan National University Hospital. HBV reactivation was defined as  $\geq$ 1 log increase in HBV replication from baseline levels or a new appearance of HBV DNA in patients with previously undetectable levels.

Results: Of the 62 patients with HBV/HCV co-infection, 34 patients (54.8%) were treated with IFN and 24 patients (38.7%) with DAA agents. Of 24 patients treated with DAA, 15 patients (62.5%) were treatment naïve. SVR was 61.8% in IFN treated patients and 85% in DAA treated patients. The rate of HBV reactivation was higher in the patients treated with DAA after interferon (IFN) failed than the patients treated with IFN only [IFN only vs. DAA only vs. DAA after IFN failed 4/25 (16.0%) vs. 4/13 (30.8%) vs. 5/9 (55.6%) P=0.011]. HBV reactivation during or after DAA treatment was statistically significant more frequent in women (male vs. female; 4 vs. 9, P=0.008). However, the mean peak elevation of ALT after HBV reactivation was 41.3 IU/L (range 11-113 IU/L), and the hepatitis due to HBV reactivation did not occur among the patient with DAA agents. After HBV reactivation, HBV DNA levels did not rise further and remained at similar levels or were not detected.

**Conclusions:** HBV reactivation occurs more frequently in HBV/ HCV co-infected patients who were treated with DAAs compared with IFN-based therapy. However, hepatitis due to HBV reactivation was not occurred.

**Keywords:** Hepatitis C virus, Hepatitis B virus, Reactivation, Direct antiviral agent

#### PO-057

#### Predictors of Major Clinical Adverse Events in Genotype 1 Hepatitis C Patients Receiving Direct-Acting Antiviral Therapy: A Multicenter Cohort Study

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**Aims:** The aim of this study was to determine the factors associated with the development of major clinical adverse events in genotype 1 hepatitis C virus (HCV) infected Korean patients who received direct-acting antiviral (DAA) therapy in real clinical settings.

**Methods:** A total of 648 genotype 1 HCV infected patients who received DAA therapy between May 2016 and January 2018 at the liver units of the Catholic University of Korea were analyzed. Primary endpoints were hepatic decompensation and/or treatment discontinuation due to adverse events and the development of de novo hepatocellular carcinoma (HCC).

**Results:** The median follow-up period was 12.8 months (range, 1.3~34.8). 70.7% of the patients had chronic hepatitis and 29.3% compensated cirrhosis. Treatment discontinuation due to adverse events occurred in 2.8% (18/648), hepatic decompensation in 1.4% (9/648) and de novo HCC developed in 3.1% (19/620) of the patients. In multivariate analysis, baseline platelet count less than 150,000/mm<sup>3</sup> (*P*=0.022), estimated glomerular filtration rate (eGFR) less than 50 mL/min/1.73m<sup>2</sup> (*P*=0.037) and baseline serum albumin less than 3.5g/dL (*P*=0.035) were independently associated with hepatic decompensation and/or treatment discontinuation due to adverse events. Also, platelet count less than 150,000/mm<sup>3</sup> was independently associated with the development of de novo HCC (*P*=0.048).

**Conclusions:** Patients with low platelet count and serum albumin level, which are indicators of portal hypertension, and patients with renal impairment were more likely to experience hepatic decompensation and/or treatment discontinuation due to adverse events. Low platelet count was associated with de novo HCC development. These patients should be meticulously followed up during and after the DAA therapy.

**Keywords:** Hepatitis C, Adverse event, Decompensation, Hepatocellular carcinoma, Direct-acting antiviral

#### PO-058

FIB-4 at Sustained Virological Response Independently Predicts Hepatocellular Carcinoma Development among Chronic Hepatitis C Patients Treated with Interferon-Based Regimen

Hosoo Chun<sup>1</sup>, Beom Kyung Kim<sup>1,2,3</sup>, Jun Yong Park<sup>1,2,3</sup>, Do Young Kim<sup>1,2,3</sup>,Sang Hoon Ahn<sup>1,2,3</sup>, Kwang-Hyub Han<sup>1,2,3</sup>, and Seung Up Kim<sup>1,2,3</sup>

<sup>1</sup>Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; <sup>2</sup>Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; <sup>3</sup>Yonsei Liver Center, Severance Hospital, Seoul, Korea **Aims:** Liver fibrosis is associated with an increased risk of hepatocellular carcinoma (HCC) development. We investigated the predictors of HCC development at the time of sustained virological response (SVR) among chronic hepatitis C (CHC) patients.

**Methods:** Between 2003 and 2016, 669 CHC patients achieved SVR through interferon-based regimens. The predictors of HCC development was assessed using Cox proportional hazards regression model.

Results: After SVR achievement, HCC developed in 19 (2.8%) patients. Patients with HCC had older age (mean 67.7 vs. 59.4 years), higher proportion of male gender (89.5 vs. 42.3%), liver cirrhosis (57.9 vs. 15.5%), hypertension (52.6 vs. 23.1%), and diabetes (36.8 vs. 16.5%), lower platelet count (mean 120 vs. 182 109/L), higher alpha-fetoprotein (mean 8.5 vs. 3.4 ng/mL), higher aspartate and alanine aminotransferase (mean 42.7 vs. 23.6 IU/L and mean 33.1 vs. 19.8 IU/L), lower total cholesterol (mean 161.8 vs. 182.7 mg/dL), and higher FIB-4 level (mean 7.0 vs. 2.2) (all P<0.05). On multivariate analysis, FIB-4 independently predicted HCC development (hazard ration=1.072; 95% confidence interval, 1.027-1.120, P=0.002), together with male gender, hypertension, and alpha-fetoprotein (all P<0.05). When the study population was stratified into three groups with different risk of significant fibrosis according to FIB-4 level (<1.45 with low-risk, 1.45–3.25 with intermediate-risk,  $\geq$  3.25 with highrisk), the cumulative incidence rate of HCC significantly different between the groups (all P<0.05 by log-rank tests).

**Conclusions:** The assessment of fibrotic burden using FIB-4 at the time of SVR might be useful for the risk stratification of HCC development in CHC patients.

**Keywords:** FIB-4, Hepatitis C, Sustained virological response, Hepatocellular carcinoma

[Group 2] June 16, 2018 | 15:00-16:00

HCV & Infectious disease

#### PO-059

Efficacy and Tolerability of Elbasvir/Grazoprevir and Ombitasvir/Paritaprevir/Ritonavir with Dasabuvir in HCV Genotype I-Infected Korean Patients : Analyses in Real-Life Settings

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<sup>1</sup>Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea; <sup>2</sup>The Catholic University Liver Research Center **Aims:** Elbasvir/grazoprevir (EBR/GZ) and ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r+DSV) were recently approved for treatment of hepatitis C virus (HCV) genotype (GT) 1 infection in Korea. This study evaluated the efficacy and tolerability of the newer direct-acting antivirals (DAAs), EBR/GZ and OBV/PTV/r+DSV, compared to daclatasvir with asunaprevir (DAC+SUN) and ledipasvir/sofosbuvir (LDV/SOF)±ribavirin (RBV) in a large real-world cohort.

**Methods:** A total of 845 patients with HCV GT 1 infection who received interferon-free DAA regimens between 2015 and 2018 were consecutively enrolled. Treatment responses and adverse events (AEs) were compared between the DAA groups. The characteristics related to sustained virological response 12 weeks off therapy (SVR12) were analyzed.

**Results:** Mean age was 59.3±12.2 years and 45.4% (384/845) of patients were male and 29.7% (251/845) of patients had cirrhosis. Among 845 patients, 531 received DAC+SUN, 128 EBR/ GZ, 64 OBV/PTV/r+DSV and 66 LDV/SOF±RBV in GT 1b. The SVR rates in GT 1b were 94.6% (423/447) in patients treated with DAC+SUN, 95.2% (20/21) with EBR/GZR, 100% (18/18) with OBV/PTV/r+DSV and 98.3% (57/58) with LDV/SOF±RBV. In subgroup analyses, there were no differences in SVR12 across DAA regimens, in terms of prior treatment experience, the presence of cirrhosis or CKD/ESRD, or patient age. However, higher SVR 12 rates were observed in patients with EBR/GZ or OBV/ PTV/r+DSV than those with other DAAs among the groups with high baseline viral load (>800,000 IU/ml) and NS5A RASs. Overall, EBR/GZ and OBV/PTV/r+DSV were well-tolerated and only one (0.78%) patient receiving EBR/GZ discontinued treatment due to skin rash and no patient receiving OBV/PTV/r+DSV discontinued treatment due to possible drug-related side effects, whereas 15 (2.82%) patients receiving DAC+SUN discontinued treatment due to possible drug-related side effects. Grade 3 AEs for AST/ALT elevation were identified in one (0.78%) patient in EBR/GZ group, no one in OBV/PTV/r+DSV group, 14 (2.64%) in DAC+SUN group and one in LDV/SOF±RBV group. For 45 GT 1a-infected patients, all (100%) achieved SVR12 with LDV/SOF±RBV (28/28) and OBV/PTV/r+DSV (4/4) regimens. All well tolerated DAAs with no grade 3 AEs or discontinuation. Conclusions: Newer DAAs, EBR/GZ and OBV/PTV/r+DSV, are safe and highly efficient for HCV GT-1 across a diverse patient population. Difficult-to-treat patient characteristics, such as cirrhosis, prior failed therapy, high baseline viral load, and NS5A RASs do not seem to impact SVR12 to these DAAs

**Keywords:** HCV, Genotype 1, Elbasvir/Grazoprevir, Ombitasvir/ Paritaprevir/Ritonavir with Dasabuvir

#### PO-060

#### Changes in Lipid Profiles of Patients with Chronic Hepatitis C after Therapy with Direct Acting Antiviral (DAA)

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**Aims:** Chronic hepatitis C virus (HCV) infection is associated with lipid metabolism, suggesting that host lipids play a central role in viral replication. The aim of this study was to investigate the influence of direct acting antiviral (DAA) treatments on lipid profiles in HCV infection.

**Methods:** In total, 107 patients were underwent DAA treatment between September. 2015 and October. 2017 at Soon Chun Hyang University Hospital. The lipid profiles of those who achieved sustained virologic response (SVR) were evaluated before DAA treatment, at the end of treatment, and 12 weeks after the end of treatment. The treatment regimen included 24wk of daclatasvir plus asunaprevir (DCV + ASV) or 12wk of sofosbuvir plus ribavirin (SOF + R) or elbasvir/grazoprevir or ledipasvir/sofosbuvir.

**Results:** SVR was achieved in 37 (97.4%) of 38 patients treated with DCV + ASV, 42 (93.3%) of 45 patients treated with SOF + R, 11 (91.7%) of 12 patients treated with elbasvir/grazo-previr and 12 (100%) of 12 patients treated with ledispasvir/ sofosbuvir. After DAA treatment, triglyceride (TG) was elevated from 108.59  $\pm$  61.53 to 132.14  $\pm$  185.60 (*P*<0.001), total cholesterol (TC) was elevated from 171.23  $\pm$  31.22 to 190.17  $\pm$  33.98 (*P*<0.001), high-density lipoprotein cholesterol (HDL) was elevated from 47.16  $\pm$  13.75 to 49.92  $\pm$  12.79 (*P*<0.001) and low-density lipoprotein (LDL) was elevated from 103.22  $\pm$  26.93 to 115.14  $\pm$  29.03 (*P*<0.001). However, there were no significant changes in the TG, TC, HDL and LDL levels regardless of the treatment regimen.

**Conclusions:** Since eradication of HCV reduces the quantity of lipid combined with HCV, comparisons of lipid profiles after treatment showed similar increases in TG, TC, HDL and LDL levels between DCV + ASV, SOF + R, elbasvir/grazoprevir and ledispasvir/sofosbuvir.

**Keywords:** Hepatitis C, Direct acting antiviral treatment, Lipid profile, Dysplipidemia

#### PO-061

#### Efficacy and Safety of Direct-Acting Antivirals for Treatment of Chronic Hepatitis C Patients

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**Aims:** Direct-acting antiviral (DAA) therapy achieves high rate of sustained virologic response (SVR) and favorable outcomes in chronic hepatitis C (CHC) patients. We investigated virologic response and its clinical impact in CHC patients.

**Methods:** CHC patients with compensated liver function who were treated with DAAs were included for the retrospective

analysis during 2016-2017. We analyzed SVR12 (undetectable HCV RNA after 12 weeks after completion of therapy) and virologic and biochemical response at baseline, treatment 4 week, end of treatment and post-treatment 12 week. Fibrosis was measured by using fibroscan. Adverse events were monitored during the treatment period.

Results: A total of 135 patients (61.5% with GT1b and 38.5% with GT2a) were enrolled and treated. 47.4% were male, 79.3% were treatment naive, and 30.4% had cirrhosis. SVR 12 was 97.6% (81/83) in the GT1b and 98.1% (51/52) in the GT2a; treatment with Daclatasvir + Asunaprevir was the most commonly used in GT1b (55/83) and with sofosbuvir + ribavirin was the most commonly used in GT2a (49/52). The median changes of liver stiffness measurement of the two time points using the signed rank test were -3.2 kPa in patients who had both fibroscan score before treatment and SVR 12. The most common adverse events were anemia, dyspepsia and nausea. One GT2a patient treated with sofosbuvir + ribavirin stopped treatment at 8 weeks due to symptomatic bradyarrhythmia, however, he recovered spontaneously and achieved SVR 12. Conclusions: Direct-acting antiviral (DAA) treatment of chronic hepatitis C genotype 1b, 2a resulted in high rate of sustained virologic response and improvement of liver fibrosis.

**Keywords:** Chronic hepatitis C, Direct-acting antiviral (DAA), SVR 12,

#### PO-062

### The Optimal Management of Pleural Effusion in Liver Abscess?

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**Aims:** We investigated the characteristics and clinical features of pleural effusion in patients with liver abscess.

**Methods:** This is a retrospective study conducted in a single center to evaluate the characteristics and management of pleural effusion in patients with liver abscess hospitalized between January 2006 and February 2018 at Soonchunhyang University Seoul Hospital. A total of 526 patients were collected. Of these, 156 patients diagnosed as eosinophilic abscess or later cholangiocarcinoma or liver metastasis were excluded from the analysis. Finally, the clinical, radiological, and laboratory findings were analyzed in total of 370 patients in liver abscess.

**Results:** Of the patients with liver abscess, 110 (29.7%) patients had pleural effusion. Among of these, 56.4% occurred in right, 5.5% in left and 35.5% in both. When pleural effusion was present, age (older age, P=0.046), liver abscess size (43.01 vs. 59.48mm, P=0.000) and location (right superior segment, P=0.000) were significantly different from those without. Most of patients (96 patients) were treated with only antibiotics and 14 patients underwent intervention with antibiotics for pleural effusion. Of the 13 patients who were able to perform fluid analysis, 11 (84.6%) were exudate and 2 (15.4%) were transudate. Duration of pleural effusion showed no significant difference between the groups that performed intervention and those who were treated with antibiotics only (17.79 vs. 12.35 days, P= 0.112).

**Conclusions:** The pleural effusion was more frequent in older patients, larger size and right superior segment. There was no statistically significant difference in duration of pleural effusion between intervention and non-intervention group. Therefore, treatment of pleural effusion is thought to be sufficient for antibiotics without special intervention in patients with liver abscess. **Keywords:** Liver abscess, Pleural effusion, Management

#### PO-063

#### The Clinical Features of Multidrug-Resistant Bacteria Induced Pyogenic Liver Abscess

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**Aims:** Pyogenic liver abscesses (PLA) remain a potentially significant clinical problem. Although multidrug-resistant organisms (MDROs) are increasingly being observed worldwide, little is known about the incidence and clinical features of MDR bacteria induced PLA. Aim of this study is to provide characteristics of PLA with MDR isolates.

**Methods:** A retrospective study of patients diagnosed with PLA from 2008 to 2017 in Hallym University Medical Center in Korea was performed to characterize PLA. The demographic and clinical features, laboratory and imaging findings, management and clinical outcomes, antimicrobial susceptibility profile of causative bacterial species were studied.

**Results:** Overall, 745 patients were included. 53.1% of PLA aspirate cultures were positive, with Klebsiella pneumonia (71% of positive cultures) being the main organism. MDROs were found in 53 (7.1%) patient, extended-spectrum beta-lac-

tamase (ESBL) producing Gram-negative bacteria was most common (77.3% of MDROs; Klebsiella pneumonia 41.5%, Escherichia coli 58.5%). The group with MDR isolates showed old age (62.3±15.1 vs. 68.9 ±14.3, P=0.002), a lower systolic/ diastolic blood pressure, hypoabluminemia (3.4±0.6 vs. 3.2±0.5, P=0.005), a higher alkaline phosphatase levels (248.1±226.8 vs. 326.9±312.2, P=0.018), a longer hospitalization (23.3±14.4 vs. 29±13.8, P=0.005) and a longer parenteral antibiotic treatment period than the non- MDR group (n=612). Biliary origin of liver abscess, previous history of hepatobiliary procedure and concomitant malignant disease were associated with MDRO induced liver abscess. In multivariate analysis, previous history of hepatobiliary procedure (relative risk, 2.73; 95% CI, 1.124 to 6.645; P=0.027) and concomitant malignancy (relative risk, 3.81; 95% CI, 1.539 to 9.47; P=0.004) were risk factors. Moreover, in-hospital mortality rate was higher in of MDR group (13.2% vs. 3.8%, P=0.007).

**Conclusions:** Our study demonstrates that patients with MDR bacteria induced PLA may have poor prognosis. Thus, microbiological diagnostics is pivotal to tailor individual treatment regimen, especially in the patient with previous history of hepatobiliary procedure and concomitant malignancy.

**Keywords:** Pyogenic liver abscess, Multidrug-resistant organisms, Extended-spectrum beta-lactamase

#### PO-064

#### Colorectal Neoplasm in Patients with Pyogenic Liver Abscess: Prevalence, Etiology and Associate Factor

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**Aims:** Pyogenic liver abscesses (PLA) is known to be caused by disruption of the colon mucosa with secondary bacteremia via the portal route, as occurs for example in tubular adenoma or colorectal cancer. This large scale population based study aim to investigate clinical characteristics of patients with both colorectal neoplasm and PLA.

**Methods:** We reviewed medical records of 256 patients with PLA who underwent screening colonoscopy but was not diagnosed cancer excluding colorectal cancer by imaging study, from January 2004 to January 2018. Differences between patients with and without colorectal cancer or high grade dysplasia were evaluated in baseline demographics, imaging, pathogens and mortality.

**Results:** Of the total patients, 7.8% (n=20) were diagnosed with adenocarcinoma, 2.3% (n=6) had adenomatous polyp with high grade dysplasia and 16% (n=41) had adenomatous polyp with low grade dysplasia only. More frequent diabetes mellitus was observed in group with colorectal cancer or high grade dysplasia (14/26 vs. 70/230 patients, *P*=0.026). There were significant differences in serum glucose, HbA1C, he-

moglobin, carcinoembryonic antigen and age, hospitalization period, mortality, compared two groups. But no significant differences were found in abscess size, abscess location, liver biochemical test excluding serum albumin. 66.8% of the patients presented growth in culture The most common isolated pathogen were Klebsiella pneumonia but was not differ between groups(15/26 vs. 118/230 patients, P=0.342).

#### Table1. Clinical characteristics of patients with pyogenic liver abscess

	Group A	Group B	p-value
N (%)	26(10.2%)	230(89.8%)	
Age (median, yr)	66	55	0.001
Sex (man, n)	18	164	0.822
DM (person, n)	14	70	0.026
HTN (person, n)	11	85	0.67
Biliary disease (person, n)	2	15	0.952
Abscess size(median, mm)	43	45	0.423
Abscess location (person, n)			
Right lobe	17	176	0.405
Lt lobe	7	38	
Both lobe	2	16	

Group A: pyogenic liver abscess with colon cancer or high grade dysplasia Group B: pyogenic liver abscess without colon cancer or high grade dysplasia

Table 2.	Baseline	laboratory f	inding of	patients	with pyoger	ic liver
abscess						

	Group A	Group B	p-value
Hb (g/dL, median)	11.8	12.6	0.037
PLT (/uL, median)	248,000	216,000	0.159
WBC (/uL, median)	12,250	12,100	0.576
AST (IU/L, median)	40.5	46.5	0.301
ALT (IU/L, median)	41	47	0.148
ALP (IU/L, median)	127	154	0.535
GGT (IU/L, median)	102.5	141	0.533
Bilirubin (mg/dL, median)	0.84	1.01	0.346
Albumin (g/dL, median)	3.4	3.7	0.035
Prothrombin time (INR, median)	1.11	1.12	0.671
CRP (mg/dL, median)	137.66	188.14	0.083
Cr (mg/dL, median)	0.71	0.8	0.495
Glocose (mg/dL, median)	149	122	0.021
HbA1C (%, median)	6.95	6.1	0.005
CEA (ng/mL, median)	1.9	1	0.001

Group A: pyogenic liver abscess with colon cancer or high grade dysplasia Group B: pyogenic liver abscess without colon cancer or high grade dysplasia

<b>Table 3.</b> Causative pathogens of patients with pyogenic liver abscess	fable 3. (	Causative	pathogens	of patients	with pyogenic	liver abscess
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Bacteria		Group A	Group B	p-value
No growth		2	11	
Klebsiella		15	118	0.342
Streptococcus		5	42	0.54
Escherichia coli		4	42	0.48
Enterococcus		2	8	
Gemella morbillorum		1	5	
Pseudomonas		1	2	
Acinetobacter		2	9	
Bacteroides		1	4	
Staphylococcus		1	11	
Enterobacter			8	
Citrobacter freundii			2	
Haemophilus			3	
Stenotrophomonas			2	

Group A: pyogenic liver abscess with colon cancer or high grade dysplasia Group B: pyogenic liver abscess without colon cancer or high grade dysplasia **Conclusions:** We found that the prevalence of colorectal neoplasm among the patients with PLA was similar or higher than other studies. Screening colonoscopy should be considered for colorectal neoplasm in patients with PLA, especially for patients with diabetes mellitus.

**Keywords:** Pyogenic liver abscesses, Colorectal neoplasm, Screening colonoscopy, Pathogen

#### [Group 3] June 16, 2018 | 15:00-16:00

#### Cirrhosis

#### PO-065

### Epidemiological Shift of Hepatitis A Infection: A Single Tertiary Center Experience

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**Aims:** As one of the most common causes of acute hepatitis, the number of hepatitis A (HAV) infection had been significantly increased from the early 1990s to the late 2000s. However, the improved socioeconomic conditions and interest for personal hygiene have contributed to the changes of incidence and epidemiology of HAV infection. Therefore, this study aimed to assess whether the epidemiology of HAV infection has been changed over the last decade.

#### Table 1. The clinical features of acute hepatitis A from 2008 to 2017

Characteristic	Total (n=625)	2008-2012 (n=473)	2013-2017 (n=152)
Sex			
Male	388 (62.1)	301 (63.6)	87 (57.2)
Female	237 (37.9)	171 (36.2)	65 (42.8)
Mean age, yr	32.1	31.2	34.7
Age1			
~19	19 (3.0)	15 (3.2)	4 (2.6)
20~29	254 (40.6)	215 (45.5)	39 (25.7)
30~39	244 (39.0)	180 (38.1)	64 (42.1)
40~49	93 (14.9)	55 (11.6)	38 (25.0)
50~59	15 (2.4)	8 (1.7)	7 (4.6)
60~	0 (0)	0 (0)	0 (0)
Season2			
Spring	227 (36.3)	171 (36.2)	56 (36.8)
Summer	185 (29.6)	157 (33.2)	28 (18.4)
Fall	104 (16.6)	65 (13.7)	39 (25.7)
Winter	109 (17.4)	80 (16.9)	29 (19.1)

Values are presented as number (%), unless indicated otherwise.

<sup>1</sup>Age:  $\chi^2$  = 29.58; P<0.001. <sup>2</sup>Season:  $\chi^2$  = 18.62; P<0.001.

Methods: Clinical information and data of the patients with acute HAV infection were collected retrospectively from 625

patients consecutively enrolled at the Chungnam National University Hospital, Daejeon, Korea, between January 2008 and December 2017. We divided the patients into two five-year-period groups and analyzed the characteristics.

**Results:** The clinical features of the patients with HAV infection are shown in Table 1. In comparison with the patients in the early five years, the incidence of HAV infection had been obviously decreased during the late five years. At the same time, age distribution and seasonal differences among study population had significantly been changed ( $\chi^2 = 29.58$ ; *P*<0.001 and  $\chi^2 = 18.62$ ; *P*<0.001, respectively).

**Conclusions:** Although the overall incidence of HAV infection has been decreased with time, the clinical characteristics apparently show the epidemiological shift to the older ages. Modification of strategies for HAV vaccination could be encouraged. **Keywords:** Hepatitis A

#### PO-066

#### The Survival of Patients with HVPG >12mmHg in Real Clinical Practice-Focusing on "with or without Gastroesophageal Varices"

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**Aims:** In patients with gastroesophageal varices (GEV), an hepatic venous pressure gradient (HVPG)>12mmHg identifies the risk of variceal hemorrhage (VH). However, although HVPG >12mmHg, some patients do not have GEV according to the different type of the portosystemic collateral vessles. We investigated the clinical outcome in patients with HVPG >12mmHg based on the presence of GEV in real clinical practice.

**Methods:** Of 572 patients performed with HVPG measurement between 2008 and 2013, 359 patients with HVPG >12mmHg were subsequently collected. The 359 patients were divided into 2 groups according to the presence of GEV. We analyzed the survival between 2 groups and the predictive factors for survival in these patients.

**Results:** Among the 359 patients, 302 (84.1%) had GEV and 57 (15.9%) had not. There were 69 cases of death (62 in GEV

group, 7 in non GEV group). The 1,3,5 year survival rate were 93.0%, 82.8% and 79.8% in GEV group, and 95.9%, 85.7% and 85.7% in non GEV group, respectively. As for the cause of death, VH was the most common (21, 33.9%), followed by hepatorenal syndrome (12, 19.4%) and hepatic failure (9, 14.5%) in GEV group. In non GEV group, hepatic failure (5, 71.4%) was the most common. However, there was no significant difference in survival between 2 groups (P=0.074)(Figure 1). To investigate the predictive factors for survival, the presence of GEV, VH, HVPG values, MELD score, CP score, and the cause of liver cirrhosis were analyzed. In multivariate analysis the CP score was the only significant factor for survival [Harzard ratio 1.343 (95% confidence interval 1.096-1.647), P=0.005].



Figure 1. Cumulative survival according to the presence of GEV in HVPG > 12mmHg

**Conclusions:** In patients with HVPG >12mmHg, 57(15.9%) patients had not GEV, and the presence of GEV did not show significance for survival. The Child-Pugh Score was the only predictive factor for the survival in these patients.

**Keywords:** Gastroesophageal varices, Hepatic venous pressure gradient, Variceal hemorrhage, Survival

#### PO-067

#### Splenoadrenal Shunt for Noncirrhotic Portal Hypertension

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**Aims:** Portosystemic shunt surgery is an established treatment option for preventing variceal rebleeding in patients with noncirrhotic portal hypertension(NCPH). The proximal splenorenal shunt is a widely performed procedure in these patients. In this study, the use of adrenal vein as an alternative conduit has been investigated.

**Methods:** A retrospective analysis of patients with NCPH who underwent proximal splenoadrenal and splenorenal shunt between 2011 and 2015. clinical presentation, intraoperative findings, postoperative morbidity, and shunt patency were studied and compared between the two groups. All patients were followed up for a minimum of 12 months. **Results:** 97 patients with NCPH underwent shunt surgery (proximal splenoadrenal shunt,8; proximal splenorenal shunt,74; and interposition mesocaval shunt, 15). Anomalous anatomy of the left renal vein was the main indication(5/8 patients) for a splenoadrenal shunt. Median fall in portal pressure in patients who underwent splenoadrenal shunt was 11.5 mmHg(range, 2-14 mmHg). The median (range) operative time was 4.5 (3-6) hours and median(range) intraoperative blood loss was 160(100-200) mL. During a median (range) follow-up of 32(12-48) months, shunt thrombosis developed in one patient. Comparison of intraoperative parameters and postoperative outcomes showed no significant difference in median fall in portal pressure( P=0.39), median operative time (P=0.51), median blood loss( P=0.80), Grade III/IV postoperative complications (P=0.56), shunt thrombosis (P=0.93), and varices regression rate (P=0.72) between patients undergoing proximal splenorenal and splenoadrenal shunt.

**Conclusions:** Left adrenal vein is a suitable vascular conduit for porto-systemic shunt surgery, particularly if the performance of splenorenal shunt is precluded because of anatomic abnormality of the renal vein.

#### PO-068

#### Evaluation of Treatment Response after Endoscopic Variceal Obturation with Abdominal Computed Tomography

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**Aims:** Current guidelines recommend endoscopic variceal obturation (EVO) as the treatment of choice for the management of bleeding from gastric varices (GV). This study was performed to evaluate the usefulness of CT for the prediction of rebleeding after EVO for GV bleeding.

**Methods:** Patients who were treated with EVO for GV bleeding and performed CT before and after EVO were included. Those with a previous history of endoscopic treatment for bleeding from GVs (n=4) and those with accompanying portal vein invasion by hepatocellular carcinoma (HCC) (n=9) or other malignancy (n=7) were excluded.

**Results:** Fifty-three patients were included. Age was 60.6±11.6 years and 40 patients (75.5%) were men. Alcoholic liver disease was the most frequent underlying liver disease (24 patients, 45.3%). Complete impaction of cyanoacrylate in GVs and in the feeding vessels were achieved in 40 (75.5%) and 24 (45.3%) of patients, respectively. During the follow-up, GV rebleeding occurred in 9 patients and the cumulative incidences of GV rebleeding at 3, 6, and 12 months were 11.8%, 18.9%,

and 18.9%, respectively. GV rebleeding rate did not differ significantly according to the complete cyanoacrylate impaction in GV, while it differed significantly according to the complete cyanoacrylate impaction in feeding vessels: the cumulative incidences of GV rebleeding at 3, 6, and 12 months were 22.3%, 35.2%, and 35.2%, respectively, in patients with incomplete cyanoacrylate impaction in feeding vessels and there was no rebleeding during the follow-up period in patients with complete cyanoacrylate impaction in feeding vessels (*P*=0.002)

**Conclusions:** Abdominal CT was useful in evaluation of treatment response after EVO for GV bleeding. Because incomplete cyanoacrylate impaction in feeding vessels is the risk factor of GV rebleeding, detailed evaluation of feeding vessels on CT after EVO and determination of additional treatment is needed.

**Keywords:** Computed tomography, Cyanoacrylate, Gastric varices, Lipiodol

#### PO-069

#### Performance of Shear-Wave Elastography to Detect High-Risk Esophageal Varices in Cirrhosis Is Improved by Spleen Stiffness Estimation

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**Aims:** There is considerable interest in developing non-invasive models to predict the presence of varices. Liver and spleen stiffness measured by 2dimensional shear-wave elastography (2D-SWE) have become Methods: of interest with good reliability in detecting portal hypertension. In this regard, measurement of the spleen stiffness reflects more accurately the dynamic changes occurring in advanced stages of cirrhosis compared to liver stiffness. We investigated the feasibility of liver- and spleen-SWE for diagnosis of esophageal varices (EV) and detection of high-risk varices.

**Methods:** A total of 191 cirrhotic patients who underwent liver stiffness, spleen stiffness measurements, using 2D-SWE (APLIO 500, Toshiba), along with endoscopic screening were included in this study. Large EV (F2 or F3) or F1 with red colour sign were defined as high-risk EV.

**Results:** EV was present in 130 patients (68.1%). For the presence of EV, the stiffness in liver-SWE had better diagnostic accuracy than the stiffness in spleen-SWE (the area under the receiver-operating characteristic curve (AUC), 0.830 vs. 0.740; Delong test, P=0.050). The best cut-off values in detecting of EV were 14.1kPa: liver-SWE and 16.5kPa: spleen-SWE. Increasing stiffness in spleen-SWE was proportionally correlated with grade of EV, whereas the stiffness in liver-SWE was not. For the presence of high-risk EV, the AUC in spleen-SWE was higher than liver-SWE (0.764 vs. 0.742), but not significantly different.

Then, the strongest association was found between high-risk EV and spleen-SWE (r=0.397, P<0.001), with the next strongest association found for Child-Turcotte-Pugh score (r=0.353, P<0.001) and liver-SWE (r=0.314, P<0.001). The best cut-off values for predicting high-risk EV were 14.3kPa: liver-SWE and 22.1kPa: spleen-SWE.

**Conclusions:** In patients with cirrhosis, stiffness measurements obtained by using 2D-SWE have effective non-invasive method for detection of EV. Moreover, the stiffness in spleen-SWE might be a better diagnostic value than liver-SWE for high-risk EV that requires prophylactic therapy.

**Keywords:** Liver cirrhosis, Esopahgeal varix, Shear-wave elastography, Spleen stiffness

#### PO-070

#### Prediction of Esophageal Varices Using Non-Invasive Methods: Including Liver Stiffness by Two-Dimensional Shear Wave Elastography

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**Aims:** The Baveno VI guidelines proposed that esophagogastroduodendoscopy(EGD) for screening esophageal varices(EV) can be avoided if liver stiffness(LS) measured by transient elastography(TE) is less than 20 kPa and platelet count is greater than 150,000 cells/ $\mu$ L. However while validation of TE is well proven, 2D-SWE has not been sufficiently validated for EV prediction. The aim of this study is to predict the presence of EV by non-invasive tools combined with 2D-SWE and to compare the diagnostic capabilities with TE.

**Methods:** Between January 2015 and October 2017, 258 patients with compensated advanced chronic liver disease(cACLD) who underwent 2D-SWE and EGD consecutively were enrolled. The AUROC was calculated to evaluate the accuracy of the prediction for the presence of EV using 2D-SWE, model combining 2D-SWE and platelet count(PC), liver stiffness to spleen/platelet score (LSPS) score and platelet-spleen ratio (PSR) score. 177 patients who underwent simultaneous TE examination were on the subgroup analysis was done.

**Results:** The mean age was 56.8±10.7 years and most common etiology was chronic hepatitis B (45.0%). 83.1% of patients were in Child class A. Prevalence of all-size varices was 41.1%. 2D-SWE alone has good ability to discriminate varices (AUROCs : 0.750, 95% CI, 0.690 to 0.809). Model combining 2D-SWE with platelet count and LSPS using 2D-SWE has better discriminative ability for varices and AUROCs were 0.793

(95% CI, 0.738 to 0.848) and 0.813 (95% CI, 0.760 to 0.865) respectively. For 177 patients who performed TE and 2D-SWE simultaneously, there was no difference in predictive abilities when other factors such as albumin, bilirubin, ALT, Platelet count, hemoglobin, spleen diameter were adjusted in multivariate analysis.

**Conclusions:** 2D-SWE combined with platelet count and LSPS seemed to be useful to predict EV. In addition, 2D-SWE has similar diagnostic performance with TE for predicting presence of EV.

Keywords: 2D-SWE, Varix, Baveno, Liver stiffness

[Group 4] June 16, 2018 | 15:00-16:00

Liver Cancer, Basic

#### PO-071

## Exosomal microRNA Derived from Hepatocellular Carcinoma Cells Regulates Pathways Associated with Cancer Progression

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**Aims:** Exosome plays important role in cell-to-cell communication. MicroRNAs in tumor-derived exosome appear to play an important role in cancer progression. The present study explored the differentially expressed microRNA profiles between hepatocellular carcinoma (HCC)-derived exosome (HEX) and normal hepatocyte-derived exosome (NEX) and investigated the target genes for microRNAs in HEX by using network analysis.

**Methods:** Exosomes were isolated from human HCC cell lines (Hep3B and Huh-7) and immortalized normal hepatocyte cell line (THLE-2). Exosomal small RNAs were extracted and differentially expressed exosomal microRNAs between HEX and NEX were screened by using Ilumina Hiseq2000 deep sequencing. Ingenuity Pathway Analysis (IPA) software was used to identify the microRNA regulatory network analysis.

**Results:** A total of 1,830 differentially expressed microRNAs in HEX were identified by deep sequencing. Among them, top 30 up-regulated and top 30 down-regulated exosomal microRNAs were identified in each Huh-7 and Hep3B. By using the differentially expressed microRNA profiles, network analyses were performed. Finally, SMAD3, IFNGR1, and WWP1 were identified as over-expressed hub gene in target network in Hep3B derived exosomal microRNA, while IGF1R, RAC1, and TNF were predicted as over-expressed hub gene in Huh-7 derived exosomal microRNA network.



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**Conclusions:** In conclusion, HCC derived exosomal microRNAs could have a central role in HCC progression by acting on the oncogenic pathways. Several key genes for HCC progression were successfully identified by regulatory network analysis of microRNA in HCC derived exosome.

**Keywords:** Hepatocellular carcinoma, Exosome, microRNA, Network analysis

#### PO-072

#### Adipocyte-Derived FABP4 Regulates of Cancer Stemness and Drug Resistance in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is one of the deadliest cancers in the world. Increasing reports showed significant cor-

relation between non-alcoholic fatty liver disease (NAFLD) and HCC development. Given cancer stem cells (CSCs) play a critical role in regulating the tumor relapse and therapeutic resistance, we hypothesize that adipocytes, one of the key cellular factors within the tumor microenvironment, may play a critical role in HCC pathogenesis via regulation of liver CSCs.

**Methods:** We have employed a co-culture system to dissect the potential cross-talk between fully differentiated adipocytes and HCC cells. The conditioned medium (CM) of adipocytes was collected to examine the potential paracrine effect of adipocytes in regulating liver CSCs. The secretome of adipocytes was analyzed by using Orbitrap Liquid Chromatography-Mass spectrometry. Molecular pathway mediating the phenotypic alterations was identified through RNA sequencing analysis and functional rescue experiments.

**Results:** Using co-culture system, we found that adipocytes enhanced the self-renewal and tumorigenicity of HCC cells through paracrine secretion. Consistently, conditioned medium of adipocytes showed enhanced tumorigenicity, self-renewal, invasiveness and resistance to doxorubicin and sorafenib treatment. By Orbitrap Liquid Chromatography-Mass spectrometry, we identified 209 proteins, among which we have focused on FABP4 as it is preferentially secreted from adipocytes. Consistently, recombinant FABP4 enhanced CSC properties of HCC cells; while FABP4 inhibitor (BMS309403) abolished the CSC enhancing effect of CM of adipocytes. Clinically, FABP4 overexpression was significantly correlated with poorer patients survival.

**Conclusions:** We demonstrated the pivotal role of adipocytes on regulation of liver CSCs through paracrine secretion. Adipocyte-derived FABP4 signaling cascade may be a novel therapeutic target for treatment of NAFLD induced HCC.

Keywords: Adipocytes, Cancer, Drug resistance, Stemness

#### PO-073

#### UBE2T: A Molecular Regulator for Cancer Stemness in Hepatocellular Carcinoma

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**Aims:** Increasing evidence showed that cancer stem cells (CSCs) play a critical role in regulating the tumor relapse and therapeutic resistance of hepatocellular carcinoma (HCC). Given high molecular similarities between liver CSCs and normal liver stem cells, we have enriched the normal stem cell populations by establishing a mouse partial hepactectomy model order to identify critical molecules involved in regulation of liver CSCs. By comparing the expression profiles between the early regenerating liver and intact one, UBE2T was found to be highly upregulated. This, together with the data showing upregulation of UBE2T in enriched liver CSC populations, suggest the role of UBE2T on regulating liver CSCs.

**Methods:** We evaluated the clinic-pathological relevance of UBE2T by qPCR, western blot and immunohistochemical analyses. Lentiviral-based overexpression and knockdown approaches were performed to characterize the functional roles of UBE2T in regulating liver CSCs. The protein binding partner of UBE2T was identified by mass spectrometry analysis.

**Results:** By qPCR analysis, UBE2T mRNA overexpression is found in over 90% of HCC samples and is associated with aggressive tumor behavior and poorer patients' survival. Overexpression of UBE2T protein level in HCC clinical samples was further confirmed by western blot and IHC analyses. Using lentiviral based knockdown approach, suppression of UBE2T inhibited liver CSC properties, including self-renewal, tumorigenicity, drug resistance and expression of liver CSC markers. Using orthotopic liver xenograft model, UBE2T suppression led to decrease in tumor burden as well as lung metastasis *in vivo*. Mechanistically, we found UBE2T interacts with E3 ligase Mule and regulates its expression via ubiquitation. Since we further found that UBE2T mediates liver CSC function through Mule-mediated  $\beta$ -catenin activation.

**Conclusions:** We have uncovered a novel UBE2T mediated signaling cascade in regulation of liver CSCs. Developing a specific inhibitor targeting this pathway may be a novel approach for HCC treatment.

Keywords: UBE2T, Cancer Stem Cell, HCC, Ubiquitination

#### PO-074

#### Targeting CD47 Enhances the Efficacy of Anti-PD-1 Immune Checkpoint Inhibition in Syngeneic Preclinical Model of HCC

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**Aims:** Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Recently, PD-1 blockade has shown promising results in the treatment of advanced HCC. However, only 15-20% of patients showed objective response, suggesting the need for development of an effective combination therapy. CD47 is an innate immune checkpoint molecule known as 'don't-eat me' signal, which plays a critical role in macrophage activation and phagocytosis. In the current study, we investigated the effects of anti-CD47 inhibition in combination with PD-1 blockade in a syngeneic preclinical model of HCC.

**Methods:** The effect of anti-CD47 and/or anti-PD-1 treatment was studied *in vitro* and *in vivo* using a syngeneic preclinical model of HCC. Flow cytometry was used to assess the phagocytic activity of macrophages.

**Results:** Phagocytosis of HCC cells by macrophages was increased after treatment with anti-CD47 and/or anti-PD-1 treatment. Further, combinatory treatment of anti-CD47 and

anti-PD-1 blockade significantly suppressed tumor growth and improved survival in the syngeneic preclinical model of HCC. **Conclusions:** Targeting CD47 in combination with anti-PD-1 immune checkpoint blockade has a potential immunotherapeutic efficacy in HCC.

Keywords: HCC, Anti-PD-1, Anti-CD47, Immunotherapy

#### PO-075

#### Prospero Homeobox 1 Drives Proliferation and Resistance to Apoptosis in Hepatocellular Carcinoma Cells

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**Aims:** Prospero homeobox 1 (PROX1) is a regulator of the development of multiple organs and has recently been known as oncogenic roles in various cancer. However, the role of PROX1 is complex and unclear in hepatocellular carcinoma (HCC). We determined whether PROX1 affected the oncogenic behavior of HCC cells and investigated its prognostic value in patients with HCC.

**Methods:** A small interfering RNA against PROX1 and pcD-NA6-myc vector was used to control PROX1 gene expression in HCCcell lines HepG2 and Huh 7. Apoptosis, proliferation and angiogenesis were determined by performing the TUNEL assay and immunohistochemical staining for Ki-67, CD34, and D2-40. Invasion and migration assay was also performed. A 62HCC tissues that obtained surgically resected were performed immuohistochemical stains of PROX1 and analyzed according to various clinical parameters.

Results: Endogenous PROX1 expression in Huh 7 was most prevalent among Hep G2, Chang, SK-HEP-1 cell lines. PROX1 knockdown suppressed tumor cell proliferation and inducing apoptosis by activating cleaved caspase-3. PROX1 knockdown induced cell cycle arrestin G2/M phase by increasing p21 and p27. Knockdown of PROX1suppressed tumor cell migration and invasion. PROX1 expressions of HCC tissues compared surrounding liver were low (13, 21%), similar (18, 29%) and high (31, 50%). PROX1 positive group of HCC tissues was 69.4% (n=43) and negative group was 30.6% (n=19) by evaluating the area and intensity of immunohistochemical stain. However, no significant difference was observed between PROX1 expression and clinical parameters of histology, recurrence, survival. Conclusions: PROX1 is associated with oncogenic roles of tumor cell proliferation and resistance to apoptosis in HCC cells. Keywords: Prospero Homeobox 1, Hepaatocellular carcinoma, Apoptosis, Proliferation

#### PO-076

### Detection of MicroRNAs Associated with EMT through Regulation CD44/TGF- $\beta$ 1 in Hepatocellular Carcinoma

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**Aims:** CD44 have known as important modulators of epithelial-mesenchymal transition (EMT) together with transforming growth factor beta1 (TGF- $\beta$ 1). Moreover, CD44 and TGF- $\beta$ 1 double positive more enhanced cancer stem cell characteristics acquisition, EMT, and metastasis. In cancer, miRNAs functions as tumor suppressors or oncogenes. This study aimed to investigate the identify microRNAs regulating the EMT with CD44/ TGF- $\beta$ 1 in HCC cells.

**Methods:** We sorted CD44<sup>-</sup> and CD44<sup>+</sup> liver cancer stem cells by fluorescence-activated cell sorting (FACs) in TGF- $\beta$ 1-positive SNU-368 cells and TGF- $\beta$ 1-negative SNU-354 cells. The miRNA profiles of CD44<sup>-</sup> and CD44<sup>+</sup> HCC cells were analyzed by nextgeneration sequencing (NGS). To investigate synergy effect of CD44 and TGF- $\beta$ 1, we induced EMT by TGF- $\beta$ 1 treatment or inhibited EMT by TGF- $\beta$ 1 inhibitors. The expression level of mRNA and protein were detected by quantitative real-time PCR (qRT-PCR) and western blot.

Results: miRNA NGS array data were compared among CD44 or TGF-B1 single expression HCC cells and CD44/TGF-B1 double positive HCC cells. The results showed that four miRNAs (miR-96-5p, miR-221-5p, miR-186-3p and miR-152-3p) were up-regulated and two miRNAs (miR-296-3p, miR-10a-5p) was down-regulated in CD44<sup>+</sup>/TGF- $\beta$ 1<sup>+</sup> cells than an expression of either one alone. These results were confirmed by gRT-PCR. TGF-β1-stimulated SNU-354 (CD44<sup>+</sup>/TGF-β1<sup>+</sup>) cells up-regulated three miRNAs (miR-96-5p, miR-221-5p, miR-186-3p) than SNU-354 (CD44<sup>+</sup>/TGF- $\beta$ 1<sup>-</sup>) cells and also, down-regulated the two miRNAs (miR-296-3p, miR-10a-5p). Inhibition of TGF-β1 in SNU-368 cells reduced miR-221-5p and increased miR-296-3p. Furthermore, TGF-β1-stimulated SNU-354 (CD44<sup>+</sup>/TGF-β1<sup>+</sup>) cells induced EMT and TGF-β1 inhibitor-treated SNU-368 (CD44<sup>+</sup>/ TGF- $\beta$ 1<sup>-</sup>) cells inhibited EMT. Overexpression of miR-221-5p in SNU-354 (CD44<sup>+</sup>/TGF- $\beta$ 1<sup>-</sup>) cells exhibited lower E-cadherin and higher  $\beta$ -catenin. Next, the loss of miR-221-5p in SNU-368 (CD44<sup>+</sup>/TGF-β1<sup>+</sup>) cells showed increased E-cadherin.

**Conclusions:** We identified CD44/TGF- $\beta$ 1-related miRNAs and confirmed regulation of EMT by miRNAs in HCC cells. The results would suggest a possible application that CD44/TGF- $\beta$ 1-regulated miRNAs may serve as specific biomarkers and therapeutic targets for hepatocellular carcinoma.

Keywords: MicroRNA, CD44, TGF-β1, EMT, HCC

[Group 5] June 16, 2018 | 15:00-16:00

Liver Cancer, Clinical

#### PO-077

#### Predictive Value of Procalcitonin for Bacterial Infection after Transarterial Chemoembolization or Radiofrequency Ablation for Hepatocellular Carcinoma

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**Aims:** The overlap of clinical findings between inflammation and bacterial infection leading to antibiotics overuse in patients with fever after intervention for treating hepatocellular carcinoma. A procalcitonin is a serum biomarker expressed by epithelial cells in response to bacterial infection, but the roles of procalcitonin have not been elucidated in HCC patients for predicting bacterial infection.

**Methods:** A prospective study was performed for a 97 HCC patients with fever ( $\geq$ 38°C) after transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) among the 563 patents. A inflammatory serum markers including C- reactive protein and procalcitonin, blood culture were measured on the fever day and 3 day and 7 day later after TACE or RFA in a enrolled 97 patients.

Results: Bacterial infection and chemical inflammation accounted for 9 (9.3%) and 88 (90.7%) respectively. Of total 9 cases of proven bacterial infection, hepatobiliary infection was most common (3 cases) followed by urinary tract infection, pneumonia (2 cases each), RFA site cutaneous abscess and bacteremia with unknown primary focus (1 case each). Serum PCT levels measured on the day of fever were significantly higher in patients with bacterial infection (median 0.2 ng/dL, interguartile range (IQR) 0.2-1.4) than those with chemical inflammation (median 0.1 ng/dL, IQR 0.1-0.3) (P=0.035). The AUC of PCT on day of fever was 0.715 (95% CI 0.538-0.892), which was higher than that of CRP [AUC, (95% CI): 0.598 (0.368-0.828)], leukocytes count [AUC, (95% CI): 0.502 (0.307-0.697)] and neutrophil percentage [AUC, (95% Cl): 0.647 (0.445-0.849)]. When the ROC curves were constructed based on peak value of inflammatory markers, AUC of peak PCT was 0.840 (95% CI 0.712-0.968), while other inflammatory markers showed relatively lower accuracy to predict the bacterial infection [CRP: AUC, (95% CI): 0.699 (0.563-0.834), leukocytes count: 0.576 (0.357-0.796), neutrophil percentage: 0.713 (0.565-0.862)] compared to PCT.

**Conclusions:** A procalcitonin is useful serum marker for differentiating bacterial infection and chemical inflammation in a HCC patients with post TACE/RFA fever. The serum level of procalcitonin is helpful for preventing overuse antibiotics. **Keywords:** Procalcitonin, Infection, Transartrial chemoembolization, Radiofrequency ablation

#### PO-078

Continuing Five or More Locoregional Therapies before Living Donor Salvage Liver Transplantation for Hepatocellular Carcinoma Is Related to Poor Recurrence-Free Survival

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**Aims:** This study was designed to analyze factors related to the success of salvage liver transplantation in hepatocellular carcinoma (HCC). While liver resection is considered the best locoregional therapy in HCC, there is a high recurrence rate. Salvage liver transplantation may be the best treatment option when feasible.

**Methods:** Patients who underwent living donor salvage liver transplantation for recurrent HCC after LR from November 1996 to May 2017 were included. Patient demographic data, clinical and pathologic characteristics, operative data, hospital course and follow-up data regarding initial liver resection, locoregional therapy after recurrence and salvage liver transplantation were reviewed. Prognostic factors for recurrence were analyzed using Cox proportional hazard ratio.

**Results:** Eighty-five of 123 salvage liver transplantation patients were included. Patients who had five or more locoregional therapies prior to salvage liver transplantation (HR=3.74, Cl=1.45-9.64, *P*=0.006), hepatitis B (HR=9.20, Cl=1.13-74.89, *P*=0.04), outside Milan criteria at the time of salvage liver transplantation (HR=2.66, Cl=1.26-5.63, *P*=0.011) and an alpha-fetoprotein level above 1,000 ng/mL at the time of recurrence after initial liver resection (HR=6.48, Cl=1.83-22.92, *P*=0.004) and at the time of transplantation (HR=3.43, Cl=1.26-5.63, *P*=0.011) were related to significant risk of recurrence.

**Conclusions:** Continuing five or more locoregional therapies for recurrent HCC after liver resection is related to poor recurrence-free survival after salvage liver transplantation.

**Keywords:** Hepatocellular carcinoma, Locoregional therapy, Salvage liver transplantation,

#### PO-079

#### Hepatocellular Carcinoma in the Elderly: Clinical Characteristics, Outcomes and Treatment Efficacy, Safety in Older than 75 Years

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**Aims:** The number of elderly patients diagnosed with hepatocellular carcinoma (HCC) has been increasing because the increase in the longevity of the general population. But there is no proper management based on age stratification in elderly patients. We compared clinical characteristics, outcomes and treatment efficacy, safety between oldest-old (aged more than 85 years), middle-old (aged between 80 and 85 years) and young-old (aged between 75 and 80 years) patients with HCC.

**Methods:** We conducted a retrospective cohort study, from January 2010 to December 2016, at Chonnam National University Hospital. A total of 550 elderly patients whose data included demographics, co-morbidity, etiology of liver disease, presence of cirrhosis, staging of HCC, treatment modality and treatment related adverse event were evaluated retrospectively. Also overall survival was assessed in enrolled patient.

Results: Fifty one patients (oldest-old; median 87 years old), 153 patients (middle-old; median 82 years old) and 346 patients (young-old; median 77 years old) were diagnosed with HCC. Both oldest- and middle-old patients, compared to young-old patients had significantly lower rate of alcohol-related disease (13.7% vs 20.9% vs 34.1%, P = 0.001). There were no significant difference in underlying sex, body mass index, presence of co-morbidity, hepatitis C-related disease and stage of HCC. The Child-Pugh class (CPT class A 88.9% vs 84.1% vs 83.6%, CPT class B 11.1% vs 15.9% vs 15.0% and CPT class C 0.0% vs 0.0% vs 1.3%, respectively, P = 0.912) and Model for End Stage Liver Disease score (mean MELD score 7.22±3.34 vs 5.88±3.01 vs 5.77±3.14, P = 0.166) were no significant difference between the patients with active treatment. The modified UICC staging (stage | 5.6% vs 17.1% vs 18.6%, stage || 55.6% vs 46.3% vs 47.3%, Stage III 22.2% vs 24.4% vs 24.8%, Stage IV-A 11.1% vs 6.1% vs 4.9% and Stage IV-B 5.6% vs 6.1% vs 4.4%, respectively, P = 0.826) and Barcelona Clinic Liver Cancer staging (stage 0 5.6% vs 9.8% vs 9.3%, stage A 16.7% vs 17.1% vs 22.1%, stage B 27.8% vs 29.3% vs 24.8%, stage C 50.0% vs 43.9% vs 41.2% and stage D 0.0% vs 0.0% vs 2.7%, respectively, P = 0.878) were no significant difference between the patients with active treatment. Furthermore, there were no difference between the age groups in treatment modality (Surgical resection 0.0% vs 3.3% vs 5.2%, P = 0.166; Radiofrequency ablation 2.0% vs 8.5% vs 11.0%, P=0.113; Transcatheter arterial chemoembolization 21.6% vs 34.6% vs 41.6%, P=0.014; Best supportive care 62.7% vs 40.5% vs 29.2%, P < 0.001, adverse event related treatment (P = 0.731) and disease-free survival days (329 .3±309.1 days vs 271.7 ± 414.2 days vs 357.2 ± 511.6 days, P = 0.336). Multivariate analysis showed that age, performance status, CTP class, MELD score, modified UICC staging, presence of portal vein thrombosis and ruptured HCC are risk factors for mortality.

**Conclusions:** Clinician should make an active treatment in elderly patients with HCC not a age but performance status, liver function and disease status of cancer.

**Keywords :** Hepatocellular carcinoma, Elderly, Treatment, Prognosis

#### PO-080

#### Risk Assessment in Patients Treated with TACE Due to Recurrent Hepatocellular Carcinoma after Curative Resection: A Retrospective Multicenter Study

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**Aims:** Few prognostic models are available for patients with recurrent hepatocellular carcinoma (HCC) following curative resection. A new postoperative hepatoma arterial-embolization prognostic (HAP) score optimized for patients treated with trans-arterial chemoembolization (TACE) due to recurrent HCC after curative resection was developed and validated.

**Methods:** A total of 448 (training cohort) and 350 (validation cohort) patients with recurrent HCC after curative resection treated with TACE between 2003 and 2016 were enrolled. Cox regression and area under the curve (AUC) analysis were used to identify risk factors and to calculate the predictive performance of risk scores, respectively.

**Results:** The median age of the study population (378 men, 70 women) was 59.4 years. The median time from resection to recurrence was 17.7 (interquartile range, 7.3–37.1) months. Alpha-fetoprotein>400ng/mL (hazard ratio [HR]=2.358), serum albumin≤3.5g/dL (HR=1.979), tumor number≥2 (HR=1.655), segmental portal vein invasion (HR=2.541), and time from resection to recurrence≤2 years (HR=1.905) independently predicted survival (all *P*<0.05). The postoperative HAP (pHAP) model established based on the rounded HR of each variable showed an AUC to predict survival at 3-years of 0.671 significantly higher than those of other HAP-based models including HAP, modified HAP, and modified HAP-II scores (0.578-0.624) (all *P*<0.05). The accuracy of pHAP was maintained in the validation cohort (n=350; AUC=0.638 at 3-years).

**Conclusions:** A new pHAP score optimized for patients treated with TACE due to recurrent HCC after curative resection showed acceptable accuracy and was externally validated. Further studies should investigate Methods: to select treatment options other than TACE for high-risk patients according to pHAP scores.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Resection, Recurrence

#### PO-081

Transarterial Chemolipiodolization for Hepatocellular Carcinoma with Central Bile Duct Invasion Causing Conjugated Hyperbilirubinemia: Safety and Prognostic Factors for Survival

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**Aims:** Bile duct invasion of hepatocellular carcinoma (HCC) is relatively uncommon. For patients with conjugated hyperbilirubinemia caused by HCC with bile duct invasion, it has been reported that effective biliary drainage followed by transarterial chemolipiodolization (TACL) may prolong survival. However, there are few reports comparing the clinical outcomes between tumors with central bile duct invasion causing conjugated hyperbilirubinemia and tumors with central bile duct invasion without hyperbilirubinemia, after TACL.

**Methods:** Between January 2005 and December 2017, a total of 50 patients with HCC invading central bile duct (right or left hepatic duct, common hepatic or bile duct) and treated with TACL were enrolled. Patients were divided into three groups: hyperbilirubinemia (total bilirubin  $\geq 2.5$ mg/dL) with pre-TACL biliary drainage group (n=12), hyperbilirubinemia without biliary drainage group (n=12), and without hyperbilirubinemia group (n=26). Tumor response to TACL, survival outcomes, length of hospitalization, adverse events recorded using Common Terminology Criteria for Adverse Events (CTCAE), and factors affecting overall survival were compared among three groups.



**Results:** The mean length of hospitalization was shorter in patients without hyperbilirubinemia compared to hyperbilirubinemia (10.2 vs 14.5 days, P=0.017), although mean CTCAE grade for laboratory parameters were not significantly increased after TACL among three groups. Significant decrease in serum bilirubin level was observed among patients who underwent pre-TACL biliary drainage (mean of differences: 5.860, P=0.002). However, there were no significant differences in serum bilirubin level between that of the TACL day and highest level within one month after TACL, in all three groups. The tu-

mor response was also not significantly different between patients with hyperbilirubinemia and without hyperbilirubinemia (*P*=0.573). Survival between patients with hyperbilirubinemia and without hyperbilirubinemia was not significantly different (*P*=0.097). In multivariate analysis,  $\alpha$ -fetoprotein less than 400 ng/dL (HR = 0.477, *P*=0.048), and highest total bilirubin < 2.5 mg/dL within one month after TACL (HR = 0.335, *P*=0.004) were significantly associated with longer survival.

**Conclusions:** TACL can be a safe and effective treatment for patients who have HCCs with central bile duct invasion, irrespective of the presence of conjugated hyperbilirubinemia.

**Keywords:** Hepatocellular carcinoma, Chemolipiodolization, Bile duct invasion, Hyperbilirubinemia

#### PO-082

#### Refractoriness to Transarterial Chemoembolization in Patients with Recurrent Hepatocellular Carcinoma after Curative Resection

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**Aims:** Identification of patients who are refractory to transarterial chemoembolization (TACE) used to treat hepatocellular carcinoma (HCC) is important. We investigated predictors of poor treatment outcomes in patients with recurrent HCC treated with TACE after curative resection.

**Methods:** A total of 428 patients with recurrent HCC after curative resection who were treated with TACE between 2006 and 2015 were enrolled (median follow-up, 59.2 months).

Results: The median age of the study population (362 males and 66 females) was 59.2 years, and the median time from resection to the first TACE was 17.8 months. On multivariate analysis, more than two TACE procedures within the first 6 months (HR=1.898), and the des-gamma carboxy prothrombin level (hazard ratio [HR]=1.000) were independently predictors of the progression to BCLC stage C in patients with BCLC stage 0-B (both P<0.05). In addition, more than two TACE procedures within the first 6 months (HR=1.863), the serum albumin level, an alpha-fetoprotein >100ng/mL, and multiple tumors, were identified as an independent predictors of mortality in the entire study population (all P<0.05). The cumulative incidence of stage progression to BCLC stage C of patients with BCLC stage O-B and that of mortality of the entire study population were significantly higher in patients undergoing more than two TACE procedures within the first 6 months compared with those undergoing fewer procedures (log-rank, P=0.003, and P<0.001, respectively).

**Conclusions:** More than two TACE procedures within the first 6 months may indicate refractoriness to TACE in patients with

recurrent HCC after curative resection. Thus, if patients meet this criterion, a switch to other treatments should be considered.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Refractoriness, Resection

[Group 6] June 16, 2018 | 15:00-16:00

Liver Cancer, Clinical

#### PO-083

#### Prognosis of Additional Hypointense Nodules Detected by EOB-MRI in a Resectable Hepatocellular Carcinoma

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**Aims:** It is known that Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid (Gd-EOB-ETPA, EOB) enhanced magnetic resonance imaging (EOB-MRI) improved the detection and diagnosis rate of hepatocellular carcinoma (HCC). In preoperative MRI, additional hypointense nodule (AHIN) is found sometimes, however there are only few studies about prognosis of curative treatments of AHIN and primary HCC lesion together. We aimed to confirm prognosis after surgical treatment in patients with these additional hypointense nodule in EOB-MRI.

**Methods:** We retrospectively reviewed medical records and preoperative images of 522 HCC patients who underwent surgical curative treatment at Hepatoma Clinic, Yonsei Cancer Center, Seoul, South Korea from January 2008 to December 2012. We analyzed general characteristics and conducted propensity score matching analysis of patients.

Results: Among 522 patients, we excluded MRI only or CT only and multiple HCC patients. Eventually, 403 patients included and 340 patients with single overt HCC and 63 patients with additional lesion in EOB-MRI were analysed. Of this 63 patients, 19 patients were confirmed HCC pathologically and 44 patients were not confirmed because of treated RFA or non-HCC lesion pathologically. Among 19 patients, non-hypervascular hypointense nodule were 7 (36.8%). Overall survival and disease-free survival analysis showed significant difference between single overt HCC patients and single overt HCC with additional hypointense nodule patients (P=0.027, P<0.001, respectively). After propensity score match analysis, there were no statistically significant differences between single overt HCC patients and and single overt HCC with additional hypointense nodule patients in overall survival analysis (mean 82 months, 95% CI [71.603-92.942] vs. mean 87 months, 95% CI [76.553-97.650], P=0.678) and disease-free survival analysis (median 62 months, 95% CI [29.164-94.836] vs. 32 months, 95% CI [21.240-42.760], P=0.070).

**Conclusions:** In general, survival probabilities of single overt HCC with AHIN patients are inferior to single overt HCC group. After propensity score matching, there were no significant difference between single overt HCC and single overt HCC with AHIN in overall survival and disease-free survival. Therefore, single overt HCC with AHIN should be considered a surgical candidate and combined active treatment is recommended if their liver function is allowed.

Variables (Mean + SD)	Single overt HCC	AHIN		
valiables (Meall ± 5D)	(N=63)	(N=63)	P	
Sex			1.000	
Male	53 (84.1%)	52 (82.5%)		
Female	10 (15.9%)	11 (17.5%)		
Age (years)	58.1 ± 8.1	57.4 ± 8.9	0.660	
Body mass index (kg/m <sup>2</sup> )	24.9 ± 3.3	$24.3 \pm 3.0$	0.327	
Serum Total bilirubin (mg/dL)	1.0 ± 0.7	1.0 ± 0.6	0.912	
Serum Albumin (g/dL)	4.1 ± 0.6	4.1 ± 0.5	0.872	
INR	1.1 ± 0.2	1.1 ± 0.1	0.704	
MELD score	8.3 ± 1.8	8.1 ± 1.8	0.687	
Platelet count	142127.0 ± 48992.6	144381.0 ± 54279.6	0.807	
AST (IU/mL)	54.6 ± 46.2	65.4 ± 58.0	0.252	
ALT (IU/mL)	49.2 ± 37.3	54.6 ± 32.3	0.391	
AFP (ng/mL)	719.4 ± 3636.4	1091.4 ± 3596.5	0.565	
PIVKA (mAU/mL)	321.7 ± 687.2	569.3 ± 2435.1	0.440	
Etiology			0.313	
Hepatitis B	48 (76.2%)	50 (79.4%)		
Hepatitis C	6 ( 9.5%)	7 (11.1%)		
Alcoholics	2 (3.2%)	4 ( 6.3%)		
Non-B, Non-C	7 (11.1%)	2 ( 3.2%)		
Cirrhosis		. ,	1.000	
No	20 (31.7%)	20 (31.7%)		
Yes	43 (68.3%)	43 (68.3%)		
10.000 million				
10 2	-/~Single overt HCC		Single event HC	
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**Keywords:** Hepatocellular carcinoma, Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid, Magnetic resonance imaging, EOB-MRI

#### PO-084

#### Metabolic Profiling Identifies Metabolic Biochemical Pathways Associated with Recurrence of Hepatocellular Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. The metabolic biochemical pathway disturbances associated with HCC progression and recurrence remain unsatisfactorily characterized. Dysregulated metabolism is a hallmark of cancer including HCC, manifested through alterations in metabolites. The emerging field of metabolomics has increased the hope of discovering metabolites and biochemical pathways as the novel biomarkers or therapeutic targets of HCC and tracking tumor recurrence.

**Methods:** Metabolomic profiling was conducted with the Metabolon platform for one hundred and twenty human recurrent/non-recurrent HCC tumor/normal paired tissues. Standard statistical analyses are performed in the Partek Genomics Suite on log transformed data. Principal component analysis (PCA) was conducted using all and dysregulated metabolites. Random Forest classification was applied to compare tumor vs. adjacent margin tissues and recurrent vs. non-recurrent tumors using named metabolites.

**Results:** We found that HCC recurrence is characterized by increasing glycolysis and glutaminolysis. Tumor recurrence was significantly associated with increasing of glucose, pyruvate,  $\alpha$ -ketoglutarate and NAD+/NADH metabolites to increase glycolysis and glutaminolysis. Higher acylcarnitine levels in non-recurrent HCC indicate elevated fatty acid  $\beta$ -oxidation. Besides, we also found that Coenzyme A levels were higher and plasmalogen lipids were uniformly lower in recurrent HCC.

**Conclusions:** Our study generates a comprehensive metabolomics dataset on HCC and highlight the massive reorganization of cellular metabolism as tumors progress and acquire recurrence feature.

Keywords: Liver cancer, Metabolomics, Recurrence, Biomarker

#### PO-085

#### Prognostic Significance of Neutrophil-Lymphocyte Ratio in Risk Prediction Model for Patients with Hepatocellular Carcinoma Undergoing Chemoembolization

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**Aims:** Neutrophil-lymphocyte ratio (NLR) has recently been reported as a predictor of hepatocellular carcinoma (HCC).<sup>1, 2</sup> We aim to investigate whether NLR is a predictor for patients with HCC undergoing transarterial chemoembolization (TACE) and develop a prediction model based upon it.

**Methods:** 1,697 HCC patients undergoing TACE as a first-line therapy were enrolled from two University Hospitals (derivation set n=1316, external validation set n=381). Serum alpha-fe-to protein (<u>AFP</u>) level, the Barcelona clinic liver cancer (<u>BCLC</u>) stage, <u>Child-Pugh Class</u>, Tumor <u>Response after TACE</u>, and <u>NLR</u>, which were selected as predictors for overall survival (OS) from a multivariate Cox-regression model were incorporated into a 9-point risk prediction model (<u>ABCRN</u> score). The prognostic performance of ABCRN score was assessed in the derivation set and in the validation set.

**Results:** The time-dependent areas under receiver-operating characteristic curves (AUROCs) for OS of ABCRN score at 1-, 3- and 5-years were 0.808, 0.724 and 0.688 in the derivation set, and those were 0.848, 0.662, and 0.717, in the validation set. ABCRN score had the highest AUROCs for OS at 1/3/5 years, compared with ART (0.577/0.505/0.655), ABCR (0.776/0.645/0.600), and SNACOR (0.770/0.662/0.634) scores, respectively, with statistical significances (all *P* values <0.05 *vs*. ABCRN score). Patients were stratified into the three risk groups according to ABCRN score (low,0-2; intermediate,3-6; high,7-9). Patients with high risk group had a significantly higher mortality risk compared to the intermediate (hazard ratio[HR], 2.8; *P*<0.001) or low-risk group (HR, 10.7; *P*<0.001)

**Conclusions:** Prognostic performance of ABCRN score in patients with HCC treated with TACE was remarkable and it was better compared to conventional scores. This score will help for further guiding future HCC treatment direction.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Neutrophil-lymphocyte ratio, Risk-prediction model

#### PO-086

#### Sex Differences in Early and Late Recurrence after Liver Resection of Hepatocellular Carcinoma (A Multicenter Study from China)

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**Aims:** There is a striking sex difference in the incidence of hepatocellular carcinoma (HCC), with a strong predominance for males. However, the impact of sex on the incidence of recurrence after curative resection of HCC remains controversial. Herein, we assess sex differences in the risks of recurrence and mortality for patients undergone curative resection of HCC.

**Methods:** Data from 1,435 HCC patients undergone curative resection (1,228 males and 207 females) between 2004 and 2014 at five institutions in China were retrospectively analyzed. Patients' baseline characteristics, operative variables, and rates of early recurrence ( $\leq$  2 years after resection), late recurrence (> 2 years) and cancer-specific mortality (CSM) were evaluated and compared. Multivariable competing-risks regression analyses were performed to identify predictors associated with CSM,

early and late recurrence.

**Results:** The early recurrence rates between males and females were similar (43.3% vs. 42.0%, P=0.728), but the late recurrence and CSM rates in males were higher when compared to females (17.2% vs. 11.2%, P=0.044; 42.8% vs. 34.3%, P=0.022). Multivariable competing-risks regression analyses revealed no sex difference in early recurrence; however, males had significantly higher late recurrence rate [hazard ratio (HR), 1.752; 95% CI, 1.145-2.682; P=0.010] and CSM rate (HR, 1.307; 95% CI, 1.015-1.683; P=0.038) than females.

**Conclusions:** Males had significantly higher late recurrence and CSM rates after curative resection of HCC than females. This suggests postoperative surveillance for HCC recurrence be varied by sex, especially for patients without recurrence at 2 years after resection.

#### PO-087

#### Serum Levels of Myostatin, Follistatin and IL-6 in the Patients with Hepatocellular Carcinoma with Their Association with Sarcopenia and Survival

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**Aims:** This study investigated the serum levels of myostatin, follistatin and IL-6 in the patients with hepatocellular carcinoma (HCC), and their association with sarcopenia and survival.

**Methods:** Using prospectively collected pretreatment serum samples obtained from 238 HCC patients from 2012 to 2015, serum levels of myostatin, follistatin and IL-6 were determined using commercialized ELISA. The cross-sectional area of the psoas muscles at the third lumbar level of CT normalized for the patient's height was presented a psoas muscle index (PMI). Sex-specific cut-offs of PMI to define the sarcopenica were ascertained by the maximal chi-square method.

Results: The subjects showed a median age of 59 years, 81% of male, and hepatitis B virus infection in 70%. The median myostatin levels for males and females were 3,979.3 pg/mL (819.33-21,652.1 pg/mL) and 2,976.3 pg/mL (901.5-15,652.9 pg/mL), respectively, with the levels of follistatin [2,118.5 pg/ mL (573.7-16,923.6 pg/mL, male); 2,174.6 pg/mL (675.1-8,337.3 pg/mL, female)] and IL-6 [2.5 pg/mL (0.11–106.79 pg/ mL, male); 2.7 pg/mL (0.01-122.97 pg/mL, female)]. PMI was  $4.48 \pm 1.25$  (males) and  $2.25 \pm 0.82$  cm<sup>2</sup>/m<sup>2</sup> (females), showing sarcopenic prevalence of 56.7%. The sarcopenic group showed a significantly higher follistatin level, larger tumor size, more advanced BCLC stage and higher overall mortality than non-sarcopenic group. On multivariate analysis, follistatin level (≥2100 pg/mL) was an independent factor for poor survival [hazard ratio, 2.197; 95% confidence interval (CI), 1.123-4.296; P=0.021] along with a low PMI, high alpha-fetoprotein level, MELD score and TNM stage. However, serum follistatin level was not correlated with PMI, while myostatin level showed a positive correlation with PMI ( $R_s = 0.271$ , P<0.001).

**Conclusions:** Serum follistatin level, rather than myostatin or IL-6, was an independent factor for poor survival in HCC patients. Further study on the role of follistatin in prognosis of HCC is warranted.

**Keywords:** Hepatocellular carcinoma, Liver cirrhosis, Sarcopenia, Myokine

#### PO-088

Preoperative Prealbumin Level as an Independent Predictor of Long-Term Prognosis after Curative Liver Resection of Hepatocellular Carcinoma (a Multicenter Study of 1,483 Patients)

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**Aims:** Serum prealbumin is more sensitive to profile nutritional status and liver function than albumin, which could hardly be affected by infusion supplement. This study aims: to identify the relationship between preoperative prealbumin level and the long-term prognosis after curative resection of hepatocellular carcinoma (HCC).

**Methods:** Patients undergone HCC curative resection between 2001 and 2014 at six institutions in China were enrolled. By using 170 mg/dl as cut-off value of serum prealbumin level, these patients were divided into the low and normal preoperative prealbumin groups. The overall survival (OS) and recurrence-free survival (RFS) were analyzed and compared. Univariable and multivariable Cox-regression analyses were performed to identify predictive factors of OS and RFS.

**Results:** Among 1,483 patients, 437 (29.5%) had a low prealbumin level within a week before surgery. The 1-, 3-, and 5-year OS and RFS rates of patients in the low prealbumin group were 83.8, 57.0, and 31.1%, and 67.0, 39.8, and19.9%, respectively, which was significantly poorer than those in the normal group (93.0, 75.5, and 42.6%, and 77.0, 56.4, and 28.4%, both *P*<0.001). Multivariable analyses revealed that preoperative prealbumin level, but not albumin level, was an independent predictor of OS (HR, 1.789; 95% CI: 1.544 -2.072, *P*<0.001) and RFS (HR, 1.420; 95% CI: 232-1.636, *P*<0.001). **Conclusions:** Preoperative prealbumin level is useful for predicting long-term prognosis in patients undergoing liver resection for HCC. Prealbumin may be suitable to displace albumin, yielding to an updated Child-Pugh grade for accessing liver function.

#### [Group 7] June 16, 2018 | 15:00-16:00

Liver Cancer, Clinical

#### PO-089

Body Mass Index and FIB-4 Score Are Risk Factors for Development of Hepatocellular Carcinoma in Liver Cirrhosis on Entecavir Therapy

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**Aims:** Prediction of development of hepatocellular carcinoma (HCC) among hepatitis B virus (HBV)-related cirrhosis patients on potent antiviral therapy is not well defined. This study aimed to investigate the incidence and predictors of HCC development in cirrhosis patients on entecavir therapy.

**Methods:** This single center, retrospective cohort study included 424 consecutive patients with HBV-related cirrhosis who underwent entecavir therapy from 2007 to 2013. Surveillance for HCC was based on semiannual ultrasonography and serum alpha fetoprotein (AFP) measurement. HCC incidence and the related factors were analyzed.

**Results:** The subjects showed a median age of 52.7±10.1 years with 63.5% of male, mean body mass index (BMI) of 24.2±3.1 kg/m<sup>2</sup>, HBeAg positivity in 41.5%, baseline HBV DNA level of  $1.39\times10^8$  IU/mL, and mostly Child-Pugh class A (80.9%). During median follow-up of 62.0 months (interquartile range, 29.0–83.0), 90.8% (385/424) reached complete virologic response of entecavir therapy. The overall incidence of HCC was 86 out of 424 patients (20.3%); incidence rate of 2.54/100 person-yr at 1 yr, 8.07/100 at 3 yr, and 8.37/100 at 5 years of follow-up. The multivariate analysis showed that the independent factors related to HCC development were BMI ≥23 (hazard ratio (HR), 1.89; 95% confidence interval (CI), 1.23-3.39; *P*=0.006), and high FIB-4 (≥3.25; HR, 5.65; 95% CI, 1.35–23.72; *P*=0.018) or intermediate FIB-4 (≥1.45 and <3.25; HR, 4.58; 95% CI, 1.08–19.41; *P*=0.039).

**Conclusions:** HCC incidence rate among HBV-related liver cirrhosis on entecavir therapy was 2.54/100, 8.07/100, and 8.37/100 person-yr at 1, 3 and 5 yr, respectively. High BMI and high to intermediate FIB-4 score were independent factors for HCC development.

**Keywords:** Hepatitis B virus, Antiviral therapy, Obesity, Hepatic fibrosis

#### PO-090

#### Surveillance for Hepatocellular Carcinoma: Is It Necessary in Low-Risk Patients with Chronic Hepatitis B?

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**Aims:** Long-term antiviral therapy significantly reduces the risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). However, whether surveillance is required for young non-cirrhotic patients exhibiting a complete virological response remains unclear.

**Methods:** We analyzed 1,349 naïve CHB patients treated with entecavir or tenofovir during a large retrospective multicenter study performed from 2012 to 2015. We defined a low-risk group as non-cirrhotic patients who commenced antiviral therapy at a young age (males <45 years, females <55 years) and achieved a complete virological response (HBV DNA <60 IU/mL). Those who had platelet counts <120,000/m<sup>3</sup> after 12 months of treatment, or who developed new cirrhosis during treatment, were excluded.

**Results:** The low-risk group (N=414) commenced antiviral therapy at a mean age of 38.2 years and all achieved HBV DNA-negativity by a median of 8.8 months of treatment. A total of 133 patients were treated with entecavir and 281 with tenofovir. The mean treatment duration was 2.9 years. The median HCC-Risk Estimating Score in CHB patients Under Entecavir (HCC-RESCUE) was 47 (range 20–59), suggesting that all patients were in the low-risk group ( $\leq$ 64). Three HCCs developed during 1,211 person-years of follow-up. The incidence was thus 248 per 100,000 person-years (0.25% per year). The ages at commencement of antiviral agents were 36, 42, and 44 years in these patients, and the HCCs were detected after 3.4, 4.4, and 1.9 years of treatment, respectively. All three patients were male, and consumed alcohol at baseline.

**Conclusions:** The risk of HCC development was not low even in highly selected patients who commenced antiviral therapy at a young age (males <45 years and females <55 years) and had no cirrhosis. Until optimal surveillance strategies based on the risk are proven, universal surveillance is needed in the CHB patients receiving antiviral therapy.

**Keywords:** Antiviral therapy, Chronic hepatitis B, Hepatocellular carcinoma,

#### PO-091

#### Comparison of Risk Prediction Model for Hepatocellular Carcinoma in Patients with Hepatitis B Virus-Related Cirrhosis Receiving Antiviral Therapy

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**Aims:** Various models for the prediction of hepatocellular carcinoma (HCC) in the patients with chronic hepatitis B (CHB) were suggested. The aim of study is to identify if the HCC risk scores are improved as antiviral therapy is prolonged in the patients with CHB-related liver cirrhosis.

**Methods:** The patients with CHB who received entecavir (ETV) or tenofovir (TDF) were investigated retrospectively. Patients with liver cirrhosis patients diagnosed by sonography, CT or biopsy were enrolled. We calculated the HCC risk scores at pre-antiviral therapy, and each year from year 1 to 5 of post-antiviral therapy. The models were GAG-HCC, CU-HCC, REACH-B, modified REACH-B (mREACH-B), LSM-HCC, and PAGE-B. The primary endpoint was decrease of the risk scores after antiviral therapy. The secondary endpoint was finding the best model by AUROC after antiviral therapy.

Results: A total of 362 patients were enrolled, and 198 and 164 patients were treated by ETV and TDF respectively. Child-Pugh scores were 5.7±1.3 and MELD were 9.9±3.8. Fifty six patient (15.5 %) occurred HCC at median 1.6 years (0.1-9.7 years). Most HCC scores (GAG, CU-HCC, REACH-B) decreased at year 1 and plateaued from year 1 to 5. mREACH-B and LSM-HCC scores decreased until year 2 and plateaued after year 2. PAGE-B showed no decrease from pre to post-antiviral therapy. The AUROC of PAGE-B was largest at baseline (GAG-HCC 0.472, CU-HCC 0.753, REACH-B 0.633, mREACH-B 0.688, LSM-HCC 0.649, and PAGE-B 0.760). After antiviral therapy, the AUROC changed. AUROCs of models employing HBV DNA levels increased (GAG-HCC, REACH-B, and LSM-HCC), that of liver stiffness based models (mREACH-B and PAGE-B) were persistent, and that of models employing hepatic function (CU-HCC) decreased (GAG-HCC 0.582, CU-HCC 0.686, REACH-B 0.689, mREACH-B 0.689, LSM-HCC 0.716, and PAGE-B 0.755 at 1year). The decrease of scores from baseline to each years were not different between ETV and TDF (all P>0.05). AUROC

were largest in PAGE-B, however the scores were not changed after antiviral therapy. Second largest AUROC is that of LSM-HCC at year 1 and its AUROC became larger after antiviral therapy

**Conclusions:** In conclusion, HCC prediction models such as PAGE-B and LSM-based models worked well in patients with HBV-related cirrhosis and decrease of the scores was associated with effects of the antiviral therapy.

**Keywords:** Hepatocellular carcinoma, Chronic hepatitis B, Liver cirrhosis, Antiviral therapy

#### PO-092

### Effect of Obesity and Statins on Liver Cancer Mortality in Patients with Chronic Hepatitis B

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**Aims:** Statins are associated with lower risk for hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). Overweight or mild obesity has also shown to be associated with lower overall mortality in population studies. We hypothesized that their protective effect might be associated with obesity or hypercholesterolemia.

**Methods:** We analyzed a Health Examination Cohort of the National Health Insurance Service of Korea from 2002 to 2013. In total, 13,063 patients aged 40–79 years with CHB and no other concurrent liver disease such as liver cirrhosis were identified. According to body mass index (BMI), underweight ( $\leq$ 18.5 kg/m<sup>2</sup>, N=263); normal (18.5 to less than 22.9 kg/m<sup>2</sup>, N=4606); upper normal (23.0 to less than 24.9 kg/m<sup>2</sup>, N=3564); overweight or mild obese (25 to less than 30 kg/m<sup>2</sup>, N = 4280); and overt obese ( $\geq$ 30 kg/m<sup>2</sup>, N = 340) were defined. Statin use was defined as  $\geq$  28 cumulative defined daily doses. Multivariate Cox proportional hazard models were used to define independent predictors for liver cancer mortality.

**Results:** Three out of 980 statin users and 190 out of 12,066 non-users were died from liver cancer during mean 10.6 years of follow-up. The mortality was 0.29 per 1,000 person-year (95% confidence interval [CI] 0.09-0.89) for statin users and 1.48 per 1,000 person-year (95% CI 1.28–1.71) for non-statin users (*P*<0.001). After adjustment for age, gender, body mass index (BMI), smoking, alcohol consumption, plasma level of glucose, cholesterol, and liver enzymes, statin use was independently associated with lower risk for liver cancer mortality (Hazard ratio [HR] 0.17, 95% CI 0.04–0.68). Only overt obese patients (BMI  $\geq$  30 kg/m<sup>2</sup>, N=340) were associated with higher risk for liver cancer mortality (HR 2.42, 95% CI 1.18–4.96) as compared with the normal patients. Overweight or mild obesity (BMI 25.0–29.9 kg/m<sup>2</sup>) have no association with the mortality

(HR 0.95, 95% CI 0.64–1.40). Cholesterol level more than 240 mg/dL was also independently associated with lower risk for the mortality (HR 0.45, 95% CI 0.23–0.86). The liver cancer mortality in patients with lower cholesterol level at baseline (< 200 mg/dL, N=7380) was 1.84 per 1,000 person-year (95% CI 1.56–2.17).

**Conclusions:** The effect of statins on the mortality doesn't seem to be dependent on BMI. However, lower cholesterol level at baseline was significantly associated with higher risk of liver cancer mortality. Statin effect among those patients need to be clarified.

**Keywords:** Chronic hepatitis B, Hepatocellular carcinoma, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Mortality, Obesity

#### PO-093

### The Diagnostic Efficacy of M2BPGi for Liver Fibrosis in HCC and NAFLD Patients

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**Aims:** Mac-2 binding protein glycan isomer (M2BPGi) is recently identified as a useful non-invasive biomarker for the diagnosis of liver fibrosis. This study aimed to evaluate the diagnostic efficacy of serum M2BPGi for liver fibrosis in hepatocellular carcinoma (HCC) and non-alcoholic fatty liver disease (NAFLD) patients.

**Methods:** M2BPGi levels were analyzed in serum samples collected from biopsy-proven HCC (*n*=135) and NAFLD (*n*=113) patients. Fibrosis was graded histopathologically in non-tumorous portion of HCC and NAFLD. Serum M2BPGi levels were determined with an automated immunoassay analyzer. Spearman's correlation and Kruskal-Wallis test were used to evaluate the correlation and comparison among groups. Diagnostic efficacy for fibrosis was evaluated by the area under the receiver operating characteristic curve (AUC).

**Results:** Median levels (range) of M2BPGi in HCC and NAFLD patients were 1.21 (0.12-14.33) cut-off index (COI) and 0.59 (0.13-5.90) COI, respectively. In HCC patients, fibrosis stages were 0 (n=22), 1 (n=10), 2 (n=11), 3 (n=16), and 4 (n=76).

The M2BPGi levels showed a significant positive correlation (r= 0.436, *P*<0.001) with fibrosis grade in HCC patients and yielded the lower AUC value, 0.787 (*P*<0.001) than transient elastography (TE), AUC value, 0.806 (*P*=0.030) to predict advanced fibrosis (F>2). In NAFLD patients, fibrosis stages were 0 (*n*=22), 1 (*n*=34), 2 (*n*=28), 3 (*n*=19), and 4 (*n*=10). The M2BPGi levels showed a significant positive correlation (r=0.578, *P*<0.001) with fibrosis grade in NAFLD patients and yielded the higher AUC value, 0.824(*P*<0.001) than TE, AUC value, 0.637(*P*=0.035) to predict advanced fibrosis (F>2).

**Conclusions:** Serum M2BPGi can be a useful non-invasive biomarker for predicting fibrosis in HCC and especially in NAFLD patients.

**Keywords:** Mac-2 binding protein, Fibrosis, Non-alcoholic fatty liver disease, Hepatocellular carcinoma

#### PO-094

#### Autologous Cytokine-Induced Killer Cells Infusion after Curative Hepatic Resection in Solitary Hepatocellular Carcinoma: An Observational Study

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**Aims:** Adjuvant immunotherapy with activated cytokine-induced killer (CIK) cell infusion has been reported to increase disease-free survival and patient survival in patients with hepatocellular carcinoma (HCC). We evaluated the efficacy of CIK cell infusion as an adjuvant therapy for solitary HCC.

**Methods:** A total of 531 patients underwent liver resection because of solitary HCC from April 2015 to September 2017. 508 patients underwent curative liver resection alone (control group) and 23 patients received surgery and at least five cycles of CIK cell infusion (case group). Multiple HCC, intraoperative RFA, synchronous abdominal surgery, re-resection, preoperative locoregional therapies such as RFA, TACE, or radiation, portal vein tumor thrombosis, bile duct tumor thrombosis, serosal involvement were excluded.

**Results:** All patients were Child-Pugh class A. In case group, 15 patients received 16 cycles of CIK cells. Median age of control and case group was 60 years and 52 years, respectively. (P=0.001). There were no statistically significant differences in the tumor size, AFP levels, and PIVKA-II levels between case group and control group. The disease-free survival rates and patient survival rates of the case group were not different those of the control group (P=0.659 and P=0.600, respectively).

**Conclusions:** CIK cell infusion as adjuvant therapy does not increase patient outcomes because patients with curative resection of solitary HCC have low HCC recurrence rate and high survival rate. More long-term follow-up is needed.

Keywords: Immunotherapy, Outcomes, Survival, Surgery

#### **Liver Transplantation**

#### PO-095

#### Continuing Five or More Locoregional Therapies before Salvage Liver Transplantation for Hepatocellular Carcinoma Is Related to Poor Recurrence-Free Survival

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Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Korea

**Aims:** his study was designed to analyze factors related to the success of salvage liver transplantation in hepatocellular carcinoma (HCC). While liver resection is considered the best locoregional therapy in HCC, there is a high recurrence rate. Salvage liver transplantation may be the best treatment option when feasible.

**Methods:** Patients who underwent salvage liver transplantation for recurrent HCC after LR from November 1996 to May 2017 were included. Patient demographic data, clinical and pathologic characteristics, operative data, hospital course and follow-up data regarding initial liver resection, locoregional therapy after recurrence and salvage liver transplantation were reviewed. Prognostic factors for recurrence were analyzed using Cox proportional hazard ratio.

**Results:** Eighty-five of 123 salvage liver transplantation patients were included. Patients who had five or more locoregional therapies prior to salvage liver transplantation (HR=2.20, Cl=1.03-4.68, *P*=0.042), outside Milan criteria at the time of salvage liver transplantation (HR=2.52, Cl=1.18-5.37, *P*=0.017) and an alpha-fetoprotein level above 1,000 ng/mL (HR=5.85, Cl=2.18-15.68, *P*<0.001) were at significant risk of recurrence.

**Conclusions:** Continuing five or more locoregional therapies for recurrent HCC after liver resection is related to poor recurrence-free survival after salvage liver transplantation.

#### PO-096

#### The Effects of Intrapatient Variability in Tacrolimus on Clinical Outcomes in Patients with Liver Transplantation during Early Stage

Eun Ji KIM, Bo Ram KIM, Jung Won CHO, Jung Hwa LEE, Eun Sook LEE, Yun Mi YU, Ho-Seoung HAN, Yoo Seok YOON, Jai Young CHOI, Euni LEE, YoungRok CHOI

Pharmacy, Seoul National University Bundang Hospital, Korea, College of Pharmacy, Seoul National University, Korea, Surgery, Seoul National University, College of Medicine, Korea, Surgery, Seoul National University Bundang Hospital, Korea

Aims: Tacrolimus has a narrow therapeutic range requiring

concentration monitoring. The purpose of this study is to evaluate the effect of tacrolimus intrapatient variability (IPV, %) on clinical outcomes in liver transplantation.

**Methods:** A retrospective analysis using electronic medical records of liver transplant recipients from 2009 to 2016 was conducted in Seoul National University Bundang Hospital. IPV was calculated by using individual tacrolimus concentration and averaged tacrolimus concentration. Patients were divided into two groups based on the median IPV; high variability (HV) and low variability (LV) groups. The rate of deviation from the therapeutic range, the incidence of acute rejection, and post-transplant diabetes, the number of infection and estimated glomerular filtration rate (eGFR) within 6 months after transplantation were compared between two groups.

**Results:** Of 82 study subjects, HV group (17.3%) has more frequently deviated from the therapeutic range than the LV group (4.5%) (P<0.001). There was no significant difference in the incidence of acute rejection, post-transplantation diabetes and eGFR in both groups, but the number of infection was significantly lower in LV group (0.4 times) than in HV group (0.9 times) for 6 months (P=0.039). The multivariate regression analysis showed that the number of infection was significantly increased as the IPV increased (P=0.003).

**Conclusions:** We compared the clinical outcomes between HV and LV groups within 6 months after liver transplantation. High IPV of tacrolimus concentration was strongly associated with increased frequency of deviation from the therapeutic range and the number of infection.

#### PO-097

#### Clinical Outcomes of Late Conversion to Once-Daily Tacrolimus after Liver Transplant

Deok Gie Kim<sup>1</sup>, Yoon Bin Jung<sup>1</sup>, Jee Youn Lee<sup>1</sup>, Jae Geun Lee<sup>1</sup>, Sung Hoon Kim<sup>2</sup>, Han Dai Hoon<sup>1</sup>, Man Ki Ju<sup>1</sup>, Gi Hong Choi<sup>1</sup>, Jin Sub Choi<sup>1</sup>, Myoung Soo Kim<sup>1</sup>, Soon II Kim<sup>1</sup>, and Dong Jin Joo<sup>1</sup>

<sup>1</sup>Department of Surgery, Yonsei University College of Medicine, Seoul, Korea; <sup>2</sup>Department of Surgery, Yonsei University Wonju Hospital, Wonju, Korea

**Aims:** Since a once-daily tacrolimus (TAC-OD) has been introduced in the field of transplantation, many studies reported advantages of the new drug, such as the better adherence and the less intrapatient variability than the twice-daily tacrolimus (TAC-TD). Recently, promising results were announced regarding better clinical outcomes of the early conversion to TAC-OD in liver transplant patients. In this study, we investigated clinical outcomes of late conversion to TAC-OD more than 6 months after transplantation.

**Methods:** A total 281 patients who received liver transplant patient from January 2012 to January 2017 took TAC-TD from operation. Of them, 38 patients were converted to TAC\_OD 6 months after transplantation, while others remained with TAC-TD. We compared graft survival and postoperative complication between two groups, especially with regard to biliary complication known as implication of chronic rejection.

**Results:** Among the patients, 151 were living donor liver transplantation. There was no difference in demographics and operative characteristics between two groups. Biliary stricture occurred later after 6 month after transplantation was 18 (7.4 %) in TAC-TD and 2 (5.3 %) in TAC-OD. The cumulative incidence was not statistically different. However, overall graft survival rate was significantly higher in TAC-OD than that in TAC-TD (P=0.049). Biliary stenosis free survival was also higher without significance (P=0.065). Adverse event of drug was similar between two groups.

**Conclusions:** Late conversion to TAC-OD was safe and feasible. It has advantages of graft survival compared to TAC-TD.



**Figur 1.** Comparison of clinical outcomes from the time point of 6 month after liver transplantation between TAC-OD conversion and TAC\_TD groups.

**Keywords:** Liver transplantation, Once daily, Tacrolimus, Outcome

#### PO-098

### Culture of a Whole Porcine Liver Ex Situ without Red Blood Cells

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**Aims:** Liver transplantation is an effective approach to end-stage liver disease. Shortage of donor liver and increased waiting time for liver transplantation necessitate the development of an organ culture system by which livers can be cultured and maintained ex *situ* for a prolonged period of time. The aim of this work is to test whether cell culture condition *in vitro* could be used to culture whole livers *ex situ* without the use of erythrocytes.

**Methods:** Eight castrated male land race/farm young porcine livers were exposed to 30 min warm ischemia and 30 min cold perfusion. Livers were isolated and connected to an *ex situ* liver culture system using a standard culture medium RPMI 1640 supplied with 10% of fetal calf serum and sufficient dissolved oxygen under a normothermic condition for 6 hours. Metabolic biomarkers, bile and urea production, hepatic cell viability, and

histology analysis of biopsies were performed and analyzed.

**Results:** Dissociated porcine hepatic cells survived and grew *in vitro* under the standard RPMI 1640 culture medium. When the same RPMI 1640 medium supplemented with 10% of FCS and sufficient oxygen was used to culture livers ex situ, over 98% of liver cells were viable for at least 6 hours during *ex situ* whole organ culture based on the results from biochemical assays.

**Conclusions:** Our data demonstrate that the liver culture system established in this work can be used to culture whole livers *ex situ* in the absence of erythrocytes.

**Keywords:** Porcine liver, Ex situ culture, Oxygen, Liver transplantation

#### PO-099

#### First Two Experiences of Pure Laparoscopic Right Hepatectomy for Adult Living Donor Liver Transplantation

Jin Woo Lee, Sung Hoon Choi

Division of Hepatobiliary and Pancreas, Department of Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

**Aims:** In recent decades, the quantitative and technological development of laparoscopic liver resection has resulted in an extension to the transplantation area. Here, we introduce our initial two experiences of pure laparoscopic living donor right hepatectomy.

**Methods:** Cases. The healthy liver donors were a 46-yearold female and 22-year-old male. The BMIs of donors were 20.83 and 25.22 kg/m<sup>2</sup>. The preoperatively estimated donor's right liver volumes were 585 and 787 ml, which were 64 and 66 %of total liver volume. The graft to recipient weight ratios were 0.8 and 1.3 %. There were no significant anatomical variant in both donors except a single right hepatic artery from superior mesenteric artery in first case.

**Operative procedure:** The donor was placed in a supine position with 30 degree reverse Trendelenburg position and slight right side up. The operator and scopist stood on left side of the donor. Total of four trocars were used. A 30-degree rigid scope in first case and 0-degree flexible scope in second case were used. Pringle's maneuver were prepared, but not used in both cases. The parenchymal transections were proceeded using the laparoscopic CUSA, bipolar coagulator, and Thurnderbeat<sup>®</sup> (Olympus) under the rubber band self-retraction method and low central venous pressure (CVP) below 5 cmH2O. Intraoperative cholangiography was performed to check a resection level of right hepatic duct. The graft was extracted through the prepared Pfannelstiel incision.

**Results:** The total operative times were 380 and 350 minutes and the estimated blood loss was 250 and 300 ml without transfusion. Postoperative recoveries were uneventful in both donor and the lengths of postoperative hospital stay were 7 and 8 days. **Conclusions:** With accumulated experience of laparoscopic hepatectomy, laparoscopic living donor right hepatectomy can be safely performed reducing the spiritual and physical burden of the healthy donors.

Keywords: Donor hepatectomy, Liver transplantation, Laparoscopy

#### PO-100

#### Comparison of Pure Laparoscopic and Open Living Donor Right Hepatectomy after Learning Curve

Boram LEE, YoungRok CHOI, Ho-Seong HAN, Yoo-Suk YOON, Jai Young CHO, Sungho KIM, Kil Hwan KIM, In Gun HYUN

Department of Surgery, Seoul National University Bundang Hospital, Korea

**Aims:** With the development of laparoscopic skills, its application has expanded to the living donor liver transplantation. However, due to technical difficulties, pure laparoscopic living donor right hepatectomy (PLDRH) is performed in few centers. In this report, we compare the early outcomes between PLDRH and open living donor right hepatectomy (ODRH).

**Methods:** Total of 78 consecutive living liver donors underwent the right hepatectomy from January 2010 to March 2017. 43 living donors underwent the ODRH and the 35 donors underwent the PLDRH. Moreover, the learning curve of each group was analyzed and compared during the experienced period.

**Results:** Except for the size of the right portal vein (PLDRH 13.4 $\pm$ 6.3 mm, ODRH 10.8 $\pm$ 3.2; *P*=0.03) donor demographic including age, sex, body mass index (BMI), fatty change and vascular and biliary anomaly were comparable. Two donors of the PLDRH group underwent open conversion due to bleeding and large graft size. There were no significant differences in the operation time, estimated blood loss (EBL), intra-operative transfusion, hospital stay and postoperative complications. However, when compared in the experience period after the learning curve (PLDRH > 15 cases, ODRH > 17 cases), EBL was lower (PLDRH 397.2 $\pm$ 302.6 ml, ODRH 511.5 $\pm$ 584.0 ml; *P*=0.04) in the PLDRH versus ODRH.

**Conclusions:** PLDRH can be performed safely without increasing the risk compared with ODRH. Moreover, after the experienced period of the learning curve, PLDRH was more favorable in terms of intraoperative blood loss.

[Group 9] June 16, 2018 | 15:00-16:00

Surgery, Technical Issues

#### PO-101

### Segmentectomy 8 for Hepatocellular Carcinoma Applied with Synapse Vincent 3D for Preoperative Evaluation

Xu-Guang HU, Hee-Jung WANG, Bong-Wan KIM, Sung-Yeon HONG, Xue-Yin SHEN

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**Aims:** The Glission pedicle of anterior section is complexity and there was no detailed description on patterns of the 3rd order of Glission branch. This presentation is attempt to describe the patterns of the 3rd order of Glission branch in right anterior sectionwith SYNAPSE VINCENT 3D and present two video clip of segmentectomy 8 which applied with SYNAPSE VINCENT 3D for preoperative evaluation.

**Methods:** A total of 106 preoperative multi detector-row computed tomography (MDCT) images were obtained from the donors of adult living donor liver transplantation and the 3D images were reconstructed by SYNAPSE VINCENT medical imaging system. The patterns of the 3rd order of Glission branch in right anterior section were investigated using SYNAPSE VIN-CENT medical imaging system.

**Results:** After analysis the patterns of the 3rd order of anterior Glission pedicle, we classified the right anterior Glission pedicle into four types. Type A: cranial-caudal type (49 cases, 46.2%); Type B: ventral-dorsal type (14 cases, 13.2%); Type C: Radial type (37 cases, 34.9%); Type D: The right anterior Glission pedicles have sliding branch to/from posterior branch (6 cases, 5.7%). Two video clip of segmentectomy 8 will be shown. The dye injection and Glissionian technique were applied seperatively and the procedure were evaluate by preoperative SYN-APSE VINCENT 3D.

**Conclusions:** The detailed description of the 3rd branch of anterior Glission pedicle enriched our understanding of Couinaud segmental anatomy. Preoperative SYNAPSE VINCENT 3D is helpful for anatomic evaluation of liver resection especially segmentectomy.

#### PO-102

#### Two-Stage Hepatectomy Combined with CRS and HIPEC: Initial Experience

### Jin Hong LIM<sup>1</sup>, Hyung Sun KIM<sup>1</sup>, Jun Seong PARK<sup>1</sup>, Dong Sup YOON<sup>2</sup>

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**Aims:** Liver and peritoneum is most common metastatic lesion in patients with colorectal cancer. Synchronous bilobar colorectal cancer liver metastases(CCLM) and peritoneal metastases(PM) is known to be unresectable and dismal prognosis. However, although two stage hepatectomy(TSH) failure rate and incomplete cytoreductive surgery(CRS) rate is still high, TSH in patient with CCLM and cytoreductive surgery with heated intraperitoneal chemotherapy(HIPEC) in patient with PM have been adopted worldwide as alternative treatment strategy.

**Methods:** Between 2017.03 and 2017.11, we have experienced six cases of TSH combined with CRS and HIPEC in our institution. Five patients received right hepatectomy after wedge resection and right portal vein ligation. One patient received associating liver partition and portal vein ligation for staged hepatectomy(ALPPS).

Results: Preoperative Mean percentage of future liver remnant

was measured as 24.2% (range 21.5~30.2%), mean liver hypertrophy period is 22.3 days (range 11~56 days). percentage of hypertrophied future liver remnant after first stage was measured as 37% (range 32.8~43.9%). Among six patients, three patient received CRS with HIPEC at first stage operation. other three patients received CRS with HIPEC at second stage operation. Complication rate (Clavien-Dinddo classification grade  $\geq$  3) was 33.3%. R0 resection of liver metastasis and complete cytoreduction of PM was achieved in all patients without mortality. **Conclusions:** Simultaneous TSH and CRS with HIPEC is feasible and considered treatments in patients with Synchronous bilobar CCRM and PM. more patients' enrollment was needed for evaluation of short and long-term outcome. Multimodal oncologic therapy can make important advances in the prognosis of these patients.

#### PO-103

#### A Primary Study for Bioprinting of Human Liver

Yilei MAO, Huayu YANG

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This study is aim to construct human liver tissue structure using 3D biological printing technology. We used the characteristics of stem cell differentiation and cell 3D printing technology to investigate the progress of stem cell differentiation, 3D printing process and training components of the environment. The biological properties of cell-cell and cell matrix in natural liver tissue were successful reproduction with realizing human liver cells mature and maintaining long-term function. In addition to this, bile duct network was widely distributed in the cellular structure, improving the three-dimensional structure of the material exchange ability, and ultimately the formation of longterm survival in vitro with drug metabolizing function of human liver tissue. The liver function of 3D printing human liver tissue in vivo was evaluated by using Fah-/- model mice with hereditary tyrosine degeneration. The results showed that the 3D printing liver tissue significantly prolonged the survival time and improve the liver function in mice. It can be concluded that the human liver tissue model based on 3D printing technology has the primary liver function of liver, which provides a new tool for drug research and disease mechanism research.

#### PO-104

#### Direct Re-Anastomosis of Right Hepatic Vein after Bisegmentectomy 7-8

#### Dong-Sik KIM, Sung-Ryong KIM, Hye-sung Jo

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**Aims:** When tumor is involving segment 7 and 8 at the same time close to right hepatic vein (RHV) or invading/abutting RHV in segment 7 or 8, absence of significant right inferior hepatic

vein usually mandates right hemihepatectomy.

**Methods:** In such cases, we prefer bisegmentectomy 7-8 with RHV reconstruction using technique of direct re-anastomosis between RHV stump on liver cut-surface and that on IVC-side by approximating both ends through folding of segment 5-6 towards caudal direction.

**Results:** This technique has several advantages over technique of RHV reconstruction using artificial graft or cryopreserved cadaveric iliac vein, which are 1) only one anastomosis is required, which is easier and quicker, 2) avoidance of using foreign material, 3) decreased risk of kinking or distortion of anastomosis when remnant liver was placed back in position.

**Conclusions:** This technique can preserve segment 5 and 6 without compromise in oncologic principle while maximizing remnant liver volume and function.

#### PO-105

#### Portocaval Anastomoses in Patients with Liver Cirrhosis and Portal Hypertension

Toshnazarov J.F., Lukmonov S.N., Madatov K.A., Toshtemirov S.G.

Department of Faculty Surgery, Tashkent Medical Academy

**Aims:** Analyze the results of partial portocaval shunting (PPS) in patients with cirrhosis of the liver.

**Methods:** 118 patients with intrahepatic form of portal hypertension (PH) undergoing liver cirrhosis underwent planned surgical treatment. Women were 21 (17.8%), men - 97 (82.2%). The average age of patients is  $58.5 \pm 17.2$  years. The following research Methods: were used in the diagnostic program: clinical and laboratory, ultrasound with duplex scanning of porto-hepatic hemodynamics, video liposcopy, MRI, CT, liver biopsy, if necessary, mesenteric and splenoportography. Patients were assessed on the basis of the Chidl-Pugh prognostic criteria: A-68 (57.6%), B-17 (14.4%) and C-33 (28.0%). With PEGD, varicose veins of the esophagus (grade II-II) were established in 79% of patients, grade III-IV in 21%. When performing duplex scanning, the volume flow rate in the portal vein averaged 292.0  $\pm$ 21.4 ml / min. Conducted morphological studies confirmed the presence of liver cirrhosis. One episode of one bleeding from the VV in a history was noted in 86% of patients, 2 and more - in 14%. In patients with Class A, splenorenal anastomoses were performed (68); Class B (42) - portocaval anastomoses were applied in 3 variants (end-to-side, side-to-side, H-type with autovenous graft from the internal jugular vein of the large saphenous vein of the thigh, and also using the reinforced Prote-Tech prosthesis <10 mm), patients of class C (8) underwent the operations of devascularization of Hassab-Sugiura and MD Patziora - stitching of the esophagus.

**Results:** Among patients of class A, 2 (2.94%) patients died, class B - 6 (35.3%), class C - 14 (42.4%). Recurrence of bleeding from the esophagus of the esophagus was observed in 1 (1.4%), 3 (17.6%) and 8 (24.2%) patients in classes A, B, C, respectively. The bleeding was stopped with the help of endoscopic sclerobliteration with 1% ethoxy-sclerol. Encephalopathy developed in 2 (11.8%) and 12 (36.3%) patients in classes B and C, respectively. Patients were observed for 5 years. The five-year survival rate was 92% in Class A, in Class B –41%.

**Conclusions:** The results of performed shunting operations in the treatment of liver cirrhosis against the background of compensated and subcompensated stages are good and satisfactory. With decompensated cirrhosis, it is necessary to perform an operation for separation, sclerobliteration.

Keywords: Ethoxy-sclerol, Portal hypertension, Liver biopsy

### The Liver Week 2018

# **Poster Exhibition**

PE-001~PE-003	Liver Failure, Acute
PE-004~PE-017	Alcoholic Liver Disease
PE-018	Genetic
PE-019	Autoimmune Liver Disease
PE-020~PE-045	HBV, Clinical
PE-046~PE-048	HBV, Basic
PE-049~PE-078	HCV, Clinical
PE-079~PE-081	HCV, Basic
PE-082~PE-149	Liver Cancer, Clinical
PE-150~PE-171	Liver Cancer, Basic
PE-172~PE-185	Liver Cirrhosis, Portal Hypertension
	with Cx. Clinical
PE-186~PE-202	NAFLD, Clinical
PE-203~PE-209	NAFLD, Basic
PE-210~PE-239	Liver Transplantation
PE-240~PE-248	Drug and Toxic Injury
PE-249~PE-251	Cell Biology / Molecular Biology
PE-252~PE-268	Liver, Infectious Disease
PE-269~PE-293	Surgery, Technical Issues
PE-294~PE-327	Biliary and Pancreatic Disease
PE-328~PE-334	Others

Liver Failure, Acute

#### PE-001

#### Analysis of Cause and Prognosis for Acute Hepatitis with High Aminotransferase Levels

Min Kyung Back<sup>1</sup>, Seok Hyun Kim<sup>1,2</sup>, Byung Seok Lee<sup>1,2</sup>, Eaum Seok Lee<sup>1,2</sup>, Hyuk Soo Eun<sup>1,2</sup>, Jong Seok Joo<sup>1,2</sup>, Woo Sun Rou<sup>1,2</sup>, Jae Ho Park<sup>1</sup>, Myung Hee Kim<sup>1</sup>, Min Seong Kim<sup>1</sup>, Deok Yeong Kim<sup>1</sup>

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**Aims:** Acute hepatitis can sometimes lead to serious complications of liver failure leading to death, and in some cases it is one of the important factors causing chronic and socioeconomic loss. This study aimed to analysis of cause, characteristics and prognosis for patients with acute hepatitis with high aminotransferase level at admission.

**Methods:** We retrospectively reviewed the medical records of 227 patients clinically diagnosed with acute hepatitis whose aminotransferase levels were elevated 10 times or more at the time of admission between January 2013 and December 2017. The recovery time of the disease was defined as the decrease in aminotransferase level and total bilirubin level within the normal range.

**Results:** The most common cause of acute hepatitis was toxic hepatitis(40.0%, n=93). The proportion of acute viral hepatitis A, acute viral hepatitis B, acute viral hepatitis C and acute viral hepatitis EBV were 23.3%(n=53), 5.7%(n=13), 1.3%(n=3) and 1.3%(n=3), respectively. In addition, Alcoholic hepatitis, Autoimmune hepatitis, HBV reactivation and acute hepatitis of un-known cause were 2.6%(n=6), 5.7%(n=13), 2.2%,(n=5) and 16.7%(n=38), respectively. The duration of hospitalization for acute hepatitis was within 2weeks, and the duration of recovery was within 2 to 4weeks. 5 patients progressed to fulminant hepatitis and died. Two of them died by HBV reactivation, and the remaining three patients died from acute hepatitis B, toxic hepatitis and acute hepatitis of unknown etiology, respectively.

**Conclusions:** The cause of acute hepatitis affects disease prognosis more than aminotransferase levels at admission. However, since aminotransferase levels may affect the patient's recovery rate or duration of hospitalization, periodic follow-up of aminotransferase levels is necessary. Especially when chronic hepatitis B is reactivated, the rate of progression to fulminant hepatitis is high. Disease control and close monitoring of chronic hepatitis B is therefore necessary.

Keywords: Acute hepatitis, Aminotransferase, Hepatitis

#### PE-002

#### Percutaneous Cholangiostomy Under Ultrasound Control in Patients with Mechanical jJundice Syndrome

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**Aim:** The results of 23 patients with mechanical jaundice syndrome who underwent percutaneous cholangiostomy were analyzed.

**Methods:** In the Department of surgery of the regional medical center of Kyzylorda in 2017, 23 patients received with mechanical jaundice syndrome had percutaneous cholangiostomy. Of these, cancer of the pancreatic head – 11 (47,8%), cancer of the large duodenal papilla of the duodenum in 5 (21,7%), choledocholithiasis – 4 (17,3%), cancer Klatskin – 3 (13.0 per cent). The age of patients from 55 years to 76 years. Of these, 9 men (39.1%), 14 women (60.8%). The level of total bilirubin = 380,0 mmol/L.

Results: After complete examination of patients, performed preventive antibiotic therapy. Under angiographic installation in the operating unit, under local anesthesia, a puncture is performed inside the hepatic bile ducts under ultrasound control in Doppler mode. Further aspires stagnant bile, a Guidewire is 0.38. According to the method of the Seldinger bile ducts biroute to 10 Fr. Then, under the control of intraoperative cholangiographies sets hydrophilic Pigtail catheter 8 Fr. Further drainage is fixed on the skin. In the early postoperative period, the cholangiostomy tube is washed with 5 ml 0.9% sodium chloride solution several times a day. In office patients receive analgesics, medications, infusion terapia, according to testimony carried zamorojennoi infusion of fresh plasma, plasmapheresis fractional. 15-25 days after surgery the level of total bilirubin is reduced to 40,0-60,0 mmol/l. Then it is possible to conduct radical surgery. The average duration of treatment was 11.5 days. There was no mortality.

**Conclusions:** Percutaneous cholangiostomy under ultrasound control is a promising direction of biliary decompression **Keywords:** Percutaneus, Cholangiostomy, Ultrasound

#### PE-003

#### Experience Using Continuous Veno-Venous Hemofiltration in Patients after Liver Transplant for 2017

Samat Issakov

CF UMC National Scientific Center for Mother and Child Health

**Aims:** To evaluate CVVH (Continuous Veno-Venous Hemofiltration) as acute renal replacement treatment in postoperative care of liver transplantation.

Retrospective study.

Intensive Care Unit, year 2017.

6 OLT performed in 2017, 3 of them underwent acute renal replacement treatment. In the same period, in the ICU were
admitted 146 patients, and 16 underwent acute renal replacement treatment (control group). Evaluation with SOFA (Sepsis-related Organ Failure Assessment) score.

**Methods:** CVVH performed heparin free, pump system, polyamide or polysulphone 0.6 mq membrane hemofilter device, blood flow 100-150 ml/min, UF rate 600-1200 ml/h, clearance 16-20 ml/min. Coagulation monitoring (PT as INR, PTT, fibrinogen, antithrombin III, d-dimer, platelet count) was performed 3 times a day or on variation of the clinical conditions.

**Results:** SOFA score did not differ between the two groups. Mortality was higher in the patients treated with CVVH. CVVH was performed from 16 to 18 hrs/day for 9.90 +/- 2.33 days. Three patients developed clinical bleeding before CVVH, 3 during CVVH but 1 of them underwent repeated surgical procedures.

**Conclusions:** We cannot demonstrate that CVVH doesn't affect bleeding, but we can say that, for the complexity of the post OLT patients, CVVH can be the treatment of choice in case of renal replacement treatment.

Keywords: Liver, Transplant, CVVH, SOFA

### Alcoholic Liver Disease

## PE-004

#### Modified Membranous Plasmapheresis in Complex Treatment of Patients with Liver Failure

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**Aims:** One of the challenging problem in modern medicine is a viral hepatitis, which can cause acute liver failure, liver cirrhosis and even HCC. In National Centre of Surgery named after acad. V. Vakhidov, we have many been conducting a number of researches dedicated to this pathology. One of them is plasmapheresis usage in complex treatment. Aim of research: to investigate the effect of advanced method of plasmapheresis conduction to patients with liver failure to efficacy of detoxication, peroxidase oxidation of lipids and antioxidant protection.

**Methods:** therapeutic membranous plasmapheresis treatment procedures were conducted at 60 patients, 34 of them were men and 26 were female. Mean age was 37,2 years old. Except standart therapy, which included hepatoprotectors, infusions, immunomodulators and antibiotics, patients were indicated therapeutic membranous plasmapheresis. Our method consists of plasmapheresis without initial heparinization of patient, neutral anolit was used instead of citrate and isotonic solutions (Invention patent NeIAP 03988 at 20.07.2009). **Results:** Most patients had high levels of average molecular peptides, bile acids, ALT, AST and CPR, which considerably decreased after 3rd procedure.

**Conclusions:** Plasmapheresis with neutral anolitis results to detoxication effect, which is presented by free radicals process recuperation and enhancement of clinical and biochemical features at earlier stages. This action is reached due to complex efferent and oxidase detoxication technologies, which in its turn approve feasibility of developed method.

#### **PE-005**

# Diagnostic Value of Transaminases and Deritis Ratio for Predicting Alcoholic Liver Disease

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**Aims:** Alcoholic liver disease is a major public health concern in Nepal. Excess alcohol consumption leads to alcoholic liver diseases. The use of test combinations significantly improves the information received with single serum enzyme determinations. Aspartate aminotransferase to alanine aminotransferase ratio (deritis ratio) is a diagnostic marker in alcoholic liver disease. The aim of the study is to rule out significance of transaminases and deritis ratio in alcoholic liver disease subjects.

**Methods:** The study was carried out in the department of biochemistry at Manipal Teaching Hospital, and kaski Sewa Hospital and Research Center Pokhara, Nepal between 5<sup>th</sup> October 2017 to 15<sup>th</sup> March 2018. Clinically 50 known cases of alcoholic liver disease patients and 50 healthy individuals were enrolled in this study. The correlations of the variables were evaluated by pearson correlation coefficient. Descriptive statistics were used for analysis of the results. Data was analyzed by using SPSS version 17. P values of < 0.05 were considered statistically significant.

 
 Table 1. Comparision of variables between study group and control group

Parameters	Study subjects (ALD) N=50 Mean± SD	Control N=50 Mean± SD	P value
Age	48.18±15.46	49.06±17.03	0.789
Total protein	7.65± 0.99	7.68±0.81	0.671
Albumin	3.85± 0.55	4.12± 0.40	0.007
Total billirubin	1.47±1.54	0.70± 0.37	0.001
Direct Billirubin	0.65± 0.88	0.26± 0.11	0.003
AST	121.9± 90.5	24.04± 8.16	0.000
ALT	61.26± 43.86	21.96±6.72	0.000
AST/ALT ratio	1.95± 1.42	$1.13 \pm 0.35$	0.000
ALP	123.58± 59.71	85.10± 29.62	0.000
GGT	155.13± 117.31	26.86± 10.86	0.000

\*P-valve < 0.05 is considered statistically significant.

**Results:** We found a significant difference between Transaminases between alcoholic liver disease patients and healthy control subjects. The mean value of AST ( $111.98 \pm 124.05$ ) was found to be highly increased incomparision to ALT (61.26  $\pm$  43.86) leading to significantly higher AST/ALT ratio (1.95  $\pm$ 1.42). The mean values of deritis ratio was 1.95 in ALD patients which was markedly increased as compared to the ratio of controls (1.13). There were significant differences in the AST/ ALT ratio between two groups (P=0.000). Patients with alcoholic liver disease had an AST:ALT ratio > 1.0.

**Conclusions:** This study suggests that high deritis ratio is the marker for alcoholic liver disease. An elevated serum AST in relation to serum ALT has been proposed as an indicator that alcohol has induced organ damage

Keywords: Alcoholic liver disease, AST, ALT, Deritis ratio

#### PE-006

#### Study of Serum Gamma Glutamyl Transferase (GGT) Activity as a Biomarker in Alcoholic Liver Disease

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Aims: Alcoholic liver diseases arise from the excessive ingestion of alcohol. It is the major cause of liver cirrhosis all over the world. It can be prevented by early diagnosis and management. Various biomarkers and enzymes are available for the diagnosis of alcoholic liver diseases. The aim of the study is to evaluate the role GGT in the diagnosis of alcoholic liver disease.

Methods: This study was conducted at Kaski Sewa Hospital and Research Centre between 2<sup>nd</sup> December 2017 to 15<sup>th</sup> March 2018. A total of 100 subjects were included in this study out of which 50 were alcoholic liver disease patients and 50 were healthy control subjects. Gamma glutamyl transferase activity was measured for all the subjects. The results were expressed as mean ± SD. The comparison between the two groups were evaluated by Pearson correlation coefficient. Statistical analysis were done by using Statistical package for social sciences version 17.0. A p values of less than 0.05 were considered statistically significant.

**Results:** The mean age of the study subjects was  $48.62 \pm 16.3$ . Male and female percentage was 71 % and 29 % respectively. A significant correlation was found between the alcoholic liver disease patients and healthy control subjects. The mean values for GGT was markedly increased 155.13 ± 117.31 as compared to healthy subjects (26.86 ± 10.86) which was statistically significant (P=0.000).

Table 1. Serum GGT activity in alcoholic liver disease and healthy controls

Parameter	Study group Mean ± SD ( n=50)	Control Group Mean ± SD (n=50)	P value	
Gamma Glutamyl				
Transferase	$155.13 \pm 117.31$	26.86 ± 10.86	0.000*	

P value < 0.05 is considered statistically significant.

Conclusions: This study suggested that serum level of gamma glutamyl transferase activity is helpful in the assessment and diagnosis of alcoholic liver disease.

Keywords: Gamma glutamyl transferase, Alcoholic liver disease, Biomarker, Enzyme

# **PE-007**

#### Incidence and Risk Factors for Alcohol Relapse after Liver Transplantation for Alcoholic Liver Disease

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**Aims:** Alcoholic liver disease is one of the most common causes of cirrhosis and indication for liver transplantation (LT). However, controversies exist over the so called "6-month abstinence rule" and LT for those with ongoing alcohol use. Also, risk factors for alcohol relapse have not been well-defined in Korea.

Methods: We analyzed consecutive 126 patients [median age: 51 years, male: 99 (78.6%)] who underwent LT between Jan. 2000 and Dec. 2016 for alcoholic liver disease at Samsung Medical Center, Seoul, Korea. We reviewed patients for alcohol relapse after LT retrospectively. Several factors that may be associated with alcohol relapse, including "6-month rule" were assessed.

Results: During a median follow-up of 43.7 months (min-max: 0.2-194.1 months), the cumulative alcohol relapse rate at 1, 3 and 5 years were 7.0%, 17.1%, and 23.1%, respectively. The 3-year cumulative alcohol relapse rate was 24.3% for those who had been abstinent from alcohol for less than six months before LT and 7.0% for those who had more than six months of abstinence (P=0.06). Patients who received deceased donor liver transplantation (DDLT) had a higher risk of alcohol relapse (34.2%) than those who received living-related donor liver transplantation (LDLT) (9.7%) (P=0.001). When stratified according to donor type and the 6-month rule, the cumulative alcohol relapse rate at 3 years was 40.0%, 16.7%, 13.7% and 5.6% for those who were abstinent from alcohol for less than six months and received DDLT, those who were abstinent for more than six months and received DDLT, those who were abstinent for less than 6 months and received LDLT, and those who were abstinent for more than 6 months and received LDLT, respectively (P=0.001).

Conclusions: About one-fourth of patients who were transplanted for alcoholic liver disease resumed alcohol consumption after LT. Alcohol relapse rate was especially high for those who were not abstinent for more than six months and received DDLT. Urgent strategies to decrease alcohol relapse are required for patients transplanted for alcoholic liver disease, especially for those who received DDLT and were not abstinent for more than six months.

**Keywords:** Liver transplantation, Alcoholic liver disease, Alcohol relapse

#### **PE-008**

# Surgical Treatment of Hepatolithiasis: Our Experience in Bangabandhu Sheikh Mujib Medical University

#### Bidhan Chandra DAS, Zulfiqur Rahman KHAN

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**Aims:** Recurrent cholangitis and sepsis are common complications after surgical treatment for hepatolithiasis as total clearance is not always possible. The present study is designed to see the effect of our treatment for hepatolithiasis on stone clearance and post operative complications.

**Methods:** We have treated 60 patients with hepatolithiasis surgically between 2010 to 2016 in the Department of Surgery, BSMMU, Dhaka. Various operative procedures were applied on the basis of location of stones. Choledocoscopic examination was performed during surgery for checking and cleaning of intrahepatic duct. Regular follow up was given and outcome was assessed.

**Results:** Lobectomy or segmentectomy is the best option for hepatolithiasis if the stones are limited to a lobe or segment. Excision of CBD-hepatolithotomy with hepaticojejunostomy is better than extended choledocholithotomy- hepatolithotomy for bilateral hepatolithiasis.

#### **PE-009**

### Effects of Oral L-Carnitine on Liver Functions after Transarterial Chemoembolization (TACE) in Hepatocellular Carcinoma (HCC) Patients

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**Aims:** Transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) is usually followed by hepatic dysfunction that limits its efficacy. L-carnitine is recently studied as hepatoprotective agent. Our aim is to evaluate the L-carnitine effects against the deterioration of liver functions after TACE.

**Methods:** 53 patients with HCC were assigned into two groups; L-carnitine group (26 patients) who received L-carnitine 300 mg tablet twice daily from 2 week before to 12 week after TACE and control group (27 patients) without L-carnitine therapy. 28 of studied patients received branched chain amino acids granules.

**Results:** There were significant differences between L-carnitine Vs control group in mean serum albumin change from baseline to 1 and 4 week after TACE (*P*<0.05). L-Carnitine maintained Child-Pugh score at 1 week after TACE and exhibited improvement at 4 week after TACE (*P*<0.01 Vs 1 week after TACE). Control group has significant Child-Pugh score deterioration

from baseline to 1 week after TACE (P<0.05) and 12 week after TACE (P<0.05). L-carnitine displayed improvement in (PT) from baseline to 1 wk, 4 w (P<0.05) and 12 wk after TACE. PT in control group declined less than baseline along all follow up intervals. Total bilirubin in L-carnitine group decreased at 1 week post TACE while in control group, it significantly increased at 1 week (P=0.01). ALT and C-reactive protein elevation were suppressed at 1 week after TACE in Lcarnitine group.

**Conclusions:** L-carnitine BCAA combination therapy offers a novel supportive strategy after TACE in HCC patients.

# PE-010

#### Activated Sorbent Hemosorption at Patients with Liver Failure

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**Aims:** In the last decade extracorporal hemosorption is successfully applied to elimination of pathological changes after liver operations complications.

**Methods:** The hemosorption method is applied at 22 patients with liver failure caused by biliary tract obturation and purulent cholangitis. At the same time at 14 patients hepatogenic encephalopathy was noted with heavy endogenic intoxication. After washing of a sorbent without preliminary geparinization of the patient the highway of a fence was connected to a vein.

**Results:** The effectiveness of a hemosorption was estimated on clinical manifestations and data of laboratory analyses which were defined prior to the procedure, after 1 and 2 sessions of a hemosorption. Clinically at all patients after 1 session of a hemosorption significant improvement of a state with decrease of symptoms of intoxication of an organism is noted. The effectiveness of holding a procedure the sorbent modified by a neutral anolyte was much higher, than an unmodified analog. The clearance of toxiferous metabolites and main markers of endogenic intoxication was higher, than at patients of control group which the hemosorption was carried out by the same sorbent, but not activated solution of a neutral anolyte. After 2 sessions of a hemosorption at most of patients, along with a normalization of the studied biochemical indexes restitution of the immunologic status was noted.

**Conclusions:** Thus, oxidizing modification of a sorbent allowed to increase effectiveness of treatment substantially at patients with liver failure.

# PE-011

#### Management of Pregnant Patients to Prevent the Graft Loss after Liver Transplantation: First Experience in National Scientific Medical Research Center

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**Aims:** There were many studies showed the successful pregnancy and delivery in patients after liver transplantation. From 2012 more than 100 living donor liver transplantations has carried out in Kazakhstan and our report represents the first successful pregnancy and delivery in recipient after liver transplantation.

**Methods:** Orthotopic transplantation of right liver lobe from a living related donor was performed to our patient from her elder brother. The main cause of liver cirrhosis was autoimmune hepatitis. After one year of LDLT the patient informed us about unplanned pregnancy.

**Results:** Among complications in early postoperative period the portal vein thrombosis was detected and successfully treated by heparin monotherapy. No other complications found in late period after transplantation. The standard third-component immunosuppressive therapy (CNI + MMF + GCS) was applied during the first year after transplantation. After the sudden information of 2 weeks pregnancy the MMF application was canceled. In first three months no significant alterations were found during the childbearing. On 18-20 weeks the first signs of liver rejection was appeared where sensitization of HLA class 1 was 0% and HLA class 2 consisted 91%. As a main treatment the pulse therapy with GCS and plasmapheresis were performed. On 40 weeks delivery was successfully done by Cesarean section. The child was male with weight - 2830 g, and height - 54.3 cm and without no visible any defects.

**Conclusions:** In our case, it was an acceptable outcome for both mother and baby, although considered a high risk pregnancy.

# PE-012

# Effect of Early and Delay Starting of Enteral Feeding in Post-Pancreatoduodenectomy Patients

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**Aims:** This study is undertaken to see the effect of early starting of enteral feeding after pancreatoduodenectomy (PD).

**Methods:** Thirty patients who underwent PD in the Department of Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2016 to December 2016 was included

in the study. They were divided into two groups; Group I (n=15): Enteral feeding was started from 2nd POD through nasojejunal feeding tube along with parenteral partial nutrition support. Group II (n=15): No enteral feeding was given up to 7-8 PODs except partial perenteral feeding. Post-operatively, serum albumin levels, total lymphocyte count, total bilirubin levels, serum alkaline phosphate levels were measured for 2 weeks postoperatively in all patients for assessing nutritional, immunological and cholestasis. Mortality, morbidity and lengths of post-operative hospital stay were also recorded.

**Results:** Both groups matched the same status pre- and per-operatively. Postoperatively serum albumin level and lymphocyte count decreased from preoperative level on 3rd POD and gradually increased from 7th POD onward in both groups but they remained persistently higher in Group I than Group II. Total bilirubin and alkaline phosphatase decreased to normal within 7 POD in Group I, but they remained still higher than normal level on POD 14 Group II. Morbidity and hospital stay is significantly lower in group I than group II.

**Conclusions:** Early enteral feeding should be considered after PD. It will improve nutritional, immunological status and cholestasis. Thus it reduces morbidity and shortens the hospital stay.

# PE-013

### Epidemiology of Pancreatic Cancer in Mongolia Last Decade

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**Aims:** Pancreatic cancer is one of the highest mortality rates in the world and often remains undiagnosed until it is at a late stage, resulting in the majority of tumors being unsuitable for surgical resection. Improving the results of chemotherapy has been slow, and novel approaches to systemic treatment are needed. The aim of the present study was to update the epidemiology of pancreatic cancer in Mongolia last decade from the National Cancer Center of Mongolia database.

**Methods:** All patients hospitalized for pancreatic cancer in NCCM from 2007 to 2016 were included. Patient and stays (length, type of support, institutions) characteristics were studied.

**Results:** A total of 1003 (52% men, median age 61 years) new cases were diagnosed for pancreatic cancer last decade, accounting for a 2.7 times increase compared with 2007 and 2016. Overall, early stage pancreatic cancer was 11.7%, among 16% of patients were operated on. Mortality rate was 86.5%.

**Conclusions:** Approximately 1003 new cases of pancreatic cancer were observed in Mongolia in last decade. The incidence and mortality rate to tendency increasing. We need more to improve diagnostic capacity and treatment rate.

### Radiofrequency Ablation Technique in Hepatic Surgery: Clinical Experience

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Aims: The Korean Association of HBP Surgery firstly launched the protocol of Korean Surgical Quality Improvement Program (KSQIP) for cholecystectomy collaborating with NECA as a multicenter prospective study. I'd like to introduce the study protocol, web based database system and outcome. Laparoscopic cholecystectomy (LC) is the standard surgical treatment of benign gallbladder disease. However, the incidence of postoperative complication varies, and the risk factor was not well thoroughly investigated. The aim of this study is to develop and evaluate the surgical risk calculator for postoperative outcomes after laparoscopic cholecystectomy. A total of 3,002 patients were registered, and 2,514 patients who underwent laparoscopic cholecystectomy for benign gallbladder disease from 18 academic institutes in Korea were included in this prospective, multicenter cohort study. Preoperative or intraoperative variables were evaluated as risk factors for various postoperative outcomes including overall complications, and tendency to increase use of medical facilities including prolonged duration of hospital stay. After risk factor analysis, risk calculator after cholecystectomy was developed using multiple logistic regression analysis. Using standard preoperative variables from this multi-institutional prospective database, we tried to construct a risk calculator for predicting adverse perioperative outcomes after laparoscopic cholecystectomy. Such information may be useful for risk stratification before laparoscopic cholecystectomy.

# **PE-015**

#### Possibilities of Retrograd Interventions in Choledocholitias and Stenosis of the Terminal Department of Choledochus

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**Aims:** To study the possibility of endoscopic retrograde interventions in choledocholithiasis and stenosis of the terminal department of choledochus.

**Methods:** From 2011 to 2016 years. on the basis of faculty surgery of the Tashkent Medical Academy. endoscopic methods of treatment of choledocholithiasis and stenosis of the terminal department of choledochus were used in 45 patients. Among the patients were 34 (75.6%) women and 11 men (24.4%) aged 24 to 80 years (mean age 54.3  $\pm$  7.22 years).

**Results:** 42 patients had mechanical jaundice when they received or in anamnesis. The diameter of the choledochus, according to ultrasound, ranged from 5 mm to 1.4 cm (8.3  $\pm$  1.42 cm). All patients underwent endoscopic retrograde chol-

angiopancreatography, in which 22 (48.9%) observations of choledocholithiasis of the terminal section of choledochus were detected, in 14 (31.1%) - stenosis and 9 (20%) - combination of choledolithiasis with stenosis of the distal section of the common bile duct duct. In 40 (88.9%) patients retrograde intervention was successful: in 33 - endoscopic papillosphincterotomy (EPST) with stone extraction and in 7 - EPST. In 5 (11.1%) observations retrograde intervention did not give the desired effect, the reasons for which were the impossibility of removing the stone.Patients of this group performed "open" operations - imposition of holedoduodenoanastomoz according to the method of Yurash-Vinogradov.

**Conclusions:** Thus, the main method for diagnosis and treatment of choledocholithiasis and stenosis of the terminal department of choledochus is ERCP with EPST. Open operations on the choledochus are performed with the imposition of biliodigistic anastomoses.

### PE-016

#### Modified Extracorporal Detoxication after Pankreatic Tumor Operations

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**Aims:** The problem of treatment of acute postoperative pancreatitis and its complications is the complex problem after pancreatic tumor operations. Mortality rate remains high, and varies from 10% to 40%. Aim of research: to increase treatment effectiveness of patients with acute pancreatitis.

**Methods:** A complex of an intensive care the modified technique of plasma exchange with reinfusion of detoxicated exfused blood by its indirect electrochemical oxidation is applied.

**Results:** All patients in a reference group had strong indications of endointoxication with multiorgan failure phenomena. After completion it was succeeded to achieve the considerable decrease in practically all studied indexes from patients of both groups. However, the tendency to a normalization was more expressed at patients of evaluated group who needed carrying out smaller number of sessions of PAS.

**Conclusions:** Neutral anolyte inclusion into technique of plasma exchange carrying out allowed us to avoid development of above-stated complications from hemostasis system and to substantially increase effectiveness detoxication. The universality of developed technique and expediency of its use was proved by the conducted researches at wide range of diseases. Thus, in all cases, irrespective of the reasons which caused the necessity of carrying out detoxication actions we managed to reduce

the number of sessions, i.e. to increase quality of detoxication. Especially it is necessary to emphasize positive influence of this technique on coagulation and anticoagulative mechanisms of hemostasis that is also the basic moment for the choice of this scheme of carrying out PAS in comparison with the working standard.

#### **PE-017**

#### Pattern of Liver Enzymes in Alcohol Dependence Syndrome Patients

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**Aims:** Alcohol dependence syndrome (ADS) has become a global public health challenge because of its high prevalence and the concomitant increase in risk of liver disease, cardiovascular disease and premature death. Influence of alcohol use on liver metabolism is well recognized. This study was aimed at examining the association of liver enzymes like  $\gamma$ -glutamyltransferase (GGT) and aminotransferase, with alcohol dependence syndrome patients.

**Methods:** This cross-sectional study was conducted in Tribhuvan University Teaching Hospital. ADS patients were screened by the consultant psychiatrist using the Alcohol Use Disorder Identification Test (AUDIT) questionnaire. A total of 89 patients scored positive on the AUDIT as having alcohol-related problems and were included in the study. Blood Pressure and other anthropometric parameters were measured while blood samples were analyzed for liver enzymes and serum protein.

**Results:** Mean age of cases and controls was  $35.42 \pm 5.6 \& 34.53 \pm 3.5$  years respectively. The mean values of Gamma GT, SGOT and SGPT were largely elevated in cases as compared to the controls with a statically significance (*P*<0.001). Among the ADS cases serum GGT level was elevated in 97% patients. The SGOT/SGPT ratio was also significantly higher in cases (2.02  $\pm$  0.39) and control (1.45 $\pm$ 0.62). It was found that 15.1 % cases had low serum protein level and 32.9% cases were low serum albumin level. Albumin to globulin ratio was also significantly decreased in cases (1.16  $\pm$ 0.29).

 
 Table 1. Comparision of liver enzymes and serum protein in cases and control

	Controls	Cases	<i>B</i> values
	Mean±SD	Mean±SD	F-values
Gamma GT	41.80 ± 10.56	181.02 ± 78.16	
SGOT	35.26 ± 14.27	114.35 ± 46.22	
SGPT	26.30 ± 10.6	60.28 ± 13.12	
SGOT/SGPT	1.45 ± 0.62	2.02 ± 0.39	<0.001
Total protein	75.19 ± 4.66	68.87 ± 4.6	
Albumin	43.27 ± 4.3	36.61 ± 5.5	
A/G Ratio	1.38 ± 0.28	1.16 ± 0.29	

Applied one way anova test, statistically significant at P-value < 0.05

Conclusions: These findings support the hypothesis that, alco-

hol may affect the pattern of liver enzymes and also damage the liver cells. Decrease in serum albumin and elevation of SGOT to SGPT ratio more than two is suggestive of development of liver cirrhosis in alcohol dependence patients.

Keywords: Alcohol dependence syndrome, Transaminases, Liver cirrhosis, Albumin

# Genetic

# PE-018

#### Autophagy Regulates the Expression of CTGF

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**Aims:** Autophagy is an intracellular lysosomal degradation process that performs important cell functions in the liver. Several studies have shown that hepatocyte-specific ATG7 or ATG5 knockout mice have increased liver injury, including liver fibrosis. However, the relationship between autophagy and liver injury and fibrosis has not been clarified so far. In this study, we investigated the genes associated with autophagy inhibition and hepatic fibrosis.

**Methods:** Hepatocyte-specific ATG7 knockout mice were generated by crossing ATG7 Flox/Flxo mice with albumin Cre mice. We isolated and cultured ATG7 K/O mouse primary hepatocyte, mouse hepatocyte and human hepatic stellate cell lines (AML12, LX2) and rat kidney fibroblast and mouse mesangial cell lines (NRK49F, SV40 MES 13). We used bafilomycin A or chloroquine as an autophagy inhibitor and MG132 as an autophagy inducer. The expression levels of CTGF, LC3, p62 and MAPK were evaluated by western blot analysis.

**Results:** Primary hepatocyte isolated from hepatocyte-specific ATG7 knockout mice showed increased expression of CTGF and phospho-ERK. MG132 decreased CTGF expression and BFM or CQ increased CTGF and phospho-ERK expression. In addition, increased CTGF expression by BFM or CQ was reduced by ERK inhibitor.

**Conclusions:** These results suggest that inhibition of autophagy may increase the expression of CTGF and ERK, while the increase of autophagy decreases the expression of CTGF. This suggests that autophagy may be involved in the progression of fibrosis.

Keywords: Autophagy, ATG7 knockout mice, CTGF

Autoimmune Liver Disease

#### PE-019

#### Autoimmune Hepatitis Aggravated by Statin

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**Aims:** Background: Although the cause of autoimmune hepatitis is unknown, drugs are believed to be potential triggers or aggravators in some patients. The exact mechanism of statin-induced autoimmune reaction is unclear. Statins, as proapoptotic drug, can release the nuclear antigen into the circulatory system and induce the production of pathogenic autoantibodies. We report a case of autoimmune hepatitis aggravated by statin.

Results: Case: The 38-year-old woman made an outpatient visit for fatigue and general weakness. On admission, BP was 100/60 mmHg, HR 72 beats/min, RR 20 breaths/min, and BT 36.5°C. Initial laboratory findings were; WBC 6,040/mm<sup>3</sup>, Hb 10.8 g/dL, PLT 291,000/mm<sup>3</sup>, PT 11.6 sec, PT (INR) 1.06, AST 75 IU/L, ALT 212 IU/L, total bilirubin 1.4 mg/dL, r-GTP 1504 IU/L, ANA titer 1:160. Abdominal ultrsono and CT showed two small hemangioma (< 2cm) in liver S2 and S3. Liver biopsy confirmed autoimmune hepatitis with severe interface hepatitis and plasma cell infiltration. She ingested prednisolone and azathioprine. During treatment with steroids and azathioprine through outpatient for 3 months, she was treated with pitavastatin for 3 weeks with newly diagnosed hypercholesterolemia (total cholesterol 504 mg/dL). Follow up liver function tests after starting pitavastatin were aggravated; AST 256 IU/L, ALT 696 IU/L, total bilirubin 2.8 mg/dL. After stopping pitavastatin treatment, the liver function test was improved.

**Conclusions:** The association of statins with immune disorders has been rarely reported. Statins are generally regarded as safe, but long-term follow-up observations of patients taking statins may trigger or exacerbate an autoimmune response.

**Keywords:** Autoimmune hepatitis, Statin, Drug-induced liver injury,

# HBV, Clinical

### PE-020

#### Risk Factors Associated with Hypophosphatemia in Chronic Hepatitis B Patient Treated with Tenofovir Disoproxil Fumarate

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**Aims:** Tenofovir disoproxil fumarate (TDF) has been considered causing hypophosphatemia as well as proximal tubular toxicity and renal dysfunction. Clinically, many patients treated with TDF experienced various degree of hypophosphatemia, and some of them should be stopped due to severe hypophosphatemia. Therefore we investigated which factors induced moderate hypophosphatemia among patients treated with TDF.

**Methods:** We conducted a retrospective study of chronic hepatitis B patients who were initially prescribed TDF at kosin university hospital, busan, korea from January 2012 to January 2017. Baseline Phosphorus and follow-up Phosphorus levels were compared. The definition of hypophosphatemia is lower than 3.0 mg/dL.

Results: 206 patients were treated with TDF. 128 patients were excluded for the following reasons. 59 patients had malignancy (including HCC), 36 patients had baseline Phosphorus check days not within 2 months of the first day of TDF administration, 14 patients were co-treated with TDF and other anti-viral agents, 14 patients were not followed up, and 5 patients had other reasons. Consequently, 78 patients were analyzed in this study. Median follow up duration was 350.5days. Follow up duration is the period from the day of tenofovir initiation to lowest phosphorus level. A total of 50 (64.1%) patients developed hypophosphatemia. There were 28 patients (35.8%) with less than 3 mg/dL, 16 patients (20.5%) with less than 2.5 mg/ dL and 6 patients (7.6%) with less than 2.0 mg/dL. Using univariate analysis, we found that male(HR= 3.397, P=0.022) and use of diuretics(HR= 12, P=0.021) and liver cirrhosis(HR=3.375, P=0.041) were significantly associated with hypophosphatemia. Using multivariate analysis, we found that male(HR= 3.836, P=0.024) and liver cirrhosis(HR= 6.062, P=0.002) was significantly associated with hypophosphatemia. Hypophosphatemia treatment was performed with nuts, dairy, protein intake(34 patients) or IV phosphorus(3 patient), or recommended stop drinking(3patient) and 25 out of 50 patients with hypophosphatemia recovered to normal levels.

**Conclusions:** When using TDF in HBV patients, hypophosphatemia may be more likely to occur in men or in patients with liver cirrhosis. Therefore, in these patients, phosphorus should be closely monitored when TDF is used and appropriate treatment should be performed in case of hypophosphatemia.

**Keywords:** Hypophosphatemia, Tenofovir, Liver cirrhosis, Hepatitis B virus

#### **PE-021**

### Modified PAGE-B Predicts the Risk of HCC in Asians with Chronic Hepatitis B on Antiviral Therapy

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**Background & Aims:** Recently, PAGE-B score has been developed to predict the risk of hepatocellular carcinoma (HCC) in Caucasian patients with chronic hepatitis B (CHB). We aimed to validate PAGE-B scores in Asian patients with CHB.

**Methods:** From 2007 to 2017, we examined 2,844 Asian patients with CHB receiving entecavir/tenofovir therapy. We assessed the performances of PAGE-B and three conventional risk prediction models (CU-HCC, GAG-HCC, and REACH-B) for HCC development.

**Results:** The 5-year cumulative HCC incidence rates were 5.6%. The PAGE- B showed similar AUROCs to CU-HCC, GAG-HCC, and REACH-B at 5 years (0.74 vs 0.70, 0.71, and 0.70 respectively; all *P*>0.05), HCC incidence rates within 5 years of antiviral therapy initiation in CHB patients were significantly higher compared with rates beyond year 5.

**Conclusion:** PAGE-B showed moderate predictablities in Asian CHB patients receiving entecavir/tenofovir therapy.

**Key words:** Chronic hepatitis B; Hepatocellular carcinoma; PAGE-B; Risk prediction model

# PE-022

#### Viral Problems of Morbidity of Hepatitis B, C, D and Its Counter Reaction among Mongolian Population

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**Aims:** It was started diagnosing HBV, HCV, and HDV since 1974 and 1998 respectively in Mongolia. HBV causes 48% of mortality caused by viral hepatitis. To make analysis on past and current situation of morbidity of hepatitis B, C, D and its counter –reaction and then deliver recommendations to decision-, markers and implementers are viral problems. To make analyze and develop recommendations on past and current situation of morbidity of hepatitis B, C, D and its counter-reaction among Mongolian population

**Methods:** We have conducted data on hepatitis and its counter-reaction in Mongolia between 1951 and 2016 using retrospective cohort. We have analyzed on morbidity of hepatitis B, C, D and its statistical data.

**Results:** Between 1992-1997ninety-sic children who have had acute hepatitis D virus infection at the department of Hepatology, National Center for Communicable Diseases (NCCD). Thirty-nine patients (40.6%) were diagnosed as co-infection of HDV (anti-HDVIgM, HBsAg, anti-HBvIGM, HBeAg all positive) while remains 59.4% were diagnosed as superinfection of

HDV. 5.9% of patients were diagnosed with HDV/HBV. 0.8% of patients were diagnosed with HBV/HCV as co-infection in 2007. There were 653 patients underwent at NCCD and Railway Central Hospital. The ninety-six (14.8%) patients were positive anti-HCV, while 324(49.6%) patients were positive HBsAg. 460 patients who underwent at NCCD and Railway Central Hospital in 2016. The sixty-seven (14.6%) patients were positive anti-HCV, while 279 (60.6%) patients were positive HBsAg. The nine patients (3.2%) were positive anti-HDVIgM, HBsAg as superinfection of HDV. While a patient (0.5%) were positive anti-HBcIgM, HBeAgas coinfection of HBV and HDV.

**Conclusions:** The patients aged between 15 and 34 and patients aged between25 qnd 54 are commonly infected by HBV and HCV infections respectively. 240 patients(71.2%) with HBV and 57(54.4%) patients with HCV have common anamnesis as who have had any risk of treatment and service.

Keywords: Co-infection, Super-infection, Morbidity

# PE-023

#### Addition of Albumin-Bilirubin Grade to PAGE-B Score Enhances Risk Assessment for Hepatocellular Carcinoma Development among Patients on Entecavir Therapy

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**Aims:** PAGE-B is a validated simple score, made of age, sex and platelet count, that can help predict the risk of developing hepatocellular carcinoma (HCC) among chronic hepatitis B patients on antiviral therapy. Yet, PAGE-B score encompass patients at intermediate risk, and requires cross-validation from Asian countries. We tested usefulness of PAGE-B score among chronic hepatitis B patients on entecavir therapy. We also tested whether performance of PAGE-B score can be improved by adding albumin-bilirubin (ALBI) grade.

**Methods:** A total of 894 treatment-naïve, chronic hepatitis B patients, who started entecavir therapy between January 2007 and June 2012 were analyzed. The virological parameters and biochemical laboratory data including platelet, albumin, bilirubin for calculation of ALBI and PAGE scores were measured at baseline and at 1 year of entecavir therapy.

**Results:** During a median 5.6 years of follow-up (range: 1.0 - 10.2 years), HCC was diagnosed in 100 patients (11.2%). The ALBI and PAGE score both at baseline and at year 1, respectively, were associated with development of HCC. After 1 year of entecavir therapy, the ALBI score improved (median: -2.69 to -2.96, *P*<0.001), whereas PAGE-B score did not (median: 14 to 14.5, *P*=0.619). Combination of ALBI and PAGE-B score showed the highest areas under the receiver operating characteristic curves (AUROCs) for the prediction of HCC development at 3 and 5 years, at baseline and at year 1, respectively,

compared with ALBI and PAGE-B alone. Especially, the ALBI grade was able to further classify patient with intermediate risk according to PAGE grade at baseline and year 1, respectively.

**Conclusions:** The use of ALBI score and PAGE-B score in combination, compared to their solitary use, was more effective in predicting HCC risk for chronic hepatitis B patients on entecavir therapy. Performance of PAGE-B score can be improved by simply adding ALBI score.

**Keywords:** Hepatocellular carcinoma, Albumin-bilirubin grade, PAGE-B grade, Entecavir, Hepatitis B

#### **PE-024**

#### Long Term Clinical Outcome of Entecavir Therapy in Patients with Chronic Hepatitis B

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**Aims:** With the availability of potent entecavir (ETV) therapy, the natural course of chronic hepatitis B has now changed and the risk of liver disease progression has been reduced, slowed down or even reversed. However, little large long-term follow-up study has investigated the effect of ETV treatment on specific liver-related events (LREs), namely, hepatocellular carcinoma (HCC), cirrhotic complications and mortality in Korea.

**Methods:** This was a 10-year longitudinal observational study of treatment-naïve patients with CHB who received ETV treatment. The primary outcome was the cumulative probability of LREs. LREs were defined as cirrhotic complications (ascites, variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS) and LT (liver transplantation)), HCC, and liver-related mortality.

Results: Data from 1,288 treatment-naïve CHB patients who received ETV were analyzed. The median follow-up period during ETV therapy was 5.4 years (interquartile range [IQR], 3.1-7.6 years). The mean age was 52.3±10.9 years, and patients were predominantly male (n=896 [69.6%]). A total of 649 patients (50.4%) had cirrhosis. During follow-up, VR was observed in 1096 patients (85.4%). One hundred sixty-nine (13.1%) patients experienced VBT, of whom 29 (2.9%) developed ETV-resistant mutations. During the median 5.4-year follow-up period (range, 1.0-10.0 years), 99 patients (7.7%) developed HCC, the majority of whom (96/99, 97.0%) had cirrhosis at baseline. Overall, 17 patients (1.3%) died during the study period. During follow-up, 165 patients (12.8%) developed cirrhotic complications, of which the most commonly encountered were HCC, followed by ascites (n=84), variceal bleeding (n=29), HE (n=21), SBP (n=21) and HRS (n=3).

Conclusions: The effective suppression of HBV replication can-

not completely eliminate the risk of HCC and cirrhotic complications, particularly in those with cirrhosis. Therefore, regular LREs surveillance is still needed even if undetectable HBV DNA is achieved.

**Keywords:** Hepatitis B virus, Hepatocellular carcinoma, Liver cirrhosis, Antiviral therapy

#### PE-025

#### Role of Fibroscan and APRI Score in Detection of Liver Fibrosis in Patients with Hepatitis B

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**Aims:** The assessment of liver fibrosis is essential for predicting the prognosis and outcome of all forms of chronic liver disease. A liver biopsy is the gold standard for the assessment of liver fibrosis, but it has its limitations which include life-threatening complications. Alternative methods of non-invasive laboratory and radiological testing for the assessment of liver fibrosis in hepatitis have evolved during the past decade and these methods may be able to overcome the limitations of liver biopsy. This study was conducted in order to asses liver fibrosis using Fibroscan and to compare these results to the AST. Platelet ratio index (APRI scores) on HBV patients.

**Methods:** A cross-sectional study was conducted on HBV patients who underwent Fibroscan examinations between March 15, 2015 and February 30, 2017 in Happy Veritas Clinic and Diagnostic Center. Demographic data was collected including sex, age, and nationality, serum alanine aminotransferase levels (ALT 6-24 U/I), serum aspartate aminotransferase levels (13-33U/L) and platelet counts (180-320-10<sup>9</sup>) wre also determined. The stages of fibrosis (F0 0-7.2; F1 7.2-8.2; F2 8.2-11; F3 11-18.3 and F4 >18.3) were in kPa. The result of APRI was compared with the Fibroscan fibrosis scores.

**Results:** The results of 228 patients were analyzed including 126(55%) males with a mean age of 42 years (SD:9.9, range :22-67). The males were significantly younger than the females (47 years (SD:10.5 ( range 18-72) (*P*<0,001). The mean stiffness score was 11:29(SD:8.7)kPa and most patients exhibited no fibrosis (37%) and mid-moderate level (38%) of fibrosis. Thirty patients(13%) had advanced fibrosis. The mean platelet and serum ALT levels were 1.11 (SD:1.42; range 0.12-3.7). There was a significant positive correlation between the Fibroscan results and the APRI scores (*P*<0,001). Similarly, there was a significant negative correlation between platelet count and stiffness score.

**Conclusions:** This study has shown that the combination of Fibroscan and APRI methods providers a valuable approach for assessing liver fibrosis in patients with hepatitis. This can elim-

inate the need for liver biopsy in patients without clear indication.

Keywords: Fibroscan, Fibrosis, HBV, APRI

#### PE-026

#### Long-Term Clinical Outcome of Tenofovir Therapy in Patients with Chronic Hepatitis B

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**Aims:** With the availability of potent tenofovir (TDF) therapy, the natural course of chronic hepatitis B has now changed and the risk of liver disease progression has been reduced, slowed down or even reversed. However, little large long-term follow-up study has investigated the effect of TDF treatment on specific liver-related events (LREs), namely, hepatocellular carcinoma (HCC), cirrhotic complications and mortality in Korea.

**Methods:** The primary outcome was the cumulative probability of LREs. LREs were defined as cirrhotic complications (ascites, variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS) and LT (liver transplantation)), HCC, and liver-related mortality. Secondary outcomes included virologic response (VR), VBT, maintained virologic response (MVR), HBeAg seroconversion (in HBeAg-positive patients) and HBsAg seroconversion during the on-treatment follow-up period.

**Results:** Data from 900 treatment-naïve CHB patients who received TDF for more than 12 months were analyzed. The median follow-up period during TDF therapy was 34 months (interquartile range [IQR], 21-47 months). The mean age was 50.8±11.2 years, and patients were predominantly male (n=571 [63.4%]). A total of 421 patients (46.8%) had cirrhosis. During follow-up, VR was observed in 795 patients (88.3%). Eightynine (9.9%) patients experienced VBT. During treatment period, 20 patients (2.2%) developed HCC, all of whom (20/20, 100%) had cirrhosis at baseline. Overall, 8 patients (0.9%) died during the study period. During follow-up, 27 patients (3.0%) developed cirrhotic complications, of which the most commonly encountered were HCC, followed by ascites (n=8), variceal bleeding (n=6), SBP (n=5), HE (n=4) and HRS (n=2).

**Conclusions:** The effective suppression of HBV replication cannot completely eliminate the risk of HCC and cirrhotic complications, particularly in those with cirrhosis.

**Keywords:** Hepatitis B virus, Hepatocellular carcinoma, Liver cirrhosis, Antiviral therapy

# PE-027

### Association of Adherence to Entecavir or Tenofovir Therapy with Cirrhotic Complications in Chronic Hepatitis B Patients with Continuous Virologic Response

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**Aims:** Treatment of chronic hepatitis B (CHB) with oral antiviral agents, especially the first line ones entecavir (ETV) and tenofovir (TDF), reduces the incidence of liver-related events (LREs), namely, hepatocellular carcinoma (HCC), cirrhotic complications and mortality. However, CHB patients with continuous virologic suppression under oral antiviral therapy are still at higher risk of developing cirrhotic complications. The aim of this study was to investigate risk predictors for development of LREs in patients with continuous virologic response (CVR).

**Methods:** We performed a retrospective analysis of data from 1362 CHB patients with CVR, treated with ETV (n=717) or TDF (n=645) therapy for >1 year. CVR was defined as having HBV DNA persistently undetectable throughout the treatment period, after achieving a virologic response (HBV DNA <12 IU/mL). The cumulative level of adherence to medication was categorized as good (=90%) or poor (<90%).

**Results:** During the median 3.7-year follow-up period (range, 1.0-10.0 years), 67 patients (4.9%) developed HCC, 14 patients (1.0%) died, and 88 patients (6.5%) developed cirrhotic complications. Multivariate analyses showed that cirrhosis at baseline, male, age, adherence rate and albumin level were significantly factors for LREs. Patients with poor adherence increased their risk of developing HCC by 2.5-fold (95 % CI, 1.507-4.386; *P*<0.001) and cirrhotic complications by 2.6-fold (95% CI, 1.603-4.055; *P*<0.001).

**Conclusions:** In addition to known risk factors (e.g. cirrhosis, age and sex), adherence was strong predictive factor for HCC and cirrhotic complications. Our study raises important clinical implications, emphasizing the benefits of adherence and the substantial harm of nonadherence to ETV or TDF therapy for patients with CHB.

**Keywords:** Hepatitis B virus, Liver cirrhosis, Antiviral therapy, Adherence

# PE-028

## Hepatic Failure by Spontaneous Reactivation of Hepatitis B Virus without a Trigger Factor in a Patient with Anti-HBs

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**Aims:** A patient who has resolved acute hepatitis B and has produced anti-HBs acquires protective immunity against hepatitis B virus. However, reactivation of hepatitis B virus may occur if the patient is exposed to an immunocompromised state by using immunosuppressive drugs or chemotherapeutic agents because cccDNA can reside within hepatocytes after recovery from acute hepatitis B. Therefore, guidelines for hepatitis B recommend the use of prophylactic antiviral agents, such as entecavir and tenofovir, in patients with anti-HBc IgG. The reactivation of hepatitis B without exposure to an immunocompromised state is very rare, and only 1 case has been reported worldwide

**Methods:** An 82-year-old male patient visited Dankook University Hospital because of high aspartate transaminase (AST), alanine aminotransferase (ALT) and total bilirubin levels. He had shown HBsAg negative/anti-HBs positive results when he underwent blood tests 1 year previously. However, the present blood test revealed HBsAg positive/anti-HBs negative findings and a high titer of HBV DNA (814,815 copies/mL). He underwent vertebroplasty 5 years previously and did not have any other medical history. Other blood and radiologic examinations failed to show other diseases that could affect host immunity. The patient started antiviral treatment with entecavir



Figure 1. Computed tomography imaging of the liver. The liver showed a normal shape without ascites one month previously (A). A moderate amount of ascites and bilateral pleural effusion had newly developed compared to the findings on the previous computed tomography scan. However, the liver still showed a normal shape without a definite surface irregularity (B).



Figure 2. Microscopic findings of needle liver biopsy. Chronic hepatitis with severe lobular activity, severe periportal activity, bridging necrosis and some fibrosis was found. (Masson's trichrome stain; original magnification, ×40 [A] and ×100 [B]).

**Results:** Patient passed away because of deteriorated hepatic function and hepatorenal syndrome 20 days after admission.

It is very rare that a patient with anti-HBs would have hepatic failure and pass away without trigger factors

**Conclusions:** The present case showed that HBV reactivation in a patient with anti-HBs can develop without trigger factors. This kind of reactivation is very rare, and only one case has been reported until now. We hope that the present case will be helpful for understanding HBV reactivations in conditions without trigger factors.

**Keywords:** Hepatic failure, Spontaneous reactivation, Hepatitis B, Anti-HBs

#### **PE-029**

#### Renal Safety of Long-Term Tenofovir Disoproxil Fumarate Therapy in Chronic Hepatitis B Patients with Conserved Renal Function (eGFR $\geq 60$ mL/min/1.73 m<sup>2</sup>)

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**Aims:** To compare renal safety of long-term tenofovir disoproxil fumarate (TDF) therapy in chronic hepatitis B patients with conserved renal function (eGFR =90 mL/min/1.73m<sup>2</sup>).

**Methods:** We reviewed both treatment-naïve or –experienced CHB patients who had treated with TDF-based therapy between August 2012 and December 2017 at Chonbuk National University Hospital. Study patients had divided into group I, normal renal function, defined as estimated glomerular filtration rate (eGFR) =90 mL/min/1.73m<sup>2</sup> or group II, mild renal dysfunction, defined as eGFR 60-90 mL/min/1.73m<sup>2</sup>. Renal impairment was defined as elevation of serum creatinine 0.3 mg/dL above the baseline level or a decrease of eGFR <60 mL/min/1.73m<sup>2</sup>.

Results: A total of 426 patients (371 patients in group I and 55 patients in group II) were included for analysis. The mean eGFR were 107.5  $\pm$  11.2 mL/min/1.73m² and 80.5  $\pm$  8.6 mL/ min/1.73m<sup>2</sup> in group I and group II, respectively. In a comparison of baseline characteristics, group II patients were older. The treatment outcomes showed favorable results for both group I and group II without significant difference between the two groups. Regarding renal safety, the incidence of renal impairment during TDF therapy was low both in group I and group II, and overall renal impairment was 2.9%, 1.8%, and 1.7% at 1-year, 2-year, and 3-year follow-ups, respectively. Although the cumulative rates of virologic response were similar between group I and group II, the cumulative rates of renal impairment were significantly high in group II (P=0.003). In a multivariate analysis, the presence of diabetes mellitus and initial mild renal dysfunction (eGFR 60-90 mL/min/1.73m<sup>2</sup>) were associated with increased risk of renal toxicity.



**Conclusions:** TDF therapy is an effective treatment option among CHB patients with conserved renal function at baseline. However, underlying diabetes mellitus and initial mild renal dysfunction (eGFR 60-90 mL/min/1.73m<sup>2</sup>) may increase the risk of renal toxicity.

**Keywords:** chronic hepatitis B, Tenofovir, Treatment outcome, Renal insufficiency

# PE-030

#### Comparative Study of Persistent Immunity to HBV after Vaccination and Naturally Acquired Immunity Post HBV Infection in Mongolia

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**Aims:** As of 2015 over 260 million people live with chronic hepatitis B in the world. Every year about 1 million people died due to liver cirrhosis, liver cancer caused by Hepatitis B virus. HBV and HCV are high prevalent in Mongolia, around one fourth Mongolian has HCV or HBV . According to the study, 39.4% of people who had HBV infection got HBV vaccination which leads to viral problem in Mongolian health care system. Since 1991 all newborns have been vaccinated with HBV vaccine. And people who born before that year did not take the HBV vaccination. To determine the generation of persistent immunity from HBV vaccination or after HBV infection.

**Methods:** 492 patients have enrolled who were investigated with quantitative HBsAb using Sysmex HISCL-800 at Happy Veritas Clinic and Diagnostic Center and MNUMS. The vaccination scheme consists of three doses. Vaccination is successful if the antibody titer is higher than 10 mlU/L. Also we have conducted questionnaires about HBV vaccination and risk factor for taking hepatitis infections from patients.

**Results:** In this study 492 patients have participated 313(63%) female and 179 (37%) male, out of which 471(96%) people born before 1991 and remaining 21(4%), people born after 1991. 12 people (57%) who born after 1991 or vaccinated within 24 hours after birth were quantification HBsAb low titer (<10mlU/L), remaining (43%) were qHBsAb titer (>10mlU/L), while 297 people (64%) who born before 1991 were qHBsAb titer (<10mlU/L), and remaining 36% of patients had persistent HBV vaccine. The 99 people who born before 1991 have enrolled in HBV vaccination voluntarily while 372 people did not take HBV vaccine at all.

**Conclusions:** Persistent immunity against HBV is generated not only in person who have taken HBV vaccination but also in person who have had slight HBV infection. It was considered that people aged between 50 and 60 years could not get persistent immunity against HBV. We assumed that persistent immunity against HBV depends on age, not other factor and sex. **Keywords:** HBV, Vaccination, QHBsAb,

**PE-031** 

## Risk of Hepatocellular Carcinoma among Chronic Hepatitis B Patients Presumed in Immune Tolerant Phase

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**Aims:** Hepatitis e antigen-positive patients with high serum hepatitis B virus (HBV) DNA but normal alanine aminotransferase (ALT) are presumed in immune-tolerant phase, and their risk of developing complication is still debatable. Recent guide-line suggested to use ALT levels, liver biopsy, elastography or liver fibrosis biomarker (eg, FIB-4) to stratify risk of complication for patients presumed in immune-tolerant phase.

**Methods:** We analyzed of 651 HBeAg positive patients with high serum HBV DNA levels (=7 log IU/mL) but normal or mildly elevated ALT levels (<80 U/L), age more than 18 years (male = 404) who were monitored for at least 1 year from 1998 to 2006. Normal ALT was defined as 35 U/L for men and 25 U/L for women. The risk of developing hepatocellular carcinoma (HCC) was assessed.

**Results:** During a median 11.2 years of follow-up (range: 1.1-18.0 years), 42 patients (6.5%) developed HCC. Age, sex, ALT and FIB-4 levels were independent factors associated with HCC development. Those with mildly elevated ALT levels showed significantly higher risk of developing HCC than normal ALT levels (3.4% vs. 9.4% at 10 years for normal ALT vs. mildly elevated ALT, *P*=0.001). Among patients with normal ALT level (n = 301), FIB-4 level was independent factor associated with HCC development (hazard ratio 2.35; 95% confidence interval 1.54-3.58, *P*<0.001). Among 301 patients with normal ALT levels, 51 patients (16.9%) had FIB-4 = 1.453. The HCC risk at 10 years was significantly higher for those with high FIB-4 levels (1.3% vs. 13.6% for FIB-4 < 1.453 vs. = 1.453, *P*<0.001).

**Conclusions:** Among patients presumed in immune tolerant phase, HCC risk was generally low but was not null. Among patients with normal ALT levels, some showed high FIB-4 levels, and their risk of developing HCC was high. Our data indicate that FIB-4 can be an useful non-invasive marker for stratifying HCC risk among patients presumed in immune tolerant phase, and those with high FIB-4 levels warrants close attention.

Keywords: Hepatitis B, Immune tolerant phase, HCC risk, FIB-4

#### PE-032

#### Increasing Age and Comorbidities in 13,639 Adult Patients with Chronic Hepatitis B (CHB) from 2011 to 2016 in Japan

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**Aims:** CHB affects approximately 1% of the general population in Japan with higher prevalence in older people. This study aims to characterize the evolving CHB patient demographics and comorbidity burden in Japan as well as their changes over 2011-2016.

**Methods:** We used the Medical Data Vision (MDV) claims database to identify patients =18 years with =1 ICD-10 codes for CHB (B18.1), having =1 HBsAg test and =1 HBeAg test, viral load test, or HB core antibody test. Patients were required to have continuous enrollment for 6 months prior and post index date (first date of CHB diagnosis) during 1/1/2011–12/31/2016. Patient demographic and comorbidity data was reported from 2011 to 2016.

**Results:** A total of 13,639 patients met inclusion and exclusion criteria. Males made up 58% of patients in 2011 and decreased to 54% in 2016 (P<0.0001). The average age of patients was 60.7±13.1 years in 2011 and increased to 63.9±13.2 years in 2016 (P<0.0001). The proportion of the population over 65 increased from 42% in 2011 to 57% in 2016 (P<0.0001). The Charlson comorbidity index, an overall measure of patient comorbidity (covering 17 conditions), increased from 2.7 to 3.7 (P<0.0001) from 2011 to 2016. In 2016, 14% of CHB patients in Japan had diabetes (DM), 16% with nonalcoholic fatty liver disease, 5% with chronic kidney disease (CKD), and 9% with fragility (non-traumatic) bone fractures; all of which have in-

creased significantly from 2011 (all P<0.05) [Figure 1]. Similarly there was a high prevalence of comorbidities in 2016 such as hypertension (38%), renal impairment (20%), hyperlipidemia (19%), liver impairment (15%), and osteoporosis (9%), although these did not show a significant increase over time.

Figure 1: Proportions of Patients with Chronic Hepatitis B (CHB) and Comorbidities in Japan between 2011 and



\*Renal Impairment: Includes acute and chronic kidney diseases, dialysis, renal failure, and nephrotic syndromes.

**Conclusions:** Between 2011 and 2016, the Japanese CHB population has aged (~80% =55) and are having more comorbidities, which may affect CHB management and should be considered in their treatment and monitoring.

Keywords: CHB, CHB cormobdities, Increasing age

#### **PE-033**

#### Evaluation of Renal and Bone and Safety in Patients with CHB and CKD Treated with TAF in Post Liver Transplantation

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**Aims:** Chronic Hepatitis B(CHB) remains a leading indication for orthotopic liver transplantation(OLT) worldwide. Common complications following OLT include renal dysfunction secondary to perioperative renal injury and post-operative nephrotoxicity from calcineurin inhibitors; osteoporosis is also observed secondary to preoperative malnutrition and post-operative corticosteroids. In this setting, antiviral prophylaxis to prevent recurrent HBV infection with TAF may have advantages over TDF due to its improved renal and bone safety profile.

**Methods:** In this Phase 2 study (NCT02862548), LT recipients with stage 2 or greater CKD and receiving antiviral prophylaxis with TDF were randomized 1:1 to either receive TAF 25 mg or continue TDF. The primary efficacy analysis was the percent of patients who maintained viral suppression at Week 24. Key pre-specified secondary safety endpoints were changes in hip and spine BMD, changes in sCr, estimated GFR and direct GFR assessment over 48 weeks.

**Results:** 51 patients were randomized and treated at a single site in New Zealand. Baseline characteristics included: mean

age 60 years, 75% males, 53% Pacific Islander and mean baseline eGFRCKD-EPI 52mL/min/1.73m2 with 53% of patients with <50mL/min/1.73m2. The median baseline surface area corrected GFRCr-EDTA was 58 mL/min/1.73m2. The median interval since transplantation was approximately 9 years. Of the 47 patients that have reached Week 12, all patients maintained viral suppression. There were no treatment discontinuations and serious adverse events were numerically lower in TAF arm compared to the TDF arm. Switching to TAF treatment resulted in a trend toward improved sCr levels (median change: -0.07 for TAF vs. -0.02 for TDF; *P*=0.09) and improved eGFRCKD-EPI (median change: 2.7 for TAF vs. 0.8 for TDF; *P*=0.14) as early as week 12 (Figure 1).

Figure 1:



**Conclusions:** Early after switching from TDF to TAF in LT recipients, viral suppression is maintained while smaller changes in renal function were observed.

**Keywords:** TAF, Post-LT, Renal safety, Bone safety, Stable switch

#### **PE-034**

#### Antiviral-Induced HBsAg-Seroclearance Might Not Necessarily Indicate a Functional Cure of Chronic Hepatitis B and Can Be Reversed

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**Aims:** The seroclearance of hepatitis B virus (HBV) surface antigen (HBsAg) is currently considered as a functional cure of chronic hepatitis B. However, there is still a lack of evidence whether the HBsAg-seroclearance is a reliable and durable indicator of HBV eradication. In this study, we aimed to evaluate the reliability and durability of NA-induced HBsAg-seroclearance.

**Methods:** Among 1,100 patients with chronic hepatitis B, 33 patients who achieved HBsAg-seroclearance with NA treatment between January 2010 and December 2017 at a single referral center were analyzed retrospectively. HBsAg was examined

using ELISA kit (ARCHITECT HBsAg Qualitative II; Abbott, Wiesbaden, Germany) and < 1.17 S/Co (0.02 IU/mL) was defined as a negativity.

**Results:** The median age at NA-induced HBsAg-seroclearance was 59.8 (range, 22.4-74.6) years and median NA treatment duration before seroclearance was 76.1 (range, 11.3-193.5) months. At the time of HBsAg-seroclearance, all patients had undetectable serum HBV DNA (< 20 IU/mL). Among them, 22 patients (66.7%) stopped NAs after HBsAg-seroclearance (the NA-off group) and the remaining 11 patients (33.3%) maintained NAs for median 23.5 (range, 5.0-49.8) months (the NA-maintenance group) after HBsAg-seroclearance. During follow-up period (median, 35.0 months; range, 4.7-89.9), two patients (one in the NA-off group and one in the NA-maintenance group) experienced HBsAg-seroreversion although their serum HBV DNA were not detectable. Of the two patents, a patient who are in the NA-maintenance group developed HBsAg-seroreversion at 19 months after HBsAg-seroclearance and again experienced HBsAg-re-seroclearance 17 months later. Interestingly, both patients experiencing HBsAg-seroreversion had hepatocellular carcinoma.

**Conclusions:** A single time negative-conversion of HBsAg might not be a reliable and durable indicator of HBV eradication since there were a few cases of detectable HBV DNA and HBsAg-seroreversion. Thus, repeated evaluation of both HBsAg and HBV DNA might be necessary to confirm the functional cure of chronic hepatitis B undergoing antiviral treatment.

**Keywords:** Chronic hepatitis B, HBsAg, Seroconversion, Antiviral agents

### PE-035

#### Laparoscopic Hemihepatectomy at Liver Tumors Children

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**Aims:** From 2010 to 2017 in Kyzylorda Regional Medical center performed 15 laparoscopic right-sided hemihepatectomy, laparoscopic segmentectomy II and III grade and laparoscopic segmentectomy V—VI art.

**Methods:** From 2010 to 2017 at the present time performed 15 laparoscopic liver surgery: segmentectomy II, III degree, laparoscopic bisegmentectomy IV—V degree and 4 laparoscopic right-sided hemihepatectomies When performing a right hemihepatectomy endoscopic instrument LigaSure complex "Force Triad" enables reliable control of hemostasis at the intersection of the short hepatic veins, stepby-step dissection of the liver parenchyma, crossing the parenchyma in the hepatic branches of the portal vein. The apparatus ENDO GIA 30 was stitched and crossed the right hepatic vein. The resected fragment of the liver was loaded into a container and evacuated through the incision in the right iliac region. The surface of the liver was covered with hemostatic mesh "Surgicel". **Results:** in right-sided hemigepatectomy surgery duration was from 150 to 240 min, blood loss of 150-400 ml. in liver resection and bisegmentectomy intervention lasted 90-120 min, and blood loss was 60-80 ml. Postoperative analgesia was provided by a constant epidural infusion of 1% lidocaine. On the second day after the operation, the patients were transferred to the Department in a satisfactory condition. Separated by drains did not exceed 80 ml per day. The drainages were removed on the 2-3 days. Activation for 1-3 days.

**Conclusions:** the Obtained results allow to conclude that video surgery of large volume on the liver in children has great prospects in clinics where there is sufficient experience of such surgical interventions in an open manner.

Keywords: Liver, Laparoscopic, Hemihepatectomy

#### **PE-036**

#### Safety of Anti TNF Therapy in Patients Receiving Anti Hepatitis B Drug

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**Aims:** There were insufficient previous studies on the use of anti TNF therapy during anti Hepatitis B drug treatment. This medical record review assessed the safety of anti TNF therapy in 4 patients with inflammatory bowel disease, ankylosing spondylitis and during nucleos(t)ide analogues(NA) treatment.

**Methods:** A retrospective analysis of patients treated with anti TNF during NA treatment was conducted. The primary outcome was markers of hepatitis B reactivation, including aspartate aminotransferase, alanine aminotransferase, and hepatitis B viral load at each follow up visit.

**Table 1.** Demographics of 7 patients at basekine(prior to start on anti TNF therapy)

	1	2	3	4	5	6	7
Sex	М	М	М	М	М	F	F
Age, years	37	37	54	41	41	57	43
Antiviral for HBV	Tenofovir	Tenofovir	Entecavir	Tenofovir	none	none	none
HBsAg	positive						
HBeAg	positive	negative	negative	negative	negative	negative	negative
HBeAb	negative	positive	positive	positive	positive	positive	positive
HBV DNA, IU/ml	95,312	ND	22	<20	ND	ND	ND
Anti-HCV	negative						
ALT, units/liter	9	9	56	31	38	14	11
AST, units/liter	17	16	35	28	20	21	22
Liver cirrhosis (yes, no)	no						
Biologic DMARD	Infliximab	Infliximab	Adalimumab	Infliximab	Infliximab	Infliximab	Etanercept
Indication for anti-TNF	CD	UC	AS	UC	CD	RA	AS
Treatment duration, months	13	12	10	6	40	26	34



**Figure 1.** (A) Aspartate aminotransferase (AST) values (units/liter) from baseline to 9 month follwup. (B) Alanine aminotransferase (ALT) values (units/liter) from baseline to 9month follwup.



Figure 2. HBV DNA level (Log, IU/mL) from baseline to 9month follwup

**Results:** In total, 7 patients with surface antigen positive were included in the study: 3 inactive carrier and 4 were being treated by NA. At baseline, 6 patients had normal liver function tests and low or undetectable HBV DNA levels, except for 1 patient with short NA administration period. Three patients received with tenofovir, and 1 received treatment with entecavir. In 4 patients with NA treatment, the HBV DNA titer was not checked or decrease and AST, ALT value remained within the normal limits throughout follwup.

**Conclusions:** Our study provides reassuring data about the safety profile of anti TNF therapy in patients with NA treatment previously. These data are encouraging and should lead to initiation of controlled trials of anti TNF therapy in hepatitis B.

Keywords: NA treatment, Anti TNF therapy, HBV DNA levels, Surface antigen positive

#### **PE-037**

### Efficacy of Prolonged Tenofovir Monotherapy for Partial Virologic Response to Tenofovir in Treatment-Naïve Chronic Hepatitis B Patients

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**Aims:** The optimal management of CHB patients exhibiting a partial virologic response (PVR) to TDF remains unclear. The aim of this study was to evaluate the long-term efficacy of prolonged TDF monotherapy in treatment-naïve CHB patients exhibiting a PVR to TDF therapy.

**Methods:** We retrospectively investigated the efficacy of prolonged TDF monotherapy in treatment-naïve CHB patients with PVR to TDF. PVR was defined as a decrease in serum hepatitis B virus (HBV) DNA of more than 2 log<sub>10</sub> IU/mL from baseline but with detectable HBV DNA by real-time PCR assay at week 48.

**Results:** A total of 155 patients treated with TDF therapy for more than 48 weeks. Virologic response (VR) was achieved in 125 patients (80.6%). PVR is evident in 30 (19.4%) of the 155 patients. Among them, 28 patients received continuous TDF monotherapy for more than 96 weeks (median duration 202 weeks, range 101-260 weeks), and 27 of these patients (96.4%) achieved a VR during prolonged TDF monotherapy (median range 68 weeks, range 52-205 weeks). The cumulative rates of VR in patients with PVR at 96, 144, 192 weeks were 82.1%, 85.7%, and 94.6%, respectively. In multivariate analysis, a high baseline HBV DNA level (OR, 1.69; 95% CI, 1.08-2.65; *P*=0.022) was independently associated with PVR.

**Conclusions:** Prolonged TDF monotherapy is effective for achieving VR in treatment-naïve CHB patients with PVR, although the time to achieve VR was delayed in those with PVR

Keywords: Chronic hepatitis B, Tenofovir, Partial virologic response

#### **PE-038**

#### The Comparison of Clinical Outcomes between Inactive Chronic Hepatitis B and HBeAg Negative Hepatitis B with Virologic Response

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**Aims:** Nucleos(t)ide analogues (NA) suppress HCC development in chronic hepatitis B (CHB) patients. This study is aimed to compare incidence of hepatocellular carcinoma and survival between inactive chronic hepatitis B (CHB) patients and HBeAg(-) CHB patients with virologic response. **Methods:** We retrospectively analyzed NA–naïve inactive CHB patients (n=80) and HBeAg(-) CHB patients on entecavir with virologic response (VR, DNA<2000 IU/mL) (n=72) at Jeju National University Hopital in Jeju, Korea, between March 2007 and December 2010. Decompensated liver cirrhosis patients were excluded.



Results: Median follow-up duration was 8.1 years (interquartile range[IQR] 7.0 – 9.0). Age, sex distribution were not different between two groups, however, patients with liver cirrhosis was higher in HBeAg(-) CHB group (8.8% versus 30.6%, P=0.001). During the follow up, one HCC (1.3%) and 10 HCCs (13.9%) were developed, in inactive group and HBeAg(-) CHB group, respectively. Estimated 10-year HCC incidence rates were 1.5% in inactive group and 25.4% in HBeAg(-) CHB group (P<0.001). Progression to decompensation was comparable (no event in inactive group, one hepatic encephalopathy in HBeAg(-) CHB group, P=0.278). Liver-related death was also similar (no death in inactive group, one death in HBeAg(-) CHB group, P=0.278). In multivariable analysis, HBeAg(-) CHB (adjusted hazard ratio[aHR] 10.17 (95% confidence interval[CI] 1.20-86.29), P=0.034) and liver cirrhosis (aHR 11.02 (95% CI 2.61-46.63), P=0.001) were significant risk factors for HCC.

**Conclusions:** Between inactive CHB patients and HBeAg(-) CHB patients on entecavir with VR, overall survival was comparable. However, HCC incidence was significantly higher in HBeAg(-) CHB patients with VR.

Keywords: Inactive, Hepatitis B, Virologic response, Outcome

#### PE-039

## Effect of Metabolic Syndrome on the Clinical Outcomes of Chronic Hepatitis B Patients with Nucleos(t)ide Analogues Treatment

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Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea **Aims:** Metabolic syndrome (MS) is a known risk factor for cirrhosis and hepatocellular carcinoma (HCC) and can bring on worse outcomes when it coexists with other liver disease. However, no data are available about the effect of MS on oral nucleos(t)ide analogues (NUCs) treatment and clinical outcomes in chronic hepatitis B (CHB) patients. We aimed to elucidate whether coexistence of MS and CHB affect the long-term prognosis of CHB patients with oral NUCs treatment.

**Methods:** We performed a retrospective data analysis for a total of 587 CHB patients who started oral NUCs treatment for the first time in our institution from January 2006 to March 2016.

Results: Among the 587 patients, 70 (11.9%) had MS, but 517 (88.1%) had no evidence of MS when oral NUCs treatment was initiated Cumulative occurrence rates of viral breakthrough, genotypic resistance, HCC, disease progression (PD), and overall adverse outcomes (OAO) were significantly higher in CHB patients with MS than in those without MS, although HBV-DNA suppression and cumulative occurrence rates of HBeAg negative conversion and seroconversion were not significantly different between the two groups. The overall survival (OS) was also significantly shorter in CHB patients with MS than in those without MS. Multivariate analysis indicated that the MS was an independent, poor prognostic factor for occurrence of genotypic resistance (adjusted hazard ratio [aHR], 22.3; 95% confidence interval [CI], 6.61-75.02, P<0.001), HCC (aHR, 3.98; 95% CI, 2.07-7.66; P<0.001), PD (aHR, 6.18; 95% CI, 3.43-11.14, P<0.001), OAO (aHR, 8.10; 95% CI, 4.68-14.02; P<0.001), and OS (aHR, 12.29; 95% CI, 2.25-67.24, P<0.001). Conclusions: MS is an independent determinant of poor prognosis in CHB patients receiving oral NUCs treatment.

**Keywords:** Metabolic syndrome, Nucleos(t)ide analogue, Disease progression, Survival

#### **PE-040**

#### Familial Hepatocellular Carcinoma in an Endemic Area: A Model for the Study of Preventive Measures

**Elroy WELEDJI** 

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**Aims:** Hepatocellular carcinoma (HCC) usually affects patients aged 50–70 years but earlier onset (25–40 years) may occur in hepatitis B endemic areas. With respect to the natural history, it takes 10 years to develop chronic hepatitis, 20 years to develop cirrhosis and 30 years to develop HCC. Thus, 70–90 % of HCC develop on a background of cirrhosis However, hepatitis B virus is directly oncogenic and can cause HCC in the absence of cirrhosis. This may represent a major cause of death from late diagnosis in resource-limited areas.

**Methods:** We report a study of a black African family in which the clinical diagnosis of HCC was made on two male siblings in an endemic area in Cameroon, W/Africa. This was accompanied by a literature search.

**Results:** HCC-prone families of the type reported here could provide powerful models for studying the preventive measures of a hepatitis B vaccination. It would seem prudent that hepatitis vaccination be given the highest priority to those individuals where the HCC yield is increased. The optimum timing for immunization in conjunction with the administration of hepatitis B immunoglobulin at a contralateral site is immediately after birth or within 12 h.

**Conclusions:** The highest risk for HCC may occur in families in which a hereditary component may be acting in concert with hepatitis B virus. We suggest a more extensive investigation of the genetic hypothesis of HCC and its fibrolamellar variant. In all cases of HCC, it is important to screen all fist degree relatives to detect early and asymptomatic disease.

#### **PE-041**

#### Liver Fibrosis by Fibroscan in Chronic Hepatitis B Patients during Tenofovir Disoproxil Fumarate in Mongolia

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**Aims:** Liver fibrosis and its sequel cirrhosis represent a major health care burden, and assessment of fibrosis by biopsy is gradually being replaced by noninvasive methods. In clinical practice, the determination of fibrosis stage is important, since patients with advanced fibrosis have faster progression to cirrhosis and antiviral therapy is indicated in these patients. To assess the performances of liver fibrosis during antiviral treatment by liver stiffness measurement (LSM)using Fibroscan in chronic hepatitis B (CHB) patients.

**Methods:** We followed and evaluated treatment outcome of 56 patients with CHB, initiating their TDF regimen at Happy Veritas Clinic and Diagnostic Center. Each patient underwent transientelastography measurements, HBV quantification and serum liver marker assays before treatment with TDF, orally once daily.

**Results:** The mean age of the patients 45±11. Before treatment LSM results indicated fibrosis stage F0 in 18(32.1%) patients, F1 in 6(10.7%), F2 in 19(33.9%), F3 in 18(16.1%), and F4 in 4(7.1%) patients. After SVR 12, SVR 24 months the mean stiffness score of F1 increased from 7.8 to 8.3kPa. F2 increased from 9.4 to 10.3 kPa, F3 decreased from 13.3 to 12.3kPa, F4 increased from 23.8 to 28.4 kPa. In table 1 shows the changes of liver stiffness by Fibroscan after treatment. There was a significant negative correlation between platelet count and liver stiffness score.

**Conclusions:** In chronic hepatitis B patients who is receiving TDF regimen, annual LSM revealed that significant advanced fibrosis improvement slows but continues during treatment.

	Liver fibrosis stage before treatment					
		FO	F1	F2	F3	F4
	n	18	6	19	18	4
Aftor	F0	16 (88.9%)	3 (50%)	4 (21.1%)	4 (22.2%)	
treatment	F1		1 (16.7%)	4 (21.1%)		
treutment	F2	1 (5.6%)	1 (16.7%)	4 (21.1%)		
	F3		1 (16.7%)	7 (36.8%)	12 (67.7%)	1 (25%)
	F4	1 (5.6%)			2 (11.1%)	3 (75%)

 Table 1. The changes of liver stiffness by Fibroscan after TDF treatment

Keywords: TDF, Cirrhosis, HBV

#### **PE-042**

#### Familial Hepatocellular Carcinoma in an Endemic Area: Prevention Is Better than Cure

#### Elroy WELEDJI

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**Aims:** Hepatocellular carcinoma (HCC) usually affects patients aged 50–70 years but earlier onset (25–40 years) may occur in hepatitis B endemic areas. With respect to the natural history, it takes 10 years to develop chronic hepatitis, 20 years to develop cirrhosis and 30 years to develop HCC. Thus, 70–90 % of HCC develop on a background of cirrhosis However, hepatitis B virus is directly oncogenic and can cause HCC in the absence of cirrhosis. This may represent a major cause of death from late diagnosis in resource-limited areas.

**Methods:** We report a case of a black African family in which clinical diagnosis of HCC was made on two male siblings in the south west region of Cameroon, W/Africa accompanied by literature search.

**Results:** HCC-prone families of the type reported here could provide powerful models for studying the preventive measures of a hepatitis B vaccination. It would seem prudent that hepatitis vaccination be given the highest priority to those individuals where the HCC yield is increased. The optimum timing for immunization in conjunction with the administration of hepatitis B immunoglobulin at a contralateral site is immediately after birth or within 12 h.

**Conclusions:** The highest risk for HCC may occur in families in which a hereditary component may be acting in concert with hepatitis B virus. We suggest a more extensive investigation of the genetic hypothesis of HCC and its fibrolamellar variant. In all cases of HCC, it is important to screen all fist degree relatives to detect early and asymptomatic disease.

#### **PE-043**

# Detection of HBV CCC-DNA in HBEAG Positive Patients with HBV-Related HCC Tumor and Peri-Tumor Tissue

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**Aims:** Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, HCC is the third leading cause of cancer death behind lung and stomach cancer, with nearly 600,000 deaths annually. Chronic hepatitis B virus (HBV) infection is considered as a major risk factor for HCC development. chronic hepatitis B disease progresses to the late stage with decreased viral replication, cccDNA becomes the predominant form of intrahepatic HBV DNA.

**Methods:** Samples of tumor and peri-tumor liver tissue were collected from 37 HBV associated HCC patients. Intrahepatic cccDNA was detected relative quantification by using the real-time PCR assay. Compare the amount of Intrahepatic levels of cccDNA in tumor tissue and peri-tumor tissue with different HBeAg states.

**Results:** In total patients the level of intrahepatic cccDNA in tumor tissue was significantly higher then the peri-tumor tissue. Furthermore, The intrahepatic cccDNA levels in the HBeAg positive group was significantly higher in the tumor tissue than peri-tumor tissue, but there was no significant difference in the HBeAg negative group.

**Conclusions:** This study demonstrated HBV cccDNA was present in both tumor and peri-tumor tissues in patients with HBV-related HCC. The tumor tissues had a significantly higher level of cccDNA compared to the peri-tumor counterpart, especially in the HBeAg positive group. Combined with the results of previous studies we can speculate that HBeAg-positive patients are more likely to cause HBV-related hepatocarcinogenesis due to the induction of cccDNA.

#### **PE-044**

Comparison of Fibrosis-Adjusted Long-Term Clinical Outcomes in Patients with Minimally Active Chronic Hepatitis B Who Did Not Undergo Antiviral Therapy vs. Those with Complete Virological Response by Antiviral Therapy

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**Aims:** The optimal criteria for commencement of antiviral therapy in patients with chronic hepatitis B (CHB) remain to be determined yet. Here, we aimed to compare the risk of hepato-cellular carcinoma (HCC) and liver-related event (LRE) between patients with minimally active CHB who did not undergo nucleos(t)ide analog (NUC) therapy according to the current treatment guidelines and HBV DNA =3.3 log<sub>10</sub> IU/mL (MA group) and those with complete virological response by NUCs (VR group).

**Methods:** We enrolled consecutive patients with CHB who underwent liver stiffness (LS) values by transient elastography

between 2006 and 2015. Patients with a history of cirrhosis or hepatocellular carcinoma at the enrollment were excluded. To adjust for imbalances between the MA and VR groups, propensity-score matching (PSM) models with 1:1 ratio were performed based on age, gender, HBeAg, presence of diabetes, and LS value. Cumulative risks of HCC or LRE development were assessed using Kaplan-Meier method.

**Results:** A total of 865 patients were enrolled. The mean age was 54.1 years old, and 61.6% were male. MA group (n=159) had higher serum HBV DNA level, alanine aminotransferase (ALT), total bilirubin, and the lower proportion of male gender and positive HBeAg compared to VR group (n=706). Regarding HCC development, MA group had the trend toward the higher risk compared to VR group (*P*=0.181). Regarding LRE, MA group showed no significant difference with VR group (*P*=0.992). Similarly, after PSM, 184 pairs were generated, showing the similar risks between two groups in terms of the cumulative risk of both HCC (*P*=0.177) and LRE (*P*=0.827) development.

**Conclusions:** After adjusting the fibrosis degree, the potential prognostic factor for HCC and LE development, MA group also showed similar, cumulative risks compared to VR group, supporting the appropriateness of the current treatment guidelines in patients with CHB.

**Keywords:** Hepatitis B, Minimally active, Virological response, Hepatocellular carcinoma

#### **PE-045**

#### Incidence of Hepatitis B Virus among Suspected Patients Attending Tertiary Care Hospital of Nepal

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Sukraraj Tropical and infectous Disease Hospital

**Aims:** Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem. HBV infection leads to a wide spectrum of liver disease ranging from acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Most adults infected with the virus recover, but 5%–10% are unable to clear the virus and become chronically infected. The aim of this study is to find the incidence of hepatitis B positive cases among suspected patients.

**Methods:** A cross-sectional study was conducted in Sukraraj Tropical and Infectious Diseases Hospital, Teku, Nepal. A total 1013 blood samples were collected by vein puncture with disposable syringe from patients attending Sukraraj Tropical Disease Hospital Teku, Kathmandu, Nepal during Dec-16-2017 to April-13-2018. All the serum samples were tested for hepatitis B surface antigen (HbsAg) by E-CLIA of Baecman Coulter Access 2 Machine.

**Results:** In the period of four months total 1013 patient's sera were tested for hepatitis B surface antigen (HBsAg), of which 295 (29.12%) sera sample were found to be positive. In the

positive cases number of males exceeded that of females. The prevalence of seropositive in male was 240 (81.3%) while in case of female 55 (18.6%).

**Conclusions:** This study shows that prevalence of viral hepatitis B was 29.12% and most commonly observed in males. Since there is no specific treatment, prevention has been the major aim in managing viral hepatitis B. Both pre-exposure and post-exposure administration of hepatitis B vaccine has been recommended. Classical example of post-exposure prophylaxis is protection of newborn infants born to carrier mothers, and individuals accidentally exposed parenterally to HBV infection through transfusion, cut, injuries and needle-sticks. The policy to give pre-exposure prophylaxis to general population should be adopted as soon as possible, to prevent it emerging as a public health problem.

Keywords: Hepatitis B Virus, Tertiary care hospital, E-CLIA, HbsAg

# **HBV**,Basic

#### PE-046

# Whole Genome Sequencing of Hepatitis B Virus: Direct Next-Generation Sequencing without Pre-Amplification

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**Aims:** In recent years, there has been various attempts to apply next-generation sequencing techniques to analyze the whole genome of hepatitis B virus. Most of the attempts were conducted by pre-amplification methods synthesizing amplicons containing fragments of HBV genome and using it for subsequent NGS test. However, there was questions whether the entire genome of HBV could be correctly detected by these methods due to polymerase errors in pre-PCR process and undetectable variants in the primer attachment sites. In this study, we tried to overcome the limitations of previous amplification methods using non-amplification method directly using serum DNA for NGS test.

**Methods:** Eight newly diagnosed, untreated naïve HBV infected patients enrolled in this study. Two serum samples (at pre & post treatment) in each person were tested. DNA extraction and quantification of HBV were conducted as follows: DNA was extracted from 200 µl of serum samples of the patients. Libraries of serum DNA was prepared using Nextera XT DNA Sample Prep Kit (Illumina, USA). The DNA were fragmented into 300 to 1000-bp, and then analyzed on a MiSeqDx sequencer (Illumina) for paired-end sequencing (2x150 bp, 300 cycles). Result data (fastq.gz) of NGS were trimmed by sickle (v1.33) based on quality score (quality score of base = 30). After trimming, BWA-MEM (v0.7.17) was used to map the reads against the human reference sequence (GRCh38.p12). The reads unmapped or not well mapped (MAPQ < 60) were extracted and re-mapped to reference sequence of HBV of Korean (DQ683578.1). GATK Mutect2 (v4.0.3) was used to call SNPs and Indels in the result. Four filters including base\_quality, read\_position, str\_contraction, strand\_artifact were applied to filter-out errorneous variant calling. We analyzed the whole genome of HBV including DNA polymerase, preS1/preS2/S, protein X, and precore/core region.

**Results:** Of the total data obtained from the NGS test, 97.3% (min–max; 90.1–99.7%) were human DNA and HBV DNA was 1.2% (min–max; 0.0–6.4%) on average. The average depth of coverage spanning 3215 nucleotides was 38.4 bp (min–max; 4.3–64.9). Total 181 variants (175 SNPs and 6 Indels) were detected in 16 samples. Among them, 57 variants in polymerase, 23 in preS1/preS2/S, 18 in X, 14 in precore/core region were non-synonymous variants or indels, which make changes in amino acid and protein.

**Conclusions:** In this study, we were able to detect the fulllength genome of HBV without pre-amplification steps. Using this non-amplification direct NGS method, errors in the PCR process can be minimized and the whole genome of HBV could be more accurately examined. However, the problem of low coverage, which takes most of the data from human DNA, is a disadvantage of this method.

**Keywords:** Hepatitis B virus, Next-generation sequeincing, Whole genome sequence, Non-human sequence

#### PE-047

# High Prevalence of Chronic Hepatitis D Virus Infection in Eastern Mongolia

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**Aims:** Hepatitis delta virus (HDV) is a serious cause of liver-related morbidity and mortality worldwide. The aim of our study was to determine the prevalence of HDV infection among patients positive for hepatitis B surface antigen (HBsAg) living in the Dornod province, which is in Eastern Mongolia.

**Methods:** We retrospectively analysed the data obtained from 121 consecutive patients with HBV infection who were referred to Dornod Medical center between 2017 and 2018. Liver transaminases were analysed using a commercial biochemistry kit. The presence of HBV and HDV infection wasinvestigated using both ELISA and polymerase chain reaction (PCR) methods. Anti-HDV-positive : ndividuals were examined to determine HDV-

#### RNA level by PCR.

**Results:** Of all patients, 53 were men (44.9%) and 68 were women (56.1%). The avarage age was 44 (between 16 and 70 years). Anti-HDV was positive in 75% (91/121) and all were checked for HDV RNA and 100% were found positive (91/91) all of the patients. HBV-DNA detected in111 all of the 121 patients. Mean HBV-DNA level was 1590177.877 IU/ml. The mean HBV-DNA level in the anti-HDV-positive patients were significantly lower than in the anti-HDV-negative patients (*P*<0.001). There were 65 patients with cirrhosis (54%) in the study group. Anti-HDV seroprevalence and HDV RNA presence were higher in those with cirrhosis 42 (64%). HDV-RNA-positive patients had significantly higher ALT (94 U/L) levels when compared to HDV-RNA-negative patients.

**Conclusions:** Our study showed hepatitis delta virus infection in HBsAg positive patients who live in Eastern province Mongolia higher than other province of Mongolia.

Keywords: Hepatitis D virus, Eastern province, Mongolia

#### PE-048

# Clinical Usefulness of Next-generation Sequencing in Whole-genome Characteristics of Hepatitis B Virus

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**Aims:** Hepatitis B virus (HBV), discovered in 1966, infects more than 350 million people worldwide. HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, accounting for 1 million deaths annually. Nevertheless, until recently, genetic testing of the hepatitis B virus is currently limited to a small fraction of the entire viral sequence. In this study, we aimed to find all variants of HBV by analyzing the whole genome sequence of it.

**Methods:** Twenty-three newly diagnosed, untreated HBV infected patients participated in this study. DNA extraction and quantification of HBV were conducted as follows: DNA was extracted from 200 µl of serum samples of enrolled patients. The amplified products were obtained by PCR. A library of PCR products of the viral genome (0.2 ng) was prepared using Nextera XT DNA Sample Prep Kit (Illumina). The PCR products were sheared into 300- to 1000-bp fragments using the kit, and then analyzed on a MiSeq sequencer (Illumina, USA) for paired-end 150-bp sequencing. After a quality check and data trimming, BWA-MEM v0.6 was applied to map the sequences against the reference HBV genome (DQ683578.1). The sequences whose quality was estimated to be greater than QD30 (quality score normalized by depth 30) were selected. GATK v3.7 Mutect 2 was used to call SNPs and indels in the sequences.



**Results:** The characteristics of the subjects were summarized in tables. We sequenced and analyzed the whole genome of HBV including DNA polymerase, preS1/preS2/S, protein X, and precore/core region. The average depth of coverage spanning 3215 nucleotides was 1359 (min–max; 389–2484). Total 1546 variants (1516 snp and 30 indels) were detected in 23 samples. Among them, 605 variants in polymerase, 360 variants in preS1/preS2/S, 94 variants in X, 165 variants in precore/core region were non-synonymous variants, which make changes in amino acid and protein sequence. The most variable region was g.1950 encoding the core protein, which showed 4 types of variants.

**Conclusions:** In this study, we could read WGS of HBV using NGS technology, and found various variants. It is expected that the next-generation sequencing technology will provide important clues to the identification of the drug resistance mechanism of HBV because it can read the entire nucleotide sequence of the HBV.

**Keywords:** Hepatitis B virus, Next-generation sequeincing, whole genome sequence



#### PE-049

### Characteristics and Clinical Outcomes of Chronic Hepatitis C among the Ex-Hansen's Disease Population in a Region of Sorokdo

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<sup>1</sup>Department of Internal Medicine, Sorokdo National Hospital, Goheung, <sup>2</sup>Department of Preventive Medicine, Sorokdo National Hospital, Goheung, <sup>3</sup>Department of Internal Medicine, Chonnam National University Hospital, Gwangju. **Aims:** Recently, group infection reports from some medical institutions and the introduction of direct acting antiviral agents are raising interest in hepatitis C in Korea. However, there are limited data about the prevalence and treatment efficacy in Hansen's disease patients who are traditionally known as the most vulnerable group of hepatitis C. Therefore, we aimed to elucidate of prevalence and clinical outcomes of hepatitis C in patients with Hansen's disease in Sorokdo.

Methods: We retrospectively reviewed medical records of 511 ex-Hansen's disease patients who were hospitalized at Sorokdo national hospital from May 2016 to March 2018. Among them, 50 patients with chronic hepatitis C were enrolled in this study. Results: Among all patients on Sorokdo national hospital, the prevalence of positivity of HCV Ab was 18.4%. The mean age of the enrolled patients was  $76.5 \pm 6.9$  years, and 28% (14/50) of the cohort was diagnosed with liver cirrhosis. 17 patients [genotype lb, RAS negative] were treated with daclatasvir(DCV) and asunaprevir(ASV), 3 patients [1b, RAS positive] were treated with DCV+sofosbuvir (SOF), 2 patients [Ib, Child B] were treated with DCV+SOF+Ribavirin(RBV). 28 patient [2a/c (n=1), 2a (n=27)] were treated with SOF+RBV. During the treatment period, there was only one (1/50, 2%) case in which the deterioration of Child score was noted. In the genotype 2 group, the number of patients experienced hemolytic anemia caused by RBV was 85.7% (24/28) and 28.5% (8/28) of them received blood transfusions. SVR was achieved at a rate of 90.1% (20/22) in genotype 1b, 92.9% (26/28) in genotype 2.

**Conclusions:** The treatment of efficacy was not different between ex-Hansen's disease population and the general public. However, it is necessary to pay attention to the development of anemia in ex-Hansen's disease population during the treatment. Therefore, active treatment is necessary in HCV patients with ex-Hansen's disease population who are medically underserved populations.

**Keywords:** Chronic hepatitis C, Hansen's disease, Direct acting antiviral agent

#### PE-050

#### Safety and Efficacy of Once-Daily Ledipasvir/Sofosbuvir (90/400 mg) for 12 Weeks in Genotype 1 HCV-Infected Patients with Severe Renal Impairment

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**Aims:** Despite higher concentrations of sofosbuvir (SOF) metabolite, GS-331007, in patients with severe renal impairment (RI), retrospective case series and claims database analyses have suggested substantial use of ledipasvir (LDV)/SOF in this population with no untoward effects described. The current study evaluated the safety, efficacy, and pharmacokinetics (PK) of LDV/SOF (90/400 mg) once-daily for 12 weeks in patients with genotype (GT) 1 HCV-infection and severe RI.

**Methods:** Treatment naïve or experienced patients with or without compensated cirrhosis and creatinine clearance (CLcr) = 30 mL/min (Cockcroft-Gault equation), not on dialysis, received open-label treatment with LDV/SOF once daily for 12 weeks. Virologic response, pharmacokinetics (PK), and safety, including echocardiograms, were assessed.

Results: Of the 18 patients enrolled and treated, mean (range) CLcr at baseline was 24.9 (9.0-39.6) mL/min. All had GT1 HCV infection (14 GT1a and 4 GT1b), 14 (78%) were treatment naïve, and 2 (11%) had cirrhosis. All patients completed 12 weeks of LDV/SOF treatment. There were no early discontinuations nor any on-treatment virologic failures. The SVR12 rate is 100% (18/18). Plasma concentrations of the terminal SOF metabolite GS-3310007 were approximately 6 fold higher than in the LDV/SOF Phase 3 trials. SOF and LDV concentrations were similar to those observed in patients with normal, mild or moderate RI. The most common adverse events (AEs) were fatigue (22%), headache (22%), and hyperkalemia (17%). Six serious AEs were reported among 4 patients (22%), including 2 renal events; no SAEs were considered related to study drugs. There were no treatment-related cardiac AEs, including bradycardia, and no meaningful changes in QTc intervals or other parameters.

**Conclusions:** Treatment with LDV/SOF (90/400 mg) for 12 weeks in genotype 1 patients with and without cirrhosis and severe renal impairment resulted in 100% SVR12 rate. The regimen was safe and well-tolerated with no treatment discontinuations and no treatment-related SAEs.

Keywords: Renal impairment, Ledipasvir, Sofosbuvir, Genotype 1

# PE-051

#### Disease Burden of Chronic Hepatitis C Virus Infection in Mongolia: Potential Impact of Attaining World Health Organization (WHO) 2030 Goals

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**Aims:** Mongolia has a large burden of viral hepatitis with the highest rates of liver cancer incidence and mortality In the

world. An estimated 95% of liver cancer patients in Mongolia are infected with HCV and/or HBV. While HCV prevalence is likely declining, the burden of advanced liver disease will continue at a high level. Direct acting antivirals (DAAs) achieve higher sustained viral response rate (SVR) than interferonbased treatment regimens. In 2015, over 10,000 patients were treated in Mongolia with DAA regimens, an important first step on the path toward HCV elimination. Implementation of new treatments requires epidemiological data and modeling to assess the potential impact of improved treatment strategies. Use a modeling approach to describe HCV-related disease progression at the national level in Mongolia through 2030. Consider the impact of two scenarios on disease burden: Base Scenario and WHO Targets 2030 Scenario.

Methods: Disease progression used age-and gender-defined cohorts to track HCV incidence, prevalence, morbidity and mortality. Data for prevalence, incidence, diagnosis, liver transplants and mortality risk factors were derived from Mongolian data sources when available, and expert consensus. A starting prevalence of 200,000 chronic cases in 2013 was used and was consistent with adult prevalence estimates collected in prevalence surveys from 2005 and 2013, after adjustment for prevalence in younger age groups. Two scenarios were considered with one based on the status quo and another designed to achieve WHO 2030 goals. Base Scenario: Treat 10,300 =F2 patients in 2016, gradually declining to 1200 treated patients by 2030. Assume 3230 new infections and 1300 newly diagnosed annually. WHO Targets 2030 Scenario: Achieve 2030 WHO Global Health Sector Strategy on viral hepatitis including a diagnosis rate of 90%, 65% decrease in liver-related mortality and a 90% decrease in new infections by 2030. Achieved in Mongolia by increasing treatment to 10,000-15,000 =F0 cases annually, diagnosing up to 10,000 cases annually, and gradually reducing new infections to 300 annually by 2025 (90% reduction) (Figure 1). The incidence and prevalence of HCV-related morbidity and mortality through 2030 were projected. Results of the WHO Targets 2030 scenario were compared to the Base scenario.

# Results:

#### Base Scenario

Viremic infections decline to 141,000 in 2030 as compared to 188,000 in 2016 (25% decrease), largely due to mortality (Figure 2). By 2030 incident decompensated cirrhosis cases will decrease by 17% from 630 cases in 2016 to 520 cases in 2030. The number of incident HCC cases was projected at 650 in 2030, a decrease of 18% as compared to 2016 (800 cases). By 2030, annual HCV-related liver deaths will decrease by 28% as compared to 2016, from 1280 deaths to 920 deaths (Figure 2). There will be 13900 cumulative liver deaths during 2016-2030 (Figure 3).

#### WHO Targets 2030 Scenario

Chronic infections decline 87% during 2016-2030 from 188,000 cases to 24,100 cases. As compared to the Base Scenario, cases decline by 83% in 2030. Incident HCC cases in 2030 were estimated at 170 respectively (74% decrease from

Base Scenario. Incident liver deaths in 2030 were estimated at 330 (64% decrease from Base Scenario). During 2016-2030, there are a cumulative total of over 2800 fewer HCV-related deaths as compared to the Base Scenario.

**Conclusions:** HCV disease is a substantial health burden in Mongolia, especially HCC and related deaths. Even under the Base Scenario, total viremic prevalence will decline by 2030, due to fewer new infections and mortality among an aging population. Scenario results emphasize the importance of increasing awareness, diagnosis and treatment of HCV, along with preventing new infections. Mongolia achieves WHO targets for HCV hepatitis elimination by 2030 under the WHO Targets 2030 Scenario, when including disease reduction achieved prior to 2016. The projected impact of the scenarios will facilitate disease forecasting, resource planning, and rational strategies for HCV management in Mongolia.

Keywords: Disease, 2030, HCV, Mongolia

#### **PE-052**

#### Predictable Factors Affecting the Virological Response Among Chronic Hepatitis C Virus Patients in Libya

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**Aims:** The global prevalence rate of hepatitis C virus (HCV) infection is 2.5 %. Approximately 21.3 million patients infected with HCV are living in Eastern Mediterranean countries. Chronic HCV patients taking interferon with ribavirin from different ethnic groups have different probabilities of reaching a sustained virological response (SVR). There are many factors, such as HCV genotype, age, gender, body weight, IL-28B single-nucleotide polymorphism, concomitant disease and liver function enzymes. The purpose of this study was to model the probability of achieving a sustained virological response in individual patients, taking into consideration various predictive factors.

**Methods:** Total of 120 subjects was interviewed and was subjective to routine laboratory investigation and abdominal ultrasound. Forty-six were excluded due to co-infection with HBC or HIV, decompensated liver disease, drug dependence, alcoholic, autoimmune disease, pregnancy, cardiac disease, age above 70 years, and poorly controlled diabetic patients. Only 72 patients with chronic HCV who received pegylated interferon and ribavirin (Peg-IFN/RBV) in Tripoli Center Hospital (TCH) in Tripoli, Libya from 2014 to 2015 were included. Quantitative HCV-RNA was assessed before the treatment and at week 1, week 4, week12, week 24, week 48 and week 72 to detect whether the patient achieved SVR. Multivariate logistic regression analysis was performed to identify variables associated with treatment response.

**Results:** At 24 weeks after the end of combination therapy, the overall SVR was detected in 49 (68%). However, 53 (73%)

of patients achieved end treatment response (ETR). Moreover, the SVR was significantly higher in patients with genotype 1b and 3a (100%) than in patients with genotype 1a and 2 (28% and 57.1% respectively). However, there was no significant difference between patients who given INFa2a and INF a2b (P=0.75). IL28B CC haplotype patient, the viral load less than 600,000 IU.ml-1(matches 5.7 logs) and the body weight < 80kg, non-detectable HCV-RNA level at week four, and genotype of the HCV were factors that predict good response for Peg-IFN/RBV combined therapy (P<0.05). However, age and gender were not a significant predictive factor.

**Conclusions:** This prediction model uses easily determined variables for a personalized estimate of the probability of SVR with Peg-IFN/RBV, allowing to identify patients who may benefit from conventional therapy.

Keywords: Hepatitis, HCV, Risk factors, Interferon

#### PE-053

Decreased of Alpha-fetoprotein Level Among Patients with Liver Cirrhosis that related to HCV Treated with Combination Therapy with Ledipasvir and Sofosbuvir

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**Aims:** Hepatocellular carcinoma (HCC) is considered one of the most lethal cancers, with most of cases diagnosed at advanced stage. The prevalence of HCC is high in Mongolia with men 116.6 cases and women 74.8 cases per 100,000 person-years. The hepatitis C virus (HCV) infection is one of the major causes of chronic hepatitis and hepatocellular carcinoma (HCC) in Mongolia. Viral infection with HCV can cause fluctuations in AFP that makes it difficult to differentiate between underlying liver disease and the development of HCC. The lack of specificity has limited the role of serum alpha-fetoprotein (AFP) for hepatocellular carcinoma (HCC) screening among patients with cirrhosis related to hepatitis C virus (HCV) infection.

**Methods:** Here we report 5 cases decreased of AFP level in patients with cirrhosis treated 24 weeks combination therapy with ledipasvir and sofosbuvir between 2017 to 2018 were referred to the Liver Unit, Dornod Medical center Mongolia. All patients had been tested for blood chemistries, liver function markers, such as alanine aminotransferase (ALT), total bilirubin, prothrombin, international normalized ratio (INR), creatinine, AFP and HCV-RNA.

**Results:** Of all patients, 53 were men (44.9%) and 68 were women (56.1%). The avarage age was 44 (between 16 and 70 years). Anti-HDV was positive in 75% (91/121) and all were checked for HDV RNA and 100% were found positive (91/91) all of the patients. HBV-DNA detected in111 all of the 121 patients. Mean HBV-DNA level was 1590177.877 IU/ml. The

mean HBV-DNA level in the anti-HDV-positive patients were significantly lower than in the anti-HDV-negative patients (*P*<0.001). There were 65 patients with cirrhosis (54%) in the study group. Anti-HDV seroprevalence and HDV RNA presence were higher in those with cirrhosis 42 (64%). HDV-RNA-positive patients had significantly higher ALT (94 U/L) levels when compared to HDV-RNA-negative patients.

**Conclusions:** Our study showed hepatitis delta virus infection in HBsAg positive patients who live in Eastern province Mongolia higher than other province of Mongolia.

Keywords: AFP, HCC, Ledipasvir, Sofosbuvir

# PE-054

#### Results of Lutasan Treatment in Mongolia

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**Aims:** Chronic liver diseases are very common among the Mongolians. Study suggests that alcohol induced pathologies composed of cirrhosis 39%, fatty liver disease 27%, and 11% chronic hepatitis respectively. "Lutasan" (reduced glutathione) injection is known as hepatoprotector, antioxidant, immune modulator and detoxifying functions. As chronic disease progresses, glutathione insufficiency leads to poor cognitive outcomes and tremor in upper limbs. Therefore, we aimed to study treatment efficacy of "Lutasan" injection for chronic liver diseases and the complications.

**Methods:** Total of ten subjects were recruited randomly from GI Department of Third General Hospital. Liver functions were evaluated by serum total bilirubin, total protein, albumin, AST, ALT, GGT, and alkaline phosphatase measures and hepatic neurocognitive deterioration was evaluated by Reitan neurophysiological test.

**Results:** 10% of the patients were alcohol induced, and 60% had combination of viral and alcoholic reasons, and remaining 20% had biliary tract disorders. Compare to the first day's results, on the 10th day of hospitalization, serum indicators were much improved within the treatment period (\*-P<0.05) including AST 3.02 times, ALT 2.21 times, ALP 2.56 times and GGT 1.78 times were decreased respectively (Table 1). Also neuro-cognitive improvements were significantly observed, by 1.74 times on Reitan neurophysiological test when comparing before and after treatment scores, 58.6±4.61 and 33.7±1.34, respectively.

**Conclusions:** These findings suggest that Lutasan, a glutathione supplement has effects of minimizing hepatic cytolysis, cholestasis in the biliary tract, reducing destruction of hepatocytes, and aiding regeneration of liver cells. Moreover, it reduces symptoms of hepatic neurocognitive disorders significantly.

Table1. Comparison of serum markers of liver functions on 10th day

	Before treatment	After treatment
n	n=10	n=10
Total bilirubin (mcmol/l)	25.38±6.58	20.32±5.17
Total protein (g/l)	70.82±2.09	71.15±2.84
Albumin (g/l)	35.7±3.04	36.7±0.74
AST (GOT) (IU/L)	132.8±28.8	65.12±13.55*
ALT (GPT) (IU/L)	146.9±21.78	66.5±15.38*
ALP (IU/L)	272.8±13.1	106.61±13.63*
GGT (IU/L)	227.5±7.27	127.17±10.98*

Significance level: \*P<0.05

Keywords: Lutasan, Treatment, HCV

# PE-055

#### A Case of Whole Body Cutaneous Erythema Multiforme Drug Eruption Induced by Sofosbuvir and Daclatasvir

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**Aims:** Direct Anti-viral Agent (DAA) has Obtained new indications of treating hepatitis C virus. Various DAA treatment regimens are selected by HCV genotype. Dermatological side effects after sofosbuvir and daclatasvir combination are rare worldwide.

Results: We report a case of cutaneous erythema which occurred after treatment of sofoubuvir and daclatasvir for hepatitis C genotype 3 treatment. The 91-year-old male patient visited our clinic complaining of new skin lesions. He was diagnosed with genotype 3a chronic hepatitis C by genetic test. Abdominal ultrasonography shows chronic hepatitis without cirrhosis. Trans Elestography showed F2, which meant that the patient had chronic hepatitis without cirrhosis. Patient was generally good condition. We started treatment daily with sofosbuvir 400mg and daclatasvir 60mg. Then, 56 days later, multiple erythematous scaly patches appeared on the patient's trunk and pelvis. He had no itching and was kept in good condition. The score of Naranjo ADR probability scale was 7, which indicated probable. The patient's skin lesions notably improved after the medications were terminated. Finally, the patient obtained SVR 12.

**Conclusions:** In treatment of hepatitis C, the rate of dermatologic side effects by DAA treatment is known around 3-8%, usually. Although in severe cases, there was a case of DRESS. However, in this case, only slight skin patches were observed. The skin side effects by DAA treatment are very rare. And this is the first report of dermatological side effects after sofosbuvir and daclatasvir combination therapy in Korea. More attention needs to be paid to prescribing DAA in the treatment of chronic hepatitis C.



Keywords: Drug eruption, Sofosbuvir, Daclatasvir

#### PE-056

# Current Status New Direct Acting Anti-Viral Treatment of Hepatitis C in Mongolia

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**Aims:** During last several years, internationally available diagnostics, treatments and medicines of HCV have changed dramatically. Interferon-based therapy for HCV has comparatively low result of treatment effect, more side effects, long treatment duration, high cost of single dose and limited option of treatment. Since introduction of direct antiviral agents including in 2011 Boceprevir, Telaprevir, in 2013 Simeprevir, Sofosbuvir, in 2014 Harvoni (ledipasvir/sofosbuvir), Daklinza (daclatasvir), Vikera Pack (ombitasvir/paritaprevir/dasabuvir), the new era HCV treatment came up. thanks to those new drugs HCV infection became one of the curable diseases, and entire world is targeting free from HCV /WHO/. Therefore, there is need of to access milestones of diagnostic and treatment development of HCV in our country. Our study aims to determine implementation of global trend for HCV diagnostic and treatment in Mongolia.

**Methods:** This study is qualitative one and we analyzed policy and strategic documents and statistics issued by Mongolian Government, Ministry of Health, National Center for Communicable Disease, Mongolian National University of Medical Sciences and other organizations.

**Results:** Ministry of Health played very large role in introduction of new management of HCV into the country. It provided all the legal ground and support to service providers at all levels of care. New guideline was approved which includes all new schemes of the treatment, diagnostic methods, new drugs were registered, specialist doctors were trained and access of the new drug were widened thanks to joining the Access program from Gilead Sciences. It can be said that the tentative result of DAA treatment is successful, compare few years ago interferon treatment effect was fewer than 20 percent to the 99 percent effective of current new treatment.

**Conclusions:** All those achievements show that Mongolia has been able to introduce a comprehensive and efficient short-term treatment for HCV and free the population of that disease which may increase the mortality level due to liver cancer. **Keywords:** HCV, DAA, Treatment

# PE-057

### SOF/VEL/VOX for 12 Weeks is a Safe and Effective Salvage Regimen for NS5A Inhibitor-experienced Patients with Genotype 1-6 HCV Infection

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**Aims:** The pangenotypic fixed-dose combination (FDC) of sofosbuvir (SOF), a HCV NS5B inhibitor, velpatasvir (VEL), a HCV NS5A inhibitor, and voxilaprevir (VOX), a HCV NS3/4A protease inhibitor, is an salvage regimen for direct acting antiviral (DAA)-experienced patients based on the safety and efficacy demonstrated in Phase 2 and Phase 3 trials in this population.

**Methods:** This was a retrospective analysis of data from 454 NS5A inhibitor-experienced patients treated with SOF/VEL FD-C+VOX or SOF/VEL/VOX FDC in the Phase 2 and Phase 3 trials. Efficacy was assessed by SVR12 and relapse rates. Safety was assessed by treatment-emergent adverse events (AEs) and laboratory abnormalities.

Results: Of 454 NS5A inhibitor-experienced patients treated, 77% were male, 41% had compensated cirrhosis, 86% had NS5A and NS3 baseline resistance-associated substitutions (RASs), 74% had genotype 1 HCV infection. Most patients (53%) had previously been exposed to NS5A inhibitor+NS5B inhibitor, with 39% exposed to NS5A inhibitor+NS3/4A protease inhibitor±NS5B inhibitor and 8% exposed to NS5A inhibitor±another DAA. Overall, the SVR12 rate was 97% with a relapse rate of 2%. The SVR12 rate in patients with compensated cirrhosis was 95% and in patients with baseline RASs was 97%. The SVR12 rates by prior regimen were: NS5A inhibitor+NS5B inhibitor 95%; NS5A inhibitor+NS3/4A protease inhibitor±NS5B inhibitor 99%; and NS5A inhibitor±another DAA 100%. Treatment-emergent RASs were uncommon, present in 3 of 10 patients who relapsed. Only 1 patient (0.2%) discontinued treatment due to an AE. No serious adverse events

attributed to study medication were reported.

**Conclusions:** Results in over 450 NS5A inhibitor-experienced patients enrolled in Phase 2 or Phase 3 trials demonstrate that the 3-DAA combination of SOF, VEL and VOX for 12 weeks is a safe, well tolerated and effective treatment for patients who previously failed an NS5A inhibitor-containing regimen, irrespective of the other drugs in the prior treatment.

Keywords: Salvage, Sofosbuvir, Velpatasvir, Voxilaprevir

#### PE-058

Adverse Events of HCV Treatment Using Ledipasvir/Sofosbuvir Combination

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**Aims:** The incidence of liver cancer in Mongolia generally caused by HBV and HCV. It is 7 times higher that that world's average in recent studies. 27% of the population has been diagnose and it is very one of four people has the virus and most prevalent cause of HCC and causing number one public health issue. Mongolia is one of the first countries that registered LED/ SOF regimen from developing countries. The HCV treatment program in Mongolia has started on January of 2016.

**Methods:** We followed and evaluated treatment outcomes of the patients with HCV infection using Harvoni (manufactured by Gilead Science). We started our prospective analysis on August until December 2016. For 3 months on 1230 patients. All patients were treated with SOF/LDV for 12 weeks and their treatment was evaluated by quantitative HCV RNA assays prior and week 4 and week 12 of treatment . Sustained Virological Response (SVR) after 12 weeks of treatment was assessed . Virus genotype analysis using cDNA microarray liver enzymes. CBC and drug related adverse events were assessed in every patient. All the tests were conducted at Happy Veritas laboratories in Ulaanbaatar, Mongolia.

**Results:** Total of 40 adverse events were observed in 527/1230 patients (43%) . Single adverse events were observed in 358/527(68%), whereas 2 events were observed in 116/527(22%) and 3 or more events were observed 52/537(10%) on patients respectively. Age wise35 or lower aged patients were 43/153 (28%), age of 36 to 55, 295/655(45%) and age of 56 of more, 190/422(45%) were adverse events were observed. Our result by gender wise, out of 406/781(52%) on female patients, on male patients 121/449(27%) were observed adverse events.

**Conclusions:** Treatment of HCV in Mongolia using all-oral dual DAA was divided in 3 phases due to shortness of drugs and logistics arrangements. We were able to include only stage-one patients in this study. We have achieved 95.5% SVR 12 week for 3 months treatment with SOF/LDV this time. Despite the

identical adverse events were found in other Asian and other regions in the world during treatment, unrecorded adverse events were observed such as the facial paralysis, paraproctitis, AFP and facial skin darkening in Mongolia.

Keywords: Adverse events, Sofosbuvir, Ledipasvir

# PE-059

# High Rates of SVR12 in Adolescents Treated with the Combination of Ledipasvir/Sofosbuvir

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**Aims:** Although direct acting antivirals have transformed HCV treatment of adults, the standard of care for adolescents and younger children with GT1 HCV is still limited to treatment with pegylated interferon+ribavirin for 48 weeks. The aim of this study was to evaluate the safety, efficacy and pharmacokinetics of the fixed dose single tablet regimen, ledipasvir/sofosbuvir (LDV/SOF), administered for 12weeks in GT1 HCV-infected adolescent patients.

**Methods:** Treatment-naive and treatment-experienced adolescent patients aged 12 to less than 18 years old with chronic GT1 HCV were enrolled into this open-label ongoing study to receive 12 weeks of treatment with LDV/SOF 90mg/400 mg once daily. The primary efficacy endpoint is SVR12 (HCV RNA<lower limit of quantitation). Safety is assessed by clinical evaluation and laboratory monitoring. Intensive pharmacokinetic (PK) sampling was done on Day 10 in the first 10 patients (PK lead-in) to confirm the appropriateness of the adult dose in the adolescent population.

**Results:** 100 GT1 patients have been enrolled and treated. The majority are GT1a (81%), female (63%), white (90%), treatment-naïve (80%), and vertically infected (84%). The mean age is 15 (range 12–17) years. In the PK lead-in, administration of 1 tablet daily of LDV/SOF provided comparable plasma exposures of LDV, SOF, and GS-331007 (SOF primary metabolite) to those observed in adults. SVR12 rate was 97% (97/100). 3 patients were lost to follow-up. No serious adverse events (AEs) have been reported. AEs are generally mild in severity and grade 3/4 laboratory abnormalities have been infrequent and transient.

**Conclusions:** The 12-week regimen of LDV/SOF 90mg/400 mg has resulted in high SVR rates and is well-tolerated. This regi-

men provides a safe and effective therapy for adolescents with GT1 HCV infection. Further evaluation is ongoing in children aged 3–11 years old.

Keywords: Adolescents, Ledipasvir, Sofosbuvir

#### **PE-060**

#### Economic Gains Related to Hepatocellular Carcinoma and Decompensated Cirrhosis Reduction in Japan is expected from Treatment of Chronic Hepatitis C

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**Aims:** Japanese chronic hepatitis C (CHC) patients are at greater risk for hepatocellular carcinoma (HCC). Highly effective oral Direct Acting Antiviral (DAA) regimens for CHC can lead to high SVR rates that reduce CHC complications and costs. This study estimated the economic benefit of CHC cure by reducing HCC and decompensated cirrhosis (DCC) in Japan.

**Methods:** A hypothetical cohort of 10,000 HCV GT1b Japanese patients with a mean age of 70 was modeled with a hybrid decision tree and Markov model capturing the natural history of HCV infection over a lifetime horizon. It was assumed that 15% of the cohort had cirrhosis and 20% were treatment-experienced. Treatment compared approved all-oral DAAs vs. no treatment (NT) with efficacy based on randomized controlled trials. Transition rates and costs were obtained from Japan-specific data. DCC, HCC and quality-adjusted life years (QALYs) were projected. QALYs were monetized using a willingness to pay (WTP) threshold which varied from ¥4 to ¥6 million. The incremental savings associated with treatment were calculated by adding the projected cost of complications avoided to the monetized gains in QALYs.

**Results:** DAA treatment avoided 1583 cases of HCC and 1162 cases of DCC, saving ¥618,076 and ¥251,329 per treated patient; respectively. Treatment leads to avoidance of 2745 cases of CHC complications and associated savings of ¥869,405 per treated patient. Additionally, DAA treatment lead to an additional 1.59 QALYs gained per patient treated. The indirect economic gains associated with treatment-related QALY improvements were estimated to be ¥6,360,000, ¥7,950,000 and ¥9,540,000 per patient at WTP thresholds of ¥4 million, ¥5 million and ¥6 million. Total economic savings of HCV GT1 treatment with DAAs (vs. NT) was ¥7,229,405, ¥8,819,405and ¥10,409,405 at these different WTP thresholds.

**Conclusions:** Treatment of HCV GT1b with all Oral DAAs in Japan can lead to significant savings related to avoidance of HCC and DCC.

**Keywords:** Chronic Hepatitis C, CHC, Economi gainsc, HCC and DC

#### **PE-061**

#### The Direct Comparison between 7th AJCC Staging System and 8th AJCC Staging System for Prediction of Survival with Korean Multicenter HCC Patients

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**Aims:** AJCC staging is the most commonly used staging system in most solid tumors, and recent AASLD hepatocellular carcinoma (HCC) guideline also endorsed this AJCC staging system based on status of tumor, node, and metastasis. Recently, 8th edition of AJCC staging system was released in December 2016. This study aimed to compare prediction of survival in HCC patients between 7th AJCC staging system and 8th AJCC staging system.

Methods: From 2004 to 2013, 2211 newly diagnosed HCC patients were consecutively enrolled in three Korea University medical centers and the medical records of patients were retrospectively reviewed. Each patients were classified following both of 7th AJCC staging system and 8th AJCC staging system. Results: Chronic hepatitis B (1523, 68.9%) was main attributable factor in development of HCC, followed by chronic hepatitis C (256, 11.6 %) and alcohol consumption (241, 10.9%). 1514 patients (68.5%) died during study period and median overall survival (OS) was 24.7 months. According to 7th AJCC staging system, 894 (40.4%) patients were included into stage I; 459 patients (20.8%) into stage II; 180 patients (8.1%) into stage IIIa; 354 patients (16.0%) into stage IIIb; 3 patients (0.1%) into stage IIIc; 119 patients (5.4%) into stage IVa; and 202 patients (9.1%) into stage IVb. According to 8th AJCC staging system, 400 (18.1%) patients were categorized into stage IA; 498 patients (22.5%) into stage IB; 442 patients (20.2%) into stage II; 193 patients (8.7%) into stage IIIa; 357 patients (16.1%) into stage IIIb; 119 patients (5.4%) into stage IVa; and 202 patients (9.1%) into stage IVb. Both 7th staging system and 8th staging system show distinct survival outcomes according to each stage. Although 7th AJCC staging system significantly well predicted 1 year of survival than 8th AJCC staging system (AUROC; 0.796 vs 0.784, P=0.013), AUROCs of 3 year and 5 year were similar in 7th and 8th AJCC staging system (0.754 vs 0.752 in 3 year, P=0.601; 0.744 vs 0.742 in 5 year, P=0.643).

**Conclusions:** Both 7th and 8th AJCC staging system show distinct survival outcome according to each stage. Moreover, both 7th and 8th AJCC staging system are similar in prediction of survival outcomes.

Keywords: HCC, AJCC, Staging

#### **PE-062**

#### The Efficacy and Safety of Sofosbuvir and Ribavirin Treatment for Genotype 2 Chronic Hepatitis C Patients

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**Aims:** A direct-acting antiviral (DAA) drug is in the spotlight for the treatment of patients with chronic hepatitis C. The combination of sofosbuvir and ribavirin is more effective than the peg IFN and ribavirin in patients with genotype 2 HCV. The aim of this study was to evaluate the treatment efficacy and safety for GT2 HCV patients treated with sofosbuvir and ribavirin in a single center.

Table1. Baseline characteristics		2
	Overall (n=92)	Cirrhosis (n=24)
Hypertesion	13 (13.98%)	4 (16.67%)
CKD	1 (1.08%)	-
HCC	1 (1.08%)	1 (4.17%)
HBV co-infection	1 (1.08%)	
Experienced peg-IFN treatment	8 (8.60%)	5 (20.83%)
SVR12	91 (96.77%)	23 (95.83%)
Genotype		
2a	89 (96.77%)	24 (100.00%)
2b	3 (3.23%)	-6
HCV RNA	2456240 ± 4337250	566210.8 ± 681911
WBC	5748.91 ± 2069.68	4935.00 ± 1441.39
Нь	13.61 ± 1.76	$12.91 \pm 1.86$
Platelets	190032.30 ± 742703.58	125000.00 ± 55905.98
Albumin	4.31 ± 0.50	$4.06 \pm 0.67$
AST	57.43 ± 65.13	$62.04 \pm 45.93$
ALT	68.71 ± 109.25	$49.71 \pm 45.71$
Bilirubin	0.96 ± 1.42	$1.12 \pm 1.43$
PT-INR	1.08 ± 0.20	$1.18 \pm 0.22$
Gamma-GTP	70.04 ± 111.61	$65.81 \pm 47.16$
AFP	21.11 ± 64.83	56.53 ± 109.41
Total cholesterol	$168.86 \pm 43.41$	$141.14 \pm 44.83$
Triglyceride	$122.65 \pm 60.78$	$112.13 \pm 54.73$
Glucose	127.61 ± 57.13	$130.25 \pm 65.20$
HbAlc	$6.74 \pm 1.11$	$6.62 \pm 1.20$
FIB-4	3.06 ± 2.51	$5.47 \pm 3.15$
Anemia	n=21	n=10
Degree of Hb decrease	2.95 ± 1.19	$2.52 \pm 1.15$
CTP		
A		23 (95.83%)
с		1 (4.17%)

**Methods:** The study was performed retrograde from May 2016 to December 2017 in GT2 HCV patients treated with so-fosbuvir (400mg) plus ribavirin (800-1200mg; based on body weight) treatment. The primary endpoint was sustained virologic response at 12 weeks (SVR12). The secondary endpoint was the occurrence of side effects during treatment.

**Results:** A total of 95 patients with GT2 HCV infection were enrolled, of which 92 were genotype 2a (96.8%) and 3 were 2b (3.2%). 2 patients were follow up loss, 1 patient discontinued treatment voluntarily. SVR12 was confirmed in 91 of 92 patients (98.91%). 1 patient with failed treatment were com-

bined LC and HCC, HCV RNA was not detected at 4 weeks and 8 weeks after initiation of treatment, but HCV RNA detected at 12 weeks. Liver cirrhosis was diagnosed on the imaging studies or clinical manifestations and 24 patients were included (CTP-A; n=23, C; n=1). SVR12 with cirrhotic patients was 95.83%. The average HCR RNA titer was  $2.46 \times 10^6$  IU/ml. Hemoglobin decrease (Mean  $\pm$  SD;  $2.95 \pm 1.19$  g/dl) occurred in 21 patients during treatment and ribavirin dose reduction was required.

**Conclusions:** This study was performed on a small group of patients compared with other studies, but showed that treatment with sofosbuvir and ribavirin was highly effective in patients with GT2 HCV infection. In aspect of safety, there was no serious side effects about treatment although hemoglobin decrease.

**Keywords:** Chronic hepatitis C, Sofosbuvir, Ribavirin, Efficacy, Safety, Sustained virologic response

# PE-063

Effectiveness of Elbasvir/Grazoprevir in Patients with Chronic Hepatitis C and Chronic Kidney Disease: Results from the Veterans Affairs System

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**Aims:** Elbasvir/grazoprevir (EBR/GZR) is indicated for the treatment of chronic hepatitis C virus (HCV) genotype (GT) 1 and 4 infections and has demonstrated high sustained virologic response (SVR) in many HCV populations, including those with chronic kidney disease (CKD). The aim of this study was to evaluate the effectiveness of EBR/GZR in people with HCV infection and CKD in a real-world clinical setting.

**Methods:** We conducted a nationwide retrospective observational cohort study of HCV-infected people in the US Department of Veterans Affairs (VA) using the VA Corporate Data Warehouse. The study population included people with RNA positive for HCV who initiated EBR/GZR between February 1 and December 1, 2016. Estimated glomerular filtration rate (eGFR), calculated per Kidney Disease Outcome Quality Initiative guidelines, was used to determine CKD stages.

**Results:** A total of 2436 HCV-infected veterans treated with EBR/GZR  $\pm$  ribavirin (RBV) were included in the evaluable population: 1611 (66.1%) had baseline eGFR >60 mL/min/1.73m<sup>2</sup>, 393 (16.1%) had CKD stage 3 (eGFR, 30-59 mL/min/1.73m<sup>2</sup>), and 407 (16.7%) had CKD stages 4-5 (eGFR <30 mL/min/1.73m<sup>2</sup>). The mean age was 63.5 years (SD=5.9). Most participants were male (96.5%), African American (57.4%), and had HCV genotype 1 infection (95.4%). Other comorbidities in these participants included cirrhosis (33.3%), diabetes (53.2%), depression (57.6%), and HIV infection (3.1%). 95.2%

(1533/1611) of those with eGFR >60 mL/min/1.73m<sup>2</sup> achieved SVR. SVR rates were 96.7% in those with CKD stage 3, and 96.3% in those with CKD stages 4-5. SVR rates were 93.3-100% in participant subgroups based on HCV genotype, HIV coinfection, baseline viral load, and cirrhosis. Full SVR data will be presented at the meeting.

 $\label{eq:table:SVR} \begin{array}{l} \textbf{Table: SVR in people with HCV infection and CKD treated with EBR/GZR±RBV in the VA system (all genotypes) - stage 3-5 (evaluable population N = 800) \end{array}$ 

Characteristics	n/N	SVR, %
HCV infection with CKD stages 3-5	772/800	96.5
Cirrhosis	319/333	95.8
Black	525/540	97.2
Hispanic	19/20	95.0
White	187/198	95.4
Genotype 1	746/773	96.5
Genotype 4	14/15	93.3
Treatment-naïve	647/664	97.4
Treatment-experienced (INF, BOC/TVR/SIM/SOF)	101/108	93.5
Treatment-experienced (NS5A-containing regimen)	24/28	85.7
HIV coinfection	40/40	100.0
Baseline HCV RNA>800,000 IU/ml	469/488	96.1
Baseline HCV RNA≤800,000 IU/mI	276/282	97.9

BOC, boceprevir; NS5A, nonstructural protein 5A; SIM, simeprevir; SOF, sofosbuvir; TVR, telaprevi

**Conclusions:** EBR/GZR was highly effective in HCV-infected veterans with moderate to severe CKD. SVR rates were high across select subgroups in a large clinical setting.

**Keywords:** HCV, Chronic kidney disease, Real world data, Elbasvir/grazoprevir

#### **PE-064**

#### Safety and Efficacy of Ledipasvir/Sofosbuvir in a Genotype 1 HCV Infected Chinese Population: Results from a Phase 3, Clinical Trial

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**Aims:** Chronic hepatitis C virus (HCV) infection remains a major health threat in China, affecting at least 10 million people, with approximately 58% having genotype (GT) 1 infection. There is a critical need for simple, all oral, direct-acting antiviral regimens to treat GT1 HCV in this region. Treatment with ledipasvir (LDV)/sofosbuvir (SOF) results in high sustained virologic response rates 12 weeks after therapy (SVR12) in GT1 HCV infected patients in clinical trials and real-world settings. This study evaluated the efficacy and safety of LDV/SOF for 12 weeks in Chinese patients with chronic GT1 HCV infection.

**Methods:** Treatment experienced and treatment naïve patients with chronic GT1 HCV infection with no cirrhosis or with compensated cirrhosis were eligible to enroll in a single-arm, openlabel trial to receive a fixed dosed combination of LDV/SOF 90/400 mg daily for 12 weeks. The primary efficacy endpoint was SVR12 using the CAP/CTM HCV 2.0 assay (LLOQ =15 IU/ mL) and the primary safety endpoint was adverse events (AEs) leading to LDV/SOF discontinuation.

**Results:** A total of 206 Chinese patients were enrolled and treated. Of these, 50% were male, 16% had compensated cirrhosis, 49% were treatment-experienced, 76% had IL28B CC genotype, and 100% had GT1b HCV infection. The mean (range) age and body mass index of enrolled subjects were 47 (21-72) years and 23 (14-34) kg/m<sup>2</sup>, respectively. The overall SVR12 rate is 100% (206/206). All 32 patients with cirrhosis (15 of whom were treatment-experienced), achieved SVR12. There were no discontinuations due to AEs. No serious or severe AEs were assessed by the investigator as related to study drug and there were no deaths.

Table: SVR12 for GT1 HCV infected Chinese Patients

N (%)	Total	Cirrhosis	No Cirrhosis
	N=206	N=32	N=174
SVR12	206/206 (100)	32/32 (100)	174/174 (100)

**Conclusions:** Treatment with the single tablet regimen of LDV/ SOF for 12 weeks resulted in 100% SVR12 and was well tolerated in treatment experienced and treatment naïve GT1 HCVinfected Chinese patients with and without cirrhosis.

Keywords: Chinese, Registrational trial, Ledipasvir, Sofosbuvir

#### **PE-065**

Safety and Efficacy of Elbasvir/Grazoprevir in Hepatitis C Virus (HCV) GT1-and GT4 infected Participants 65 Years and Older

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Aims: Safety and efficacy of HCV therapy in older individuals is

of growing importance as the population with HCV infection ages. The objectives of this study were to compare the safety and efficacy of elbasvir (EBR)/grazoprevir (GZR) in participants aged  $\geq$ 65 and <65 years.

**Methods:** Safety and efficacy data from participants with HCV genotype (GT)1 or 4 infection receiving EBR (50 mg/day)/GZR (100 mg/day) for 12 weeks in 12 clinical trials were pooled and analyzed according to age ( $\geq$ 65 years vs <65 years). Sustained virologic response (SVR) 12 was defined as HCV RNA <lower limit of quantification 12 weeks after end of treatment (CO-BAS® AmpliPrep/COBAS® Tagman® v2.0).

**Results:** In participants aged  $\geq$ 65 years (n=339), mean age was 70 years (range, 65-82) versus 49 years (range, 18-64) in those <65 years (n=2139). Demographic parameters in participants aged ≥65 years versus <65 years were noncirrhotic (85% vs 83%), treatment-naive (72% vs 85%), HCV GT1 infection (99% vs 95%), male (44% vs 61%), and white (26% vs 59%), black (12% vs 13%), and Asian (61% vs. 26%) race, respectively. SVR12 rates were 323/339 (95.3%) and 2041/2139 (95.4%) in participants with HCV GT1 or 4 infection aged ≥65 and <65 years, respectively (Table). Rates of serious adverse events (SAEs), discontinuations due to adverse events (AEs), drug-related SAEs, and deaths were similar in both age groups (Table). AEs (occurring in >5% of either age group) in participants aged  $\geq$ 65 versus <65 years were headache (7.1% vs 13.0%), fatigue (6.8% vs 11.3%), nasopharyngitis (6.5% vs 4.9%), nausea (4.1% vs 7.2%), and diarrhea (3.5% vs 5.8%), respectively.

Parameter	≥65 years of age (n=339)	<65 years of age (n=2139)
SVR12, n/N (%)		
GT1a	48/52 (92.3%)	863/929 (92.9%)
GT1b or GT1-other	270/282 (95.7%)	1071/1097 (97.6%)
GT4	5/5 (100%)	107/113 (94.7%)
Safety, n/N (%)		
Serious adverse events	18/339 (5.3%)	68/2139 (3.2%)
Discontinuations due to adverse events	5/339 (1.5%)	11/2139 (0.5%)
Drug-related serious adverse events	1/339 (0.3%)	5/2139 (0.2%)
Deaths	1/339 (0.3%)	3/2139 (0.1%)

GT, genotype; SVR12, sustained virologic response 12 weeks after end of treatment

**Conclusions:** The efficacy of EBR/GZR for 12 weeks was similar in participants aged  $\geq$ 65 years versus those <65 years. Treatment was well tolerated in both age groups, with low rates of SAEs, discontinuations due to AEs, drug-related SAEs, and deaths. **Keywords:** HCV, GT1 GT4, Elbasvir/grazoprevir, Elderly patients

#### PE-066

## Efficacy and Safety of Daclatasvir and Asunaprevir in Patients with Hepatitis C Virus Genotype 1b Infection on Hemodialysis

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**Aims:** We evaluated the efficacy and safety of daclatasvir (DCV) and asunaprevir (ASV) in patients with chronic hepatitis C virus (HCV) infection on hemodialysis.

**Methods:** We performed a single-arm, multicenter prospective study. Twenty-one chronic hemodialysis patients with HCV infection were prospectively enrolled from February 2016 to April 2017. We evaluated the virological responses at each weeks 4, 12, and 24 (end of treatment [EOT]) and the sustained virological response at week 12 after the EOT (SVR12). The tolerability and safety of the drugs were also assessed.

**Results:** None of the 20 patients had a resistance-associated variants of NS5A (NS5A RAVs) and 1 patient showed indeterminate NS5A RAVs. Seventeen patients (80%) completed the 24 weeks of treatment with DCV and ASV. Four patients discontinued the study prior to week 12. In an intention-to-treat analysis, the SVR12 was 76.1%. In a per-protocol analysis, patients who completed DCV and ASV treatment achieved an SVR12 of 100%. DCV and ASV were well tolerated by the majority of patients. Three patients discontinued treatment due to adverse events (AEs) including dizziness, dyspnea, and neutropenia. The patient with indeterminate NS5A RAVs showed viral break-through and discontinued treatment.

**Conclusions:** DCV and ASV combination therapy in chronic hemodialysis patients with HCV infection achieved a high SVR12 rate with few AEs. To maximize the SVR12 rate, it is important to identify candidates by baseline RAVs testing. Close monitoring of the safety and tolerability of DCV and ASV may be necessary in HCV-infected patients on hemodialysis. ClinicalTrials. gov ID NCT02580474

**Keywords:** Daclatasvir, Asunaprevir, Chronic hepatitis C virus, Hemodialysis

### PE-067

### Impact of Treatment Duration and Addition of Ribavirin on Real-World Effectiveness of Elbasvir/Grazoprevir: Retrospective Analyses from the Trio Network

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**Aims:** Lengthening treatment with elbasvir/grazoprevir (EBR/ GZR) to 16 weeks and/or adding ribavirin (RBV) is recommended for select patients with HCV GT1 infection. However, realworld data (J Hepatol 2017;66:S295) suggest that utilization of this regimen is low. This study examined the use of 12- and 16week EBR/GZR ±RBV regimens in different patient subgroups.

**Methods:** Data were collected from providers and specialty pharmacies through Trio Health's disease management program. Patients (n=442) with HCV GT1 infection who initiated EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Dec 31, 2016 were included.

Results: 401 (91%) patients received EBR/GZR for 12 weeks, 12 (3%) received EBR/GZR+RBV for 12 weeks, 11 (2%) received EBR/GZR for 16 weeks, and 18 (4%) received EBR/GZR+RBV for 16 weeks. Possible baseline NS5A resistance was identified in 13/285 patients with GT1a infection: 3 (23%) received EBR/ GZR for 12 weeks, 1 (8%) received EBR/GZR+RBV for 12 weeks, 2 (15%) received EBR/GZR for 16 weeks, and 7 (54%) received EBR/GZR+RBV for 16 weeks. Across all patients, the +RBV subgroup had a higher proportion of treatment-experienced patients (43%, 13/30) than the -RBV group (17%, 69/412); and the 16-week subgroup had a higher proportion of GT1A subtype (93%, 27/29) than the 12-week group (62%, 258/413). Other characteristics including gender, age, baseline viral load, and cirrhosis were similar between regimens and between groups defined by RBV addition or therapy duration. SVR12 results at time of abstract submission were available for 262/442 patients. Overall per protocol (PP) SVR12 was 97% (253/262). Across GT1 subgroups (defined by subtype, prior treatment experience, and fibrosis) that received EBR/GZR for 12 weeks without RBV, the PP SVR12 was  $\geq$  94% (TABLE).

**Conclusions:** In real-world practice, EBR/GZR was highly effective, with the majority of patients treated for 12 weeks without RBV. Full SVR12 data will be presented at the conference.

Table: Per Protocol SVR1	2 with 12-week	EBR/GZR without RBV
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Patient subgroups	SVR12 (n/N (15)
All GT1, n/N (%)	232/238 (97%)
GT1a	138/139 (99%)
GT1b	91/96 (95%)
Treatment-naïve	193/198 (97%)
Treatment-experienced	39/40 (98%)
FO-F3	174/177 (98%)
F4	57/60 (95%)
Treatment-naïve, F0-F3	150/153 (98%)
Treatment-naïve, F4	42/44 (95%)
Treatment-experienced, F0-F3	24/24 (100%)
Treatment-experienced, F4	15/16 (94%)

Keywords: HCV, Real World Data, Elbasvir/grazoprevir

#### PE-068

# A Systematic Review of the Extrahepatic Manifestations of Hepatitis C Infection in East Asia

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**Aims:** Chronic hepatitis C (CHC) infection causes a systemic infection with hepatic and extrahepatic manifestation (EHMs). Although the prevalence of EHMs in Western countries is well described, the same is not well known in East Asian countries. We performed a systematic review to quantify the prevalence of selected EHMs among CHC patients in East Asia.

**Methods:** PubMed, Medline, and Japan databases searched (1990-Dec 2016) with "hepatitis c virus" "chronic hepatitis C", "extrahepatic manifestations", and respective EHM's. Data were collected and reviewed by two per PRISMA guidelines. EHMs were by ICD-9 codes or clinically: depression:BDI-2 score>19, chronic kidney disease (CKD): eGFR of < 60 mL/min/1.73 m2 per MDRD, diabetes (DM):fasting blood glucose level > 126 mg/dL. Pooled prevalence determined by random effects models.

**Results:** 75 articles were identified. After applying inclusion and exclusion criteria, 23 articles remained (Japan=6; China=3, Korea=4, Taiwan=9, Asia=1) with a total of 468,656 subjects (n= 51,160 CHC and n= 417,496 non-HCV controls). HCV patient age ranged from 44-70 (mean age 55), 50% were male (range 0%-67%), and over 80% of diagnosis was established through positive HCV anti-body. CHC subjects had higher risk of lymphoma (n=2) 4.6% vs. 2.3%, OR=1.79 (1.47-2.19), P<0.0001; DM (n=11) 16.7% vs. 9.4%, OR=1.84 (1.52-2.21), P<0.0001; SS (n=2) 9.6% vs. 3.5%, OR=9.80 (1.25-76.56), P=0.0295; LP (n=5) 8.2% vs. 4.2%, OR=2.45 (1.36-4.41), P=0.0027; depression (n=1) 51.6% vs. 27.7%, OR=2.77 (1.25-6.15), P=0.0121; CKD (n=5) 3.8% vs. 1.7%, OR=2.00 (1.09-3.70), P=0.026; RA (n=2) 0.9% vs. 0.3%, OR=2.41 (1.54-3.76), P=0.0001; CVA (n=2) 25.3% vs. 19.3%, hazard ratio 1.38 (1.24-1.53), P<0.05; IHD (n=1) 25.3% vs 11.6%, OR=1.76 (1.04-2.96), P=0. 0.034.

Additionally, the prevalence of MC (symptomatic and asymptomatic; n=1) in CHC was 46.9% in CHC vs. 1.9% in general population with a risk ratio of 24.7 (17.2-32.2).

**Conclusions:** Our review found that CHC in East Asia is associated with increased risk for EHMs.

**Keywords:** Extrahepatic manifestation, Chronic Hepatitis C, CHC, EHM

# PE-069

### Multiple Comorbidities and Significant Pill Burden in Hepatitis C Patients in a Large US Insured Population

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**Aims:** Decreasing pill burden and regimen complexity have been associated with improved adherence and clinical outcomes in other diseases and this may extend to hepatitis C virus (HCV). This study describes the pill burden and comorbidities in patients treated for HCV.

**Methods:** Commercial and Medicare Advantage insurance claims were used to identify patients who filled HCV medications between11/1/2013 and 7/31/2016 (index date =first fill date of HCV medication). Patients were continuously enrolled in the health plan for 9 months prior and 6 months after index date. Pill burden was calculated as mean ±SD daily pill count for chronic, oral medications in the 90 days prior to (pre-HCV) and after index date (post-HCV).



Figure 1. The differences in pre-index and post-index pill counts per day were significantly different among index HCV medications (p<0.0001).

**Results:** Descriptive statistics were used to compare patient demographics and pill burden changes by HCV medication. The study population included 9,815 patients (mean ±SD age 59.1±9.7, 63% male, 56% commercial). Highly prevalent comorbidities included pain (61%) and hypertension (50%). Preand post-HCV pill burden was 5.4 ±9.3 and 7.7 ±9.6, respectively. Pill burden was significantly higher among older patients and in those with more comorbidities (*P*<0.001). A greater proportion of Medicare patients had a post-HCV pill burden of  $\geq$  8 pills/day than in commercial (52% vs. 29%, *P*<0.0001). Post-

HCV pill burden was higher among patients treated with more complex regimens, such as ombitasvir/paritaprevir/ritonavir±dasabuvir (Figure; P<0.001). As such, patients with HCV have a substantial pill burden even prior to their initiation of HCV treatment, and more complex HCV regimens further increase the burden by up to 300%.

**Conclusions:** The majority of Japanese CHC patients are elderly with several comorbidities and high pill burden pre-DAA treatment. Patient pill burden may be an important consideration for HCV regimen selection.

Keywords: CHC, HCV, Pill burden, HCV comorbidities

# PE-070

#### Patient Characteristics and Medication Burden of Chronic Hepatitis C Patients in Japan from a Nationwide Real World Hospital Claims Database

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**Aims:** Japanese patients with CHC are elderly and may possess more comorbidities and higher pill burden. This study describes the pill burden and comorbidities in Japanese CHC patients in the Medical Data Vision (MDV) claims database.

**Methods:** This was a retrospective cohort study of  $\geq$ 18 years old patients with CHC (ICD-10: B18.2) from 2008-2016. Age and gender were derived from the database for the most recent CHC visit. Comorbidity prevalence was assessed using ICD-10 codes. Patients who had received all oral direct acting antiviral (DAA) therapy were identified through receipt code for a prescription for a DAA. The average number of tablets ('pill burden') taken by DAA-treated patients was calculated for the 90 days prior/post first prescription date of a DAA.

Table 1							
Comorbidity (% of patients)	All patients	Age group (years)					
		18-34	35-44	45-54	55-64	65-74	75+
	n=173,796	4,171	7,437	14,797	28,130	48,604	70,657
Hypertension	41.4	3.5	9.5	20.5	32.2	42.5	54.4
Gastroesophageal Reflux Disease	30.6	10.4	16.0	22.4	28.0	31.9	35.1
IBS and Constipation	29.5	11.8	13.7	17.0	21.5	28.6	38.6
Chronic Gastritis	26.7	12.7	16.8	21.0	24.6	28.4	29.4
Insomnia	23.9	9.1	14.7	19.5	21.2	24.7	27.1
Chronic Pain Syndromes	23.8	12.2	16.1	19.2	22.5	24.7	26.3
Type 2 Diabetes	18.3	4.4	8.6	13.5	18.5	20.8	19.3
Dyslipidemia	17.9	6.4	11.3	14.9	18.4	19.9	18.3
Hepatocellular Carcinoma	14.1	0.5	0.7	3.0	9.7	15.3	19.6
Congestive Heart Failure	13.5	2.9	4.4	5.7	8.5	11.5	20.2

**Results:** The study population included 173,796 patients (mean  $\pm$ SD age 69 $\pm$ 14, 51.7% male), with a large proportion  $\geq$ 75 years old (40.7%). Prevalent comorbidities included hyperten-

sion (41.4%) and type 2 diabetes (18.3%). Patients within the sample experienced a mean of  $3.54\pm2.98$  comorbidities, with elderly HCV patients experiencing more comorbidities than younger HCV patients (age group 18-34 vs. 75+;  $1.17\pm1.64$  vs.  $4.33\pm3.09$ ; *P*<0.001). The 10 most prevalent comorbidities are displayed in Table 1, with most increasing with age. 19,683 patients satisfied criteria for pill burden analysis. Pre- and post-DAA treatment initiation mean pill burden was  $4.23\pm11.4$  pills/ day and  $6.72\pm12.17$  pills/day, respectively. Pill burden was higher among older patients, with those aged over 75 experiencing mean pill counts of  $5.2\pm13.27$  and  $7.12\pm12.05$  pre- and post-index, respectively. A greater proportion of elderly patients had a pill burden of >10 after initiating DAA treatment, compared to those in younger age groups (age group 18-34 vs. 75+; 4.2% vs. 21.6%; *P*<0.001).

**Conclusions:** The majority of Japanese CHC patients are elderly with several comorbidities and high pill burden pre-DAA treatment, which may be an important consideration for CHC regimen selection.

Keywords: CHC, Patient characteristics, Medication burden

# PE-071

#### Sofosbuvir and Ledipasvir is Associated with High Sustained Virologic Response and Improvement of Health-Related Quality-of-Life in East-Asians with Hepatitis C

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**Aims:** We aim to assess HRQL in east Asian (EA) HCV patients treated with different anti-HCV sofosbuvir (SOF)-based regimens.

**Methods:** 1070 EA HCV subjects were enrolled in two phase 3 clinical trials [China: 55.6%, S. Korea: 20.7%, Taiwan: 16.1%, Vietnam: 4.7%, and Hong Kong: 2.9%]. Patients received IFN+SOF+RBV for 12 weeks (n=155, GT 1 and 6) or SOF+RBV for 12-24 weeks (n=531, GT 1, 2, 3 and 6) or IFN-free RBV-free LDV/SOF (n=384, GT1 only). The SVR-12 rates were 95.5%, 96.0%, and 99.2%, respectively (*P*=0.008). EA HCV patients completed Short Form-36 before, during, and after treatment

and HRQL scores compared between regimens.

Results: Baseline HRQL scores were similar between treatment groups. After 2 weeks of treatment, HRQL scores for the IFN+R-BV-containing regimen became significantly lower as compared to the IFN-free regimens (average decline up to -11.2 points, P<0.0001). By the end of treatment, IFN-treated group experienced significant declines in most HRQL scores (up to -13.3 points, P<0.02 for 7/8 HRQL scales). Patients on SOF+RBV had milder HRQL impairments (up to -5.4 points, P<0.05 for 5/8 scales). However, patients receiving LDV/SOF had improvement in their HRQL scores (up to +4.3 points by the end of treatment, P<0.001 for 3/8 scales). Achieving SVR-12 with IFN+RB-V+SOF and SOF+RBV was associated with improvement in General Health (GH) and Vitality (VT) (up to +2.9 points, P<0.05), while SVR-12 with LDV/SOF was associated with improvement in Physical Functioning, GH, VT, Mental Health, and Role Emotional (up to +5.9 points, P<0.03). In multivariate analysis, receiving IFN was independently associated with HRQL impairment during treatment ( $\beta$ : -10.4 to -17.3 points, P<0.0001).

**Conclusions:** Treatment of EA HCV patients with IFN or RBV containing regimens is associated with HRQL impairment, while treatment with LDV/SOF is associated with improvement of HRQL during treatment. SVR-12 was associated with greater improvements in HRQL.

Keywords: LDV/SOF, Harvoni, SVR, HRQL

#### PE-072

Interferon-Free Treatment Achieves High Rate of Sustained Virological Response in Kidney and Liver Transplanted Patients Infected with Hepatitis C Virus

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**Aims:** Recently, several studies have shown that direct acting antivirals (DAAs) can be effective in treating patients with relapsed hepatitis C virus (HCV) infection after liver or kidney transplantation. In this single center study, we aimed to evaluate the sustained virological response (SVR) rates among Korean liver or kidney transplant recipients.

**Methods:** We identified 15 liver or kidney transplant recipients (mean age 57  $\pm$  8.4 yeas, 7 males) treated with DAAs. Nine patients received liver transplantation (LT) and 6 patients received kidney transplantation (KT). Among them, 11 patients were infected with genotype 1B HCV and 4 patients with genotype 2. The mean interval between transplantation day and DAA start day was 876 days. Mean HCV RNA level was 3,010,319 IU/ mL. Eleven patients received combination therapy of DAA and ribavirin and 4 patients were treated with DAA monotherapy. Most patients were taking Tacrolimus or Cyclosporin as immunosuppressant. The primary endpoint was sustained virologic response at 12 weeks after the end of treatment (SVR12).

**Results:** The SVR12 rate by an intention-to-treat analysis is 92% (11/12). Patient who failed to reach SVR12 (genotype 1B) was initially treated with Ledipasvir/sofosbuvir and ribavirin. At 12 weeks, HCV RNA level was 0, but after 24 weeks, the level increased to 315,222 IU/mL, and at 36 weeks, 1,719,237 IU/mL. Interestingly, 5 patients treated with DAA monotherapy all reached SVR12. Patients did not show increase in AST/ALT and serum creatinine level or decrease in hemoglobin.

**Conclusions:** Treatment of HCV with the DAAs provided high rates of SVR12 in Korean liver and kidney transplant recipients on immunosuppression. ITT analysis SVR12 was 92% across different treatment regimens.

Keywords: Hepatitic C, Transplantation, DAA, SVR

### PE-073

The Effectiveness and Safety in Genotype 1b HCV Infected Treatment Naïve Patients Who Are Treated by Ledipasvir/Sofosbuvir

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**Aims:** Combination of ledipasvir (LDV)/sofosbuvir (SOF) has been approved in Mongolia for the treatment of genotype 1b hepatitis C virus (HCV) infected patients.

**Methods:** This retrospective study analyzed 627 patients with HCV infection who were treated with LDV/SOF from February 2016 to January 2018, were retrospectively enrolled from Dornod Medical center. Virologic response was measured at 4 weeks (rapid virologic response, RVR), at 12 weeks (end of treatment response, ETR), and at 12 weeks after the end of treatment (sustained virologic response, SVR12). Safety was assessed by review of adverse events, physical examinations, and laboratory findings.

**Results:** Of the 627 patients (male, n=282 [45%] female n=344 [55%]; mean age, 52.7 years; liver cirrhosis 169 [27%]), 458 patients (73.0%) were chronic hepatitis, mean AST (74.4 IU/L), mean ALT (66.8 IU/L), and mean HCV RNA level (3,678,490 IU/mL). In all patient, SVR12 was achieved in 622 (99.2%). 2 patients early stopped the treatment because of headache problem, 2 patient were over 70 year old, stopped the medication due to gastrointestinal troubles. During or after DAA treatment, hepatocellular carcinoma developed in 1 patients whose age was 67 years.

**Conclusions:** LDV/SOF treatment for HCV GT1b infected Mongolian subjects achieved very high SVR rates. However, in some older patients, HCC can develop during or after DAAs treatment.

**Keywords:** Hepatitis C, Ldipasvir (LDV)/sofosbuvir (SOF), Sustained virologic response

# PE-074

#### Effectiveness of Hepatitis C Virus (HCV) Screening Laws in United States [US]: Evidence from Paid Claims Data from 2010 to 2016

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**Aims:** The World Health Organization [WHO] has set a goal of having 90% of the world's population screened for chronic hepatitis C (HCV) infection by 2030. Starting from 2014 in the United States (US) 5 states (NY, CA, CT, MA, CO) implemented new HCV screening policies. This study assesses the effective-ness of these screening laws and projects states' progress toward the WHO target.

Methods: Claims data for 2010-2016 from Optum Clinformatics® Data Mart, a de-identified claims database from the US were analyzed. HCV screening was identified by paid claims for CPT codes 86803, 86804, or G0742. Logistic regression models of the likelihood of a patient being screened were estimated, controlling for patient demographic and clinical characteristics. Three time periods [2010; 2011-13 and 2014-16] were used to measure the effect on screening of the availability of the newer curative agents. Variables identifying states with screening policies were entered as interaction terms with the post-2014 time period to test if new screening policies enhanced screening rates, independent of the availability effect of the newer agents. Further, the proportion of the population screened in each state was extrapolated to 2050 using each state's 2014-16 screening rates applied to an assumed baseline diagnosis rate of 50%.



**Results:** Relative to the annual screening rate in 2010, annual screening rates were increased by 19.9% post 2014. In the states that passed screening laws, the annual post 2014 screening rates were increased by an additional 6.4%. Among the states that passed screening laws, MA and CT increased

annual screening rates but policies in NY, CA and CO had no significant effect. Other factors that increased the likelihood of a patient being screened were female gender, Medicare enrollment and presence of comorbidities like chronic kidney disease, mixed cryoglobulinemia, fatigue and coinfection with HIV and/ or HBV. Projections of screening rates suggest that NY and 4 other states without screening laws were on track to reach the WHO target by 2030 with 8 additional states attaining WHO target by 2040. 29 states would not attain this target by 2050. **Conclusions:** The availability of curative therapies has increased the likelihood of screening for HCV. While current efforts to increase annual HCV screening have had positive impact, over 90% of states in the US are still not on track to reach WHO target by 2030.

Keywords: Hepatitis C, Mass screening, Epidemiology

#### PE-075

#### Real-World Single Center Experience with Grazoprevir-Elbasvir for Chronic HCV Genotype 1b Infection

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**Aims:** Grazoprevir-elbasvir is direct-acting antiviral agents (DAA) with an FDA-approved indication for the treatment of chronic HCV genotype 1 and 4 in adults. Grazoprevir-elbasvir showed high efficacy for patients of chronic HCV infection and sustained virological response 12 weeks post treatment (SVR<sub>12</sub>) was observed in 95% of the randomized control trial. This study aimed to evaluate the clinical effects of grazoprevirelbasvir in the real world single center setting for the treatment of chronic HCV genotype 1b.

**Methods:** The medical records of patients treated for HCV genotype 1b with grazoprevir-elbasvir in the Chungnam National University, Korea from June 2017 to april 2018 were reviewed retrospectively. We assessed the  $SVR_{12}$  and  $SVR_{24}$  of the treatment of grazoprevir-elbasvir.

**Results:** A total of 25 patients with HCV genotype 1b were treated with grazoprevir-elbasvir for 12 weeks. All of them were HCV treatment naive and 20% had cirrhosis.  $SVR_{12}$  rate were 92% (23/25) with 1 relapse and 1 null response.  $SVR_{24}$  rate were 66% (2/3) and 1 relapse case was observed with HCV N55A mutation (Y93H).

**Conclusions:** In the real-world setting, grazoprevir-elbasvir had similar effects to HCV genotype 1b compared with the results of the randomized control trials. Since relapse case occurred in  $SVR_{24}$ , it seems necessary to continue serial assessments after the treatment followed by at least until 24weeks even after achieving  $SVR_{12}$  rates.

Keywords: Chronic hepatitis C, Grazoprevir, Elbasvir, Real-World

#### PE-076

Efficacy and Safety of 12 Weeks of Daclatasvir, Asunaprevir Plus Ribavirin for the Treatment of HCV Genotype 1b Infection without Baseline NS5A Resistance-Associated Variants (DARING)-Interim Report

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**Aims:** The current study aims to elucidate the treatment efficacy (defined as undetectable HCV RNA throughout 12 weeks of post-treatment follow-up, SVR12) and safety DCV/ASV plus ribavirin for 12 weeks in HCV-1b patients without NS5A RAS.

**Methods:** This is a single-arm, open-label phase 2 study. Seventy directly acting antivirals (DAA)-naïve HCV-1b patients without L31/Y93 RAS are planned to receive daclatasvir (60 mg/ day) and asunaprevir (100 mg twice daily) plus weight-based ribavirin (1000-1200 mg/day) for 12 weeks. After treatment they were followed up for 12 weeks.

Results: As of 31 Oct 2017, 58 eligible patients are allocated to treatment, with a mean age of 59.3 years and female predominance (67.2%, 39/58). The mean HCV RNA was 5.87+0.77 log<sub>10</sub> IU/mL; 23 patients (39.7 %) had significant hepatic fibrosis (>F2). In the modified intention-to-treat analysis, the rate of undetectable HCV at week 1, week 2, week 4, week 8 and endof-treatment was 25 % (14/56), 84.8 % (39/46), 100 % (46/46), 100 % (38/38) and 100 % (27/27), respectively. Undetectable HCV RNA were observed in all of the patients with HCV RNA assessable 4 weeks (SVR4, 18/18) and 12 weeks (SVR12, 12/12) post treatment. None of the 18 patients who completed the 12-week treatment experienced relapse during post-treatment follow-up. The most common adverse event was fatigue (78.3 %), followed by pruritus (65.2 %) and dizziness (52.2 %), of which were considered as ribavirin related. None of the participating subjects withdrew treatment or follow-up throughout the trial peroid. Three serious adverse events were reported which included urosepsis, appendicitis and left ureteral stone. All were unrelated to the investigating drugs.

**Conclusions:** 12 weeks of DCV/ASV plus ribavirin was highly effective and safe in HCV-1b patients without NS5A RAS in the interim analysis. The satisfactory results would be anticipated in the full patient set.



Updated on 2017/10/31

Keywords: HCV, DAA, NS5A, RAS

# PE-077

#### Long-Term Prognosis for Chronic Hepatitis C: Clinical Follow-Up after Achieving and Non-Achieving Sustained Virologic Response with Peginterferon Plus Ribavirin Combination Therapy

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**Aims:** Peg-interferon and ribavirin combination therapy was once the treatment standard for patients with chronic hepatitis C and is an option that is still used today. Its ultimate goal is to achieve a sustained viral response (SVR). Several studies have shown about 42 to 82% SVR with less than 1% relapse rate. However, there are not many cases of SVR of HCV in Korea, and also there is no definite study on SVR maintenance and observation period. Aim of this study was to evaluate the achievement rate and the prognosis of patients with achievement of SVR or not during the period of 5 years for peg-interferon and ribavirin combination therapy.

**Methods:** 94 patients successfully treated with peg-interferon and ribavirin combination therapy Patients with HCV genotype 1 (34 patients, 36.2%) at a constant dose received treatment for 48 weeks, whereas non-1 genotype patient (60 patients, 63.8%) received treatment for 24 weeks. The ratio of each achievement and non-achievement of SVR and the incidence rate of liver cirrhosis as well as HCC for each patients during 5-year follow-up periods were evaluated.

**Results:** Among the whole patients, 86 patients (86/94, 80.8%) achieved SVR. However, relapse of HCV RNA occurred in 4 patients (4/86, 4.7%), including two patients with persistent viremia (2/86, 2.3%). The SVR rates of genotype 1 and non-1 genotype were 70.6% (24/34) and 91.7% (55/60), respectively. All of the 8 patients (8/94, 8.5%) who did not achieve SVR had persistent viremia and 7 patients (7/8, 87.5%) were genotype 1 and rest of the patients were genotype IIa. Six patients (6/8. 75%) with genotype 1 progressed to cirrhosis and four of them (4/8, 50%) progressed to HCC.

**Conclusions:** Our results suggest that HCV patients who did not reached SVR, have a high risk for liver cirrhosis or HCC. However, although there are not many cases, our study showed that the risk of liver cirrhosis or HCC is still present in case of non-genotype I, even if SVR is reached. Therefore, longterm outpatient follow-up is recommended for patients chronic hepatitis C, and appropriate treatment and management are required for relapse.

**Keywords:** Peginterferon and ribavirin, Sustained viral response, Chronic hepatitis C, HCV genotype

# PE-078

Real-World Sustained Virologic Response Rates (SVR12) with Interferon (IFN)-Free Direct Acting Antiviral (DAA) Therapy in East Asia- Results from REAL-C (Real-World Effectiveness from the Asia Liver Consortium for Chronic Hepatitis C)

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**Aims:** Since their recent introduction in Asia, IFN-free DAAs have revolutionized treatment of chronic hepatitis C across all HCV genotypes. However, experience from large and diverse routine clinical practice is still limited. The aim of this study was to report real-world outcomes from a large multinational co-
hort of East Asian HCV patients treated with IFN-free DAAs.

**Methods:** Data were obtained using a required case report form from the REAL-C registry of patients who were initiated on IFN-free DAA therapy in routine practice and represented 10 study centers inclusive of 30 clinical sites in Hong Kong, Japan, Korea, and Taiwan. Cirrhosis was determined by liver biopsy, noninvasive tests (elastography/fibroscan, fibrotest), or the presence of clinical, radiologic, endoscopic, laboratory evidence of cirrhosis and/or portal hypertension.

Results: A total of 3702 patients have been registered. Table 1 displays the patient characteristics. The average age was 63.6±12.8; 17.7% had diabetes, 8.7% had chronic renal impairment, 26% had cirrhosis (5.1% decompensated cirrhosis), and 5.4% had HCC at baseline or prior to DAA treatment initiation. The majority of patients were HCV GT1 (68.7%), followed by HCV GT2 (30.4%). Ten different DAA regimens were used, with the majority receiving LDV/SOF (43.7%), followed by SOF+RBV (27.8%). One-third were treatment experienced (24.8% with prior PEG-IFN+RBV, 4.5% with prior DAA). SVR12 overall rate was 96.6%. Significant decreases noted in all major liver enzymes at week 12 and 24 post treatment. No increase in creatinine noted across treatments; 3.2% stopped treatment and 13.4% had an adverse event with fatigue (5.6% in patients treated with RBV vs. 6.4% in those treated without RBV, P=0.61) and anemia (5.6%) the most reported. Table 2 displays SVR12 rates by cirrhosis and prior treatment status for the most commonly used DAA treatments for GT1 and GT2 patients. SVR12 rates were excellent ranging from 97.1% (95%CI: 94.1-98.8%) to 99.7% (95%CI: 99.0-99.9%) for GT1 patients treated with LDV/SOF who did not have cirrhosis regardless of prior treatment history and who were treatment-naïve with cirrhosis but lower in the cirrhotic treatment-experienced group (92.2%; 95%CI: 86.7-95.9%) (P<0.0001). Sub-analysis results for GT1b were similar, with SVR12 99.7% for non-cirrhotic treatment-naïve, 99.5% for non-cirrhotic treatment-experienced, 97.4% for cirrhotic treatment-naïve, and 93.0% for cirrhotic treatment-experienced, (P<0.0001). For GT2 patients, SVR12 was excellent for all groups (96.8-98.0%) except for cirrhotic treatment-experienced patients (n=66) who experienced an SVR12 of 87.9% (95%CI: 77.5-94.6%) (P=0.002).

**Conclusions:** HCV cure rates were high overall in the REAL-C cohort-LDV/SOF GT1 98%; SOF+RBV GT2 96% except for cirrhotic, treatment-experienced patients especially in GT2, suggesting alternative therapy is needed.

Keywords: HCV, IFN-free DAA

HCV, Basic

#### PE-079

#### Role of Interleukin 28B Polymorphisms in Response to Interferon Based Therapy for Hepatitis C Virus Clearance in Libya

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**Aims:** The Single-nucleotide polymorphism in interleukin genes have been reported to be associated with clearance of HCV and sustained virologic response (SVR). Interleukin 28B (IL28B) gene polymorphism is responsible for immune protection against viruses. IL28B gene polymorphism in HCV infection determines the fate of infection toward spontaneous clearance or chronic infection. This study aims to determine that IL28B gene polymorphism is associated with HCV clearance as well as response to interferon treatment in Libyan patient.

**Methods:** Total of 72 patients with chronic HCV infection who received interferon plus ribavirin combination therapy were enrolled in the study. Viral RNA was checked at one, the third and sixth month of treatment. Genotyping of single-nucleo-tide polymorphism (SNP) rs12979860 of IL-28B gene was performed using DNA isolated from blood plasma. Detection was performed using Applied Biosystem® Real-Time PCR.

Results: Twenty-four patients (33%) had CC genotype, 36 (50%) had CT, and 12 (17%) had TT. CC patients obviously had achieved the SVR (91%) more than that of CT/TT (58% and 50%) respectively (P<0.005). This had reported with HCV genotype 1 and HCV genotype 4 infected patients similar to other findings reported by several studies. The studied patients who have infected with HCV genotype 3 had achieved RVR and succeeded to achieve the SVR irrespective of their IL28B genotypes where the relapse there after had reported only with the CC patients. On the other hand, CC/TT (haplotype) patients infected with HCV genotype 2 significantly achieved the RVR that eventually translate to SVR achievement. However, the rate of the RVR for CT patients was indeed lower that consequently translated into a lower SVR rate and higher of the thereafter relapse. IL28B CC genotype was the independent predictive factor for SVR with an (odds ratio [OR] 10.59; (95% confidence interval [CI]: 1.47-76.43; P=0.019). These findings were indeed consistent with several studies using the IL28B with various genotypes as predictive factors for the SVR.

**Conclusions:** The CC patients showed a trend toward higher viral decline more than the CT and TT patients. Therefore, IL28B genotyping may be used as a predictor of IFN-based therapy outcomes, and a strategy for developing personalized treatment of hepatitis C patients in Libya.

Keywords: Hepatitis, Interleukin 28B, Interferon, HCV

### **PE-080**

#### The HCV-Associated Hepatocarcinogenesis in Intracellular Low Viral Load Cells

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**Aims:** There are differential viral load distribution in HCV infected liver tissues. We conduct the present study aimed to dissect the different viral load cells to investigate the viral-host resistance on the HCV associated hepatocarcinogenesis.

**Methods:** The study was performed using a replicated *in vitro* HCV-fluorescence infection model to discuss HCV-high viral load (HVL) cells and the HCV-low viral load (LVL) cells by Flow sort system. The next generation RNA sequence and miRNA array were used to explore the gene profiles and miRNA expression on different HCV-viral load cell populations.

**Results:** The ROS indicator shows that the ROS abundantly in low viral load cells. The RNA-Seq analysis showed that significant enrichment in Cancer (*P*=5.00E-02 - 2.76E-04; 40 molecules) and a network of the Cellular Movement, Immune Cell Trafficking, Inflammatory Response (Score: 18) by IPA analysis. Protein analysis results confirmed the GADD45A and iNOS overexpression in the LVL cells which verified the oxidative stress qPCR array data in LVL cells. We also found the up-regulated Src oncoprotein expression and down-regulated E-cadherin expression in LVL cells. The miRNA array showed that miR-194, miR-192/215 and miR-10a were preferentially expressed in low viral load cells.

**Conclusions:** With our established cell sorting system, this study provided the gene network between viral and host cells resistance by different viral load cells. The findings show the activated oxidative stress related-gene expression in hepatocytes is associated with the HCV-infected epithelial-to-mesenchymal transition (EMT), providing an important link between HCV viral load and liver cancer. The miRNA-gene intergraded dada need further studies.

Keywords: HCV, HCC

#### PE-081

# Hepatitis C Virus Genotypes and Subtypes Circulating in Libya

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Aims: Hepatitis C virus (HCV) infection is a global important

health issue affecting around 150–170 million patients around the world, around 1-1.3% of the Libyan population are affected by HCV. HCV genotyping plays an important role in the clinical decision and epidemiological studies; there are six major genotypes worldwide. The aim of the study was to establish the local genotypic profile and characterize the associated treatment response rate for patients on pegylated interferon and ribavirin in Tripoli Center Hosptial (TCH) Tripoli, Libya.

**Methods:** A total of 72 patients with a measurable serum HCV-RNA were enrolled between 2014 and 2015. HCV Genotyping was performed by the Abbott Real-Time HCV assay v2.0 using Applied Biosystem Real-Time PCR.

**Results:** HCV with genotype 4 forms the highest incidence rate of infection, presented with 41.6%, followed by 1a (9.7%), 2 (9.7%) and 1b (6.9%). While other HCV genotype 1 and genotype 3 subtypes were detected in (27.7%). The HCV genotype 1b had achieved SVR with higher rate representing 100% of the treatment more than that of the HCV genotype 1a that displayed 28%. In contrast, the HCV genotype 3a infected patients had succeeded to achieve the SVR (100%) than other HCV genotype 3 subtypes. However, HCV genotype 2 have fully achieved the ETR with a rate of 100%.

**Conclusions:** The sustained virological response rate with different HCV genotypes was indeed 92%, 73%, 57% and 50% of patients infected with HCV genotypes 3, 4, 2 and 1 respectively. This would reflect that the screening for HCV genotyping predicting the treatment response. Nevertheless, the HCV genotype 1a displayed the minimum level of the SVR. These results were consistent with previous reports.

Keywords: Genotype, HCV, Hepatitis, Interferone

#### Liver Cancer, Clinical

# PE-082

Complete Response Induced by Multidisciplinary Treatment Modalities and Anaphylaxis in a Hepatocellular Carcinoma Patient with Right Atrium and Pulmonary Metastasis

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**Aims:** Hepatocellular carcinomas (HCC) with the right atrium and pulmonary metastasis are rare, but have a dismal prognosis. The treatment outcomes of patients with advanced HCC remain unsatisfactory.





**Methods:** A 46-year-old man was diagnosed with huge HCC and extra-hepatic metastasis including multiple lung metastasis, and right atrium. He received treatment with multidisciplinary modalities such as radiotherapy (RT), trans-arterial chemoembolization (TACE), and sorafenib. After initial treatment follow up computed tomography (CT) using radio-contrast media was

checked for evaluation of tumoral response. At that time, he experienced radio-contrast induced anaphylaxis. After anaphylaxis event and additional treatment, the patient's tumor burden decreased and eventually achieved complete response by mRECIST criteria.

**Results:** Subsequent blood tests showed increased NK cell (CD56) activity, which were significantly more active than those in other HCC patients who had same stage and ages. This suggests that antitumor effect of the NK cell induced by anaphylaxis affected the tumor burden and contributes to long term survival of the patient. The patient has survived for 830 days thus far and he is still alive.

**Conclusions:** Herein, we report a rare case of long term survival in a HCC patients with multiple metastasis treated with multidisciplinary modalities that experienced anaphylaxis.

**Keywords:** Antitumor effect, Anaphylaxis, NK cell, Hepatocellular carcinoma

#### PE-083

How to Treat Single Very Large Hepatocellular Carcinoma without Portal Vein Thrombosis: A Single Center Retrospective Study

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**Aims:** In the treatment of hepatocellular carcinoma (HCC), single very large carcinoma ( $\geq$ 7cm) is still difficult for clinician to choose treatment modality due to concern of recurrence. In this study, we aimed to evaluate the survival across treatment modalities in single large carcinoma without portal vein thrombosis (PVT).

**Methods:** From 2002 to 2013, 1,685 patients were newly diagnosed HCC patients in Seoul St. Mary's hospital. Of them, 1,628 patients were excluded with following reasons: metastasis (187 patients), less than 7cm (1,095 patients), PVT (249 patients) and multiple HCC (93 patients). 57 patients were included and evaluated on overall survival according to treatment mortalities. Moreover, response rate using RECIST 1.1, recurrence free survival and risk factor for survival were also examined

**Results:** Fifty-seven included patients had mean 59.7 years and hepatitis B (50.9%) was the main etiology. The majority were CTP class A (86.0%) and 18 patients had cirrhosis. The median tumor size and AFP were 10.0cm (7.0-14.9cm), 70.6ng/mL (0.7-200,000), respectively. There were no significant difference in baseline characteristics between treatment modalities. Surgery based group (n=11) had higher survival than other treatment group (*P*=0.008). In subgroup analysis, surgery based group showed higher survival than TACE only group (n=21), TACE based group (n=6) and conservative group (n=4). However, compared with TARE based group (n=5), there was no

significant difference. Better response (complete response [CR] rate: 91%) was note in surgery based group than that of TACE only group (CR rate: 41%) and TACE based group (CR rate: 19%). Surgery based group had better recurrence free survival than other treatment group without significance (P=0.062). In multivariate analysis, surgery based treatment (P=0.027), creatinine (P=0.016) and AFP (P=0.004) were independent prognostic factors for survival.

**Conclusions:** In the treatment of single large ( $\geq$ 7cm) HCC without PVT, surgery based treatment was better treatment modality than other treatments.

Keywords: Hepatocellular carcinoma, Large, Treatment

#### PE-084

#### Clinicopathologic Characteristics of Hepatocellular Carcinomas with BAP1-Loss

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**Aims:** BAP1 is a tumor suppressor gene that is mutated in several tumor types. BAP1 loss has been noted in 20% of intrahepatic cholangiocarcinomas and has been used in support of a diagnosis of cholangiocarcinoma (CCA) in intrahepatic masses. We sought to determine if BAP1 loss occurs in hepatocellular carcinoma (HCC) and to characterize the features of cases that show BAP1 loss.

**Methods:** We screened 133 HCCs (1994-2012) for loss of BAP1 by immunohistochemistry (clone C-4) using tissue microarrays and followed up all abnormal (non-nuclear expression) cases and a group of control normal cases (n=24) by performing BAP1 IHC on full tissue sections. Loss of BAP1 IHC nuclear expression in the entire tumor was recorded as negative while loss in >5% but less than the entire tumor section was scored as heterogeneous loss. BAP1 chromogenic in situ hybridization (CISH) was performed on cases of BAP1 loss and scored as follows: negative (no staining), equivocal (rare cytoplasmic dots only at x40) and positive (cytoplasmic dots readily seen).

**Results:** 35 (26%) HCC were abnormal on the initial screen. BAP1 IHC on full sections showed 7 (5.3%) HCC were negative, 8 (6.0%) showed heterogeneous for BAP1 loss and 20 were intact. CISH was successful in 6 and 8 cases with complete and heterogeneous BAP1 loss by IHC respectively. CISH was negative in 4 of 6 IHC negative cases and equivocal in 2 of 6, and was negative in 2 of 8 IHC heterogeneous cases, equivocal in 2 and positive in 4. CISH was positive in 14 (61%) of cases with controls, equivocal in 9 (38%) and negative in 1 (1%). HCC with BAP1 loss and heterogeneous loss are compared in the Table below. HCC with BAP1 loss were conventional type while HCC with heterogeneous BAP1 loss were conventional in 4 (50%) cases and steatohepatitic in 4 (50%) cases.

Characteristic	HCC with BAP1 loss N=7	HCC with heterogeneous BAP1 loss N=8
Sex	4 (57%)	6 (75%)
Age (years)	64	76
Median max. tumor Size (cm)	9.6	4.6
Poorly differentiated	4 (57%)	6 (75%)
Multifocal	3 (43%)	2 (25%)
Viral hepatitis C positive	1 (14%)	2 (25%)
Median overall survival (months)	64	26

**Conclusions:** BAP1 loss is seen in 5-10% of HCC limiting its usefulness in the diagnosis of intrahepatic CCA particularly on biopsy specimens. The complete loss of BAP1 in a subset of cases raises consideration for targeting BAP1-related pathways in the treating HCC.

Keywords: BAP1, Hepatocellular carcinoma, Liver

# PE-085

# The Hepatocellular Carcinoma Developed in a Patient with HCV Infection After Direct-Acting Antiviral Agents

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**Aims:** Interferon (IFN)-free direct antiviral agents (DAAs) effectively eradicate hepatitis C virus (HCV) and rapidly improve liver functions. Current HCV eradication rates have exceeded 98% in a very short time. Since DAAs for treatment of HCV were introduced, conflicting data emerged about the risk of HCC after IFN-free treatments.We report a case of HCC early detection after HCV treatment with DAAs in a cirrhotic patient from Dornod, Mongolia.

**Methods:** We report a case of HCC early detection after HCV treatment with DAAs in a cirrhotic patient from Dornod, Mongolia.

**Results:** We report the history of a 58-years-old women, affected by HCV (1b genotype) related liver chronic hepatitis, who was followed-up since 2013 in our Internal Medicine Departmentas an outpatient of Dornod Medical Center. She was monitored with an ultrasound examination and liver function tests every six months. In 2016, she was treated with sofosbuvir plus ledipasvir to reach sustained virological response (SVR) with a complete clearance of the virus. At baseline and at the end of HCV treatment, computed tomography (CT) scan of abdomen excluded any lesions suspected for HCC. Alpha-fetoprotein (AFP) was 53.0 ng/mL before DAAs, increasing up to 253.1 ng/mL at 6 month of follow-up after the end of therapy. An ultrasound examination of the liver detected a new nodule, 5cm in the maximum size, located in the sixth segment.

**Conclusions:** In our case, the increase of AFP was the first signal of HCC. Patients with previous HCC should be carefully investigated to confirm complete HCC remission before starting, and proactive follow-up should be performed after DAA

#### treatment.

Keywords: AFP, Direct-acting antiviral agents

#### **PE-086**

### Remained Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Receiving Entecavir/Tenofovir

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**Aims:** We aimed to identify the incidence rate of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients treated with entecavir or tenofovir in South Korea, and to identify predictors of HCC development in these patients.

**Methods:** Between January, 2007 and December, 2015, 582 CHB patients initially received entecavir (n=406, 69.8%) or tenofovir (n=176, 30.2%) for CHB were retrospectively analyzed.

Results: During a median follow-up of 57.1 months, HCC developed in 38 (6.5%) of the 582 patients, regardless of antiviral agent type. Entecavir and tenofovir treated patients had similar HCC development rates (P=0.471). For the 582 patients, 2-, 4- and 6-year cumulative HCC development rates were 2.6%, 4.4 %, and 8.3%, respectively, and the 2-, 4-, and 6-year cumulative HCC development rates of patients with liver cirrhosis were significantly greater than those of patients without liver cirrhosis (6.2%, 9.8%, and 18.4% vs. 0.3%, 1.1%, and 2.2%, respectively, P < 0.001). Older ( $\geq 60$  years) patients regardless of the presence of cirrhosis and cirrhotic patients with age of  $\geq$ 40 years showed significantly higher risk of HCC development compared to others (P<0.05, respectively). ≥Multivariate analysis showed that an older age ( $\geq$ 50 years; hazard ratio [HR] 5.02, P=0.009), and the presence of cirrhosis (HR 4.95, P=0.002) independently predicted HCC development.

**Conclusions:** The HCC development rate was 6.5% in CHB patients treated with ETV or TDF over a median follow-up of 6 year in South Korea, a predominantly HBV genotype C area. An age of  $\geq$ 50 and liver cirrhosis were found to predict HCC development in these patients.

**Keywords:** Chronic hepatitis B, Hepatocellular carcinoma, Entecavir, Tenofovir

#### **PE-087**

#### Prognostic Comparison of the 7th and 8th Editions of the American Joint Commission on Cancer Staging System for Intrahepatic Cholangiocarcinoma

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**Aims:** Several important changes were made to the 8th edition of American Joint Commission on Cancer (AJCC) tumor staging system for intrahepatic cholangiocarcinoma (ICC). We assessed the prognostic impact of this new tumor staging system compared to the 7th edition.

**Methods:** A retrospective single-institution study was performed with 626 patients who underwent R0 resection for ICC over 20-year period.



**Results:** Anatomical resection and concurrent bile duct resection were performed in 571 (91.2%) and 62 (9.9%) patients, respectively. Cumulative tumor recurrence and patient survival rates were 40.6% and 73.3% at 1 year; 66.7% and 43.8% at 3 years; 73.6% and 30.4% at 5 years; and 74.4% and 20.3% at 10 years, respectively. Independent prognostic factors for tumor recurrence and patient survival were multiple tumors, CA 19-9 >200 U/mL, tumor size >5 cm, direct invasion to extrahepatic structure, and lymph node metastasis. For TNM stages in the 7th versus the 8th editions, C-index was 0.615 and 0.625 for tumor recurrence and 0.626 and 0.628 for patient survival, respectively.

**Conclusions:** The 8th edition AJCC appears to provide high prognostic contrast for T stage categories, except for T3. However, overall prognostic performance of the 8th edition was not markedly improved over the 7th edition.

Keywords: Tumor staging, Intrahepatic cholangiocarcinoma, Prognosis

#### **PE-088**

#### Comparison of Long-Term Outcome for Single Small Hepatocellular Carcinoma between Different Treatment Modalities According to the Size and Tumor Marker

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**Aims:** For single small hepatocellular carcinoma (HCC), different therapeutic modalities can be tried for patients with preserved liver function. We aim to identify prognostic factors associated with overall survival, that can be used to guide treatment selection.

**Methods:** Between 2010 and 2013, we analyzed 896 patients who received resection, radiofrequency (RF) ablation or transarterial chemoembolization (TACE) as a first-line therapy for single, small (<3cm) HCC. We first identified risk factors associated overall survival in patients who were treated with RF ablation, and then compared long-term outcome according treatment modalities, stratified based on risk factors.

Results: Among 425 patients treated with RF ablation, tumor size and PIVKA-II levels were independent factors associated with overall survival. When patients were stratified according to the tumor size and PIVKA-II levels, overall survival of patients treated with RF ablation was significantly different by subgroups (group 1: tumor sized = 2 cm with low PIVKA-II levels (< 30 mAU/ml); group 2: tumor sized 2-3 cm with low PIVKA-II levels (< 30 mAU/ml) or tumor sized = 2 cm with elevated PIV-KA-II levels (= 30 mAU/ml); group 3: tumor sized 2-3cm with elevated PIVKA-II levels (= 30 mAU/ml)). When compared to resection, overall survival of those treated with RF ablation was not different to those who received resection in group 1 or group 2, but was significantly lower in group 3. When compared to TACE, those treated with RF ablation showed better survival in group 1 or group 2, but was not different in group 3. Conclusions: Tumor size and PIVKA-II levels were associated with overall survival of patients treated with RF ablation. When patients were stratified according to tumor size and PIVKA-II levels, different long-term outcome by treatment modalities was observed. Our data suggests that these two factors can be a valuable factors in choosing first-line treatment option for single small HCC.

Keywords: HCC, RFA, Resection, Treatment modality

# PE-089

### HCC Screening Program in Mongolia Single Center Data

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**Aims:** : Incidence of liver cancer in 4<sup>th</sup> rate of common cancers and 3<sup>rd</sup> rate of deaths due to cancer incidence in the world. In the Mongolia, cases of liver cancer are 44.1% of all cancer cases and mortalities are 43.3%, which is the first leading cause of mortality among cancer. In Mongolia, 81.2% of the liver cancer was diagnosed at an advanced stages (stage 3 or 4) and the 5-year survival rate (after diagnosed) of 19.5% are associated with lack of high risk population screening. The most common causes of liver cancer are hepatitis B, C and co infections. Screening and diagnosis in early stage of liver cancer in high risk population group

**Methods:** In our study we used single center patient data. These patients are controlled in screening in early stage of liver cancer in Happy Veritas Clinic and Diagnostic Center. In this center, patients are included for HCC screening, when they have liver fibrosis stage higher than F2 (over 7.2kPa) that indicates higher likehood of developing HCC. Fibrosis stage was measured using a Fibroscan (Fibroscan 502 Touch, Echosens, Paris, France). The total number of patients included for screening was 10682 patients such as abdominal ultrasound and to identify serum AFP every 3 months. 181 patients were included in this study, who had complete set of data and are regularly controlled for screening in early stage of liver cancer. Medical history, results of blood test, liver function tests, AFP, liver fibrosis stage and abdominal ultrasound examination results were collected for each patient.

**Results:** 181 patients with an average age of  $54\pm11$  (range 23-89 years old) were included the study. In the result, causes of liver fibrosis were HCV 59.1%(107), hbv 24.9%(45), HBV/HDV 13.3%(24), HCV/HBV 2%(3), HCV/HBV/HDV 0.6%(1) and without hepatitis viruses 0.6%(1). According to the study F2 stage was 64.6%(117), F3 stage 27.1%(49) and F4 stage 8.3%(15). We studied the changes in laboratory tests and depending on the patients fibrosis stage . Increasing fibrosis stage of liver cirrhosis has decreased platelets aalbumin and total protein level (*P*<0,001). However, we observed ALT level, which increased in F3 stage and decreased fibrosis stage F4. Liver cancer nodule is detected in 4 patients from 181 patients during the follow-up. Those 4 patients had fibrosis stage F4 in Fibroscan analysis and average level of AFP was 86.

**Conclusions:** We conclude that patients in F4 stage in Fibroscan analysis have higher risk of developing liver cancer. Therefore, health care providers need regularly screening and testing in early stage of liver cancer in high risk population.

Keywords: HCC, Screening, Program

#### PE-090

# Association of Non-Alcoholic Fatty Liver Disease with Hepatocellular Carcinoma

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**Aims:** This study was performed to evaluate the association between non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) development between 2005 and 2015 in a hepatitis B virus (HBV) endemic area.

**Methods:** The medical records of 1,327 patients initially diagnosed with HCC at our institution between January 2005 and December 2015 were retrospectively analyzed. Patients with other malignancies in addition to HCC were excluded. During the study period, changes in the proportion of NAFLD-associated HCC among all HCCs were assessed longitudinally. In addition, the clinical characteristics of NAFLD-associated HCC were evaluated.

**Results:** Among the 1,327 subjects, HBV was the most common (65.5%) cause of HCC, and the overall rate of NAFLD-associated HCC was 4.7%. As compared with HBV-associated HCC patients, NAFLD-associated HCC patients were older, had a higher median body mass index, and a larger median tumor size (*P*-values for all<0.05). Liver cirrhosis was less frequent in NAFLD-associated than in HBV-associated HCC patients (*P*<0.05). The annual proportions of NAFLD-associated HCC patients were 3.4% in 2005, 3.6% in 2006, 3.5% in 2007, 3.2% in 2008, 4.2% in 2009, 4.4% in 2010, 5.6% in 2011, 5.2% in 2012, 5.8% in 2013, 7.0% in 2014, and 6.7% in 2015. From 2008 to 2015, the percentage of them steadily increased.

**Conclusions:** Annual proportion of NAFLD-associated HCC patients among all HCC patients ranged from 3.2% to 3.5% before 2008, but thereafter, it increased gradually and had doubled to 7.0% by 2014. In addition, NAFLD-associated HCC was found to develop more commonly in non-cirrhotic liver and to present with larger tumor sizes than those of HCCs associated to other causes.

**Keywords:** Hepatocellular carcinoma, Non-alcoholic fatty liver disease

#### PE-091

#### A Comparative Study between Platelet-Albumin-Bilirubin (PALBI) and Albumin-Bilirubin (ALBI) Grade in Predicting Overall Survival for Hepatocellular Carcinoma

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Aims: Child-Turcotte-Pugh (CTP) class is well-known grade to

reflect the liver function in hepatocellular carcinoma (HCC). Recently, albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI) was introduced to access the liver function and predict survival. We aimed to validate the PALBI grade and compare with ALBI grade on overall survival (OS) and its applicability according to treatment modalities.

**Methods:** The 6,669 patients were randomly extracted from the national cohort of Korean Central Cancer Registry during 2008-2012. Of them, The 6,507 patients were evaluated on OS with CTP class, model for end stage liver disease (MELD), ALBI and PALBI grade. Moreover, OS according to treatment modality was evaluated with PALBI grade and compared with ALBI grade, MELD, and CTP class.

**Results:** The mean age was 59.7 years and 79.1% were male. The major cause of HCC was hepatitis B (63.4%) and majority was CTP class A (71.8%). Median survival time of PALBI grade 1 (38.4%), grade 2 (33.2%) and grade 3 (28.4%) were 81, 30 and 5 months, respectively (*P*<0.001). PALBI grade had higher area under receiver-operator-characteristic curve (AUC) at 1, 3, 5 years-mortality than CTP class, MELD grade and ALBI grade (overall AUC; 0.722 vs. 0.633, 0.645, 0.642, respectively, *P*<0.001). In multivariate analysis, PALBI and ALBI grade were also significant risk factor for overall survival. Comparing ALBI and PALBI grade according to treatment modalities, PALBI could predict survival in treatment of trans-arterial chemoembolization and supportive care. Meanwhile, ALBI grade could predict survival in treatment of surgical resection, radiofrequency ablation.

**Conclusions:** This study showed PALBI and ALBI grade was reliable model to access liver function and survival. According to treatment modalities, ALBI may predict OS better in curative treatment. On the other hand, PALBI showed more applicable to the locoregional therapy.

Keywords: Hepatocellular carcinoma, Grade, PALBI, ALBI

#### PE-092

# Effects of Metformin in Sorafenib-Administered Patients with Hepatocellular Carcinoma Recurrence after Hepatic Resection and Liver Transplantation

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**Aims:** Hepatocellular carcinoma (HCC) recurrence following hepatic resection (HR) and liver transplantation (LT) remains a great concern. We investigated metformin-induced cytotoxic effects in *in vitro* study and assessed the synergistic antitumor effects of metformin in patients administered with sorafenib for HCC recurrence after HR or LT.

**Methods:** This research included an *in vitro* study and two clinical retrospective studies involving metformin administration including 304 HR patients and 74 LT recipients who were administered with sorafenib.

**Results:** The *in vitro* study used one HepG2.2.15 liver tumor and two patient-derived graft HCC cell lines and showed noticeable synergistic cytotoxic effects of metformin and sorafenib on cell viability and cytokine levels. In the clinical study with patients who had undergone HR, the metformin HR group (group 1; n=40) did not show any prognostic difference in progression-free and overall survival rates compared with the all-HR control group (group 3; n=241) and propensity score-matched HR control group (group 4; n=80). In the clinical study with recipients of LT, the metformin LT group (group 5; n=14) did not show any prognostic difference in progression-free and overall survival rates compared with the all-LT control group (group 7; n=43) and propensity score-matched LT control group (group 8; n=28).

**Conclusions:** Our *in vitro* study demonstrated cytotoxic effects of metformin and synergistic antitumor effects of sorafenib. However, our clinical studies demonstrated absence of synergistic antitumor effects of metformin. Further high-volume studies are necessary to assess the role of metformin in patients administered with sorafenib for advanced HCC.

Keywords: Hepatocellular carcinoma, Meformin, Sorafenib, Recurrence





#### PE-093

#### Pathologic Predictive Factors for Late Recurrence of Hepatocellular Carcinoma in Chronic Hepatitis

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**Aims:** Hepatocellular carcinoma (HCC) has poor outcome, with a cumulative 5-year recurrence rate > 70% even after curative resection. Late recurrence (> 2 years after resection) is regarded as de novo HCC that typically develops from chronic liver disease through a multistep process. It was recently reported that the molecular genetic profile of the background liver rather than HCC itself predicts late HCC recurrence. In this study, we developed and validated a predictive model based on histopathologic features and immunohistochemical marker expression, which is practically useful.

**Methods:** The training (402 cases) and validation (243 cases) cohorts of patients who underwent curative resection for HCC were independently established. Histopathologic features including lobular and porto-periportal inflammatory activity, fibrosis stage, and small or large liver cell changes were evaluated. To evaluate changes in protein expression of genes related

to late recurrence, 95 non-tumor liver tissue samples from HCC patients were screened by reverse phase microarray analysis. Expression of phosphorylated signal transducer and activator of transcription (pSTAT)3, phosphorylated extracellular signal-regulated kinase (pERK)1/2, plasminogen activator inhibitor (PAI)-1, and spleen tyrosine kinase (SYK) was detected by immunohistochemical staining. A predictive model was constructed using independent parameters selected by multiple Cox proportional hazards regression analysis. The same analysis was performed in the validation cohort to verify the reliability of the model for predicting late recurrence.

Results: In the training cohort, late recurrence of HCC was observed in 74 (18%) patients, with a median follow-up period of 82 months. Late recurrence in HCC patients was correlated with cirrhosis (fibrosis stage 4), small and large liver cell changes, and upregulation of pSTAT3, pERK1/2, and PAI-1 levels (P<0.05 for all). Cirrhosis (odds ratio [OR] = 2.0; 95% confidence interval [CI]: 1.2-3.2), moderate or severe lobular activity (OR = 21.4; 95% CI: 4.4-104.2), and expression of one or more of pSTAT3, pERK1/2, and SYK (OR = 6.0; 95% CI: 2.0–17.5) as detected by immunohistochemical staining were independently associated with late HCC recurrence according to the multivariate Cox regression analysis (P<0.05 for all). A nomogram was based on these variables to predict late recurrence of HCC, and Harrell's c index was 0.701 (95% CI: 0.64-0.75). In the validation cohort, 47 patients (19%) showed late recurrence with a median follow-up period of 56 months and the Harrell's c index was 0.719 (95% CI: 0.64-0.79) for predicting late recurrence of HCC, demonstrating that the predictive model is highly reliable.

**Conclusions:** Our predictive model based on cirrhosis (fibrosis stage 4), moderate or severe lobular activity, and expression of one or more of pSTAT3, pERK1/2, and SYK in non-tumoral tissue of background liver is useful for predicting late recurrence of HCC after curative resection.

**Keywords:** Chronic hepatitis, Hepatocellular carcinoma, Late recurrence

#### **PE-094**

#### Albumin-Bilirubin Grade Predicts Survival of Advanced HCC Patients Treated with Sorafenib in a Hepatitis B-Virus Endemic Area

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Aims: Hepatocellular carcinoma (HCC) patients often have

cirrhosis, and the severity of liver dysfunction influence the prognosis of HCC. Albumin-Bilirubin (ALBI) grade is a recently introduced measurement for hepatic reserve in HCC patients. We aimed to investigate the prognostic value of ALBI grade in advanced HCC patients in a hepatitis B-virus endemic area.

**Methods:** A total of 411 consecutive advanced HCC patients in Child-Pugh A receiving sorafenib monotherapy from September 2008 to October 2017 were evaluated. Overall survival (OS) was assessed using the Kaplan-Meier method and a Cox proportional hazard model.

**Results:** Hepatitis B virus-related HCCs comprised 73.9% (304/411) of enrolled patients. Among 411 enrolled patients, 113 patients (27.5%) were classified as ALBI grade 1 and 298 patients (72.5%) were classified as ALBI grade 2 in baseline. Majority of the patients with ALBI grade 1 (110/113, 97.3%) had a Child-Pugh score of 5. Among patients with ALBI grade 2, 60.7% (181 patients) had a Child-Pugh score of 6. The median OS was 24.5 and 10.8 months for ALBI grade 1 and 2, respectively (*P*<0.001). Cox regression analysis showed that baseline ALBI grade 2 strongly influenced the mortality of HCC patients receiving sorafenib [Hazard ratio = 2.29 (95% CI: 1.60-3.27, *P*<0.001)].

**Conclusions:** ALBI grade could predict the overall survival of advanced HCC patients in Child-Pugh A treated with sorafenib in a hepatitis B virus-endemic area.



**Keywords:** Hepatocellular carcinoma, Sorafenib, Hepatitis B, Albumin-bilirubin grade

#### **PE-095**

#### Tumor Marker Response and Radiologic Response Can Predict Survival Following Radioembolization: A Landmark Analysis

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#### Seoul, Korea

**Aims:** It remains unclear whether alpha-fetoprotein (AFP), Des-gamma-carboxy protein (DCP), and modified Response Evaluation Criteria in Solid Tumor (mRECIST) can be used as predictors for overall survival (OS) after radioembolization.

**Methods:** Between 2009 and 2016, 63 patients with AFP >20 ng/mL, DCP >20 mAU/mL, and Child-Pugh A were analyzed. AFP or DCP responders were defined as decrease > 50% from baseline at 1, 3, 6 month landmark after radioembolization. mRECIST responders were defined as complete response or partial response.

Results: At 1month landmark, OS was not statistically different between AFP, DCP, and mRECIST responder and nonresponders. From 3month landmark, AFP (75.8 vs 7.6 months, P=0.001), DCP (75.8 vs 7.1 months, P<0.001), and mRECIST responders (75.8 vs 10.0 months, P=0.001) live longer than nonresponders. From 6month landmark, AFP (72.8 vs 9.4 months, P<0.001), DCP (72.8 vs 3.9 months, P<0.001), and mRECIST responders (not reached vs 12.1 months; P=0.012) also showed better OS than nonresponders. At 6 month risk of death from each landmark, there was statistical difference only between DCP responders and nonresponders (9.5% versus 36.8%, P=0.010 at 1month landmark, 2.9% versus 33.3%, P=0.002 at 3month landmark, and 4.3% versus 40.0%, P=0.009 at 6month landmark). In multivariate Cox proportional hazard analysis, at 3month landmark, DCP responder (hazard ratio [HR] 0.21, 95% confidence interval [CI] 0.072-0.593, P=0.003) and mRECIST responder (HR 0.19, 95% CI 0.065-0.571, P=0.003) were independent predictors for OS. At 6month landmark, only DCP responder (HR 0.02, 95% CI 0.001-0.392, P=0.010) was an independent predictor for OS.

**Conclusions:** AFP, DCP, and mRECIST responder showed better OS than nonresponder at 3month and 6month landmark after radioembolization, and DCP responder was the most potent predictor among them.

Keywords: Hepatocellular carcinoma, AFP, DCP, mRECIST

# PE-096

#### Single-Stage Extended Right Hemihepatectomy with Low Anterior Resection of the Rectum in Patients with Colorectal Cancer with Liver Metastases

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**Aims:** Colorectal cancer (CRC) occupies the 4th place in the structure of cancer morbidity in Kazakhstan. From 35 to 57% of patients with colorectal cancer with primary treatment have metastases to the liver. However, active surgical treatment of metastatic liver invasion allows achieving 5-year survival in 27-47% of patients.

**Methods:** We present the clinical observation of successful surgical treatment of rectal cancer with liver metastases with

simultaneous execution of extended right hepatectomy and "low" anterior rectal resection. Patient E., 64 years old, male. From anamnesis: the above complaints are noted within 6 months. Ultrasonography of the abdominal cavity revealed a focal lesion in the right lobe of the liver, with a colonoscopy: in the middle-ampullar rectal section, a tumor up to 5 cm in length is located 8 cm above the anus, which closes the colon lumen of the gut by 2/3; the result of a biopsy: moderately differentiated adenocarcinoma. By PET – no other metastatic problems.

**Results:** Was performed extended right hepatectomy (cholecystectomy) and "low" anterior rectal resection. After operation recommended adjuvant chemotherapy. At the control examination 3 months later after the operative treatment the condition is satisfactory, the laboratory parameters are within the norm. With ultrasound of the abdominal cavity signs of progression of the disease is not revealed.

**Conclusions:** Thus, the using of one-step operations on the primary tumors of CRC and liver metastatically lesions makes it possible to perform the surgical treatment in a shorter time and earlier to start adjuvant chemotherapy. With hepatic metastases of CRC, it is justified to perform extended liver resections.

**Keywords:** Liver metastases, Colorectal cancer, Hemihepatectomy, Single-stage

# PE-097

#### Different Survival Outcomes between Patients with Treatment-Naïve HCC versus Recurrent HCC after Curative Resection Undergoing TACE

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**Aims:** Trans-arterial chemoembolization (TACE) improves survival of patients with hepatocellular carcinoma (HCC). However, the treatment outcomes of TACE in patients with treatment-naïve HCC versus recurrent HCC after curative resection has not been compared.

**Methods:** A total of 448 patients with treatment-naïve HCC and 275 patients with recurrent HCC after curative resection treated with TACE as the first-line anti-cancer treatment were recruited. Cox regression analysis was used to identify independent factors affecting overall mortality.

**Results:** Patients with treatment-naïve HCC at the time of TACE showed a significantly higher proportion of liver cirrhosis (61.9% vs. 49.3%), higher aspartate aminotransferase level (median 48 vs. 31 IU/L), higher alanine aminotransferase level (median 38 vs. 26 IU/L), higher alpha-fetoprotein level (median 96.6 vs. 7.7 ng/mL), higher total bilirubin level (mean 0.97 vs. 0.84 mg/ dL), longer prothrombin time (1.05 vs. 1.01 INR), higher tumor

number (mean 2.1 vs. 1.7), larger tumor size (3.1 vs. 1.6 cm), and lower proportion of BCLC stage 0-B (vs stage C) (55.6% vs. 71.9%) (all *P*<0.05). Multivariate analysis showed that TACE for treatment-naïve HCC (vs. recurrent HCC after curative resection) was one of independent risk factors of mortality (hazard ratio, 1.328; 95% confidence interval, 1.038-1.700; *P*=0.024), together with higher alpha-fetoprotein level and higher tumor number (all *P*<0.05).

**Conclusions:** Patients with treatment-naïve HCC showed poorer clinical characteristics than those with recurrent HCC after curative resection at the time of TACE and TACE for treatment-naïve HCC (vs. TACE for recurrent HCC after curative resection) was independently associated with the increased risk of mortality.

**Keywords:** Hepatocellular carcinoma, Curative resection, Trans-arterial chemoembolization, Outcome

#### PE-098

Alpha-Fetoprotein Response after Selective Internal Radiation Therapy versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB)

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**Aims:** Alpha-fetoprotein (AFP) is considered to be an indicator of tumor activity in hepatocellular carcinoma (HCC). We present a novel correlation of AFP response to radiologic response and overall survival (OS) in patients treated with Selective Internal Radiation Therapy (SIRT) and Sorafenib therapies.

**Methods:** Participants from a phase III multicenter randomized trial of SIRT versus Sorafenib in HCC were studied. Thirty five patients with HCC were treated with selective internal radiation therapy or Sorafenib at our institution. Thirty one patients with baseline AFP higher than 20ng/ml were studied for analysis. AFP response was defined as more than 50% decrease from baseline. Twenty six patients with follow-up imaging were studied for the AFP imaging correlation analysis. We studied the relationship between AFP response and treatment outcome in terms of radiologic response and overall survival.

**Results:** Of 39 patients, 31 patients (79.4%) with elevated serum AFP (>20ng/ml) and documented radiologic evaluation every 12 weeks. AFP response was seen in 3 (17.6%) of 17 and 6 (40%) of 15 of patients treated with Sorafenib and Selective internal radiation therapy, respectively (P=0.16). The hazard ratio in AFP nonresponders compared with responders was 1.12 (95% CI, 0.46-2.69). AFP responders had better survival than nonresponders (15 and 6.95 months, respectively; P<.79), and AFP response was strongly associated with survival (hazard ratio, 1.12; 95% CI, 0.46 to 2.69; P<0.79). AFP response were frequently observed in patients with radiologically stable disease (SD) and tended to indentify a subgroup of SD patients with better survival.

**Conclusions:** The data presented support the use of AFP response seen after locoregional therapy as an ancillary method of assessing tumor response and survival, as well as an early objective screening tool for progression by imaging. **Keywords:** AFP, Liver cancer, Radiation, SIRT

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#### PE-099

#### A Case of Repeated Transcatheter Arterial Chemoembolization in a Patient with Hepatocellular Carcinoma Accompanying Incidental Aortic Dissection

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**Aims:** Transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) in patients with aortic dissection is a potentially risky and demanding technique. Access to the true aortic lumen might not be allowed by the arterial entry route chosen.

**Methods:** Here we report a case of repeated sessions of TACE through true and false lumens in a HCC patient with chronic aortic dissection.

Results: A 56-year old male presented with infiltrative HCC with right portal vein tumor thrombosis. Abdominal computer tomography scan also revealed an incidental asymptomatic aortic dissection involving descending aorta from proximal segment to superior mesenteric artery (SMA) origin level. Celiac trunk was supplied by false lumen, and SMA was supplied by true lumen. On SMA angiography, right hepatic artery was originated from SMA. HCC was supplied by segment 7 and 8 branch of right hepatic artery. Infusion of adriamycin and lipiodol mixture and subsequent embolization was performed to superior branches of right hepatic artery. Catheterization to celiac axis was failed due to its origin from pseudolumen caused by aortic dissection. Complete response was achieved after sequential radiation therapy. After 1 year, nodular HCC recurred at segment 4. On this session of repeated TACE, catheterization to false lumen was successful. Left hepatic angiography showed tumor stain supplied by segment 4 branch, and embolization was performed. One year later, viable portion was noted in infiltrative HCC at segment 7. Repeated TACE was performed to embolize segment 7 branch supplying infiltrative tumor.

**Conclusions:** In this case, we presented our experience with selective hepatic angiography and SMA angiography in a HCC patient with descending aortic dissection. To our knowledge, this is the first description of hepatic angiography using true and false lumen in a HCC patient with a concomitant aortic dissection.

**Keywords:** Transarterial chemoembolization, Hepatocellular carcinoma, Aortic dissection

# **PE-100**

Comparison of Selective Internal Radiation Therapy versus Sorafenib in Patients with Locally Advanced Hepatocellular Carcinoma in Mongolia

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**Aims:** Mongolia has one the highest hepatocellular carcinoma (HCC) incidence in the world due to widespread hepatitis B and C endemic along with high alcohol consumption rate. However, local data on optimal therapeutic regime for these patients is scarce. The objective of this study is to evaluate the efficacy of Selective Internal Radiation Therapy (SIRT) using SIR-Spheres yttrium-90 microspheres versus sorafenib in Mongolian patients with locally advanced HCC patients at Barcelona Clinic Liver Cancer (BCLC) stage B and C patients without extra-hepatic metastasis.

**Methods:** It was a subgroup analysis based on patients enrolled from the National Cancer Center, Mongolia in the SIRveNIB study. SIRveNIB was a multi-center, randomized trial in which eligible patients with locally advanced inoperable HCC was randomized (1:1) to either single injection of SIRT or Sorafenib (oral 400mg BD) and patients were followed up till progressive disease or unacceptable toxicity. Key endpoints were overall survival (OS) (primary endpoint), tumor response rate, time-totumor progression, progression-free survival and toxicity

**Results:** 39 patients (20 SIRT, 19Sorafenib) were enrolled from Mongolia. BCLC C patients without extra-hepatic metastasis comprised 62% of patients, 18% had portal vein thrombosis, 85% were Child-Pugh A, 45% were hepatitis B and 30% were hepatitis C. Altogether 4 of 20 patients (20%) in the SIRT arm failed to receive the study therapy. Intention-to-treat analysis was carried out with the OS in the SIRT and Sorafenib arms being 9.2 and 15.6 months, respectively, (Hazard ratio [HR]0.95, *P*=0.889).Tumour response rate (TRR) was 10% and 0% (*P*=0.487) respectively. Time-to-tumor progression(TTP) was 6.2 vs 8.5months (HR 1.01, *P*=0.971) and progression-free survival (PFS) 5.9 vs 8.5 months (HR 1.07, *P*=0.842 for SIRT and Sorafenib, respectively.At least one severe adverse event (=3 grade) was found in 56% and 47% of patients in the SIRT and Sorafenib arms, respectively.

**Conclusions:** In this subgroup analysis of a single center which is part of a larger multi-center, randomized controlled trial, 20% of the patients assigned to the SIRT arm failed to receive SIRT. On intention-to-treat analysis, there was no significant difference in OS, TRR, TTP and PFS between the SIRT and sorafenib arms. **Keywords:** Liver cancer, Sorafenib, SIRT

# PE-101

Bridging and Downstaging Role of Transarterial Radioembolization (TARE) for Expected Small Remnant Volume after Liver Resection in Hepatocellular Carcinoma

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**Aims:** Hepatectomy is the best treatment to improve survival in liver cancer. However, if the tumor is located in the central portion or the remaining remnant liver volume is small, there is a risk of complications such as hepatic failure after surgical treatment. Transarterial radioembolization (TARE) is a radiosurgical technique using yttrium-90 to induce primary tumor necrosis and hypertrophy of remnant liver to reduce the risk of liver failure and enable safe hepatic resection. In this study, we report a case of patients with hepatic resection after TARE.

**Methods:** Between January 2017 and December 2017, we performed hemihepatectomy in 5 patients who had unresectable causes like central located, small remnant liver volume, vascular invasion to major vessel. We performed TARE 3 month before surgical resection. Then we check tumor volume and expected remnant liver volume after surgical resection. Re-evaluating of liver function test, CT scan 4 weeks after TARE, and ICG test for patient safety, then we performed surgical resection.

**Results:** None of the 5 patient had recurrence during observation period. There was no hepatic failure after surgical resection 4 cases underwent Rt. hemihepatectomy and 1 case underwent extended Rt. hemihepatectomy. The mean operative time was 160 minutes. Mean hospital day was 7.5 days and mean blood loss 120 cc. Mean tumor shrinkage rate was -21.1 % and mean remnant liver hypertrophy rate was 39.5%. Only 1 case had wound complication, but the others had no postoperative complication. **Conclusions:** Surgical resection after TARE is feasible technique for surgically unresectable cases of hepatocellular carcinoma.

**Keywords:** Hepatocellular carcinoma, Transarterial Radioembolization, Hepatectomy

#### PE-102

#### Outcome and Safety of Nivolumab in Real Life in the Treatment of Far-Advanced Hepatocellular Carcinoma: A Single Center Experience

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**Aims:** Sorafenib has been the only approved systemic agent for advanced hepatocellular carcinoma (HCC) for the past decade and multiple new drugs were recently approved. Out of these, nivolumab, a programmed cell death protein-1 inhibitor, is the first immune checkpoint inhibitor approved for the second-line

therapy for advanced HCC. The aim of this study is to describe our experience with nivolumab in patients who have progressed on or been intolerant of prior sorafenib.

**Methods:** Thirty consecutive patients with advanced HCC receiving nivolumab were enrolled between October 2017 and March 2018. Enrolled patients were given nivolumab 3mg/kg intravenously every 2 weeks. Assessment of response was based on the Immune-Modified Response Evaluation Criteria In Solid Tumors (iRECIST) and RECIEST version 1.1 every 8 weeks.

**Results:** The median age of patients was 65.5 years (range, 46-81 years) and the predominant etiology was hepatitis B (64%). Most patients had preserved liver function (Child-Pugh class A, 93%) and good performance status (ECOG score of 0 or 1, 100%). Portal vein invasion and extrahepatic spread was present in 54% and 67%, respectively. Sorafenib was given all patients as a first-line treatment. Before nivolumab treatment, 6 patients received 2 systemic agents and another 6 patients received 3 or more. As of the cutoff date of April 5 2018, the median duration of nivolumab treatment was 61 days. Eleven out of 30 patients (36.7%) are on treatment, while 19 patients stopped treatment because of disease progression (n=9, 30%), serious toxicity (n=7, 23.3%), treatment refusal (n=2) and follow up loss (n=1). Of 22 patients available for evaluating tumor response, 2 showed partial response (PR; 9.2%); 8 stable response (SD; 36.3%); 4 immune unconfirmed progression (iUPD; 18.2%) and 8 immune confirmed progression (iCPD; 36.3%). One of the four iUPDs was identified as iCPD and discontinued treatment, while three patients are still on treatment awaiting the next evaluation. Median overall survival (OS) was not reached because of short follow up duration (83 days). Mean OS was 117.7 days (95% confidence interval [CI]; 105.4-129.9) and median progression free survival (PFS) was 97 days (95% CI; 72.9-121.1). Survival rate and PFS rate at 3 months were 90.2% and 64.9%, respectively. Most common adverse reactions included abdominal discomfort (20%), general weakness (13%), constipation (13%), ascites (13%), skin eruption or pruritus (13%), anorexia (10%), nausea (10%), myalgia (7%), diarrhea (7%), peripheral edema (7%), fatigue (3%), dyspnea (3%). Treatment-emergent grade 3 adverse events (n=7) included hepatotoxicity, azotemia, hematochezia, anorexia, hyperbilirubinemia, and hypercalcemia, which necessitated treatment cessation.

**Conclusions:** In real life practice of a single center, nivolumab as a second- or a third-fourth-line therapy appears to have meaningful efficacy and acceptable tolerability in patients with far-advanced HCC. Further follow-up studies are warranted. **Keywords:** Nivolumab, Advanced hepatocellular carcinoma

#### **PE-103**

#### Pathological Response, Rather than Radiological Response, to Chemoembolization for Hepatocellular Carcinoma Predicts Survival after Curative Surgery

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\* Contributed equally to this work

**Aims:** We aimed to confirm the prognostic significance of a pathological response (PR) achieved with preoperative transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) preceding liver resection (LR) or liver transplantation (LT). **Methods:** Between 2005 and 2016, 124 patients underwent preoperative TACE before LR, and 166 underwent preoperative TACE before LT. PR was defined as the mean percentage of necrotic tumor area within each tumor. A complete PR (CPR) was defined as the absence of viable tumor in the surgical specimens. **Results:** A total of 34 (27%) and 38 (23%) patients had CPR

before LR and LT, respectively. Five-year overall survival (OS) was higher in patients with CPR than in those without CPR after LR (87% vs. 63%, *P*=0.005) and LT (91% vs. 75%, *P*=0.021). The 5-year recurrence-free survival (RFS) rates were also significantly higher in patients with CPR (71% vs. 38% after LR, *P*=0.001 and 97% vs. 75% after LT, *P*=0.008). Among patients with complete radiological remission, those with CPR had better prognosis than those without CPR. Subgroup analyses showed that PR  $\geq$  90% predicted OS and RFS in patients with a single resected tumor. On multivariate analyses, PR  $\geq$  90% remained an independent predictor of better OS and RFS in both groups. Independent factors associated with CPR were a preoperative alpha-fetoprotein level < 100 ng/mL and a single tumor.



**Conclusions:** Overall, CPR or nearly CPR improves long-term survival after LR and LT, independent of other pathological and clinical variables.

**Keywords:** Hepatocellular carcinoma, Chemoembolization, Hepatectomy, Liver transplantation

#### PE-104

#### Initial Treatment Response is Significantly Associated Survival Outcomes in Patients Treated with TACE for Recurrent HCC after Curative Resection

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**Aims:** Trans-arterial chemoembolization (TACE) prolongs the survival of patients with hepatocellular carcinoma (HCC). We evaluated whether the initial treatment response by TACE for recurrent HCC after curative resection is associated with better survival.

Methods: Between 2003 and 2015, 385 patients with recurrent HCC after curative resection who were treated with TACE were recruited for this retrospective study. Modified Response Evaluation Criteria in Solid Tumor (mRECIST) was used for response evaluation. Results: After the first TACE, 266 (69.1%), 75 (19.5%), 18 (5.7%), and 26 (6.7%) showed complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively. Patients with CR achievement after the first TACE had significantly better survival than those with PR/SD and PD (median 83.7 vs. 45.6 and 13.7 months; all P<0.05, log-rank tests). Similarly, patients with CR achievement as the best response during repeated TACE showed significantly better survival than those with PR/SD and PD (median 78.8 vs. 28.2 and 7.8 months; all P<0.05, log-rank tests). On multivariate analysis, CR achievement after the first TACE (hazard ratio [HR]=0.629; 95% confidence interval [CI], 0.454-0.872; P=0.005) or during repeated TACE (HR=0.354; 95% CI, 0.237-0.528; P<0.001) was independently associated with the reduced risk of mortality, whereas multiple tumors, BCLC stage C (vs. A-B), and Child-Pugh class B liver function (vs. A) were associated with the increased risk of poor outcomes (all P<0.05).

Variables	Mul	tivariate analysis	Mul	tivariate analysis
variables	P value	HR (95% CI)	P value	HR (95% CI)
Baseline variables				
AFP, ng/mL	0.283	1.255 (0.829-1.898)	0.203	1.303 (0.867-1.958)
PIVKA-II, mAU/mL	0.382	1.275 (0.740-2.197)	0.126	1.545 (0.885-2.696)
Multiple tumor	0.022	1.465 (1.058-2.029)	0.073	1.349 (0.972-1.873)
Max. tumor size > 3cm	0.244	1.426 (0.784-2.594)	0.566	1.190 (0.657-2.157)
BCLC stage C (vs. 0-B)	0.002	3.007 (1.487-6.082)	0.021	2.328 (1.133-4.780)
Child-Pugh class B (vs. A)	0.035	3.030 (1.081-8.495)	0.029	3.108 (1.123-8.601)
< 2 year between	0.425	1 170 (0 705 1 722)	0.901	0.051 (0.645 1.402)
resection and the first	0.425	1.170 (0.795-1.725)	0.801	0.951 (0.045-1.405)
Complete response after the	0.005	0 620 (0 454 0 972)		
first TACE	0.005	0.029 (0.454-0.872)	-	-
Complete response as the				
best response during	-	-	< 0.001	0.354 (0.237-0.528)
repeated TACE				

TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; BCLC, Barcelona-clinic liver cancer. Figure. Kaplan-Meier curves generated among entire population to compare survival, according to the (Left) initial and the (Right) best response.

\* X-axis means Overall survival (months), and y-axis means cummulative survival propability.



**Conclusions:** CR achievement after the first TACE or during repeated TACE strongly predicted favorable survival outcome in patients with recurrent HCC after curative resection.

**Keywords:** Recurrence, Complete response, Trans-arterial chemoembolization, Hepatocellular carcinoma

#### **PE-105**

#### Treatment and Prognosis of Hepatic Epithelioid Hemangioendothelioma Based on SEER Data Analysis from 1973 to 2014

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**Aims:** Malignant hepatic epithelioid hemangioendothelioma (HEH) is a rare malignant tumor of vascular origin with unknown etiology and a variable natural course. This study evaluated the current management and prognosis of HEH status based on SEER data analysis from 1973 to 2014. In addition, we also evaluated the changes of treatment modalities of HEH over 30 years.

**Methods:** Using SEER database, a total 79 patients with HEH were analyzed from 1973 to 2014. The extent of disease was classified by SEER Stage: local (confined to the liver), regional (either direct tumor extension or confined to regional lymph nodes), or distant (metastatic). Patient survival was calculated using Kaplan-Meier survival curves with log rank test.

**Results:** The mean age of patients with HEH was 53.0 years, and the male to female ratio was 1:2.6. About one third (40.8%) of patients were diagnosed at regional metastatic stage followed by local (30.3%) and distant metastatic stage (28.9%). Median tumor size was 3.85cm (IQR, 2.50–7.93cm). Thirty four (43.0%) of patients received no treatment or the treatment information was missing. Of the 45 treated patients, the most common treatment was chemotherapy (48.9%) followed by resection (22.2%). About 22.2% of patients were treated with more than one method. The 1-year and 5-year survival rates were 88% and 88%, respectively in resection or liver transplan-

tation group; 72% and 49%, respectively in other treatment or observation group. Resection or liver transplantation based treatment was only independent predictive factor for survival (hazard ratio 0.17, 95% confidence interval 0.04-0.75, *P*=0.020)

**Conclusions:** Resection or liver transplantation is worth considering for treatment of patients with HEH.

**Keywords:** Hemangioendothelioma, Epithelioid, Liver Transplantation, Survival rate, Prognosis

#### PE-106

#### Consecutive Increment of Serum AFP Level Is a Useful Surrogate Marker in Predicting HCC in Liver Cirrhosis Patients

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**Aims:** The role of alpha-feto protein (AFP) in the diagnosis of hepatocellular carcinoma (HCC) is getting smaller due to the advances of imaging modalities. However, consecutive increment of AFP level in liver cirrhosis patients is presumed to be associated with the higher risk of developing HCC in clinical settings. Such a notion instigated us to analyze serial AFP levels of HCC patients in a retrospective manner.

**Methods:** From January 2002 to December 2016, 2259 patients were diagnosed with HCC in Seoul St. Mary's hospital. Among them 236 cirrhotic patients were found to have a serial record of AFP measurements for over one year. We assessed AFP levels at the time the diagnosis of HCC was made and compared them with that of patients at 3,6 and 12 months prior to the diagnosis.

**Results:** At the time the diagnosis was made, the patients' baseline characteristics were as follows; mean age was 58.89 years (32-87), median tumor size was 2.1cm (0.7-26.3), median AFP level was 20.35 ng/mL (0.75-32134). Median AFP level of 12 months, 6 months and 3 months before the diagnosis of HCC was 6.26 ng/mL (0.6-513), 8.73 ng/mL (0.66-1287.86), 12.95 ng/mL (0.91-1461), respectively. We divided patients by two groups; one was AFP over 20 ng/mL at the time of diagnosis of HCC, and the other one was not. In elevated AFP group (n=119), median AFP level of 12 months, 6 months and 3 months before the diagnosis of HCC and at the time of the diagnosis of HCC was 12.79 ng/mL (0.81-513), 24.58 ng/ mL (1.25-1287.86), 43.41 ng/mL (2.54-1461), 278.03 ng/mL (11.8-19017), respectively. In non-elevated AFP group (n=115), median AFP level of 12 months, 6 months and 3 months before the diagnosis of HCC and at the time of the diagnosis of HCC was 4.54 ng/mL (0.6-74.78), 4.68 ng/mL (0.66-91), 5.04 ng/mL (0.91-17.9), 4.99 ng/mL (0.75-18.29), respectively. Repeatedmeasure ANOVA was used to analyze the significance of increase in consecutive AFP levels in HCC surveillance. In elevated AFP group, Consecutive increment of AFP level was statistically significant in time dependent manner ( $P \le 0.000$ ) with linear relationship ( $P \le 0.000$ ). There was no significant change of consecutive AFP level In non-elevated AFP group. Consequentially, there was significant difference of AFP level between the two groups in time dependently ( $P \le 0.000$ ).

**Conclusions:** Early detection of HCC with relatively smaller sizes was possible due to the close observation of increase in serial AFP levels. We suggest increase in serial AFP level as a strong surrogate marker in the prediction of HCC and that those with consecutive increments of AFP levels for more than 2 times should be candidates for active surveillances for HCC. **Keywords:** AFP, Liver cirrhosis, HCC

PE-107

#### Autologous Cytokine-Induced Killer Cells for Longer Recurrence Free Survival for Hepatocellular Carcinoma as an Adjuvant Therapy: A Case Series

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**Aims:** Autologous cytokine-induced killer cells were used to reduce recurrence in hepatocellular carcinoma as an adjuvant therapy. Our study aimed to evaluate the efficacy of Autologous cytokine-induced killer Cells after curative therapy in primary hepatocellular carcinoma(HCC) in CNUH cases retrospectively.

**Methods:** The study included HCC patients who visited CNUH after surgery, Radiofrequency ablation(RFA), or Transarterial chemoembolization(TACE) from Jan. 2016 to Mar. 2018. The autologous CIK(created by incubation of patient's peripheral blood mononuclear cells with interleukin 2 and an antibody against CD3) were treated as an adjuvant drug within 2.3 months after curative therapy. Clinical characteristics at baseline and after CIK treatment, and adverse events and recurrence free survival period were collected.

**Results:** Eight of HCC patients were treated with CIK immunotherapy. Patient's median age was 50 (range 45-67) and 6 of 8 patients were HCC stage II according to the AJCC staging system (7<sup>th</sup> ed). Before taking immunotherapy, 6 patients received surgery, one patient received RFA and the other received TACE. All patients received average 10 months of CIK as an adjuvant therapy. The median time of recurrence-free survival (RFS) was 10.0 months. 5 patients experienced tumor recurrence or death by the time of the data cut-off date. 4 patients who experienced tumor recurrence underwent additional RFA or TACE and three of these 4 patients were constantly receiving one to eight CIK treatments after additional therapy. There was one death in the study period, which was due to recurrence of liver cancer. Adverse events were reported for 2 and were mild to moderate grade of diarrhea and vomiting. No patient discontinued treatment due to an adverse event.

**Conclusions:** In this CNUH case series using the autologous CIK cells for HCC patients as an adjuvant therapy, the median time of recurrence-free survival (RFS) was 10.0 months. It also offers a new option that can be used as an ongoing therapy even after the first recurrence.

**Keywords:** Hepatocellular carcinoma, Cytokine-induced killer cells, Recurrence-free survival

### PE-108

# Immediate Results of Surgical Treatment of Metastasis of Colorectal Cancer of the Treatment

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**Aims:** Evaluation of the results of surgical treatment of CRC 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  $37 \pm 85$  yearsold. 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 lwatsukiS.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  $\pm$  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).

**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  $\pm$  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 cancer, Colorectal metastasis, Liver resection

# PE-109

### Feasibility of Surgeon Performed Intraoperative Radiofrequency Ablation for the Treatment of Hepatocellular Carcinoma

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**Aims:** There are multiple modalities of treatment for hepatocellular carcinoma (HCC), including resection, transplantation, transarterial embolization (TAE), and radiofrequency ablation (RFA). RFA is performed either percutaneously or surgically, and many authors have reported on the feasibility of surgical RFA (S RFA). Generally, S RFA is performed by a radiologist, on tumors less than 3cm in diameter. We report our experience of S RFA performed by a single surgeon, with no size limitations.

**Methods:** This study was a retrospective case series. The study period was March 2012 to November 2017. S RFA was performed in patients with a clinical diagnosis of HCC, who were not amenable to resection or transplantation. The indications of S RFA were Child either A or B, ECOG 0 to 2, no vascular or bile duct involvement. There were no limitations regarding number or size.

**Results:** During the study period a total of 58 patients received S RFA. The average age was  $60.7 \pm 9.5$  years. 32 patients (55%) received open RFA, and 26 patients (44%) received laparoscopic RFA. The average size of tumor was  $1.64 \pm 0.63$  cm. There was one case (1.7%) with a major complication. This patient had bile duct injury. The 5 year overall survival rate was 78%, and the 5 year disease free survival rate was 17%.

**Conclusions:** The results of S RFA performed by a surgeon were comparable to those previously reported, with a favorable complication rate and overall survival rate. S RFA is a feasible treatment option that can offer cure for patients not amenable to resection. S RFA can also be a valuable bridging therapy for patients awaiting transplantation.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation

# PE-110

#### Multiple Hepatocellular Carcinoma within the Milan Criteria: When to Consider Surgical Resection?

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**Aims:** Although surgical resection is usually considered for single tumor, several reports suggested that resection can be considered for multiple tumor and may provide better outcome. We analyzed whether resection can provide better long-term outcome for patients with multiple hepatocellular carcinoma

(HCC) within the Milan criteria, and looked for factors that may guide treatment selection.

**Methods:** A total of 314 consecutive patients with multiple HCCs within Milan criteria and had preserved liver function, defined by Child-Pugh class A, who underwent resection (n=49), radiofrequency ablation (RFA) (n=97) or transarterial chemoembolization (TACE) (n=168), as an initial treatment, between January 2009 and December 2013 were analyzed.



Figure 2. Overall survival by **initial** treatment modality



# Figure 3. Overall survival rates based on **ALBI grade** and **PIVKA-II**





Results: The 5-year overall survival rates were 91.3%, 69.1%, and 61.0%, for patients received resection, RFA and TACE. respectively (P=0.003). Patients who received resection were younger and had more preserved liver function assessed by albumin-bilirubin (ALBI) grade, showed different tumor characteristics (more frequently two tumors and had higher PIVKA-II levels) compared to those received RFA or TACE. Resection was rarely performed for those with ALBI grade 2 (n=2). In multivariable analysis, initial treatment modality was independent factor associated with overall survival, along with ALBI grade and PIVKA-II levels. When stratified according to ALBI grade and PIVKA-II levels, long-term outcome was significantly different (5-years survival rates: 90.7%, 72.6% and 45.7% for resection, RFA and TACE, respectively, P=0.004) by initial treatment modality for those with ALBI grade 1 and high PIVKA-II levels (>40 mAU/ml). For other subgroups, there was no significant different of overall survival by initial treatment modalities.

**Conclusions:** Our findings suggest that resection can provide better long-term outcome than RFA or TACE in selected multiple HCC patients within the Milan criteria. ALBI grade and PIVKA-II levels were factors that can be used to guide initial treatment modalities in this situation, which warrants prospective validation.

**Keywords:** Multiple hepatocellular carcinoma, Resection, Radiofrequency ablation, Transarterial chemoembolization, Albumin-bilirubin grade, PIVKA-II

### PE-111

#### Outcome of Sorafenib Treatment in Patients with HBVversus Non-HBV-Related Hepatocellular Carcinoma: A Single-Center Cohort in an HBV-Endemic Area

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Aims: Sorafenib has been the only approved systemic agent for advanced hepatocellular carcinoma (HCC). A recent metaanalysis suggested that sorafenib benefit may depend on viral status and was observed only in hepatitis B virus (HBV)-negative and hepatitis C virus (HCV)-positive patients. The aim of this study is to investigate sorafenib response between HBV and non-HBV patients with HCC in real-world practice.

Methods: From June 2007 to March 2018, 703 patients with unresectable HCC who had been treated with sorafenib for more than 4 weeks in the National Cancer Center, Korea were enrolled. Patient demographics and overall survival (OS) were compared between HBV-related HCC and non-HBV-related HCC.

Results: Among 703 patients, 518 (73.7%) were HBV-related and 185 (26.3%) were non-HBV-related (HCV, 8.0%; alcoholic, 8.4%; others, 9.9%). The HBV-related group was younger (median age, 54.5 vs. 66; P=0.210). The majority of both group had good liver function (Child-Pugh class A, 92.3% vs. 94.6%; P=0.293) and performance status (ECOG score of 0, 64.0% vs.65.8%; P=0.667). In HBV-related group, 33.6% and 48.3% were modified UICC stage IVa and IVb, respectively, while 33.5% and 43.8% of non-HBV-related group were modified UICC stage IVa and IVb, respectively. The median duration of sorafenib treatment was 2.9 months in HBV-related group (range, 0.9 - 73.0 months) and 3.7 months in non-HBV-related group (range, 0.9 - 72.8 months). The median OS of HBV-related and non-HBV-related group was 8.7 months (95% confidence interval [CI], 7.7 - 9.6) and 11.0 months (95% CI,9.3 -12.6); however, it was not statistically significant (P=0.292). Multivariable analysis indicated that prior history of anti-tumor therapy, Child-Pugh class B, presence of portal vein invasion, and alpha-fetoprotein level  $\geq$  100ng/ml were independent predictors for OS in patients treated with sorafenib; however, etiology of HCC failed to show the impact on OS.

Conclusions: In comparison to non-HBV status, the HBV infection status did not affect the outcomes of sorafenib treatment in patients with advanced HCC in an HBV endemic area.

Keywords: Hepatocellular Carcinoma, Sorafenib, HBV

# PE-112

#### Control of Intracranial Disease Is Associated with Improved Survival for Patients with Brain Metastases from Hepatocellular Carcinoma

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Aims: We performed a retrospective study to identify prognostic factors and determine outcomes for patients with brain metastases from hepatocellular carcinoma (HCC).

Methods: A total of 72 patients with brain metastases from HCC were identified from two institutions; 26 of 72 patients received tumor-removing surgery or stereotactic radiosurgery with or without whole-brain radiotherapy (WBRT), 23 of 72 received WBRT only, and 23 of 72 received conservative treatment. Estimates for overall survival (OS) after brain metastases were determined and clinical prognostic factors were identified by Cox proportional hazards modeling.

Results: Median OS after development of brain metastases was 48 days (one day to 536 days). The median age at the time patients were diagnosed with brain metastasis was 54 years. Fiftyone patients (71%) were male, and 62 patients (86%) were infected with hepatitis B virus. Median time from diagnosis of HCC to brain metastasis was 17.2 months, and 4 patients had brain metastases at the time diagnosis. Intracranial hemorrhage was frequently associated (42%) with brain metastasis. The most common presenting symptoms were motor weakness, mental change, and headache. Sixty-three patients (88%) had lung metastases, 25 patients (35%) had bone metastases, 18 patients (25%) had metastatic lymphadenopathy, and 7 (10%) patients had peritoneal seeding when diagnosed with brain involvement, and there was only one patient without metastasis to other organs. Univariate analyses showed that treatment with curative intent (surgery or SRS) and serum AFP levels were associated with improved survival (P<0.001, and 0.045, respectively), whereas a single brain metastasis, size of metastatic tumor, or intracranial hemorrhage were not. We further divided patients with three groups by the treatment modality; surgery or radiosurgery (group1), WBRT (group 2), or conservative treatment (group 3). Group 1 showed best survival, followed by group 2 and group 3, sequentially (P<0.001). Subgroup analysis with patients with single brain metastasis showed similar results. Multivariate analysis showed that treatment modality was the only factor that is associated with improved OS (P=0.001)



Overall Survival (days)

**Conclusions:** When patients with lung metastases from HCC present neurologic symptoms, brain imaging is required to confirm intracranial metastases. Although the overall prognosis of patients with brain metastases from HCC is extremely poor, patients actively treated with surgery or radiosurgery have prolonged survival, suggesting that interventions to control intracranial disease are important treatment modalities.

Keywords: Hepatocellular carcinoma

#### PE-113

#### Hepatocellular Carcinoma with Extrahepatic Metastasis: Who Are Still Candidates for Locoregional Therapy?

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**Aims:** Nowadays, sorafenib is available for hepatocellular carcinoma (HCC) patients with extrahepatic metastasis (EHM). We aimed to find out whether locoregional treatment is still valid for patients with EHM, and if so, which subgroup may benefit from locoregional treatment.

**Methods:** A total of 187 consecutive HCC patients (median: 55 years, male: 86.1%, hepatitis B virus: 81.2%, Child-Pugh Class A: 82.9%) with EHM between 2010 and 2014 were analyzed. We categorized patients according to initial treatment modality: sorafenib or locoregional treatment. Overall survival was compared between two groups.

**Results:** During a median follow-up of 6.6 months (range: 0.2-94.6 months), mortality was 90.4% (169/187). Type of EHM was nodal metastasis in 114 patients (61.0%) and distant metastasis with/without nodal metastasis in 73 patients (39.0%). Tumor morphology was nodular in 156 patients (83.4%) and diffuse in 31 patients (16.6%). Initial treatment modality was locoregional for 118 patients (63.1%), of which 116 patients underwent transarterial chemoembolization, and was systemic for 69 patients (36.9%). Median survival was better for patients who received locoregional treatment than systemic treatment (8.9 months vs. 4.6 months, P<0.001). However, once the different baseline characteristics of the two groups were adjusted, treatment modality was no longer a risk factor for overall survival (hazard ratio: 1.09, 95% confidence interval: 0.75-1.57, P=0.63).

When stratified, there was no difference in survival according to treatment modality for patients with distant metastasis or diffuse tumor (6.6 vs. 3.9 months for locoregional vs. systemic, P=0.63). However, for nodular tumor with nodal metastasis, the survival was better in locoregional treatment group than systemic treatment group (11.7 vs. 5.2 months, P=0.027).

**Conclusions:** Locoregional treatment offered survival benefit for HCC patients with EHM compared to systemic treatment when tumor showed nodular morphology without distant metastasis. Our data indicate that nodal or distant metastasis should be differentiated, which may have therapeutic implication on initial treatment.

**Keywords:** Hepatocellular carcinoma, Extrahepatic metastasis, Locoregional treatment, Systemic treatment, Sorafenib

#### PE-114

#### Effectiveness of Antiviral Therapy in Hepatitis B Virusrelated Hepatocellular Carcinoma Initially Treated with Transarterial Chemoembolization: a Multicenter Retrospective Study

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**Aims:** It remains uncertain whether antiviral treatment improve surivival in hepatitis B virus (HBV)-hepatocellular carcinoma (HCC) patients receiving palliative therapy. The purpose of this study is to evaluate the role of antiviral therapy in HBV-HCC patients after diagnosis of HCC.

**Methods:** This retrospective study analyzed 113 HBV-HCC patients who underwent transarterial chemoembolization (TACE) in two university hospital. Overall survival (OS) was compared in patients treated with/without antiviral treatment after diagnosis of HCC. Subgroup analysis and Cox regression analysis were performed to determine the efficiency of antiviral treatment and prognostic factors for OS.

**Results:** OS was not different between the patients treated with antiviral treatment (n = 67) and the patients who received no antiviral treatment (n = 46) (P=0.103). Barcelona Clinic Liver Cancer (BCLC) was independent prognostic factors for OS of HBV-related HCC patients who were treated with TACE. By subgroup analysis, antiviral therapy achieved better survival improvement in BCLC stage B and C (P<0.001) but had no survival improvement in BCLC stage 0 and A (P=0.605). Antiviral therapy was one of the independent prognostic factors for patients with BCLC stage B and C (HR 0.230, 95% CI 0.094-0.565, P=0.001).

#### Table 1. Baseline characteristics

Variable	Antiviral Treatment (n=67)	No treatment (n=46)	Total (n=113)	P-value
Sex				0.707
Male	55 12	39 7	94 19	
Female				
Mean age (mean ± SD)	60.36±8.95	59.76±9.82	60.12±9.278	0.738
Number of tumor				0.348
1 2	22 20	22 9	44 29	
3 >4	11 14	5 10	16 24	
Size of largest tumor (mean ± SD)	4.43±3.48	4.30±3.69	4.38±3.55	0.853
Child-pugh score (mean ± SD)	5.63±0.99	5.67±0.94	5.65±0.97	0.082
MELD score	9.61±6.45	9.40±3.73	9.52±5.49	0.845
HBeAg				0.500
Positive Negative	5 62	2 44	7 106	
Liver cirrhosis				0.054
Yes	48	40	88	
No	19	6	25	
mUICC stage				0.032
1	5	10	15	
2	24	13	37	
4	5	8	48	
BCIC stage	0	Ū	10	0.082
0	6	11	17	0.002
A	28	18	46	
В	27	11	38	
С	6	6	12	
HBV DNA (IU/mL)	3726±5786	1344±2897	2756±4948	0.011
ECOG performance status				0.425
0	51	34	85	
1	14	12	26	
2	2	0	2	

MELD, Model For End-Stage Liver Disease; mUICC, modified Union for International Cancer Control ; BCLC, Barcelona clinic liver cancer; ECOG, Eastern Cooperative Oncology Group

Veriable	Un	ivariate analy	sis	Mu	ultivariate ana	aylsis
variable	HR	95% CI	P value	HR	95%CI	P value
Antiviral therapy						
No	1.000					
Yes	0.593	0.313-1.124	0.109			
Age	0.945	0.919-0.990	0.012	0.956	0.921-0.992	0.017
Sex, male	1.127	0.496-2.561	0.776			
HBeAg Negative Positive	1.000 0.699	0.415-1.178	0.179			
Child-pugh class A B	1.000 1.342	0.613-2.934	0.462			
MELD score	0.994	0.942-1.048	0.813			
Number of tumor 1	1.000		0.005			
2	1.223	0.503-2.974	0.657			
≥3	3.372	1.535-7.410	0.002			
Size of largest tumor	1.183	1.095-1.279	<0.001			

	<b>C</b> 1					
≥2000 IU/mL	1.318	0.680-2.554	0.413			
<2000 IU/ml	1.000					
Baseline HBV DNA						
B and C	2.873	1.482-5.573	0.002	2.773	1.431-5.376	0.003
0 and A	1.000			1.000		
BCLC stage						

HR, hazard ratio; CI, confidence interval; MELD, Model For End-Stage Liver Disease; BCLC, Barcelona clinic liver cancer

#### Table 3. Prognostic factors for overall survival in BCLC B and C

Variable	U	nivariate analy	sis	Mu	ultivariate ana	ylsis
	HR	95% CI	P value	HR	95%CI	P value
Nucleotide analogue						
No	1.000					
Yes	0.236	0.098-0.568	0.001	0.230	0.094-0.565	0.001
Age	0.955	0.910-1.003	0.068			
Sex, male	1.568	0.528-4.652	0.418			
HBeAg Negative Positive	1.000 2.689	0.650-12.661	0.164			
Child-pugh class						
A	1.000					
В	1.342	0.613-2.934	0.462			
MELD score	0.931	0.803-1.079	0.341			
Number of tumor			0.248			
1	1.000					
2	0.510	0.113-2.303	0.381			
≥3	1.321	0.367-4.571	0.670			
Size of largest tumor	1.135	1.024-1.257	0.016	1.148	1.026-1.285	0.016
Baseline HBV DNA						
<2000 IU/ml	1.000					
≥2000 IU/mL	1.381	0.558-3.419	0.486			

HR, hazard ratio; CI, confidence interval; MELD, Model For End-Stage Liver Disease; BCLC, Barcelona clinic liver cancer



#### *P*=0.103

Fig. 1 Overall survival for patients with and without antiviral therapy











**Figure 2.** Overall survival of antiviral therapy and non-antiviral therapy in subgroup analysis stratified by BCLC stage

**Conclusions:** Antiviral therapy did not improve survival of HBV-related HCC patients treated with TACE. However, antiviral therapy shows survival benefit only in BCLC stage B and C disease.

**Keywords:** Hepatocellular carcinoma, Antiviral therapy, Transarterial chemoembolization, Survival

# PE-115

#### Sorafenib Therapy for Hepatocellular Carcinoma in Real Practice: Treatment Outcome and Prognosis

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<sup>1</sup>Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, Korea; <sup>2</sup>Center for Liver Cancer, National Cancer Center, Goyang, Korea **Aims:** Sorafenib is recommended as the treatment of choice for advanced hepatocellular carcinoma (HCC) in most global guidelines, including those of Korea, according to phase III Western and Asian studies. Although outcomes of several phase III clinical trials or phase IV studies have been reported, real practicebased, single institution, and large-scale studies are rare. This study investigated the outcomes and prognosis of sorafenib treatment in patients with HCC who received sorafenib for at least four weeks, in real practice, at a single institution.

**Methods:** From June 2007 to December 2017, 704 patients with HCC were treated with sorafenib for at least four weeks. Eight subgroups within larger cohorts were retrospectively analyzed according to tumor stage, underlying liver function, serum alpha-fetoprotein (AFP) levels, portal vein tumor thrombosis status, prior therapy, hand-foot syndrome (HFS) development after sorafenib, post-sorafenib therapy, and extra-hepatic metastasis (EHM) status such as metastasis in lymph nodes or distant organs. Overall survival (OS) was assessed for subgroups within each category using a log-rank test.

Results: In the total patient population (n=704) treated with sorafenib, the median OS was 8.9 months and median duration of sorafenib treatment was 3.0 months. According to the modified Union for International Cancer Control (mUICC) staging system, the median OS was 17.3, 10.6, 7.7, and 9.2 months in patients with Child-Turcotte-Pugh (CTP) class A who had mUICC stage II (n=39), III (n=117), IV A (n=225), and IV B (n=271) tumors, respectively. Median OS was 6.4, 3.5, 3.7, and 5.7 months in patients with CTP class B who had mUICC stage II (n=4), III (n=11), IV A (n=19), and IV B (n=18) tumors, respectively. In subgroup analyses according to serum AFP levels (≥200 vs. <200 ng/mL), patients with low serum AFP levels (<200 ng/mL) showed a significantly longer OS of 11.7 months than the duration of 6.0 months that was observed for those with high serum AFP levels ( $\geq$ 200 ng/mL) (P<0.001). Regarding portal vein invasion (PVI) status, patients without PVI showed a significantly longer OS duration of 11.1 months, compared to the 7.2 months observed for those with PVI (P<0.001). When extent of PVI was divided into none, type I-segmental/ sectoral branches, type II-left and/or right portal vein, and type III-main portal vein trunk, the median OS in patients with type I, II, and III disease was 9.7, 6.4, and 5.4 months, respectively (all P<0.05). Patients who had prior therapy before sorafenib showed a significantly longer OS of 9.2 months than the OS of 5.8 months that was observed for those without prior therapy before sorafenib (P<0.001). Patients with HFS after the start of sorafenib showed a significantly longer OS of 11.7 months than the OS of 5.5 months that was observed for those without HFS (P<0.001). The median OS for patients who had post-sorafenib therapy was 12.6 months, which was significantly longer than the 5.8 months observed for patients who did not have postsorafenib therapy (P<0.001). Patients with any mUICC T stage with extra-hepatic metastasis showed a similar OS of 8.3 months, compared to the 7.7 months observed for those with mUICC T4 stage without extra-hepatic metastasis (P=0.65).

**Conclusions:** In real practice, survival outcomes after sorafenib treatment were similar to or shorter than that of recent phase III clinical trials. This study may help determine the proper counseling for patients with HCC in actual clinical practice by suggesting patient characteristics that may show better response to sorafenib.

Keywords: Hepatocellualr carcinoma, Sorafenib

# PE-116

Validation of Risk Prediction Model of HCC Development for Indeterminate Nodules (LIRADS 2 and 3) in Patients with Chronic Hepatitis B

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**Aims:** A risk model for indeterminate nodules on computed tomography (CT) (Rad<sub>CT</sub> score) in chronic hepatitis B (CHB)-related cirrhotic patients was proposed. We validated this model for indeterminate nodules on magnetic resonance imaging (MRI) (LIRADS 2/3).

**Methods:** Between 2014 and 2016, LIRADS 2/3 nodules were detected in 78 CHB patients.  $Rad_{CT}$  score including arterial enhancement on CT was calculated.

Results: The median age of the study population (59 men and 19 women) was 57 years. Previous HCC history and liver cirrhosis was found in 33 (42.3%) and 31 (39.7%), respectively. The median Rad<sub>ct</sub> score was 108, 4. Patients who developed HCC (n=35, 44.9%) showed significantly higher Rad<sub>ct</sub> score than those (median 120 vs. 98; P=0.003), whereas CU-HCC an REACH-B score was statistically similar (all P>0.05). Arterial enhancement, T2 hyperintensity, and diffusion restriction on MRI was not significant even in univariate analysis. On multivariate analysis, previous HCC history was the only independent predictor of HCC development (hazard ratio [HR]=3.193; P<0.05). In addition, only unadjusted HR of Rad<sub>ct</sub> score was statistically significant (1.021; P=0.001), whereas those of CU-HCC and REACH-B score were not (P>0.05). When the study population was stratified intro three risk groups based on Rad<sub>ct</sub> score (<60, 60-105, >105), the cumulative HCC incidence was not significantly different among groups (all P>0.05 by log-rank tests).

**Conclusions:** Rad<sub>CT</sub> score was not validated for LIRADS 2/3 nodules and previous HCC history was the only predictor of CHBrelated HCC development. New risk models optimized for MRIdefined indeterminate nodules are required.

**Keywords:** LIRADS, Indeterminate nodule, Hepatitis B, Hepatocellular carcinoma

# PE-117

Multi-Disciplinary Approach including Hepatic Arterial Infusion Chemotherapy and Conventional Systemic Chemotherapy for Inoperable Metastatic Hepatocellular Carcinoma

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**Aims:** Introduction: The only proved treatment for inoperable metastatic hepatocellular carcinoma (HCC) is targeted therapy such as sorafenib. We experienced a case of sorafenib-refractory, recurrent metastatic HCC, surviving more than 4 years after curative hepatectomy by multi-disciplinary therapies including lung wedge resection, hepatic arterial infusion chemotherapy and conventional systemic chemotherapy.



2016.6.1

2017.1.18

Methods: Case: A 50-year-old male patient was diagnosed with 8cm sized HCC on the right lobe of the liver on Jan 14, 2014. He received right hepatectomy. HCC recurred on the left lobe of the liver with the size of 2.5cm. and three lung metastasis with the sizes of 2cm, 1cm and 4mm on 31 Oct, 2015. He received wedge resection of the liver, and metastasectomy for lung metastasis. After then, he took sorafenib. However, infiltrative HCC developed on May 5, 2016. He received 6 cycles of hepatic arterial infusion chemotherapy (HAIC) using 5-FU and cisplatin. The HCC disappeared completely on CT and angiography. Complete remission state maintained until Sep 26, 2017. However, multiple lung and peritoneal metastasis were found on Dec 26. 2017. He has been receiving conventional chemotherapy using 5-FU plus cisplatin. The tumor size and number decreased much after 2 cycles of chemotherapy (partial response).

**Conclusions:** The infiltrative HCC of the patient showed complete remission by HAIC. Also, extrahepatic metastasis of lung

and peritoneum showed good response by conventional systemic chemotherapy using 5-FU plus cisplatin.



**Keywords:** Hepatocellular carcinoma, Multi-disciplinary, Chemotherapy

#### PE-118

#### Second Line Treatment for Recurrent Hepatocellular Carcinoma after Curative Treatment: Single Center Experience

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**Aims:** We investigated the recurrence of hepatocellular carcinoma (HCC) after curative treatment and the efficacy of second line treatment.

**Methods:** This study included 230 patients who had been diagnosed with HCC and had curative treatment such as radiof-requency ablation (RFA), resection or liver transplantation. Data on recurrence, survival, and second line treatment after curative treatment were collected and analyzed. Recurrence rates were compared with the chi-square test, and cumulative survival rates were compared with log-rank and Kaplan-Meier test. P-values <0.05 were considered statistically significant.

**Results:** Average follow up duration was 46.37 months (1-180 months). The total recurrence rate after curative treatment for HCC was 41.3%. The recurrence rates after surgery including liver transplantation and RFA were 43.4% and 38.6%, respectively. There was no significant difference in recurrence rate after surgery and RFA (*P*=0.463). However, the cumulative survival rate after surgery including liver transplantation was

significantly higher than that after RFA (P=0.032). Transarterial chemoembolization (TACE) was performed in 50 of 95 patients (52.6%), as second line treatment. Other patients received local treatment (RFA or CyberKnife) (17.9%), sorafenib (14.7%), or other treatments (14.8%) as second line treatment. Surgery was performed in 1 patient with recurrent HCC after RFA. The 5-year survival rate in patients with recurrent HCC was 64.1%. The survival rate was not significantly different between patient treated with TACE and non-TACE as second line treatment (P=0.760) (Figure 1).

**Conclusions:** Although recurrence rates after surgery and RFA were not significantly different, the cumulative survival rate was significantly different between the two groups. TACE was the most common second line treatment, but the cumulative survival rate was not significantly different between patients treated with TACE and non-TACE.



**Keywords:** Hepatocellular carcinoma, Curative treatment, Recurrence, Second line treatment, Survival

# PE-119

#### Sorafenib Treatment for Advanced Hepatocellular Carcinoma: The First-Line versus Second-Line Treatment Following Transarterial Chemoembolization

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**Aims:** A number of Asian-Pacific centers perform transarterial chemoembolization (TACE) as the first treatment for advanced hepatocellular carcinoma (HCC), although sorafenib is the standard first-line treatment. In this study, we aimed to compare the overall survival (OS) according to initial treatment (TACE vs sorafenib) among patients experiencing sorafenib treatment in advanced HCC.

**Methods:** We included 200 consecutive patients treated with sorafenib for >4 weeks with or without TACE for advanced HCC at a single tertiary hospital in Korea. The primary endpoint was OS and secondary endpoints included time to progression (TTP) and objective response rate (ORR) and disease control rate (DCR). The risk was compared between groups using a Cox proportional hazards model and inverse probability weighting (IPW) analysis.

Results: Eighty-seven patients were initially treated with sorafenib (the sorafenib-first group: 54 treated with sorafenib only and 33 treated with sorafenib followed by TACE) and 113 patients were treated with TACE followed by sorafenib therapy (the TACE-first group). Twenty-eight patients (14%) were Child-Turcotte-Pugh class B and there was no significant difference in baseline characteristics between two groups except sorafenib-first group had more ascites (17.2% vs 7.1%, P=0.04) and prolonged prothrombin time (1.2±0.1 vs 1.1±0.1, P=0.02). The TACE-first group showed significantly longer OS than the sorafenib-first group (hazard ratio [HR]=0.62, 95% confidence interval [CI]=0.45-0.85, log-rank P=0.004). Median OS was 11.6 months in the TACE-first group and 6.9 months in the sorafenib-first group. The TACE-first group had significantly longer OS in multivariable analysis (adjusted HR=0.58; 95% CI=0.41-0.80, P=0.001 and IPW analysis (HR=0.63, 95% CI=0.44–0.91, P=0.01). There was no significant difference in TTP between two groups (HR=0.89, 95% CI=0.62-1.28, P=0.53). ORR was 6.9% in the sorafenib-first group and 10.6% in the TACE-first group (P=0.27 by chi-square test). DCR was 56.3% in the sorafenib-first group and 73.5% in the TACE-first group (P=0.01 by chi-square test).









	Sorafenib-first group (n=87)	TACE-first group (n=113)	P-value
PD, n (%)	38(65.5%)	3080.5%)	
SD, n (%)	43(27.6%)	70(12.4%)	
PR, n (%)	4(4.6%)	11(9.7%)	
CR, n (%)	2(2.3%)	2(0.9%)	
			0.06
Disease control rate, n (%)*	49(56.6%)	83(73.5%)	0.01
Objective response rate, n (%)†	6(6.9%)	13(11.5%)	0.27

Table 1: Best overall response between treatment groups

Abbreviation: PD=Progressive disease; SD=stable disease; RR=partial response; CR=complete response \* Disease control rate = CR + PR + SD. †Objective response rate = CR + PR

**Conclusions:** For patients with advanced HCC, second-line sorafenib treatment following TACE has significantly longer OS than first-line sorafenib treatment. An initial aggressive intrahepatic tumor control with loco-regional therapies followed by sorafenib treatment may be a potent strategy for advanced HCC.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Sorafenib, First-line

#### **PE-120**

#### Risk Factor of the Recurrence for Hepatocellular Carcinoma after Intra-Operative Radiofrequency Ablation

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**Aims:** Despite the highly complete tumor necrosis rate of radiofrequency ablation (RFA), tumor recurrence, either locoregional or newly developing lesion, was regarded as significant issue. Recurrence reduction through appropriate procedure selection as well as patients' selection could improve survival of patients. Therefore, we analyzed the conditional factor for recurrence after intra–operative RFA treatment on hepatocellular carcinoma (HCC).

**Methods:** We investigated 98 patients who were treated with intra-operative RFA as initial treatment for HCC. The mean follow-up period was  $33 \pm 14.5$  months. We evaluated the disease-free survival of recurred patients, including local tumor progression (LTP) and intrahepatic distant recurrence (IDR). For these patients, multiple factors were assessed to their significance for recurrence and survival.

**Results:** Almost baseline characteristics were not shown statistically significant difference, except for few factors between the groups. The incidence of overall recurrence was 47.9 %. LTP was found in 20 of 47 patients (20.4%) and occurred 4 - 33 months [median period: 14 months] after RFA. IDR was found in 27 of 47 patients (27.5%) and occurred 6 - 88 months [median period: 22 months] after RFA. Interestingly, on multivariate analysis for whole recurred patients, serum  $\alpha$ -fetoprotein (AFP)

was significantly associated factor with recurrence of the tumor [P=0.006, 95% C.I.: 1.001-1.007, HR=1.004]. In addition, INR and Child-Pugh scores, factors representing severity of underlying liver disease status, were significantly associated with survival of the patients (P=0.039 and P=0.046). Especially, AFP was also significantly associated factor with patients' survival. [P=0.016, 95% C.I.: 1.001-1.006, HR=1.004]. After subgroup analysis for recurred patients, we found that patients with higher AFP levels had more recurrence patterns of LTP rather than IDR.

**Conclusions:** Patients with high AFP level received intraoperative RFA for HCC should be carefully followed-up and considered more active radical treatment modality because of higher risk of recurrence and mortality.

**Keywords:** Recurrence, Intra-operative radiofrequency ablation, Alpha-fetoprotein, Local tumor progression, Survival

#### PE-121

#### Reduction of Intrahepatic Tumor Burden by Hepatic Arterial Infusion Chemotherapy Prolongs Survival in Advanced Hepatocellular Carcinoma

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**Aims:** There are limited studies on the impact of intrahepatic tumor control on patient survival in advanced hepatocellular carcinoma (HCC). The purpose of this study is to confirm survival benefits of reduced intrahepatic tumor burden by hepatic arterial infusion chemotherapy (HAIC) in advanced HCC patients. **Methods:** Between January 2012 and December 2017, a total of 138 consecutive patients with advanced HCC treated with HAIC were enrolled. Thirty-six patients (26.1%) had extrahepatic metastasis when HAIC was started. Survival outcomes and tumor response rate (both intrahepatic and extrahepatic) after HAIC were analyzed. Multivariate analysis was performed to estimate clinical factors associated with survival outcomes.

**Results:** Most of the patients (86.2%) included in the study were on Barcelona Clinic Liver Cancer stage C. The presence of extrahepatic metastasis at the start of HAIC had no significant effect on overall survival (*P*=0.17). The intrahepatic objective response rate (ORR) (complete response + partial response) of all the enrolled patients to HAIC was 17.4%. The intrahepatic OR was 13.8% for patients with extrahepatic metastasis, and 18.6% for patients without extrahepatic metastasis. Patients with intrahepatic OR by HAIC showed significantly better survival outcomes than those without OR did, irrespective of the initial distant metastases. On multivariate analysis, the achievement of intrahepatic OR by HAIC and Child-Pugh classification at the time of first response evaluation were two independent

factors affecting better overall survivals.



**Conclusions:** HAIC-induced intrahepatic tumor reduction prolongs patient survival irrespective of the status of distant metastasis. Our study demonstrates that it is critical to reduce intrahepatic tumor burden in advanced HCC even when patients have initial extrahepatic metastasis.

**Keywords:** Hepatocellular carcinoma, Hepatic arterial infusion chemotherapy, Objective response, Metastasis

#### PE-122

Association of Diabetes Mellitus with Hepatocellular Carcinoma in Patients of Chronic Liver Disease of Non-viral Etiology: A Case-control Study from North India

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**Aims:** Hepatitis B, hepatitis C, alcohol, and non-alcoholic steatohepatitis are important etiological factors for hepatocellular carcinoma (HCC). Role of diabetes mellitus (DM) as a contributory factor for HCC in patients with viral etiology has been adequately demonstrated, however its role in HCC due to alcohol and NASH remains controversial. This case-control study aimed to investigate the association of DM with HCC in patients with alcoholic liver disease and cryptogenic (including NASH-related) liver disease.

**Methods:** We conducted this case-control study at Sir Ganga Ram Hospital, Delhi, India. Consecutive patients of HCC due to alcohol or cryptogenic etiologies presenting between 2011 and 2017 were included in the study as cases. Age and sex matched patients of chronic liver disease of same etiologies, presenting during the same period, were chosen as controls. Cases and controls were in the ratio of 1:2. Patients of any other etiologies were excluded. Prevalence of DM among cases and controls were compared.

**Results:** A total of 138 patients of HCC (mean age 61±9 years, 95% males) were included in the study. The etiologies of HCC were cryptogenic (including NASH) 54%, and alcohol 46%. DM was present in 48% of patients. A total of 276 controls (mean age 61±7 years, 92% males; *P*=NS compared to cases) were included in the study. Among patients of HCC due to cryptogenic / NASH etiology, the prevalence of DM was significantly higher than in controls (*P*=0.012; OR 2.3, 95% CI 1.2, 4.3). Among

patients of HCC due to alcohol etiology the prevalence of DM was similar to that of controls (*P*=NS).

Cryptogenic / NASH	etiolog	y					
		HCC (n=75)		Controls (n=86)	P value	Odds ratio	95% C.I.
Diabetes present	45	(60%)	34	(40%)	0.012	2.3	1.2, 4.3
Diabetes absent	30	(40%)	52	(60%)			
	1	(1070)	52	(0070)			
Alcohol etiology		(1070)	52	(00%)			
Alcohol etiology		HCC (n=63)	52	Controls (n=190)	P value	Odds ratio	95% C.I.
Alcohol etiology Diabetes present	21	HCC (n=63) (33%)	45	Controls (n=190) (24%)	P value	Odds ratio	95% C.I.

**Conclusions:** DM is strongly associated with the increased risk of HCC in patients of cryptogenic / NASH etiology. Therefore, these patients represent a high HCC risk population and should be considered for closer HCC surveillance program. DM does not seem to increase the risk of HCC in patients of chronic liver disease due to alcohol etiology.

Keywords: HCC, Diabetes

### PE-123

#### Prediction of Hepatocelluar Carcinoma Using Decision Tree Classification in Treatment Naïve Patients for Chronic Hepatitis B

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**Aims:** This study aimed to develop prediction model for the development of hepatocellular carcinoma (HCC) in treatmentnaïve patients receiving entecavir or tenofovir for chronic hepatitis B (CHB).

**Methods:** We enrolled 3184 patients treated with chronic hepatitis B. We analyzed 1350 patients who were treated with entecavir or tenofovir as initial treatment, those with initial clinical records, and those without cancer within one year after treatment. HCC prediction decision tree was constructed through logistic regression using 90 variables including demographic, laboratory data, and cirrhosis. We also analysis with support vector machine (SVM) analysis and random forest analysis.

**Results:** Eighty-four patients were diagnosed with hepatocellular carcinoma. Age (OR=12.3, P=0.001), family history of HBV (OR=7.2, P=0.006), cirrhosis (OR=35.1, P=0.001), diuretics use (OR=4.1, P=0.04), WBC count (OR=4.1, P=0.04), hemoglobin (OR=4.6, P=0.03), admission history (OR=6.2, P=0.01), and ascites (OR=10.7, P=0.001) were the significant predictors of hepatocellular carcinoma development. Cirrhosis, family history of HBV, serum albumin, serum alkaline phosphatase, smoking history, platelet count, and WBC count were selected to set up a decision tree as the prediction model. Decision tree algorithm showed high HCC prediction [96% (95% CI, 93.0-98.0)]. Decision tree algorithm show better area under the curve (AUC) than other analysis.

**Conclusions:** Proposed decision tree algorithm produces high accuracy for prediction of hepatocellular carcinoma in chronic hepatitis B patients.

**Keywords:** Hepatocelluar carcinoma, Chronic hepatitis B, Decision tree

# PE-124

# Is Surgical Resection Justified for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus? (A Systematic Review and Meta-Analysis)

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**Aims:** The prognosis of hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) is very poor. According to the BCLC treatment recommendations, sorafenib or other palliative treatment (PT) is recommended as the first-line therapy when it happens. In real world, however, a significant number of selected patients with HCC and PVTT suffered from surgical resection (SR).

**Methods:** PubMed, Embase, Medline and Cochrane library were searched for studies comparing SR with PT (including TACE, sorafenib, etc.) for HCC with PVTT, which were published before September 2017.

**Results:** 4,810 patients from 7 studies were enrolled in this meta-analysis, which divided into the SR group (n = 2,344) and the PT group (n = 2476). When compared with the PT group, the pooled hazard ratio (HR) for the 1, 3 and 5-year OS rates of the SR group were 0.56 (95% CI 0.52–0.60, *P*=0.03), 0.56 (95% CI 0.53–0.59, *P*<0.001) and 0.55 (95% CI 0.54–0.57, *P*<0.001). For subgroup analysis, when compared with the mere TACE group, the pooled HR for the 1, 3 and 5-year OS

rates of the SR group were 0.54 (95% CI 0.43–0.67, *P*=0.81), 0.75 (95% CI 0.65–0.87, *P*=0.25) and 0.76 (95% CI 0.67–0.88, *P*=0.25).

**Conclusions:** This meta-analysis demonstrated SR had better OS than TACE or other palliative therapy for HCC with PVTT. SR may be suitable as the first-line treatment for selected patients with resectable HCC and removable PVTT.

### PE-125

# Treatment of Intermediate Stage HCC Patient: Impact of Deviation from BCLC Treatment Guidelines

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**Aims:** The intermediate stage hepatocellular carcinoma (HCC) comprises a highly heterogenous patient population. Despite the recommendation of transarterial chemoembolization (TACE) as first-line treatment, adherence to the recommended treatment option is low. Four substages (B1-B4) of intermediate HCC based on up-to-seven and Child Pugh Score was proposed by Bolondi et al. and different treatments modalities are recommended according to the stages. We aimed to compare the prognosis of patients who adhere to BCLC guideline impact of substagings in the management of intermediate HCCs.

**Methods:** A retrospective chart review was conducted for 136 patients newly diagnosed with HCC BCLC stage B from year 2004 to 2016. Patients were categorized into three groups: adherent, over-treated and under-treated group based on BCLC guideline and Bolondi substage treatment recommendation. Survival analysis was performed using cox regression to determine the effects of overtreatment in intermediate HCC patients.

Results: Among 136 patients, 84.1% were male patient with mean age of 60 years and overall survival was 35 months. Out of 136 patients, 86 patients (63%) adhere to TACE while 44 patients were over-treated (liver transplantation, resection, radioembolization and radiotherapy in addition to TACE) and 6 patients were undertreated (best supportive care) according to BCLC guideline. No patient had systemic therapy as initial treatment. When patients who adhere to TACE were compared to those who were over-treated according BCLC guideline, a higher proportion of patients with greater number of tumors, increased MELD score ( $\geq$ 10), and prolonged INR with lower platelet count were observed in TACE treatment group (all, P<0.05). Factors significantly associated with prolonged survival using multivariate analysis revealed that bolondi substages, over-treatment according to BCLC guideline, baseline AFP level and serum sodium level predictors of survival. Subgroup analysis with those who were treated with TACE only following BCLC guideline revealed that adherence to Bolondi treatment strategy improved survival compared to those who did not adhere to Bolondi treatment (P<0.001).

Conclusions: BCLC practice guideline alone is not practiced

in real life management of intermediate HCC patients. Our result indicate that overtreatment according to BCLC stage has impact in the prolongation of patient survival and treatment according to Bolondi's substage could improve survival.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, BCLC, Survival

#### PE-126

Transarterial Infusion of Epirubicin and Cisplatin Combined with Systemic Infusion of 5-Flurouracil versus Sorafenib for Hepatocellular Carcinoma with Failure of Transarterial Chemoembolization Using Doxorubicin

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Aims: Transarterial chemoembolization using doxorubicin (TAC-DOX) has been recognized as effective therapy for advanced hepatocellular carcinoma (HCC). However, there are few limited options in the patients with TACE failure. We compared the efficacy between sorafenib and transarterial chemoembolization using epirubicin and cisplatin combined with systemic infusion of 5-flurouracil (TAC-ECF) in the patients with TAC-DOX failure. Methods: We analyzed the consecutively enrolled 742 patients who received TAC-DOX as the first-line therapy for HCC between January 2007 and December 2017. Among the patients who failed with TAC-DOX, 49 patients were treated with TAC-ECF and 37 patients were treated with sorafenib as a rescue therapy. The regimens of TAC-ECF consisted of transarterial infusion of epirubicin (50 mg/m<sup>2</sup>) and cisplatin (60 mg/m<sup>2</sup>) combined with systemic infusion of 5-FU (200 mg/m<sup>2</sup> or 1000mg/m<sup>2</sup>). Overall survival and progression-free survival were analyzed.

Results: Of 86 patients, 22 and 64 patients were in Barcelona Clinic Liver Cancer (BCLC) stage B and C, respectively. The patients with Child-Pugh class A (CPC A) were 70.9%. There was no difference of baseline stage or CPC in both group. The median duration of sorafenib administration was 2.8 months (1.0-17.8 months) and the median number of TAC-ECF was 2 times (1-10 times). Overall survival after rescue therapy did not differ between sorafenib group and TAC-ECF group (4.7 vs. 6.4 months, P=0.730). When we performed subgroup analysis by same CPC or BCLC stage, there is no difference of overall survival after rescue therapy in both groups (P>0.05). In multivariate analysis for predicting poor survival, the patients with CPC B (P=0.016, HR 1.863, 95% CI 1.124-3.087) and BCLC stage C HCC (P<0.0001, HR 2.999, 95% CI 1.653-5.440) showed shorter survival than those with CP A and BCLC stage B HCC. There was no difference in progression-free survival

between the sorafenib group and TAC-ECF group (3.0 vs. 3.5 months, P=0.598). In the multivariate analyses, male gender (P=0.034, HR 1.991, 95% CI 1.054-3.762) and BCLC stage C HCC (P=0.035, HR 1.822, 95% CI 1.044-3.180) were proved as unfavorable factors for progression-free survival.

**Conclusions:** The present study showed that the overall survival and progression-free survival in patient with rescue TAC-ECF therapy were consistent with sorafenib therapy among the HCC patients who failed with TAC-DOX. TAC-ECF might be considered as an alternative therapy for the patients with TAC-DOX failure, especially CPC B patients who are not indicated for sorafenib therapy.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Failure

#### **PE-127**

# Management of a Surgical Treatment of Patients with Pancreatic Cancer

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**Aims:** In this study our purpose is analysis of retrospective patients with I-III stages which went to the surgery and postoperative chemo – and radiotherapy in Kazakh Scientific Research Institute of Oncology and Radiology.

**Methods:** Totally 64 patients between 2009 and 2016 underwent surgical treatment of pancreatic cancer and follow-up. Which of them: pancreatoduodenal resection was performed in 37 patients, corpocaudal resection in 12 patients, distal pancreas resection in 12 patients, total pancreatectomy performed to 3 patients. Resequence in pancreatic head cancer was 25.5%, with carcinoma of the body and tail - 10.1%.

**Results:** Postoperative mortality for pancreatoduodenal resection was 8.7% (in the last 5 years - 3.5%), distal resection was 13.3%. The average life expectancy after pancreatoduodenal resection was 17.4 months, pancreatectomy - 8 months, distal subtotal pancreas resection - 11.2 months. Three years after pancreatoduodenal resections, 14.7% lived, and the 5-year survival rate was 4.4%. After palliative surgery, the average life expectancy was 5.2 months. The best long-term results were observed when applying a complex and combined treatment. In distal pancreas resection postoperative use of SBRT/IMRT radiation therapy or induced chemotherapy, give almost same results. In this way, improvement of the treatment results of pancreatic cancer is possible with early diagnosis and applying of complex and combined treatment. Patients should be classified and treated with a multidisciplinary approach at specialized centers.

**Conclusions:** In this way, improvement of the treatment results of pancreatic cancer is possible with early diagnosis and applying of complex and combined treatment. Patients should be classified and treated with a multidisciplinary approach at specialized centers.

# PE-128

#### Differentiation of Small Hepatocellular Carcinomas from Small Benign Nodules in Cirrhotic Liver on Gadoxetic Acid-Enhanced and Diffusion-Weighted Magnetic Resonance Images

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**Aims:** To identify imaging characteristics that differentiate small (£2 cm) HCCs from small (£2 cm) benign nodules in cirrhotic liver on gadoxetic acidenhanced and diffusion-weighted (DW) magnetic resonance (MR) images.

**Methods:** On gadoxetic acid-enhanced and DW MR images, we analysed signal intensity of 222 small HCCs and 61 benign nodules (diameter, 0.5–2 cm) at each sequence and rim enhancement during portal or equilibrium phases. Univariate and multivariate logistic regression analyses identified predictors of HCC. Combinations of significant MR findings in multivariate analysis were compared with American Association for the Study of Liver Disease (AASLD) practice guidelines.

**Results:** In multivariate analysis, arterial enhancement (adjusted odds ratio [aOR], 8.6), T2 hyperintensity (aOR,5.8), and hyperintensity on DW images (aOR, 3.8) were significant for differentiating small HCCs from benign nodules (p  $\pm$  0.004). When two or all three findings were applied as diagnostic criteria for differentiating small HCCs from benign nodules, sensitivity and accuracy were significantly higher compared with AASLD practice guidelines (91% vs. 78% and 89% vs. 81%, respective-ly;each *P*<0.0001).

**Conclusions:** On gadoxetic acid-enhanced MR imaging, arterial enhancement and hyperintensity on T2-weighted and DW MR images are helpful for differentiating small HCCs from benign nodules in liver cirrhosis.

**Keywords:** Magnetic resonance imaging, Contrast Media, Heoaticellular carcinoma, Cirrhosis

# PE-129

### Protective Effects of Influenza Vaccination on the Admission Outcomes of Liver Cancer: A Nationwide Matched Study

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**Aims:** Limited information is available on the association between influenza vaccination (IV) and cancer outcomes. The purpose of this study is to evaluate the effects of IV on the outcomes of liver cancer.

**Methods:** Using reimbursement claims data of National Health Insurance in Taiwan in 2008-2013, we conducted a matched cohort study including 32330 patients aged  $\geq$ 20 years underwent inpatient care of liver cancer and 5841 of them received IV within previous one year. Using propensity score matching procedure, we selected 5621 patients with IV and 5621 patients without IV for comparison. Logistic regressions were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of IV associated with complications and in-hospital mortality during admission of liver cancer.

**Results:** Patients with liver cancer receiving IV showed less pneumonia (P<0.0001), septicemia (P<0.0001), urinary tract infection (P<0.0001), and in-hospital mortality (P<0.0001) compared with unvaccinated patients with liver cancer. IV was associated with decreased risk of in-hospital mortality during the cancer admission (OR, 0.60; 95% CI, 0.47-0.76) after adjustment. Vaccinated patients with liver cancer also had shorter length of hospital stay (P<0.0001) and lower medical expenditure (P<0.0001) than non-vaccinated patients.

Table 1. Characteristics of hospitali	ized liver cancer patients with
and without influenza vaccination	

	No IV (	N=5621)	IV (N	=5621)	p-value
Sex	n	(%)	n	(%)	1.0000
Female	1872	(33.3)	1872	(33.3)	
Male	3749	(66.7)	3749	(66.7)	
Age, years					1.0000
20-29	2	(0.04)	2	(0.04)	
30-39	16	(0.3)	16	(0.3)	
40-49	51	(0.9)	51	(0.9)	
50-59	147	(2.6)	147	(2.6)	
60-69	1559	(27.7)	1559	(27.7)	
70-79	3109	(55.3)	3109	(55.3)	
≥80	737	(13.1)	737	(13.1)	
Low income					1.0000
No	5579	(99.3)	5579	(99.3)	
Yes	42	(0.7)	42	(0.7)	
Number of hospitalizations					1.0000
0	3346	(59.5)	3346	(59.5)	
1	1321	(23.5)	1321	(23.5)	
2	502	(8.9)	502	(8.9)	
≥3	452	(8.0)	452	(8.0)	
Number of emergency visits					1.0000
0	3516	(62.6)	3516	(62.6)	
1	1162	(20.7)	1162	(20.7)	
2	448	(8.0)	448	(8.0)	
≥3	495	(8.8)	495	(8.8)	
Medical conditions					
Hypertension	2248	(40.0)	2248	(40.0)	1.0000
Diabetes	1325	(23.6)	1325	(23.6)	1.0000
Mental disorders	844	(15.0)	844	(15.0)	1.0000
Ischemic heart disease	531	(9.5)	531	(9.5)	1.0000
Heart failure	61	(1.1)	61	(1.1)	1.0000
Renal dialysis	74	(1.3)	74	(1.3)	1.0000
COPD	417	(7.4)	417	(7.4)	1.0000

IV, influenza vaccination.

 Table 2. Adverse outcomes of liver cancer patients with and without influenza vaccination

	No IV (N=5621)		IV (N=5621)		Risk of outcomes	
	Events	%	Event	%	OR	(95% CI) <sup>a</sup>
30-day in-hospital	170	3.0	99	1.8	0.57	(0.44-0.73)
mortality						
Postoperative						
complications						
Pneumonia	196	3.5	153	2.7	0.77	(0.62-0.96)
Septicemia	289	5.1	262	4.7	0.90	(0.76-1.07)
Acute renal failure	129	2.3	97	1.7	0.75	(0.57-0.97)
Pulmonary embolism	8	0.1	7	0.1	0.88	(0.32-2.42)
Stroke	108	1.9	105	1.9	0.97	(0.74-1.28)
Urinary tract infection	218	3.9	193	3.4	0.88	(0.72-1.07)
Deep wound infection	8	0.1	4	0.1	0.50	(0.15-1.66)
Acute myocardial	8	0.1	8	0.1	1.00	(0.38-2.67)
infarction						
Postoperative	32	0.6	29	0.5	0.91	(0.55-1.50)
bleeding						
ICU stay	1056	18.8	993	17.7	0.93	(0.84-1.02)
Medical expenditure,	3270±3606		3290±4130		P=0.7814	
Length of hospital stay,	12.2±11.5		11.7±12.9		P=0.0340	

Cl, confidence interval; IV, influenza vaccination; OR, odds ratio.

<sup>a</sup>Adjusted for all covariates listed in Table 1.

<sup>\*</sup>Mean±SD

Table 3. The stratification analysis for liver cancer patients w	ith
and without influenza vaccination associated with adverse ever	nts

			Adverse events			
		n	Events	Incidence, %	OR (95% CI)*	
Female	No IV	1872	124	6.6	1.00 (reference)	
	IV	1872	90	4.8	0.70 (0.53-0.94)	
Male	No IV	3749	313	8.4	1.00 (reference)	
	IV	3749	231	6.2	0.71 (0.60-0.85)	
Age 20-59 years	No IV	216	3	1.4	1.00 (reference)	
	IV	216	3	1.4	1.00 (0.19-5.28)	
Age 60-69 years	No IV	1559	68	4.4	1.00 (reference)	
	IV	1559	67	4.3	0.98 (0.69-1.40)	
Age 70-79 years	No IV	3109	251	8.1	1.00 (reference)	
	IV	3109	181	5.8	0.70 (0.57-0.85)	
Age =80 years	No IV	737	115	15.6	1.00 (reference)	
	IV	737	70	9.5	0.56 (0.41-0.77)	
0 medical condition	No IV	1767	136	7.7	1.00 (reference)	
	IV	1767	94	5.3	0.66 (0.50-0.88)	
1 medical condition	No IV	2501	192	7.7	1.00 (reference)	
	IV	2501	144	5.8	0.73 (0.58-0.91)	
≥2 medical conditions	No IV	1353	109	8.1	1.00 (reference)	
	IV	1353	83	6.1	0.74 (0.55-1.00)	
0 hospitalization	No IV	3346	202	6.0	1.00 (reference)	
	IV	3346	150	4.5	0.73 (0.58-0.90)	
1 hospitalization	No IV	1321	122	9.2	1.00 (reference)	
	IV	1321	86	6.5	0.68 (0.51-0.91)	
2 hospitalizations	No IV	502	51	10.2	1.00 (reference)	
	IV	502	36	7.2	0.67 (0.42-1.06)	
≥3 hospitalizations	No IV	452	62	13.7	1.00 (reference)	
	IV	452	49	10.8	0.76 (0.50-1.14)	
0 emergency visit	No IV	3516	185	5.3	1.00 (reference)	
	IV	3516	133	3.8	0.71 (0.56-0.89)	
1 emergency visit	No IV	1162	106	9.1	1.00 (reference)	
	IV	1162	85	7.3	0.78 (0.58-1.06)	
2 emergency visits	No IV	448	57	12.7	1.00 (reference)	
	IV	448	47	10.5	0.80 (0.53-1.21)	
≥3 emergency visits	No IV	495	89	18.0	1.00 (reference)	
	IV	495	56	11.3	0.58 (0.40-0.83)	

CI, confidence interval; IV, influenza vaccination; OR, odds ratio. \*Adjusted for all covariates listed in Table 1. **Conclusions:** Among patients with admission of liver cancer, vaccinated patients showed lower risks of complications and in-hospital mortality compared with unvaccinated patients. Further studies are needed to explain how IV improves outcomes of liver cancer.

Keywords: Influenza vaccination, Liver cancer, Admission, Outcome

#### PE-130

Recurrence after Curative Resection of Small Hepatocellular Carcinoma: Histology as Potent Prognostic Factors

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**Aims:** Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide despite the improvement in diagnostic methods and treatment modality. Curative treatment is recommended for patients with small HCCs and good liver function based on Milan criteria, but nevertheless the risk of tumor recurrence is still high in these selected patients. Therefore, we aimed to identify the factors that could predict HCC recurrence after resection focusing on the histologic findings.

**Methods:** A total of 99 HCC patients who had undergone resection from June 2003 to December 2015 with HCCs  $\leq$  3cm and total number of tumors  $\leq$  3 were retrospectively reviewed. Patients with child pugh grade A were included in the study. Histologic features including gross pattern, Edmonson grade, microvascular invasion, capsule invasion, free resection margin for tumor while presence of cirrhosis in non-tumor lesion were analyzed. Predictive efficacy of HCC recurrence were also analyzed using clinical variables and lab findings including tumor markers.

**Results:** Forty patients (40.4%) exhibited HCC recurrence following resection. In univariate analysis, factors associated with recurrence were presence of DM, increased baseline PIVKA level, prolonged INR and histological microvascular invasion, high Edmonson grade (grade4), cirrhosis. In multivariate analysis, presence of DM, increased PIVKA level and high Edmonson grade were associated with HCC recurrence. In subgroup analysis, presence of microvascular invasion and increased PIVKA level were associated with early recurrence ( $\leq 2$  years) (both, P<0.05) while presence of DM and low albumin level tended to be associated with late recurrence (>2 years). When recurrence free survival was analyzed, presence of DM and microvascular invasion (both, P<0.05) remained as associated factors.

**Conclusions:** Our findings show that in addition to tumor marker, histologic findings and presence of DM are important prognostic factors that could help in identifying patients who will recur from resection.

Keywords: Hepatocellular carcinoma, Histology, Prognosis

#### PE-131

# Outcome of Radiotherapy for Bone Metastasis from Hepatocellular Carcinoma

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**Aims:** Recently, bone metastasis from hepatocellular carcinoma (HCC) has been noted much more frequently as survival and imaging technology have been improved. The aim of current study is to investigate the outcome of patients with HCC who underwent radiotherapy for bone metastasis.

**Methods:** Sixty-five patients who received radiotherapy for bone metastases from HCC were retrospectively analyzed between January 2013 and March 2018 at the Pusan National University Hospital.

Results: During the study period, 65 patients received 90 sessions of radiotherapy for bone metastasis from HCC. The most common treatment site was spine (46%), followed by pelvic bone (20%) and rib (12.2%). The average number of radiotherapy per patient was 1.4 sessions (range, 1-4) per patients and 30 sessions (33.3%) were performed on multiple sites in one session. The median total dose per radiotherapy was 30.0 Gy (range, 3-120 Gy). In 22 (24.4%) among total session, radiotherapy was prematurely interrupted mostly due to poor general condition. No severe adverse event due to radiotherapy was not observed. Pain was the most common symptom before radiotherapy, and overall rate of pain control after radiotherapy was 53.0%. Overall survival rate was 10.8% (7/65) and median survival time from the beginning of radiotherapy was 3.0 months (95% CI, 1.75-4.24 months). In univariate analysis, the presence of concurrent metastasis other than bone and multiple session of radiotherapy was significant factor for survival (P=0.042, P=0.049, respectively). In multivariate analysis, multiple session of radiotherapy was significant factor for survival (P=0.024).

**Conclusions:** Radiotherapy for bone metastasis from HCC is relatively safe and effective for pain relief. The greater number of radiotherapy reduced the risk of death.

**Keywords:** Hepatocellular carcinoma, Bone metastasis, Radiotherapy

### PE-132

### The Advanced Multidisciplinary Team (MDT) in the Management of Stage IV Colorectal Cancer

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**Aims:** The management of stage IV colorectal cancer would be optimized by bringing together all relevant specialties in-

volved in colorectal liver metastases (CRLM) management in a centralized high volume liver cancer surgery centre. The major objective is to increase resectability so as to achieve long-term patient survival (> 5years). 80% of CRLM are initially non-resectable due to tumour size, location and functional liver reserve. New chemotherapy regimens including biologicals are bringing more patients to resection. Including resectable extrahepatic disease, resectability is the complete removal of liver metastases while leaving at least 30% of remnant liver.

**Methods:** A BASO Ronald Raven travelling fellow '2 week' observational study on the role of the advanced MDT in the management of Stage IV Colorectal Cancer (CRC) at the Aintree hepatobiliary centre, Liverpool (UK).

**Results:** There are 4 clinical scenarios of stage IV colorectal cancer; (1) asymptomatic CRC and resectable colorectal liver metastases (CRLM), (2) asymptomatic CRC and unresectable synchronous CRLM, (3) symptomatic CRC and resectable synchronous CRLM, (4) symptomatic CRC and unresectable synchronous CRLM. 10 -20% of patients with liver limited disease are resectable with curative intent, 10% are amenable to resection with ablation or two stage hepatectomy, with concomitant resectable extrahepatic disease (i.e. borderline resectable) and thus requiring induction chemotherapy and 30-40% of patients with initially limited unresectable disease are made resectable by chemo/biological therapy.

**Conclusions:** The major end-point of the advanced MDT approach to stage IV colorectal cancer management is resectability due to the impact on patient survival ( 40% > 5years, 20-30% in 10yrs).

# PE-133

#### Association of Family History with Cancer Recurrence and Survival in Patients with Hepatitis B-Related Hepatocellular Carcinoma (A Propensity Score Matching Analysis)

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**Aims:** A family history of liver cancer is regarded as a risk factor for hepatocellular carcinoma (HCC) development. We investigated the association between family history and cancer recurrence and survival in patients with hepatitis B virus (HBV)-related HCC.

**Methods:** Patients who underwent curative resection of HBVrelated HCC between 2003 and 2013 from a tertiary hepatobiliary center in China were enrolled in this study. A family history was defined as a self-reported history of primary liver cancer in the first-degree relatives. Propensity score matching (PSM) and multivariable Cox-regression analyses were performed to compare the overall survival (OS) and recurrence-free survival (RFS) between patients with and without a family history of liver cancer.

**Results:** Of 1,112 patients, 183 patients (16.5%) had a family history of liver cancer. A family history was not associated with OS and RFS (P=0.994 and 0.428) in the entire cohort. Using PSM, 179 pairs of patients with and without a family history but with comparable baseline characteristics and operative variables were created. A family history was associated with decreased OS and RFS (P=0.042 and 0.006) in the PSM cohort. On multivariable Cox-regression analyses, a family history was significantly associated with decreased OS (HR: 1.574, 95% CI: 1.171-2.116, P=0.003) and RFS (HR: 1.534, 95% CI: 1.176-2.002, P=0.002) after adjusting for other prognostic factors.

**Conclusions:** A family history of liver cancer was associated with decreased OS and RFS rates after curative resection in patients with HBV-related HCC.

#### PE-134

#### Three Decades' of Experience in the Surgical Management of Hepatoblastoma

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**Aims:** This study reviewed the clinical outcomes in the surgical management of hepatoblastoma over the past 30 years.

**Methods:** Pediatric patients with hepatoblastoma who underwent surgery (1985-2015) were reviewed (n=45). The outcomes of operation at different eras (I: 1985 to 1994; II: 1995 to 2003; III: 2004 to 2015) were compared.

**Results:** The most frequent type of liver resection was extended right hepatectomy (n = 10, 22.2%). The overall operative morbidity and mortality rates were 22.2% (n=10) and 0%. The median follow up was 157 months. The overall 5-year disease free survival was 77.8% (n = 35). Comparing the three study eras (l: n = 8; II: n = 15; III: n = 22), there was no significant difference in the pre-op disease status. Patient operated in era III had the shortest operative duration (I: 423+/-132 vs II: 368 +/- 103 vs III: 296 +/- 84 minutes, *P*=0.03) as well as the least blood loss (I: 680+/180 vs II: 452 +/- 84 vs III: 250 +/-86 minutes, *P*=0.02). The incidence of major surgical complications was highest in era II (I: 25.0% vs II: 26.6% vs III: 18.2%, *P*=0.73). The 5-year disease free survival appeared to be the best in era III (I: 75.0% vs II: 73.3% vs III: 81.8%, *P*=0.61).

**Conclusions:** With the advancement in perioperative care and surgical techniques, the operative outcome of hepatoblastoma has significantly improved in recent years.

# PE-135

# The First Experience of Radiotherapy on the Pancreas Cancer in KazlOR

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**Aims:** Despite the improvement of special treatment methods, the 5-year survival rate according to different authors is 1-10%. In 2016 in Kazakhstan, the number of people who fell ill at the PCa was 1028, while the one-year mortality rate was 65,1%. Radiation therapy (RT) is one of the treatment options for malignant neoplasm of the pancreas. Our purpose is to improve the treatment results of patients with PCa.

**Methods:** The method of IMRT was applied in 8 patients with adenocarcinoma of the third stage. 5 of them (62.5%) are primary patients without any treatment, 3 (37.5%) - after not radical operations. At the end of the course of treatment with a patient with PCa, the quality of life did not worsen. There are no early radiation reactions of high toxicity (RTOG 3-4). The evaluation of the quality of the conducted RT was carried out by Multispiral Computed Tomography (MSCT) with contrast enhancement (bolus + per. os).

**Results:** The best results are observed in a patient whose tumor size decreased from 6.1x5.1x3.8 cm to 4.1x3.8x3.7 cm in 1 month after radiation therapy. As a result, in 5 primary patients after 2,0 Gy per fraction to 55-60 Gy observed partial regression of the lesion, 3 patients underwent postoperative radiation therapy for prevention of disease recurrence (they are follow-up).

**Conclusions:** The application of the technique of intensively modulated radiotherapy in patients with malignant neoplasm of the pancreas, increases access to new methods of treatment, and improves the quality of life and the survival rate.

# PE-136

# Predictors of HCC Recurrence beyond MILAN Criteria after Primary Liver Resection

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**Aims:** There is a controversy whether to undergo liver resection or transplantation at early stage HCC. Thus, we aimed to find factors that reliably predict HCC recurrence beyond MILAN criteria which could help prioritizing transplantation as initial therapy.

**Methods:** This is a retrospective study including patients who were diagnosed with HCC within MILAN criteria and had liver resection as initial treatment from year 2002 to 2016. In total, 152 patients were enrolled for analysis. The primary endpoint

of this study is to find factors that enable prediction of HCC recurrence beyond MILAN criteria at the time of first recurrence. Secondary endpoints were factors associated with recurrence and recurrence free survival. Cox regression model was employed to select factors associated with recurrence.

**Results:** Out of 152 patients, 56 patients developed HCC recurrence. Out of 56 patients 12 patients (21.5%) showed HCC recurrence beyond MILAN criteria at the initial time of recurrence. Time to recur was significantly shorter in patients out of MILAN criteria compared to those recur within MILAN (14±10 vs 28±23 months, P=0.005). HCC recurrence was independently associated with increased baseline tumor size, ALT levels (>35 IU/L) and degree of AFP decrease after resection (all, P<0.05). Factors associated with HCC recurrence beyond MILAN criteria were greater tumor number, higher child pugh score, and increased baseline serum ALT levels (all, P<0.05). Lastly, independent factors associated with recurrence free survival rate were recurrence beyond MILAN criteria, remote recurrence from resection site and degree of AFP decrease (all, P<0.05).

**Conclusions:** HCC recurrence pattern (within versus beyond MILAN) has significant impact in the recurrence free survival even when patients are cured at early stage. Therefore, to prolong survival, prediction of patients who would lead to HCC recurrence beyond MILAN criteria is important and early liver transplantation could be an alternative treatment in this group. **Keywords:** Hepatocellular carcinoma, Milan, Resection, Recur

# PE-137

#### An Uncommon Finding; Bleeding Extrahepatic Recurrence of Hepatocellular Carcinoma

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**Aims:** Introduction : Recurrence of Hepatocellular carcinoma (HCC) can mainly be divided into intrahepatic recurrence (IHR) and extrahepatic recurrence (EHR). EHR being the less common of the two.

**Results:** In a post-hemihepatectomy patient with routine surveillance at 6 months, was noted to have elevated Alpha-Fetoprotein and complained of vague lower abdominal pain. CT scan revealed a 6cm heterogenous mass located at pelvis. During laparotomy for resection, the tumour was found to be bleeding.

**Conclusions:** In conclusion, a high index of suspicion and early surgical intervention can help in detecting possible bleeding extrahepatic recurrence in the background of a patient with history of HCC.

#### PE-138

#### Successful Resection for Huge Combined Hepatocellular-Cholangiocarcinoma after Portal Vein Embolization – A Case Report

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**Aims:** Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare primary hepatic cancer with poor prognosis. Aggressive surgical planning with complete resection of cHCC-CC plays an important role in treatment. We presented one case of successful resection of huge cHCC-CC after portal vein embolization (PVE).

**Methods:** This is a 46-year-old man with alcoholic liver cirrhosis. CT scan showed one 10cm infiltrative tumor in right liver with right anterior portal venous tumor thrombosis enhanced in arterial phase and washed out in portal venous phase. Regional enlarged lymph nodes is also noted. Under the preoperative diagnosis of HCC, right hepatectomy is planned. CT volumetry showed future liver remnant(FLR) is 480ml, 38.5% of standard liver volume. The ideal percentage of FLR in cirrhotic liver is more than 40% in our institution. Because of tumor thrombosis with total occlusion in right anterior portal pedicle, we performed PVE to right posterior portal vein for inadequate FLR. Two weeks after PVE, left liver enlarged from 480ml(38.5%) to 620ml(49.7%). There was no complication during PVE.

**Results:** Right hepatectomy and regional lymph node dissection were performed two weeks after PVE. The post-operative course was smooth without any evidence of hepatic insufficiency. Pathology reported combined hepatocellular-cholangiocarcinoma but no malignant lymph nodes. There is no evidence of recurrence in follow-up CT scan 17 months after the operation until now.

**Conclusions:** Aggressive surgical planning with PVE is effective for patient with cHCC-CC without adequate FLR even in cirrhotic liver. Complete resection may provide longer overall survival in this disease with dismal prognosis.

# PE-139

# Evaluation of the Clinical Usefulness of Adding Serum AFP-L3 and/or PIVKA-II Levels to Serum AFP Level

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Aims: This study was performed to investigate the clinical use-

fulness of the tumor-markers for hepatocellular carcinoma (HCC), including alpha-fetoprotein (AFP), AFP-L3, and prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II).

**Methods:** Patients who underwent serum AFP, AFP-L3, and PIVKA-II for elevation of space-occupying lesion (SOL) in the liver or elevated serum AFP level without liver SOL were retrospectively reviewed. AFP >5 ng/mL, AFP-L3 >5%, PIVKA-II >40 mAU/mL were used as the cut-off value, respectively.

**Results:** Two-hundred fifty-two patients were included; patients with liver SOL were 219 (86.9%) and those with elevated AFP without liver SOL were 33 (13.1%). In patients with liver SOL, 85 (38.8%) patients were diagnosed as HCC. Twenty-four (17.9%) patients with benign SOL and 53 (62.4%) patients with HCC had elevated AFP level (P<0.001). AFP-L3 was elevated in 5 (3.7%) patients with benign SOL, and 30 (35.3%) patients with HCC (P<0.001). 6 (4.5%) patients with benign SOL and 43 (50.6%) patients with HCC had abnormal PIVK-II level (P<0.001). Sensitivity and specificity of AFP for the HCC diagnosis were 62.4% and 82.1%, respectively. Combination of AFP-L3 to AFP increased sensitivity to 68.2% without change in the specificity. Combination of PIVKA-II to AFP increased sensitivity to 76.5% with slight decrease in specificity (78.4%). Combination of all three tumor-markers increased the sensitivity to 80.0% with 78.4% of specificity. In patients with elevated AFP without liver SOL, 5 (15.2%) and 4 (12.1%) patients had increased AFP-L3 and PIVKA-II, respectively, while, no one had increased both markers.

**Conclusions:** In patients with liver SOL, combination of AFP, AFP-L3, and PIVKA-II improved sensitivity of AFP, not having a significant effect on specificity. None of patients with elevated AFP without liver SOL showed parallel elevation of AFP-L3 and PIVKA-II. Therefore, combined evaluation of these tumor-markers would be beneficial in differential diagnosis.

Keywords: AFP, L3 fraction, PIVKA-II, Hepatocellular carcinoma

# PE-140

# Effectiveness of Hypofractionated Proton Beam Therapy for Inoperable or Recurrent Hepatocellular Carcinoma

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**Aims:** To evaluate the optimal time of tumour response and effectiveness of hypofractionated proton beam therapy (PBT) for hepatocellular carcinoma (HCC).

**Methods:** Seventy-one inoperable or recurrent HCC patients underwent hypofractionated PBT using 66 GyE in 10 fractions. The tumour responses were defined as the maximal tumour response observed during the follow-up period using the modified Response Evaluation Criteria in Solid Tumors criteria.

Results: Overall, treatment was well tolerated with no grade

toxicity  $\geq$ 3. Of 71 patients, 66 patients (93%) eventually reached complete response (CR) after PBT: 93.9% (62 of 66) of patients who reached CR within 12 months, and the remaining 4 patients (6.1%) reached CR at 12.5, 16.2, 19.1 and 21.7 months, respectively. The three-year local progressionfree survival (LPFS), relapse-free survival (RFS) and OS rates were 89.9%, 26.8%, and 74.4%, respectively. Multivariate analysis revealed that the tumour response was an independent prognostic factor for LPFS, RFS, and OS.

**Conclusions:** Most CR was achieved within 1 year after PBT and further salvage treatments in PBT field might be postponed up to approximately 18 - 24 months. Hypofractionated PBT could be good alternative for HCC patients who are unsuitable for surgical or invasive treatments with curative intent.

**Keywords:** Hepatocellular carcinoma, Proton beam therapy, Hypofractionation, Overall surival

# PE-141

#### Predictive Factors to Trans-Arterial Radioembolization Based Treatment with Yttrium-90

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**Aims:** Trans-arterial radioembolization (TARE) is a form of radiation therapy performed by selective intra-arterial injection of microspheres loaded with Yttrium-90. TARE has been shown in many clinical trials to be safe and effective in the management of unresectable HCC. The aim of this study is to identify prognostic factors for overall survival (OS) and time to progression (TTP) in patients with HCC undergoing TARE.

**Methods:** This study included 65 consecutive HCC patients who underwent TARE from Jul 2009 to Jan 2018. The tumor responses to TARE were assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).

**Results:** Study cohort comprised nineteen patients (29.2%) in BCLC-A stage, 21 (32.3%) patients in BCLC-B stage and 25 (38.5%) patients in BCLC-C stage. Among 65 patients, 4 (6.2%) obtained complete response (CR) and 27 (41.5%) showed partial response (PR) at 3 months after TARE. Median OS was 19.47 months and TTP was 4.83 months. Fifty-one patients underwent salvage treatment after TARE and 18 achieved objective response (OR); 14 achieved CR and 4 achieved PR. Multivariate analysis showed that the presence of portal vein tumor thrombus (PVTT) (hazard ratio [HR], 5.862; 95% confidence interval [CI], 2.380-14.437, P=0.000) and multiplicity of HCC nodules (HR, 2.205; 95% CI, 1.058-4.594, P=0.04) were independent factors for OS. The presence of PVTT (HR, 3.961; 95% CI, 1.924-8.155, P=0.000) and tumor diameter >10 cm

(HR, 2.167; 95% CI 1.152-4.076, P=0.016) were independent prognostic factors for TTP. Subgroup analysis of 40 patients without PVTT showed that the degree of tumor burden (HR, 44.317; 95% CI, 5.042-389.505, P=0.001), the achievement of OR at 3 months after TARE (HR, 8.561; 95% CI, 3.321-103.738, P=0.001) and receiving salvage treatment (HR, 24.307; 95% CI, 4.709-125.481, P=0.000) were shown to affect OS.

**Conclusions:** TARE is an effective therapy for patients with advanced HCC. And PVTT before TARE is an independent predictive factor for both OS and TTP.

Keywords: TARE, Prognosis, PVTT

# PE-142

#### Efficacy of Radiotherapy in Addition to Chemoembolization with Hepatic Arterial Infusion Chemotherapy versus Sorafenib in Advanced Hepatocellular Carcinoma with Portal Vein Thrombosis

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**Aims:** Sorafenib is the only standard treatment for advanced hepatocellular carcinoma with (HCC). However, its efficacy is not satisfactory and other treatment options are required. This study investigated the efficacy of chemoembolization and hepatic arterial infusion chemotherapy (HAIC) with or without radiotherapy versus sorafenib alone in patients with portal vein thrombosis (PVT).

**Methods:** This single-center retrospective study involved 105 patients of advanced HCC with portal vein tumor thrombosis (PVT). Enrolled patients had either child-pugh (CP) class A or B liver cirrhosis whom were classified into 3 groups: 1) Sorafenib alone, n=20; 2) Chemoembolization and HAIC, n=26; 3) Chemoembolization and HAIC with radiotherapy, n=59. Sorafenib was initiated with 400mg twice daily and HAIC was based on cisplatin and 5-fluorouracil regimen, performed every 4 weeks. Response of PVT was determined 3 months after completion of treatment and was regarded as responsive when there is at least partial response. Overall survival (OS) was analyzed among the treatment groups and factors associated with mortality were evaluated using multivariate analysis.

**Results:** The median radiation dose, sorafenib treatment duration and chemoembolization sessions were 50 Gy, 40 days, and 4 sessions, respectively. Proportion of patients according to the degree of PVT (main/both vs. first order vs. segmental PV) and bilobar tumor mass involvement did not differ among the three groups of treatment. However, PVT response rate was significantly higher in group 3 (13.5% vs. 6.7% vs. 55%, P=0.014) with lower incidence of solid organ metastasis (60% vs. 23.1% vs. 18.6%, P=0.001) and child pugh class B (70%, 50%, 25.4%%, P=0.001) compared to other groups. In univariate cox analysis, treatment modalities, presence of either lymph node or other organ metastasis, CP class B, decrease in

AFP levels were associated with survival. However, multivariate analysis revealed that treatment modalities (group 1 vs. 2, HR, 0.244; 95% CI, 0.06-0.999, *P*=0.05, group 1 vs. 3, HR 0.121; 95% CI 0.028-0.51, *P*=0.004 and group 2 vs. 3, HR 0.495; 95% CI, 0.25-0.98, *P*=0.044) and decrease in serum AFP level within 2 months of treatment (HR, 1.813; 95% CI, 1.204-2.72; *P*=0.004) were the only independent factors associated with survival. Median OS was significantly higher in patient treated with radiotherapy (group3, 11.1 months) than group 2 (3.6 months, log rank *P*<0.001) and group 1 (2 months, *P*<0.001). Furthermore, median OS survival was still significantly greater in group 2 than group 1, *P*=0.008.

**Conclusions:** Radiotherapy with chemoembolization and HAIC can be alternative treatment option to sorafenib in patients with advanced HCC and PVT.

**Keywords:** Portal vein thrombosis, Hepatocellular carcinoma, Sorafenib, Radiotherapy

#### PE-143

Analysis of Results after Liver Resection for Metastasis from Non-Colorectal and Non- Endocrine Tumors

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**Aims:** Liver metastasis from colorecal cancer and endocrine organs relatively well researched and reported. However, there have been few reports on outcome of liver metastasis from noncolorectal and non endocrinee organs. In this study ,we evaluate the prgosnostic factor among the patient who underwent hepatic resection with noncolorectal nonendocrine liver metastasis.

**Methods:** The overall study period was September 2005-July 2015. A total of 23 patients were selected from the two different hospital database and included in the analysis Patients and tumors characteristics were reported. Overall survival and subgroup analyses based on different characteristics were performed .

**Results:** Them Mean age of the patients was  $57.9 \pm 11.5$  years. Male was 15 (65.2%) and female 8 (34.8%). Primary malignancies distribution resulted as follows: Genitourinary 7 (30.4%) Gastrointestinal 6 (26.1%) Pancreatic cancer 3 (13.0%) Lung cance 2 (8.7%) Breast cancer 2 (8.7%) CBD cancer 1 (4.3%) Melanoma 1 (4.3%) and Nasopharyngeal cancer 1 (4.3%) The overall survival rates at 1, 3, 5 years, were 68.5%, 38.0% and 19.0% respectively .Presence of Neoajuvant treatment and recurrence after hepatic resection were significant different between Death and Survival groups (21.4% vs 77.8%, *P*<0.05) ,(78.6% vs 22.2%, *P*<0.05) and Overal survival rate was high in the patients with Neoajuvant treatemnt (1, 3 and 5yr: 88.9%, 77.8% and 51.9% vs 53.8%, 23.1% and 0 % *P*<0.05).

**Conclusions:** Neoajuvant treatemnt could have survival benefit in the patient of noncolorectal nonendocrine liver metastasis.

### PE-144

#### Validation of Risk Factors Affecting the Early Recurrence of Single Lesion Hepatocellular Carcinoma with HBV Related Liver Cirrhosis Patients after Curative Resection

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**Aims:** Early recurrence is associated with poor prognosis after curative resection for hepatocellular carcinoma (HCC). This study was designed to validate the risk factors affecting the early recurrence of single lesion HCC with HBV related liver cirrhosis (LC) patients.

**Methods:** 132 cases of consecutive HCC patients were enrolled in our institution between Jan 2005 and Dec 2015. We divided the cohort into two groups: early recurrence group(ER) which has recurrence within 12 months after resection, and non-early recurrence group (NER). Survival rate, univariate and multivariate analysis were performed to identify variables associated with early recurrence.

**Results:** The selected cut-off values with sufficient sensitivity and specificity were 1.99 for Neutrophil-to-Lymphocyte Ratio (NLR). When comparing the ER group with NER group, significant differences were observed in the level of PIVKA (P=0.007), NLR (P=0.001), GPS (P=0.001), Edmonson-Steiner (ES) grading (P=0.002), tumor necrosis (P=0.004) and lymphovascular invasion (LVI) (P=0.001). ER groups has statistically significant lower overall survival rate than NER groups (P=0.000). By multivariate analysis, there were significant differences in NLR more than 1.99 (P=0.000), elevated Glasgow Prognostic Score (GPS) (P=0.004) and presence of lympho-vascular invasion (P=0.0002) for affecting the overall survival of the ER group.

**Conclusions:** Preoperative NLR more than 1.99 and elevated GPS and presence of lymphovascular invasion were independent risk factors for ER of single lesion HCC with HBV LC patients after curative resection.

#### **PE-145**

#### Bilobar Liver Metastasis with Portal Vein Tumor Thrombus of Colorectal Cancer

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**Aims:** Treatment of Liver metastasis of colorectal cancer (CLM) is now evolving rapidly with regards to oncological and technical resectability. Little is known about multiple CLM with tumor thrombus in the portal vein (PVTT). On the literatures, Authors suggested at least that macroscopic PVTT is not a contraindication to liver surgery. Herein, we report the clinical outcomes of two patients with progressive PVTT and multiple CLM underwent hepatectomy.

**Results:** Case 1. A 73-year-old man presented with a metastatic liver tumor accompanied by a macroscopic tumor thrombus in the right portal branch and multiple CLM on both lobes. Extended right hemi-hepatectomy with and removal of the tumor thrombus were performed, and the liver metastasis and tumor thrombus were successfully resected. The patient had the multiple CLM on remnant lobe with left main PVTT at 8 months after the liver surgery. Case 2. A 64-year-old woman who had previously undergone palliative chemotherapy for ascending colon cancer presented with CLM accompanied by a macroscopic tumor thrombus in the left portal branch. Tumor and PVTT were progressed regardless of various chemoagents. Left hemihepatectomy with radiofrequency ablation on right lobe and right hemicolectomy were performed. But, CLM occurred just at 3 months after the liver surgery.

**Conclusions:** The prognosis of patients with liver metastasis accompanied by a PVTT remains unknown. Considering previous our cases, a poor prognosis may be expected even though the tumor is successfully removed by liver resection. We introspected whether surgery is the treatment option for such pattern of liver metastasis in this era.

### PE-146

#### Two Cases of Uncommon Hepatic Tumor Mistaken for a Hepatocellualr Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) shows typical findings in imaging studies such as computed tomography (CT) and magnetic resonance image (MRI). However, there are some cases which show different postoperative pathologic results from preoperative imaging diagnosis. Herein, we introduce two cases of rare hepatic tumor mistaken for a HCC.

**Methods:** First case of this report is a 62-year-old female and another case is a 67-year-old female patient. Two cases had similar clinical courses and we describe clinical course of these patients who received liver resection for rare hepatic tumor mistaken for a HCC.

**Results:** These patients visited for liver tumor diagnosed in medical check-up. Computed tomography (CT) scan and Magnetic resonance images (MRI) showed single mass on segment 6 which was in accordance with diagnostic criteria of HCC. Liver biopsy was performed because these patients had no risk factor of HCC such as HBV, HCV and liver cirrhosis, and suspicious HCC was reported in pathologic results. These patients received liver resection (posterior sectionectomy for first case, tumorectomy for second case) and postoperative pathologic exams revealed adrenal cortical carcinoma in both cases.

**Conclusions:** Adrenal cortical carcinoma is a rare malignant tumor, but similar to a HCC on the basis of imaging and histologic features. For these reasons, this tumor can be mistaken for a HCC in cases of direct invasion or hepatic metastasis. Therefore, this tumor should be suspected once in case of suspicious HCC on segment 6 in imaging without risk factors.

# PE-147

#### A Case of Primary Non-Hodgkin B-Cell Lymphoma Mimicking Cholangiocarcinoma

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**Aims:** Primary hepatic lymphoma (PHL) is rare and accounts for only 0.01% of Non-Hodgkin lymphomas(NHL). Primary hepatic lympoma presenting with non specific symptoms and radiological imaging, PHL was often misdiagnosed. This article presents a case of PHL mimicking cholangiocarcinoma that was treated by resection and subusequent chemotherapy.

**Methods:** A 61 years old female visted our hospital for epigastric pain. Abdominal CT and MRI scan revealed lobulating hypodense mass involving left hepatic lobe and S8/4 liver, which was suggested cholangiocarcinoma. There was no evidence of retroperitoneal lymphadenopathy. The patient underwent Extended left lobectomy with caudate lobectomy.

**Results:** The operative findings showed no evidence of a mass originating from any other organs. Microscopically, atypical large lymphoid infiltrates at edges of portal tract, with disruption of hepatic parenchyma and uniform population of lymphoid cells of large size with many mitotic figures. Immunohistochemically, tumor cells were positive for CD20, MuM1, and Ki-67, while CD3, CD10, and anaplastic lymphoma kinase were negative. CT scan of the thorax and abdomen did not reveal any lymphadenopathy or mass lesion. Thus, the tumor was diagnosed as Primary non-Hodgkin lymphoma of the liver, large cell type (diffuse large B-cell lymphoma). She received six cycles of rituximab, cyclophosphamide, hydroxydaunorubicin(Adiramycin), oncovin(Vincristine), prednisolone (R-CHOP), and has disease regression.

**Conclusions:** Primary non-Hodgkin lymphoma of the liver, although rare, should be considered in the differential diagnosis of patients with large, hypovascular liver lesions. Although the mainstay of therapy for PHL patients is chemotherapy with R-CHOP regimen, surgical resection followed by chemotherapy has a valid role in the treatment.

#### PE-148

# Effect of Preoperative Treatment for Hepatic Resection in Patient with HCC

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**Aims:** Hepatic resection is a cornerstone in the treatment of HCC patients. However, after resection, low resection rate and high recurrence rate are problematic. In liver transplantation, preoperative treatment has a good outcome, but it is doubtful whether resection shows the same result.

**Methods:** From January 2005 to December 2015, 274 patients who underwent curative hepatic resection in our center were included. And then, they were divided into hepatic resection only (HRO) group (n=208, 75.9%) and preoperative treatment (PT) group (n=66, 24.1%). Preoperative treatment was TACE, and effect after treatment was analyzed by changes by mRECIST and tumor marker (AFP, PIVKA). Also, PT group was divided into responder (complete response/partial response in mRECIST or reduction of tumor marker) and non-responder (stable disease/progressive disease in mRECIST or increase of tumor marker). Then, we evaluated recurrence, the disease-free survival rate (DFS), the overall survival rate (OS), and various other factors based on the characteristics of patients and tumors according to two groups.

**Results:** Of the 274 patients, the recurrence rate was 48.2% and related factors were tumor size, MVI, TNM stage, and preoperative treatment. 5-year DFS and OS rates were 42.6% and 69.8%. We found no statistically significant difference in the DFS (P=.397) and OS (P=.373) rates between HRO and PT group. Also, classification by Milan criteria did not affect DFS or OS. HRO and responder in PT group showed no difference between DFS and OS, but non-responder in PT group showed significantly worse in both DFS and OS. (DFS, P=.029, OS, P=.003 in mRECIST, DFS, P=.079, OS, P=.002 in AFP)

**Conclusions:** Hepatic resection is still an effective tool for initial treatment of HCC. Preoperative treatment did not affect the outcome after resection. If there was no response after pre-operative treatment, resection should be considered carefully since postoperative results were statistically poor. To further ensure this result, further studies will be needed to collect more cases.

**Keywords:** Hepatocellular carcinoma, Rresection, Transarterial chemoembolization

#### PE-149

# Prospective Multicenter Observational Analysis for Postcholecystectomy Complication and Development of Predictive Model in Korea

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**Aims:** The Korean Association of HBP Surgery firstly launched the protocol of Korean Surgical Quality Improvement Program (KSQIP) for cholecystectomy collaborating with NECA as a multicenter prospective study. I'd like to introduce the study protocol, web based database system and outcome. Laparoscopic cholecystectomy (LC) is the standard surgical treatment of benign gallbladder disease. However, the incidence of postoperative complication varies, and the risk factor was not well thoroughly investigated. The aim of this study is to develop and evaluate the surgical risk calculator for postoperative outcomes after laparoscopic cholecystectomy. A total of 3,002 patients were registered, and 2,514 patients who underwent laparoscopic cholecystectomy for benign gallbladder disease from 18 academic institutes in Korea were included in this prospective, multicenter cohort study. Preoperative or intraoperative variables were evaluated as risk factors for various postoperative outcomes including overall complications, and tendency to increase use of medical facilities including prolonged duration of hospital stay. After risk factor analysis, risk calculator after cholecystectomy was developed using multiple logistic regression analysis. Using standard preoperative variables from this multiinstitutional prospective database, we tried to construct a risk calculator for predicting adverse perioperative outcomes after laparoscopic cholecystectomy. Such information may be useful for risk stratification before laparoscopic cholecystectomy.

Liver Cancer, Basic

#### PE-150

# ROS Induced-Activation of YAP-1 through a C-Myc Pathway Is a Therapeutic Target in Hepatocellular Carcinoma

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**Aims:** The Hippo signaling pathway regulates organ size by controlling both cell proliferation and apoptosis via effectors such as yes-associated protein (YAP). Dysregulation of the Hippo pathway has been suggested as one of the therapeutic target in hepatocarcinogenesis. Reactive oxygen species (ROS) levels increase during the progression from early to advanced hepatocellular carcinoma (HCC). Activated YAP-1 by ROS-induced damage has been hypothesized to aggravate progression of HCC, but it remains unclear which signaling pathway is involved. Here, we investigated ROS-induced YAP-1 activation in HCC and the signaling pathway which is associated.

**Methods:** The expression of YAP-1 was quantified using realtime PCR and immunoblotting. Human HCC cells (Huh-7, HepG2, and SNU-761) were grown under  $H_2O_2$  treatment which is a major component of ROS in living organisms, either with YAP-1 siRNA or with control siRNA. MTT assays were performed to evaluate the role of YAP-1 in HCC under  $H_2O_2$  treatment. To investigate the signaling pathway responsible for the activation of YAP-1, immunoblotting was performed.

**Results:**  $H_2O_2$  treatment increased the mRNA and protein expressions of YAP-1 in HCC cells (Huh-7, HepG2, and SNU-761). Suppression of YAP-1 using siRNA transfection resulted in significant decrease in tumor proliferation under  $H_2O_2$  treatment both *in vitro* and *in vivo*. The oncogenic action of YAP-1 occurred via activation of the c-myc pathway, leading to upregulation of unfolded protein response (UPR), including the 78-kDa glucose-regulated protein (GRP78/BiP) and activating transcription factor 6 (ATF-6).

**Conclusions:** These results indicate that ROS-induced activation of YAP-1 via the c-myc pathway, which leads to activation of the UPR pathway, is a therapeutic target in HCC.

Keywords: Hepatocellular carcinoma, YAP, C-myc, ROS

# PE-151

#### Functional and Mechanistic Characterization of PRMT6-Regulated Autophagy in Hepatocellular Carcinoma

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**Aims:** Autophagy is a critical survival factor for cancer cells, whereby it maintains cellular homeostasis including degradation of damaged organelles and unwanted proteins as well as the support of cellular biosynthesis in response to environmental stress, preventing cells from undergoing apoptosis. We investigated the functional role of protein arginine methyltransferase 6 (PRMT6) in regulation of autophagy and sorafenib resistance, aiming to provide novel therapeutic insights for HCC.

**Methods:** We characterised the regulatory role of PRMT6 in autophagy by immunofluorescence puncta staining, transmission electron microscopy and immunoblot analyses. Identification and validation of potential PRMT6-interacting partners were performed through tandem affinity purification coupled with mass spectrometry profiling followed by co-immunoprecipitation. Subsequent *in vitro* and *in vivo* methylation assays found PRMT6 to methylate its binding partners to mediate arginine methylation for post-translational modification of proteins. Lentiviral-based overexpression and knockdown approaches were utilised to examine and explore the functional role of PRMT6-downstream effector in PRMT6-mediated autophagy deregulations in HCC.

**Results:** Upon autophagy induction by Earle's Balanced Salt Solution (EBSS) to mimic nutrient deprivation, hypoxia to mimic oxygen deprivation and sorafenib treatment, we demonstrated a negative correlation between expression of PRMT6 and LC-3BII in HCC. Intriguingly, we identified and validated a number of autophagy-related proteins from mass spectrometry-based proteomics, including Bcl-2 associated athanogene 5 (BAG5), as PRMT6-binding partners. Mechanistically, PRMT6 methylates BAG5, leading to its protein degradation. We later confirmed

that, BAG5, a downstream effector of PRMT6, promotes HCC tumorigenesis through autophagic alterations *in vitro* and *in vivo*. More importantly, data-mining in The Cancer Genome Atlas (TCGA) – Liver Cancer dataset found patients with higher BAG5 expression to display a significantly worst survival outcome, indicating its potential translational values.

**Conclusions:** Our findings suggest PRMT6 down-regulation in HCC tumors to promote tumorigenicity and sorafenib resistance through an altered autophagic flux via BAG5 de-regulation. **Keywords:** HCC, Autophagy, Sorafenib resistance, PRMT6

# <u>PE-</u>152

# UBE2T: A Molecular Regulator for Cancer Stemness in Hepatocellular Carcinoma

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**Aims:** Increasing evidence showed that cancer stem cells (CSCs) play a critical role in regulating the tumor relapse and therapeutic resistance of hepatocellular carcinoma (HCC). Given high molecular similarities between liver CSCs and normal liver stem cells, we have enriched the normal stem cell populations by establishing a mouse partial hepactectomy model order to identify critical molecules involved in regulation of liver CSCs. By comparing the expression profiles between the early regenerating liver and intact one, UBE2T was found to be highly upregulated. This, together with the data showing upregulation of UBE2T in enriched liver CSC populations, suggest the role of UBE2T on regulating liver CSCs.

**Methods:** We evaluated the clinic-pathological relevance of UBE2T by qPCR, western blot and immunohistochemical analyses. Lentiviral-based overexpression and knockdown approaches were performed to characterize the functional roles of UBE2T in regulating liver CSCs. The protein binding partner of UBE2T was identified by mass spectrometry analysis.

**Results:** By qPCR analysis, UBE2T mRNA overexpression is found in over 90% of HCC samples and is associated with aggressive tumor behavior and poorer patients' survival. Over-expression of UBE2T protein level in HCC clinical samples was further confirmed by western blot and IHC analyses. Using lentiviral based knockdown approach, suppression of UBE2T inhibited liver CSC properties, including self-renewal, tumorigenicity, drug resistance and expression of liver CSC markers. Using orthotopic liver xenograft model, UBE2T suppression led to decrease in tumor burden as well as lung metastasis *in vivo*. Mechanistically, we found UBE2T interacts with E3 ligase Mule and regulates its expression via ubiquitation. Since we further found that UBE2T mediates liver CSC function through Mulemediated  $\beta$ -catenin activation.

**Conclusions:** We have uncovered a novel UBE2T mediated signaling cascade in regulation of liver CSCs. Developing a specific inhibitor targeting this pathway may be a novel approach for

#### HCC treatment.

Keywords: UBE2T, Cancer Stem Cell, HCC, Ubiquitination

# PE-153

#### PI3Kγ Inhibition Enhances the Anti-Cancer Effect of Cytokine-Induced Killer or Natural Killer Cell

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**Aims:** Phosphoinositide 3-kinase (PI3K $\gamma$ ) signaling through the Akt and mTOR pathways promotes immunosuppression by inhibiting activation of nuclear factor kappaB and stimulating CCAAT/enhancer-binding protein  $\beta$  activation. In contrast, inactivation of macrophage-elicited PI3K $\gamma$  activates immunostimulatory signals that restore CD8+ T cell activation and cytotoxicity. Cytokine-induced killer (CIK) or natural killer cell (NK) infusion therapy alone is insufficient for treating advanced cancers. Thus, this study evaluated whether inhibiting PI3K $\gamma$  enhances the anti-cancer effects of CIK and NK cell therapy in a mouse hepatocellular carcinoma (HCC) model.

**Methods:** CIK and NK cells were generated from mouse splenocytes using interferon gamma, a CD3 monoclonal antibody (CIK cells), and interleukin 2 (CIK and NK cells). The potential synergistic effect of CIK or NK cell therapy with a PI3K $\gamma$  inhibitor was evaluated in a mouse HCC model.

**Results:** A synergistic anti-cancer effect was observed by measuring tumor volume following treatment with CIK or NK cells and/or a PI3K- $\gamma$  inhibitor. Relative tumor volume increased to 41.49 ± 14.41 in the control group, whereas that in the CIK plus PI3K- $\gamma$  inhibitor group increased to only 16.48 ± 8.58 (*P*=0.004). Relative tumor volume in the NK plus PI3K- $\gamma$  inhibitor group increased to 20.30 ± 3.98, whereas that in the control group was 47.63 ± 7.38 (*P*=0.016). TUNEL assays revealed that the combined treatment group (CIK or NK cells plus the PI3K $\gamma$  inhibitor) demonstrated significant increases in the proportion of apoptotic cells compared to the control (both *P*<0.05).

**Conclusions:** This study demonstrates that inhibiting PI3K $\gamma$  enhances the anti-cancer effect of CIK and NK cell therapy in a mouse model of HCC; therefore, PI3K $\gamma$  may be a potential immunotherapeutic target for HCC.

**Keywords:** PI3Kγ, Cytokine-induced killer cell, Natural killer cell, Hepatocellular

#### PE-154

## Prognostic Subclasses of Intrahepatic Cholangiocarcinoma by Integrative Molecular – Clinical Analysis and Potential Targeted Approach

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**Aims:** Although molecular characterization of intrahepatic cholangiocarcinoma(CCA) has been studied recently, integrative analysis between molecular and clinical characterization has not been established yet. We analyzed RNA sequencing data with annotated clinical data for clarifying genomic features of intrahepatic CCA, molecular specific clinical features and evaluating therapeutic potential based on molecular subtypes.

**Methods:** We performed next generation RNA sequencing of 30 surgically resected intrahepatic CCA from Korean patients. RNA expression, variants and fusions were analyzed with clinical, pathologic features. RNA sequences from 32 intrahepatic CCA resected from USA were used for validation.

**Results:** Patients were classified into 2 subclasses based on unsupervised clustering, which showed a significant difference 5year survival. The validation cohort of USA data also revealed two subclasses with significant differences in survival. Two subclasses had different clinical and pathologic features for higher CEA and CA19-9 levels, underlying cholangitis and bile duct type pathology in the poor prognostic subclass and more frequent hepatitis and cholangiolar type of pathology in better prognostic subclass. On pathway analysis, liver related signatures were enriched in better prognosis subclass. In poor prognosis subclass, inflammation related pathways were enriched and KRAS mutation was more frequent. Cholangiocarcinoma cell lines which have similar gene expression pattern with better prognosis subclass were sensitive to gemcitabine.

**Conclusions:** Two molecular subtypes of intrahepatic CCA with distinct clinical, biological and prognostic differences were identified. With clinical and pathological characteristics, molecular subtypes can be predicted and different signaling pathways of subtypes may lead to more rational targeted approaches to treatment. **Keywords:** Cholagniocarcinoma, RNA

# PE-155

# T-Cell Exhaustion Determined by PD-1 Expression on Tumor-Infiltrating CD8 T-Cells in Hepatocellular Carcinoma

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**Aims:** Phenotypic and functional characteristics of tumor-infiltrating CD8 T-cells (CD8 TILs) has not been well studied in the context of heterogeneity of exhausted T-cells and patient stratification in hepatocellular carcinoma (HCC).

**Methods:** We identified distinct T-cell exhaustion profiles determined by PD-1 expression levels on CD8 TILs from 48 HCC patients undergoing surgical resection by multi-color flow cytometry and RNA sequencing.

Results: CD8 TILs from HCC patients significantly overexpressed immune checkpoint receptors such as PD-1, TIM-3 and LAG-3. CD8 TILs could be further stratified into PD-1<sup>hi</sup>, PD-1<sup>int</sup> and PD-1<sup>neg</sup> subpopulations, and TIM-3 and/or LAG-3 were exclusively expressed on PD-1<sup>hi</sup>, not PD-1<sup>int</sup>, subpopulation. RNA expression profiles were distinct among PD-1<sup>hi</sup>, PD-1<sup>int</sup> and PD-1<sup>neg</sup> CD8 TILs and a gene module of T-cell exhaustion was significantly enriched in PD-1<sup>hi</sup> CD8 TILs. HCC patients could be classified into two distinct subgroups based on the proportion of PD-1<sup>hi</sup> CD8 TILs; High PD-1 expressers and Low PD-1 expressers. High PD-1 expressers had more severely dysfunctional CD8 TILs with exhaustion profiles that were observed in PD-1<sup>hi</sup> CD8 TILs, compared to Low PD-1 expressers. High PD-1 expressers were associated with aggressive biologic tumor features. Combination blockades of Tim-3 or LAG-3 in addition to PD-1 blockade further enhanced proliferative responses of CD8 TILs from High PD-1 expressers.

**Conclusions:** CD8 TILs displayed heterogeneous exhaustion profiles determined by differential PD-1 expression levels in HCC patients. A certain subgroup of HCC patients expressing multiple immune checkpoint receptors appears to be eligibly indicated for immune checkpoint inhibitors for effective reinvigoration of anti-tumor immunity.

**Keywords:** Hepatocellular carcinoma, PD-1, Checkpoint immunity, Immunotherapy

# PE-156

#### Hepatitis B Virus X Protein Stimulates Expression of PD-L1 in Hepatocellular Carcinoma via a MyD88-Dependent Pathway

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**Aims:** Hepatitis B virus (HBV) X protein (HBx) has been implicated in HBV-related hepatocellular carcinoma (HCC). Recently, immune checkpoint inhibitors have showed effective in solid cancers. However, the expression of immune checkpoint proteins has not been clarified, especially in HCC with HBV. We aimed to investigate the mechanism for expression of immune checkpoint proteins in HBx expressing HCC cell lines via my-

eloid differentiation factor 88 (MyD88) pathway.

**Methods:** We compared HBx-expressing HCC cell lines (SNU354, SNU368) with HCC cell lines (Hep3B, HepG2) through measuring expression of immune checkpoint proteins including programed death-ligand1 (PD-L1), CD80/86, and galectin9 by western blotting. The role of MyD88 in these processes was analyzed by MyD88 siRNA.

**Results:** HBx-HCC cell showed high expression of PD-L1 compared HCC cell. Expression of CD80/86 and galectin9 also showed more in HBx-HCC cell. HBx expression activated downstream signaling proteins of MyD88 including STAT3, interleukin-6 (IL-6). Inactivation of MyD88 reduced IL-6 synthesis and PD-L1 and CD86, and galectin9, respectively.

**Conclusions:** In HBx-HCC cells, HBx stimulates the immune checkpoint proteins including PD-L1, CD86, and galectin9 in a MyD88 dependent pathway. MyD88 could be involved in HBV-related HCC. Further study of clinical feature according to expression of PD-L1 in HBV related HCC tissue by immunochemical stain may be necessary.

**Keywords:** Hepatitis B virus X protein, Hepatocellular carcinoma, Myeloid differentiation factor 88, Programmed deathligand1

# PE-157

#### Kinase Suppressor of Ras 1 Promotes YAP/TAZ-Mediated Tumorigenesis in the Liver

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**Aims:** Liver cancer is the second most common cause of cancer-related deaths worldwide. The Hippo signaling pathway is tumor suppressive, as its inactivation leads to tissue overgrowth and tumor formation via YAP- or TAZ-mediated transcriptional activation. YAP is overexpressed in 62% of patients with hepatocellular carcinoma (HCC) and in almost 90% of human cholangiocarcinoma (CCC). Kinase Suppressor of Ras 1 (KSR1) is a scaffold protein for the Ras/Raf/MEK/ERK signaling pathway, promoting activation of MEK and ERK. Pro-tumorigenic roles of KSR1 in Ras-activated cancers have been verified in murine models for lung, skin, and pancreatic cancers. In this study, we have investigated the role of KSR1 in YAP/TAZ-mediated hepatocarcinogenesis.

**Methods:** Transposons were constructed encoding KSR1 and an activated from of TAZ (TAZ<sup>S89A</sup>). Transposons were hydrodynamically delivered to livers of 6-week-old C57BL/6 mice. Mice were monitored at least twice per week and sacrificed when moribund. Tumor-bearing livers were formalin fixed for hematoxylin–eosin staining and immunohistochemistry. **Results:** Analysis of gene expression levels in human HCC and CCC samples deposited in The Cancer Genome Atlas (TCGA) revealed that KSR1 was significantly upregulated both in human HCC and CCC, compared with non-tumoral surrounding livers (P<0.0001 in HCC and P=0.0063 in CCC). Co-expression of KSR1 and an activated form of TAZ (TAZ<sup>S89A</sup>) led to the development of both HCC and CCC in the murine livers, while expression of TAZ<sup>S89A</sup> alone failed to induce hepatic tumors.

**Conclusions:** KSR1 promotes hepatocarcinogenesis, both in HCC and CCC. Suppression of KSR1 might be an attractive therapeutic option for both types of hepatic malignancies. **Keywords:** Liver cancer, KSR1, YAP/TAZ

# PE-158

#### Proteomic Approaches to Investigate the Regulation of Human Telomerase Reverse Transcriptase in Hepatocel-Iular Carcinoma Cells

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**Aims:** Human telomere transferase (hTERT) is expressed during early fetal development and then turned off in most adult tissues, but it becomes reactivated in almost all human cancers, such as hepatocellular carcinoma (HCC). However, the exact mechanism regulating these changes in expression remains unknown. We evaluated whether knockdown of hTERT in HCC cell lines inhibits cell cycle and proliferation, and analyzed hTERT-regulating proteins using proteomic analyses.

**Methods:** HCC cell lines were transfected with hTERT small interfering RNA (siTERT) and cultured under normal conditions. Following transfection, the expression levels of hTERT, steroidogenic acute regulatory protein (StAR), and human Kruppel-related 3 (HKR3) were further investigated in the proteomic analysis of hTERT through western blotting, and tumor growth was measured by cell proliferation and cell cycle (PI staining) assays.

**Results:** The upregulation of StAR expression and downregulation of HKR3 expression led to increased hTERT expression and telomerase activity. Inhibition of hTERT by siRNA led to the inhibition of tumor growth.

**Conclusions:** Our results suggested that StAR is positively correlated with telomerase activity, whereas HKR3 may be a negative regulator. Our results facilitate further exploration of the pathways regulating human telomerase activity.

Keywords: HCC, TERT, StAR, HKR3

# PE-159

#### CKD5, a Novel Pan-Histone Deacetylase Inhibitor, Synergistically Enhances the Efficacy of Sorafenib for Hepatocellular Carcinoma

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**Aims:** Histone deacetylase inhibitor (HDACi) is a promising candidate with distinctive epigenetic targets involved in hepatocarcinogenesis and chemoresistance. Recent phase I/II study reported the possibility of HDACi as a chemosensitizer in sorafenib-resistant patients. In this study, we evaluated whether CKD5, a novel pan-HDACi, can potentiate the efficacy of sorafenib.

**Methods:** Human hepatocellular carcinoma (HCC) cell lines (SNU-3058 and SNU-761) cultured under normoxic or hypoxic conditions were used. Cell viability was assessed by MTS assay and gene expressions by microarray analysis and real-time PCR. Small interfering RNA (siRNA) transfection and immunoblot assays were used to identify the mechanism of cell death. For *in vivo* experiments, C3H mice implanted with MH134 cells were treated with weekly CKD5 (60 mg/kg, intraperitoneal) with/ without sorafenib (20mg/kg) for 2 weeks and tumor volumes were compared by each treatment.

**Results:** CKD5 treatment significantly suppressed human HCC cell growth in both normoxic and hypoxic condition, and peripherin expressions in the HCC cells were markedly increased after CKD5 treatment. When the peripherin expression was downregulated by siRNA, CKD5-induced apoptosis of HCC cells was decreased. In immunoblot assay, neither acetylation of HSP90 nor p21 expression were altered following CKD5 treatment, suggesting HSP90 and p21 were not related with the anti-cancer mechanism of CKD5. In *in vivo* experiments, combination therapy of CKD5 with sorafenib decreased tumor volume more effectively than sorafenib or CKD5 mono therapy (Figure 1). Histological and biochemical analysis demonstrated that CKD and sorafenib combination therapy was well tolerated *in vivo*.



#### Figure 1. The efficacy of tumor suppression in each treatment

**Conclusions:** CKD5 may enhance sorafenib efficacy through epigenetic regulation by increasing peripherin expression. Combination therapy of CKD5 with sorafenib could be a novel therapeutic option for HCC treatment.

Keywords: CKD581, Sorafenib, Hepatocellular carcinoma

# PE-160

# Dickkopf-1 Is the Potential Therapeutic Marker for Sorafenib Response in Hepatocellular Carcinoma

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**Aims:** Sorafenib, the multi-kinase inhibitor, is the only standard 1<sup>st</sup> line targeted anti-cancer agent for advanced hepatocellular carcinoma (HCC). Dickkopf-1 (DKK1) which is an antagonist of Wnt signaling has been known to be overexpressed in HCC tumors and serum of patients with HCC. In this study, we aimed to investigate whether DKK1 is a sorafenib therapeutic biomarker and to clarify whether DKK1 is a good therapeutic target.

**Methods:** Five Human HCC cell lines (Hep3B, HepG2, Huh7, SNU-449 and SNU-475) with different DKK1 expression were used in this study. Cell viability and proliferation level were determined by MTT assay. Expression of DKK1 after sorafenib treatment was analyzed by qRT-PCR, western blot and ELISA. To compare with clinical data, tissues and serum from patients with HCC treated sorafenib were collected and DKK1 level was analyzed using ELISA and qRT-PCR.

**Results:** The viability and proliferation of the sorafenib treated cells was decreased. Among them, Hep3B, which secretes the greatest amount of DKK1, showed the highest resistance.mRNA level of DKK1 estimated by qRT-PCR was displayed down regulation in all sorafenib-treated HCC cell lines. In addition, the sorafenib altered expression level of secreted DKK1 in Hep3B and HepG2 and these were confirmed by ELISA and western blot. Taken together, our results showed that Sorafenib inhibits DKK1 expression in a dose-dependent manner. Next, to identify on human sample, we investigated that DKK1 level in patients' sera using ELISA. As a results, DKK1 levels were lower in treated patients andthe expression level of DKK1 in HCC patients' tissue was significantly reduced after liver section or treatment for HCC.

**Conclusions:** We found that sorafenib down-regulated DKK1 expression in HCC cells and human samples. Our results indicate that DKK1 might be a useful serum biomarker for monitoring the therapeutic efficacy of sorafenib for HCC treatment. **Keywords:** Hepatocarcinoma, Dickkopf1, Biomarker, Sorafenib

# PE-161

# Silencing Alpha-Fetoprotein Augments the Effects of Sorafenib and Regorafenib in Human Hepatocellular Carcinoma Cells

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**Aims:** Tyrosine kinase inhibitors (TKIs), such as sorafenib and regorafenib, were approved as effective treatments for patients with advanced hepatocellular carcinoma (HCC). However, primary resistance towards these agents is observed in approximately 50% of patients and secondary resistance is expressed 3–4 months after treatment in many patients. Moreover, sorafenib provides a lower survival rate for patients having high serum alpha-fetoprotein (AFP) levels. AFP is a diagnostic marker, and also has a variety of biological functions. This study investigated whether AFP inhibition enhanced the anti-proliferative effects of TKIs in human HCC cell lines.

**Methods:** AFP-producing human HCC cell lines, Huh-7 and Hep3B, and non-AFP-producing SNU-series cell lines were used in this study. AFP expression was suppressed via AFP siRNA transfection. Cellular growth was analyzed via MTS assay and kinase signaling pathways were examined via immunoblot analysis.

**Results:** Lenvatinib, regorafenib, dasatinib, and sorafenib inhibited HCC cellular growth. Huh-7 and Hep3B cells were more susceptible to sorafenib and regorafenib than the other drugs. After AFP siRNA transfection, sorafenib or regorafenib treatments showed a synergistic anti-proliferative effect in Huh-7 and Hep3B cells. This growth inhibition was associated with the suppression of Akt phosphorylation

**Conclusions:** AFP suppression increases the anti-proliferative effect of sorafenib and regorafenib in human HCC cells. These results suggest that AFP silencing may play a synergistic role in the anti-tumor effect of some TKIs in human HCC cells. **Keywords:** Hepatocellular Carcinoma, AFP

# PE-162

# Establishment of 3D Multicellular Tumor Spheroids (MCTS) using Hepatocellular Carcinoma and Stromal cells for Screening Anti-cancer Therapeutic Agents

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**Aims:** Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and the second leading cause of cancer-related deaths worldwide. Tumor microenvironment is composed of myofibroblasts, fibroblasts, immune-

inflammatory cells, extracellular matrix, blood vessels, etc. and closely involved in multiple facets of tumorigenesis. Studies have shown that response to chemotherapy is highly affected by drug penetration through tumor tissue, highlighting the role of tumor microenvironment in cancer chemotherapy. Compared with tumor cell monolayer culture, multi-cellular tumor spheroid (MCTS) is superior in mimicking tumor microenvironment and thus a suitable model for studying drug penetration into tumor. The purpose of this study is to establish the MCTS model to investigate the interaction with the microenvironment in tumor and to investigate the effect of microenvironment on drug permeability.

**Methods:** To generate multicellular tumor spheroids, HCC cells were seeded at a density of 6 × 103 cells/well in 96-well roundbottom ultra-low attachment microplates. The plates were incubated for 3 days at 37 °C in a humidified atmosphere of 5% CO2. To generate MCTS, HCC cells and stromal cells (LX2, WI38, and HUVECs) were mixed at a 1:1 ratio. Diameter was measured using a confocal microscope and an image analyzer to determine the compactness of spheroid. Protein expression levels in MCTS were determined by immunoblots. For drug penetration study, fluorescent chemicals (e.g., verteporfin) were used and the distribution of drug within MCTS was determined by a LSM700 confocal microscope with a 425 to 440nm excitation and a 700 to 730nm emission filter set.

**Results:** Various multi-cellular tumor spheroid (MCTS) models were developed using HCC cell lines with various degrees of differentiation such as SNU449 (Well differentiated), SNU3059 and SNU3160 (moderately differentiated), and Hep3B (poorly differentiated). The volume, shape, and compactness of HCC MCTS were heterogeneous depending on the differentiation degree. Well differentiated SNU449 MCTS showed the least compactness of tumor spheroids, while Hep3B MCTS had the highest compactness. Of note, YAP/TAZ levels in HCC MCTS were significantly different. SNU449 MCTS model had a low level of YAP/TAZ, while Hep3B MCTS model had the highest level of YAP/TAZ expression. Drug penetration into tumor spheroids was significantly retarded due to the multi-cellular components within HCC MCTS. HCC MCTS with higher YAP/TAZ levels increased the compactness and inhibited drug penetration.

**Conclusions:** In this study, diverse MCTS models have been developed using HCC of different degrees of differentiation and stromal cells such as HSCs, fibroblasts, and endothelial cells. MCTS with poorly differentiated HCC showed an increased compactness of spheroids, an elevated level of YAP/TAZ and a limited drug penetration. Reducing tumor compactness or stromal activation should be considered to improve a response to chemotherapy in patients with advanced HCC.

**Keywords:** Multicellular tumor spheroid, 3D cell culture, Tumor microenvironment, Drug screening

#### PE-163

#### Dysregulated Fatty Acid Metabolism in Hepatocellular Carcinoma

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**Aims:** Studies are urgently needed on it molecular pathogenesis and biological characteristics of hepatocellular carcinoma (HCC). Dysregulation of fatty acid (FA) metabolism, in which aberrant activation of oncogenic signaling pathways alters the expression and activity of lipid-metabolizing enzymes, is an emerging hallmark of cancer cells, and it may be involved in HCC development and progression.

**Methods:** We summarize the characteristics of FA metabolism in HCC, focusing on the pathways of FA synthesis, oxidation, uptake and transport. We also provide a brief review of the relationship between NAFLD and HCC development.

Results: The current review summarizes the dysregulated FA metabolism in HCC and pathways through which this dysregulation may regulate HCC survival and growth. Aberrant activation of oncogenic signaling pathways regulates the expression and activity of lipid-metabolizing enzymes, thus reprogramming FA metabolism to promote HCC development and progression. Intracellular FAs are required for biosynthesis of most biological membrane lipids and signaling molecules, and are also used to provide energy to support HCCs survival and proliferation, when necessary, through  $\beta$ -oxidation process. HCC cells can employ appropriate metabolic pathways as different situation demands. Intrahepatic cholangiocarcinoma (ICC) and HCC exhibits differential requirement for de novo lipogenesis and distinct response to therapeutic approaches focusing on inhibition of exogenous FA uptake. Non-alcoholic fatty liver disease related obesity and diabetes have increasingly emerged as two major factors responsible for the rise in prevalent of HCC.

**Conclusions:** Our understanding of dysregulated FA metabolism and associated signaling pathways may contribute to the development of novel and efficient anti-tumor approaches for patients with HCC.

# **PE-164**

# Preoperative Neutrophil-Lymphocyte Ratio (NLR) and CEA as a Prognostic Factor in Patients with Synchronous Colorectal Cancer with Liver Metastasis

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**Aims:** Recently, the neutrophil-to-lymphocyte ratio (NLR), which is considered to be an inflammatory response marker, has been reported to be associated with the prognosis in patients with

various type of cancer including colorectal cancer. CEA is also widely accepted as a clinically significant prognostic indicator of recurrence and therapeutic benefit in colorectal cancer. So, our study determines the prediction ability of a combination of NLR and CEA in sCRLM patients.

**Methods:** Eighty-three patients who histologically diagnosed as CRLM were selected. Their laboratory and clinical data were collected retrospectively. NLR was defined as the neutrophil to lymphocyte ratio. Using ROC curve analysis, the cutoff value of NLR was calculated based on which patients were assigned to a high NLR (more than 1.94) group and low NLR (less than 1.94) group. A cutoff value of 100 ng/mL for serum CEA level was used in light of the previous literature.

**Results:** Poorly differentiated histology and CEA level of colon cancer was strongly and significantly correlated with high NLR (P=0.026 and P=0.005, respectively). The multivariate analysis identified the lymph-node metastasis, inflammatory complication, and high NLR as independent prognostic factors for OS and DFS in all patients (P=0.037, P<0.001, P=0.010, respectively). Survival rate were compared into three groups according to their NLR and CEA levels. Patients with both levels low were assigned to group 1, both high were group 3, and the rest were group 2. Patients in group 1 had a significantly longer OS and DFS than group 3 did (P=0.026 and 0.009, respectively)

**Conclusions:** In conclusion, elevated preoperative NLR is strongly correlated with both survival and recurrence in patients who have been diagnosed with resectable synchronous colorectal cancer with liver metastases. The combination of NLR and CEA level could be a more powerful prognostic marker than NLR alone. **Keywords:** Colon cancer, Liver, Metastasis, NLR

# PE-165

# Hypomethylation of Long Interspersed Nuclear Element-1 (LINE-1) Leads to Activation of CD133 and ST18 in Hepatocellular Carcinoma

Yu Rim Lee<sup>1</sup>, Kyunghwa Kim<sup>2</sup>, Se Young Jang<sup>1</sup>, Won Young Tak<sup>1</sup>, Young Oh Kweon<sup>1</sup>, Bina Jung<sup>1</sup>, Gyoun Eun Kang<sup>1</sup>, Sang Kyung Seo<sup>1</sup>, Jung Gil Park<sup>3</sup>, Hye Won Lee<sup>4</sup>, Young Seok Han<sup>5</sup>, Jae Min Chun<sup>5</sup>, Soo Young Park<sup>1</sup>, and Keun Hur<sup>2</sup>

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**Aims:** Long interspersed nuclear element-1 (LINE-1) hypomethylation, representing global DNA methylation level, is associated with prognosis via activation of oncogenic functions of genes. This experiment was performed to evaluate prognostic implication of LINE-1 methylation in patients with hepatocellular carcinoma (HCC) and the possible mechanisms related to oncogene activation. **Methods:** Ninety-six HCC patients between October 2014 and September 2015 at Kyungpook National University Hospital, Daegu, South Korea were enrolled for this prospective study. Quantitative pyrosequencing was performed to quantify the methylation level of for CpG sites in the LINE-1 promotor. The expression of CD133 and ST18 were measured by immunohistochemistry and their correlation with LINE-1 methylation levels were analyzed.

Results: LINE-1 was significantly hypomethylated in tumor tissues compared with nontumor tissues (64.0 ±11.6% vs. 75.6 ±4.0%, respectively, P<0.0001). In this study population, LINE-1 hypomethylation group had a large proportion of female gender, smaller tumor size, and nonexistence of ascites (P<0.05). Contrary to previous reports, LINE-1 hypomethylation was not an independent risk factor for overall survival and disease progression (all P>0.05). A total of 81 (84.4%) patients had demethylation of LINE-1 ( $\Delta$ MI<0), and 15 (15.6%) patients had hypermethylation of LINE-1 ( $\Delta$ MI $\geq$ 0). HCC with demethylation of LINE-1 ( $\Delta$ MI<0) had higher CD 133 expression than HCC with hypermethylation of LINE-1 ( $\Delta$ MI $\geq$ 0) (*P*=0.011). Moreover, when patients divided into two groups based on the mean value of tumor line-1 methylation, ST18 showed borderline significance in distinguishing the LINE-1 hypomethylation group than the other (P=0.053).

**Conclusions:** LINE-1 demethylation is associated with expression of CD133 and ST18 in Hepatocellular carcinoma. In this study, LINE-1 hypomethylation was not related to overall survival and disease progression, this is probably due to the enrollment of HCC patients with various tumor stages and liver function.



Keywords: Long interspersed nuclear element-1, Hepatocellu lar Carcinoma

# PE-166

#### Autophagy Inhibitor, Chloroquine Did Not Affect Tumor Development in a Transgenic Mouse Model of HCC

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**Aims:** Autophagy is an intracellular recycling process by which damaged or superfluous proteins are delivered to lysosomes for degradation, and then utilized as energy resources and macromolecular precursors. Autophagy in cancer is a highly debated subject. Research has shown that autophagy can become either tumor-promoting or tumor-suppressive depending on cellular or genetic context. Here, we investigated the role of autophagy in hepatocellular carcinoma (HCC) by applying an autophagy inhibitor, chloroquine to a transgenic mouse model of HCC.

**Methods:** Transposons were constructed encoding an activated from of RAS (HRAS<sup>G12V</sup>) and short hairpin suppressing P53 (shp53). Transposons were hydrodynamically delivered to livers of 6-week-old C57BL/6 mice. Mice were administered intraperitoneally with chloroquine at a daily dose of 60mg/kg for five weeks. Control mice were given a phosphate buffered saline (PBS). Mice were monitored at least twice per week.

**Results:** The sizes and numbers of tumor nodules were similar between chloroquine group and control when livers were harvested at 5 weeks after the delivery of oncogenes. Animal survivals were not significantly different between the two groups, suggesting that the treatment with chloroquine does not affect liver tumorigenesis induced by HRAS<sup>G12V</sup> plus shp53.

**Conclusions:** Our study suggests that autophagy inhibition has a minimal role in HCC under the genetic context of RAS signaling activation and P53 downregulation.

Keywords: Autophagy, HCC, Transgenic mouse, Chloroquine

#### **PE-167**

#### Down-Regulation of Non-Coding circHIPK3 RNA as Human Hepatocellular Carcinoma Biomarker

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**Aims:** Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with poor prognosis and high risk of recurrence. Previous studies have shown that various microR-NAs (miRNAs) are frequently dysregulated in HCC, which contributes to cancer development and progression. Nonetheless, it is still unclear the regulation mechanism of miRNAs. Circular non-coding RNA (circRNA) is highly conserved and stable covalently closed RNA circles with gene-regulatory potential. Recently, one abundant circRNA from *HIPK3* gene, circHIPK3, has been identified, and its function has been elucidated as multiple miRNAs sponge. Thus, we aim to investigate the clinical relevance of circHIPK3 in HCC.

**Methods:** We analyzed clinical specimens from 152 pairs of HCC and corresponding normal liver (NL) tissues. Total RNAs were isolated from clinical tissues using qiagen kit. CircHIPK3 expression levels were determined by quantitative real-time PCR (qRT-PCR), and its expression was normalized with GAPDH. In addition, we analyzed the correlation between circHIPK3 expression and various clinicopathological features of HCC patients.

**Results:** CircHIPK3 expression was significantly down-regulated in HCC tissues compared to corresponding NL tissues (P=0.036). In HCC patients, circHIPK3 expression was strongly suppressed in more advanced tumors (P<0.001). Further correlation analysis showed that circHIPK3 expression was significantly associated with T-stage (P<0.001), TNM stage (P<0.001), BCLC stage (P<0.001), and alpha-fetoprotein (AFP) expression (P=0.033).

**Conclusions:** We have determined clinical significances of circHIPK3 expression in HCC, which may provide clinical evidence for the potential of circHIPK3 as novel markers for diagnosis and predicting prognosis in HCC patients.

**Keywords:** Human hepatocellular carcinoma, Biomarker, Non-coding RNA,

#### **PE-168**

#### The Adequate Resection Margin of Hepatocellular Carcinoma According to the Tumor Microenvironment

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**Aims:** There is no consensus on the safe resection margin in patients with hepatocellular carcinoma (HCC). We investigated the change of tumor microenvironment according to the resection margin.

**Methods:** We prospectively collected the specimen of 60 patients with HCC. We selected three portions of specimens as follows: tumor, 1cm and 2cm margin normal tissue. We investigated the expression status of tumor microenvironment genes. We compared the expression status according to recurrence, HCC gross type and positron emission tomography (PET) positivity. We divided the patients into two groupsas follows: group 1 included expanding and vaguely nodular types whereas group 2 included nodular with perinodular extension, multinodular confluent and infiltrative types.

**Results:** Group 2 had a higher prevalence of PET positive [6 (37.5%) vs 10 (62.5%)] and recurrence [5 (16.7%) vs 17 (56.7%)]. However, in cases with more than 1cm resection margin, there was no difference of recurrence rate [9 (75%), P=0.017 vs 8 (44.4%), P=0.06]. Beta-catenin was significantly

decreased and E-cadherin was significantly increased according to the resection margin in group 1. Group 2 and PET positive patients showed Group 1 did not show any significant change of beta-catenin and E-cadherin until 2cm resection margin.

**Conclusions:** Our data suggest that patients with HCC of expanding and vaguely nodular gross types may safely undergo surgical resection with a narrow resection margin and patients with HCC of nodular with perinodular extension, multinodular confluent and infiltrative gross type must undergo surgical resection with more than 2cm resection margin because of tumor microenvironment condition.

# PE-169

## AFP and Histologic Grade Are Significant Predictors for Intrahepatic Recurrence of Hepatocellular Carcinoma after a Hepatectomy

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**Aims:** The alpha fetoprotein(AFP) elevation in hepatocellular carcinoma(HCC) has been shown to correlate with poor tumor differentiation, early intrahepatic recurrence after a hepatectomy. We aimed to examine the AFP levels, tumor burden, histologic grade, and other clinicopathological variables compare with two groups of HCC patients either with low or high AFP. This comparison helps us to predict intrahepatic recurrence of HCC.

**Methods:** We retrospectively reviewed medical records of HCC patients who received hepatectomy between January 2009 and December 2015. Perioperative data were collected from the patients.

**Results:** Of 181 recipients, we divided two groups either with low or high AFP. Histological variables were analyzed with serum AFP. We observed intrahepatic recurrence rates, disease free survival, and 3years/5years overall survival rates for 7years.

**Conclusions:** In high AFP and poorly differentiated HCC patients had early intra-hepatic recurrence and low survival rates. Prospective study for AFP genes of HCC patients would be planned.

# PE-170

# Lipids-Induced Exosomal lincRNA-ROR Released from Hepatocellular Carcinoma Cell Promotes Tumor Cell Growth through the PI3K/Akt Pathway

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**Aims:** The lipid-related metabolic dependence is a hallmark of cancer. Exosomes in tumor microenvironment are enriched in lipids and their accumulation in cells might modulate recipient cell homeostasis. We investigated whether lipids and lipids-in-

duced exosomes released from HCC cells can induce a tumorpromoting phenotype and the underlying mechanisms.

**Methods:** Human HCC cell lines (Huh-7, SNU-761, and SNU-3058) were incubated with oleic acid (OA) or control vehicle. The released exosomes were isolated, quantified, and applied to HCC cells.

**Results:** Incubation of HCC cells with OA enhanced proliferation, migration and invasion of cells. Furthermore, OA upregulated long noncoding RNA regulator of reprogramming (lincRNA-ROR) mRNA expression in Huh-7 and SNU-3058 cells, whereas its expression in SNU-761 cells did not change. Exosomes collected form OA-treated cells were enriched with lincRNA-ROR mRNA, and upregulated proliferation and invasion of HCC cells through the activation of PI3K/Akt pathway.

**Conclusions:** These findings suggest that lipids-induced exosomal lincRNA-ROR released from hepatocellular carcinoma cell promotes tumor cell growth through the PI3K/Akt pathway. **Keywords:** Hepatocellular carcinoma, Oleic acid, lincRNA-ROR

# PE-171

# Second Mitochondria-derived Activator of Caspases, Lysine Demethylase 3A, and P21 are Responsible for Sorafenib Resistance in Hepatocellular Carcinoma

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**Aims:** Sorafenib treatment is regarded as a first-line chemotherapy in patients with advanced hepatocellular carcinoma (HCC), although most patients are refractory to this drug. In this study, we aimed to establish Sorafenib-resistant HCC cell line and explore various signals involved in cell survival in order to investigate the mechanism of Sorafenib resistance in HCC.

**Methods:** Huh7-Sorafenib resistant (SR) HCC cell line was established by culturing Huh7 HCC cells in increasing doses of Sorafenib. Gene expression, cell proliferation, and protein expression were determined by RT-PCR, MTS assay and Western blot. To identify the role of each signaling involved in Sorafenib resistance, cells were treated with LCL161 (a second mitochondria-derived activator of caspases (Smac) mimetic) and/or lysine demethylase 3A (KDM3A)-specific small interfering RNA (siRNA), or p21-specific siRNA.

**Results:** Huh7-SR cells exhibited lower gene and protein expression of Smac than Huh7 cells. Sorafenib sensitivity of Huh7-SR cells as well as Huh7 cells was increased with LCL161, and the Sorafenib sensitizing effect of LCL161 was more potent in Huh7-SR cells than in Huh7 cells. KDM3A gene expression was higher in Huh7-SR cells than in Huh7 cells. Huh7-SR cells demonstrated improved sensitivity to Sorafenib following siRNA-mediated KDM3A knockdown. Moreover, Sorafenib sensitivity was further increased after KDM3A knockdown in

combination with LCL161 treatment. Huh7-SR cells showed increased expression of p21 compared to Huh7 cells. Proliferation of Huh7-SR cells was markedly decreased with Sorafenib treatment after p21 knockdown, although there was no change in the antitumor effect of Sorafenib before and after p21 knockdown in Huh7 cells.

**Conclusions:** Smac, KDM3A and p21 are involved in Sorafenib resistance mechanism in HCCs, which might be new therapeutic targets to overcome Sorafenib resistance.

Keywords: Smac, KDM3A, P21, Sorafenib resistance

#### Liver Cirrhosis, Portal Hypertension with Cx. Clinical

#### **PE-172**

#### Prospective Analysis of Transjugular Portosystemic Shunt in Difficult-to-manage Hepatic Hydrothorax

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**Aims:** Pleural effusions complicate end-stage liver disease in 5% of patients. Early and careful identification of cause and related complications is imperative for appropriate management and patient survival. Unlike refractory ascites, data is limited on safety and efficacy of TIPS in cirrhotic patients with refractory refilling pleural effusion.

**Methods:** We analyzed a consecutive cohort of hospitalized cirrhotic patients having pleural effusion (PE) at admission. Baseline HVPG and PE tap was done to determine etiology and presence of infection. We determined the rate and predictors of PE resolution with standard medical treatment (SMT), need for intercostal drainage (ICD) for repeated pleurocentesis, and efficacy and safety of TIPS in hepatic hydrothorax.

Results: Of 1149 admissions involving 762 cirrhotics (mean CTP- 10.6±1.8) with PE, 967(84.2%) had hepatic hydrothorax (HH), 181(15.8%) had tubercular PE (TBPE) and despite comparable HVPG, CTP and MELD scores at baseline, patients with HH in comparison to TBPE developed more complications (HE-41.6% vs. 30.2%, AKI- 48.6% vs. 37%, pneumonia- 16.1% vs. 7.2%, bacteremia-11.7% vs. 6.1% and septic shock-14.1% vs. 8.3%; all P<0.01) on follow up. Among admissions with HH, 475(49.2%) were symptomatic (mainly dyspnea-30.1%, cough-24% and chest pain-16.9%), 24.7% were isolated left sided and PE tap revealed SBE in 219(22.9%). Presence of co-existing SBP (52.5%; Odd's ratio, OR: 5.2) and ICD placement (24.2%; OR: 3.1) were independent predictors for SBE. Baseline HVPG (16.6 ± 4.4 vs. 16.4 ± 5.1; P-0.6) and MELD scores (22.3  $\pm$  6.9 vs. 21.9  $\pm$  7.3; P-0.1) were comparable in SBE versus no SBE. In 43% of admissions, HH responded to SMT

alone and 133(13.8%) required ICD for repeated pleurocentesis. 41 patients were carefully selected for TIPS [based on lower CTP score (TIPS vs no TIPS-  $9.9 \pm 1.6$  vs  $10.7 \pm 1.8$ ; P-0.02), lower MELD (18.7  $\pm$  5.5 vs. 21.5  $\pm$  7.5; P-0.03) and higher HVPG (19  $\pm$  4.7 vs. 16.4  $\pm$  4.8; P-0.08)]. Despite reduction in pressure gradient (mean portal venous – mean right atrial pressure) from 23.1  $\pm$  3.8 mm Hg to 7.2  $\pm$  2.5 mm Hg), only 20(48.2%) had complete resolution of HH, with no difference in mortality rates. Main complications of TIPS in HH were post TIPS encephalopathy (8 patients, 6 resolved) and ischemic hepatitis (4 patients, 2 resolved). 321(35.9%) patients with HH had in-hospital mortality and independent predictors were MELD >25, SBE non-response to SMT and septic shock requiring vasopressors

**Conclusions:** Only one-half of hepatic hydrothorax resolve with standard medical therapy and need for any intervention including TIPS generally herald poor outcome. Role of hepatic hemodynamics in predicting complications and resolution of hydrothorax is limited. Early referral for liver transplantation is imperative. **Keywords:** Cirrhosis, Portal hypertension, Bleed, Shunt

# PE-173

#### Comparative Study of Cirrhosis Stage in Patients with HBV Infection and HBV/HDV Co-Infection in Mongolia

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**Aims:** There are about 350 million people with HBV infection in the world.. 5% or about 15-20 million people of them are co-infected HDV. Every year an average of 7500 people are detected HDV new infection and 1,000 people die due to HDV infection in the United States. The Middle East, Pakistan, Central and Northern Asia, some areas of Africa, have high prevalence of HDV infection. North America, Northern Europe, Southern Africa and East Asia have low prevalence of HDV infection. There is 70-90% higher risk of liver cirrhosis in patients with HBV/HDV co-infection than patients with HBV infection. Comparative study of cirrhosis stage in patients with HBV infection and HBV/HDV co-infection

**Methods:** Our study continued from January 2015 to March 2017 and we measured liver fibrosis stage in patients with HBV infection and HBV/HDV co-infection using a Fibroscan (Fibroscan 502 Touch, Echosens, Paris, France) who are controlled in Happy Veritas Clinic and Diagnostic Center. When we measured liver fibrosis stage in 5504 patients with HBV infection, 20% or 1115 of the patients is determined HDV co-infection . In our study in random sampling cases are selected 354 patients with HBV monoinfection and 177 of all patients have HBV/HDV co-infection. We selected parameters from patients medical histories in our study, such as serologic markers of HBV quantification of HBV and HDV in serum samples, blood test,

liver function tests, and liver fibrosis stage. Summary statistics were perfomed using sPSS 22.0 siftware.

**Results:** 354 patients 47.7 %(169) was men. Range with an average age of 44±17 (range 18-75 years old) were included the study. According to the comparative study in laboratory tests, ALT level was HBV - 44 (36; 51.5) and HBV/HDV co-infection 61 (39.8; 97.5), AST level was HBV – 39.1(30; 83) and HBV/HDV co-infection – 50 (33.1; 77.8), Platelet count was HBV-193±66 and HBV/HDV - 181±62.8. When we compared liver fibrosis stage were HBV- F0 67(37.9%), HBV/HDV-F0 57(32.2%), HBV-F1 22(12.4%), HBV/HDV-F1 17(9.6%), HBV-F2 39(22%), HBV/HDV-F3 29(16.4%), HBV/HDV-F3 41(23.2%), HBV- F4 20(11.3%) and HBV/HDV – F4 23(13%). In table 1 shows the difference of liver fibrosis by age group.

**Conclusions:** 65.5% of all patients with HBV/HDV co-infection are from 30 to 50 years old. Liver fibrosis of patients with HBV/ HDV co-infection is a higher 11.88kPa than patients with HBV mono-infection. Our study shows that, the hepatitis is more severe in patients with HBV/HDV co-infection and the platelet count is less than HBV infection only.

Keywords: Co-infection, Cirrhosis, HBV, HDV

# PE-174

#### Platelet Count Spleen Diameter Ratio to Predict Esophageal Varices in Mongolian Patients with Liver Cirrhosis

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**Aims:** Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices is one of the major complications of portal hypertension. To validate whether the platelet count/spleen size ratio can be used to predict the presence of esophageal varices in Mongolian patients with hepatic cirrhosis.

**Methods:** This was a cross-sectional study to validate the diagnostic test for hepatic cirrhosis and was performed between 2017 to 2018. Only stable patients were included in the study. Patients with active gastrointestinal bleeding at the time of admission were excluded. All patients underwent screening upper gastrointestinal endoscopy. Biochemical parameters were evaluated, and ultrasound was used to measure the longest diameter of the spleen. The platelet count/spleen diameter ratio was calculated and analyzed to determine whether it can predict the presence of esophageal varices.

**Results:** A total of 31 patients were included. The mean age was  $51.23 \pm 14$  years; 17 (55%) were men, and 14 (45.0%) women. Child-Pugh classification, 18 (58%) patients were classified as class A, 11(37%) as class B, and 2 (5%) as class C. The platelet count/spleen diameter ratio to detect esophageal varices independent of the grade showed using a cutoff value of  $\leq$  884.3, had 82% sensitivity, 71% specificity, and positive and negative predictive values of 93% and 41%, respectively.

**Conclusions:** The platelet count to spleen diameter ratio may be a useful tool for diagnosing EVs in liver cirrhosis noninvasively when endoscopy facilities are not available.

Keywords: Platelet count/spleen diameter ratio, Esophageal varices

# PE-175

# Natural History of Patients with Compensated Cirrhosis and a Hepatic Venous Pressure Gradient >20 mm Hg: A Prospective Longitudinal Cohort Study

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**Aims:** HVPG >10 mm Hg predicts clinical decompensation (CD) in compensated cirrhotics. A few cirrhotics exhibit high HVPG (>20mm Hg) despite no CD. Their natural history, pattern of CD (ascites, hepatic encephalopathy, variceal bleed) and complications (HCC, mortality) is largely unknown.

**Methods:** Consecutive compensated cirrhosis patients with HVPG >5 mm Hg (n=747) were followed up every 3-6 monthly for CD. They were sub-classified at baseline based on HVPG (<12 mmHg (low HVPG group), 12-20 mmHg (Intermediate HVPG group) and >20 mmHg (High HVPG group). We analyzed only the low and high HVPG groups. Multivariate Logistic regression was used to identify predictors

Results: 295(39.4%) patients developed clinical decompensation (CD) at mean follow up of  $1.9 \pm 0.3$  years. In comparison to low HVPG group, first CD in high HVPG group developed early  $(1.4 \pm 0.3 \text{ years vs } 2 \pm 0.3 \text{ years}, P=0.02)$ , more frequently (ascites- 27.1% vs 13.2%, variceal bleed- 31.9% vs 7.9%, AKI- 31% vs 12.8%, HCC- 12.4% vs. 3.9%; all P<0.05) with higher mortality (15.9% vs 1.9%; P<0.05). There was no significant correlation between baseline HVPG level and grade of esophageal varices (P=0.457). All patients in high HVPG group received carvedilol (maximum dose-25 mg/d, divided) and a repeat HVPG measured after a mean duration of  $1.8 \pm 0.4$  years showed suboptimal HVPG response (≥20% reduction in HVPG or <12 mmHg) in 26.6% patients (mean HVPG reduction, 3.3± 1.3 mm Hg). Etiology of cirrhosis and grade of varices were not significantly associated with CD or HVPG response. On multivariate analysis, baseline HVPG >20 mm Hg (hazard ratio [HR], 5.09; 95% confidence interval [CI], 2.909-8.926, P=0.001) and high MELD score (HR, 1.125; 95% CI, 1.066- 1.187, P=0.001) were independent predictors of CD.

**Conclusions:** An HVPG of >20mm Hg independently predicts early and more frequent CD in compensated cirrhotics. Only a quarter of these patients respond to carvedilol and hence mandates us for careful HVPG monitoring and low threshold for additional drugs or interventions.

Keywords: Cirrhosis, Portal hypertension, Bleed, Ascites

# **PE-176**

#### Treatment of a Duodenal Variceal Bleeding by Transjugular Intrahepatic Portosystemic Shunt

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**Aims:** Bleeding from duodenal varix is a rare complication of portal hypertension but potentially serious and can cause massive gastrointestinal bleeding. Because of the low incidence of cases, most effective treatment methods have not been established.

**Methods:** This is a case report of successful treatment of duodenal variceal bleeding by transjugular intrahepatic portosystemic shunt (TIPS).



**Results:** Case: A 61 year old male was admitted to hospital due to hematemesis and melena. He had been diagnosed with alcoholic liver cirrhosis 10 years ago. Six years ago, he had experienced gastric variceal bleeding, which was treated by balloon-occluded retrograde transvenous obliteration (BRTO). At presentation, vital signs were as follows: blood pressure 148/70 mm Hg, heart rate 89 bpm, temperature 36.5°C and saturation > 98%. Digital rectal examination showed fresh blood. Initial laboratory results as follows: hemoglobin (Hb) 6.5 g/dL, WBC 8.3 x10<sup>3</sup>/mL, platelet 174x10<sup>3</sup>/mL. The patients received terlipressin and broad-spectrum antibiotics. Esophagogastroduodenoscopy was performed on the day of admission. It showed grade 1 esophageal varices without any stigma of recent bleeding (Fig. A). The stomach showed only previous BRTO-induced scar on fundus. Duodenum was evaluated up to 2<sup>nd</sup> portion, there was no evidence of old or recent bleeding. There was no evidence of bleeding focus on the colonoscopy which was performed on the on the next day. He remained stable for 2 days even though melena persisted. At 3 days after admission, hematochezia developed again and blood pressure drop to 108/60. Gastrointestinal bleeding CT scan was performed immediately and showed venous dilatation on 3<sup>rd</sup> portion of duodenum (Fig. B). We performed esophagogastroduodenoscopy again, which showed stigma of recent bleeding from duodenal varices on the 3<sup>rd</sup> portion (Fig. C). We have successfully treated a patient with duodenal variceal bleeding by TIPS (Fig. D).

**Conclusions:** This case brings further evidence that duodenal variceal bleeding can be treated with TIPS.

Keywords: Liver cirrhosis, Variceal bleeding, TIPS,

# PE-177

Reappraisal of the Accuracy of Diagnostic Criteria for Spontaneous Bacterial Peritonitis in Cirrhotic Patients with or without Hepatocellular Carcinoma: A Preliminary Result

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**Aims:** We aimed to reevaluate whether the traditional cutoff count of polymorphonuclear-leucocyte(PMN, $\geq$ 250/mm<sup>3</sup>) would be still optimal to diagnose spontaneous bacterial peritonitis(SBP) in cirrhotics having a hepatocellular carcinoma(HCC) or not.

**Methods:** This preliminary study included 136 consecutive patients having cirrhosis with(n=60) or without HCC(n=76) and a positive ascitic-fluid(AF) culture at the first exploratory paracentesis between 2007 and 2016 as the SBP group; and 202 cirrhotics with neither bacterascites on the first AF specimen nor any typical symptoms suggestive of peritoneal infection as the non-SBP control group. Among the SBP group, none had clinical suspicion of secondary or tertiary peritonitis and malignant ascites, and history of non-HCC cancers.

Results: Fever(28%) and E. coli(22%) were the most common symptom and isolated pathogen, respectively in the SBP group. There was no patient with ascitic-PMN≥250/mm<sup>3</sup> in the control group. Ascitic white-blood-cell and PMN counts, and lactatedehydrogenase were significantly higher in the SBP group, whereas glucose and serum-ascites-albumin-gradient were higher in the control group Ps<0.05). Total-protein and pH in the AF were similar in both groups. For the entire SBP patients, receiver-operating-characteristic analysis to determine the diagnostic performance of ascitic-PMN≥250/mm<sup>3</sup> showed a sensitivity of 87% and a specificity of 95%, comparably between the LC and HCC subsets. There were no differences in both AF results and symptoms between SBP patients with cirrhosis and HCC. The 90th-percentile limits for the ascitic-PMN counts were 246 and 466/mm<sup>3</sup>, respectively for the LC and HCC subsets with SBP. The number of SBP patients with ascitic-PMN<250/ mm<sup>3</sup> was 11(8%), consisting of 6 cirrhosis and 5 HCCs.

**Conclusions:** Based on our results, an update or revision of the old threshold count for ascetic-PMN may be taken into consideration to be timely treated with antibiotics in not only HCC

patients but cirrhotics who have established or suspected SBP, leading to prevention of undertreatment of serious infection and overtreatment of sterile ascites.

**Keywords:** Spontaneous bacterial peritonitis, Liver cirrhosis, Hepatocellular carcinoma, Ascites polymorphonuclearleucocyte

# PE-178

#### Correlating Abdominal Ultrasound and Upper GI Endoscopic Findings of Schistosomiasis

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**Aims:** This study aims to correlate the ultrasound and endoscopic findings of portal hypertension in patients with schistosomiasis and to determine which among these findings showed the best predictive values for the presence of endoscopic signs of portal hypertension. This study also aims to determine the correlation of Hepatitis B and/or Hepatitis C co-infection with the endoscopic and sonographic characteristics of patients with schistosomiasis.

**Methods:** This is a prospective, cross-sectional study of 82 adult patients diagnosed with schistosomiasis. Each patient underwent screening upper endoscopies to assess the presence of varices and portal hypertensive gastropathy and holoabdominal ultrasound with doppler studies to assess the extent of hepatosplenic involvement. One-way ANOVA, Chi-square, Fischer's exact test were performed to determine which ultrasound findings showed the best predictive values for the presence of endoscopic signs of portal hypertension.

**Results:** Of the 82 patients, almost half (47.6%) had esophageal varices (54% small vs 46% large), 8.5% had gastric varices, and 46.3% had portal hypertensive gastropathy (PHG) on screening upper endoscopy. A significant correlation was found between the presence of esophageal varices, gastric varices, and PHG with the following ultrasonographic findings: grade of liver appearance, surface irregularity, spleen length, and size of right lobe. Seventeen percent tested positive for HbsAg while none tested positive for anti-HCV. Among the patients with hepatitis B/schistosomiasis co-infection, grade III (severely coarsened) echopattern, irregular liver surface, and the presence of short gastric vein collateral had a significant correlation with findings of portal hypertension on endoscopy.

**Conclusions:** Among patients with schistosomiasis, the grade of liver appearance, surface irregularity, spleen length, and size of right lobe on abdominal ultrasound strongly predicts the presence of endoscopic signs of portal hypertension.

**Keywords:** Schistosomiasis, Portal Hypertension, Ultrasound, Endoscopy

# PE-179

# Treatment of Esophageal-Gastric Bleeding in Patients with Portal Hypertension Syndrome

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**Aims:** The aim of the study was to improve the results of treatment of patients with bleeding from varicose veins (VV) of the esophagus and stomach.

**Methods:** Over the past 12 years, we have experience in treating 110 patients with esophageal and gastric bleeding from the esophagus and cardiac gastric divisions on the basis of the faculty surgery of the Tashkent Medical Academy. The age of the patients ranged from 19 to 79 years. The men were 68 (61.8%), women - 42 (38.2%). The cause of cirrhosis of the liver in 90% of patients was viral hepatitis. Clinical laboratory and instrumental methods of investigation, including endoscopic, ultrasound (ultrasound) and magnetic resonance imaging (MRI), have been performed to diagnose esophageal-gastric bleeding in patients with cirrhosis.

Results: According to the methods of treatment, patients were divided into two groups: treatment was started with conservative hemostatic therapy with the use of drugs that reduce portal pressure (ednit, nitroglycerin, octreotide); To stop bleeding from the BPV of the esophageal-gastric zone, the Sengstacken-Blackmore probe was used in combination with hemostatic therapy. The results of treatment showed the effectiveness of conservative hemostatic therapy in combination with drugs that reduce portal pressure in 37.3% of patients. A lethal outcome occurred in 10% of cases. After using the Sengstacken-Blackmore probe in combination with conservative methods, a lethal outcome was noted in 7.3% of observations. It should be noted that against a background of esophageal-gastric bleeding, a mixed form of hypoxia is observed due to disruption of transport and utilization of oxygen by tissues, and therefore studied the state of homeostasis in the posthemorrhagic period in 27 patients with esophageal-gastric bleeding of various severity. It turned out that the leading factor in the development of disturbance of homeostasis is the posthemorrhagic hypoxia of tissues, especially the liver, due to a decrease in the oxygen tension in the mixed venous blood and in the blood of the portal system. Based on this in 14 patients in the complex of conservative therapy included a drug that reduces hypoxia (the carrier of oxygen perfluorane). The positive effect of perfluorane on the gas transport function of blood was detected, a significant increase in oxygen tension was observed not only in the arterial blood, but also in mixed venous and portal blood. The beneficial effect of perfluorane on ischemic liver tissue is due to its positive effect on hepatocytes. In recent years, in the treatment of esophageal-gastric bleeding, along with the stitching of bleeding perforated varicose veins and in order to reduce portal pressure, stem vagotomy with pyloroplasty at the height of esophagealgastric bleeding with good immediate results was performed in 7 patients. To the above, it should be added that the hemostatic effect of stem vagotomy is due not only to the hypotensive effect on portal pressure, but also to the suppression of the peptic activity of gastric juice, which is one of the leading factors in the development of esophageal-gastric bleeding.

**Conclusions:** Diagnosis of esophageal-gastric bleeding should be complex (ultrasound, endoscopy and MRI). In the complex of conservative therapy of esophageal-gastric bleeding it is expedient to include preparations - carriers of oxygen. A promising method of surgical treatment of esophageal-gastric bleeding is the flushing of the bleeding BPV of the esophagus and cardia in combination with stem vagotomy and pyloroplasty.

Keywords: MRI, Varicose veins, Ultrasound, Gastric bleeding

# PE-180

#### Validation of Usefulness for Korean Paper and Pencil Test to Detect Minimal Hepatic Encephalopathy in Korea

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**Aims:** We recently developed a new Korean paper and pencil test (KPPT) as a 'copyleft' test. The aim of this study is to validate the usefulness for a KPPT to detect minimal hepatic encephalopathy (MHE) in Korea.

**Methods:** Two hundred twenty five patients with hepatitis B virus related cirrhosis without overt HE were prospectively enrolled in 13 centers for two years. All patients underwent psychometric hepatic encephalopathy score (PHES, gold standard),

KPPT and Korean stroop test. MHE was defined as  $\leq$  -5 points in PHES. And MHE in KPPT defined an impaired performance under - 1.5 standard deviations from the mean on more than 2 tests in short version (number connection test-A, number connection test-B, digit span test-forward, digit span test-backward and symbol digit modality test) and long version (short version + word list memory test and MCG complex figures test).

**Results:** The mean age of the patients was 53.4 years with males predominant (67.1%). Prevalence of MHE was 20.9% in using PHES, 25.3% in using KPPT short version, and 41.3% in using KPPT long version. There was significant difference between patients with MHE and those without MHE in all tests that constitute KPPT (P<0.05). Also, all tests that constitute KPPT except copy value of MCG Complex Figures test showed a statistically significant difference between patients with MHE and those without MHE, according to OnTime+OffTime (word+inhibition) of Korean stroop test. In the diagnosis of MHE, the concordance between PHES and KPPT short version was 85.8% (sensitivity 76.6%, specificity 88.2%), and the concordance between PHES and KPPT long version was 73.3% (sensitivity 85.1%, specificity 70.2%). The area under the curve of total score of KPPT short version and long version were 0.809 (95% C.I 0.737-0.880, P<0.001) and 0.820 (95% C.I 0.755-0.884, P<0.001) in the diagnosis of MHE.

**Conclusions:** KPPT have good correlation with conventional PHES to detect MHE in patients with cirrhosis. Also, the diagnostic performance of the KPPT short version is comparable to the diagnostic performance of the long version.

**Keywords:** Liver cirrhosis, Hepatic encephalopathy, Diagnosis, Psychometry test

# PE-181

#### A Case of Acute Hemoperitoneum Due to Spontaneous Rupture of the Umbilical Vein in Cirrhosis

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**Aims:** In patients with portal hypertension, acute hemoperitoneum due to spontaneous rupture of umbilical vein was rarely reported. We report a case of spontaneous rupture of umbilical in a cirrhotic patient without extrinsic trauma history.

**Methods:** A 50-year-old male without previous *trauma* was transported to the emergency department after experiencing sudden crampy whole abdominal pain.

**Results:** He has had a regular check up for liver cirrhosis. The abdomen was distended with generalized tenderness but without peritoneal signs. Laboratory data showed a hemoglobin of 6.8 g/dl; the white blood cell count was 13260/mm3 and the platelets were 128000/mm3. Liver function tests were normal,

except for aspartate aminotransferase 70 U/L, a prothrombin time of 18.5 s, with a control of 11.2, and an albumin of 2.2 mg/dl. Abdominal CT scan showed a umbilical vein with a massive contrast leakage to the peritoneum and the presence of a large amount of hemoperitoneum. An emergent angiographic embolization procedure was performed to stop bleeding from paraumbilical vein. The patient recovered well after angiographic embolization procedure and was discharged home on the sixth day after the procedure.

**Conclusions:** In a cirrhosis patient who has rapid onset of abdominal distention and pain, as well as hypotension and tachycardia, intraperitoneal hemorrhage must be considered. Computed tomography scan typically represent a dilated umbilical vein and periumbilical contrast leakage. Early recognition and their intervention with embolization of the ruptured vessel are critical for the successful management of these patients.

**Keywords:** Liver cirrhosis, Hemoperitoneum, Umbilical vein, Rupture

# PE-182

#### Adverse Events after Non-Hepatic Surgeries in Patients with Liver Cirrhosis Undergoing General or Neuraxial Anaesthesia

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**Aims:** Limited information is available on the outcomes after surgery in patients with liver cirrhosis receiving general or neuraxial anaesthesia. The purpose of this study is to compare the postoperative complications and mortality between cirrhotic patients with general and neuraxial anaesthesia.

**Methods:** From the claims data from the National Health Insurance program in Taiwan, we identified cirrhotic patients aged  $\geq$  20 years who underwent non-hepatic surgery in 2008-2013. Using propensity-score matching procedure, we selected 8194 cirrhotic patients with neuraxial anaesthesia and 8194 cirrhotic patients with general anesthesia during the same period for comparison. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of postoperative complications and mortality were calculated between cirrhotic patients with general anesthesia.

**Results:** Compared with patients received neuraxial anaesthesia, patients received general anesthesia had increased risk of postoperative pneumonia (OR, 2.08; 95% CI, 1.48-2.90), septicaemia (OR, 1.24; 95% CI, 1.04-1.48), acute renal failure (OR, 2.31; 95% CI, 1.57-3.42), intensive care (OR, 4.63; 95% CI, 3.73-5.75), and 30-day mortality (OR, 2.09; 95% CI, 1.15-3.82). Longer length of hospital stay (*P*<0.0001) and higher medical expenditure (*P*<0.0001) were also noted in patients with general anesthesia than patients with neuraxial anaesthesia.

**Conclusions:** Cirrhotic patients received general anesthesia had more complications and higher mortality after non-hepatic

surgeries than those received neuraxial anaesthesia. Physicians in gastroenterology and perioperative care team need to pay attention to the anesthesia type for this susceptible population. **Keywords:** Liver cirrhosis, Surgery, General anesthesia, Neuraxial anesthesia

# PE-183

# Longitudinal Outcomes of the Application of Non-Selective Beta-Blockers in Portal Hypertension: Real Life Data in Gangwon-Do Province

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**Aims:** The effect of non-selective  $\beta$ -blockers (NSBB) on survival in cirrhosis is still disputed. Moreover, most physicians use low-dose NSBB for cirrhosis due to decreased systemic pressures. We investigates whether low-dose NSBB can have beneficial effects in cirrhosis and the NSBB impact on survival in both primary prophylaxis (PP) and secondary prophylaxis (SP).

**Methods:** We conducted study involving 890 consecutive patients with/without NSBB treatment in either PP or SP; 596 patients in PP (NSBB = 371, non-NSBB = 225) and 291 patients in SP (NSBB = 217, non-NSBB = 74). The NSBB group was divided into two sub-groups: low-dose NSBB group ( $\leq$  80 mg) and high-dose NSBB group (> 80 mg).

**Results:** In the PP group, 273 received only NSBB, while 98 received NSBB + endoscopic band ligation (EBL) in NSBB patients; 170 patients were in the low-dose and 201 patients were in the high-dose group. During the median follow-up of 40.0 months (Interquartile range [IQR], 15.0–58.8), NSBB showed similar survival rates to non-NSBB (log-rank, P=0.685). In addition, there was no difference in survival between low-dose NSBB compared to high-dose NSBB (log-rank, P=0.311). In the SP group, 217 received NSBB + EBL among the NSBB patients; 87 patients in the low-dose group and 130 patients in the high-dose group. The probability of survival was higher in patients who received NSBB (P<0.001). Multivariate analysis also revealed that NSBB significantly prolonged survival (adjusted hazard ratio, 0.490; P<0.001). However, overall survival did not significantly differ between low-dose NSBB and high-dose NSBB (P=0.131).

**Conclusions:** In cirrhosis, NSBB therapy was associated with a reduced risk of mortality in SP but not in PP. Moreover, our study showed that there was a similar effect on survival when low-dose NSBB was used in SP.

**Keywords:** Portal hypertension, Non-selective beta-blockers, Survival

#### PE-184

# Predictors of Fifty Days In-Hospital Mortality in Patients with CNNA

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**Aims:** Culture negative neutrocytic ascites is a variant of spontaneous bacterial peritonitis. But there are conflicting reports regarding the mortality associated with culture negativeneutrocytic ascites. Therefore we aim to determine the predictors of mortality associated with culture negativeneutrocytic ascites in a larger sample population.

**Methods:** We analysed 170 patients consecutively admitted to intensive care unit with diagnosis of culture negative neutro-cyticascites. The clinical, laboratory parameters, etiology of liver cirrhosis was determined along with the scores like model for end stage liver disease, child turcotte pugh were recorded.

**Results:** The 50 day in-hospital mortality rate in culture negative neutrocytic ascites was 39.41% (n=67). In univariate analysis, means of parameters like total leucocyte count, urea, bilirubin, alanine aminotransferase, aspartate aminotransferase, international normalized ratio, acute kidney injury, septic shock, hepatic encephalopathy and model for end stage liver disease were significantly different among survived and those who died (P value ≤0.05). Cox proportional regression model showed the hazard ratio (HR) of acute kidney injury was 2.212 (95%CI: 1.334-3.667), septic shock (HR = 1.895, 95%CI: 1.081-3.323) andmodel for end stage liver disease (HR = 1.054, 95%CI: 1.020-1.090). Receiver operating characteristics curve showed aspartate aminotransferase had highest area under the curve 0.761 (95%CI: 0.625-0.785).

**Conclusions:** Patients with culture negative neutrocytic ascites have a mortality rate comparable to spontaneous bacterial peritonitis. Aspartate aminotransferase, alanine aminotransferase, acute kidney injury, model for end stage liver disease and septic shock are the independent predictors of 50 days in-hospital mortality in culture negative neutrocytic ascites.

#### **PE-185**

#### Comparative Study of Bone Mineral Density between Chronic Liver Disease and General Population

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**Aims:** Chronic liver disease (CLD) may be associated with decrease in bone mineral density (BMD) in several studies. However, there is no specific guideline or data for the surveillance of osteoporosis in CLD patients. The aim of this study is to compare BMD between general population and CLD, and to evaluate the change of BMD according to liver disease status. **Methods:** A total of 440 subjects were enrolled in the study.

Among those, 148 CLD patients at Daejeon St. Mary's hospital were enrolled from January 2006 through December 2017, and 292 people without underlying liver disease who had taken general health care program at Daejeon St. Mary's hospital from January 2016 through December 2017 were selected by age and sex matching based on the enrolled CLD patients. BMD was measured by dual X-ray absorptiometry (DEXA) in femur and lumbar spines. The 10 year fracture risk was calculated using fracture risk assessment tool (FRAX).

Results: The BMD of both spine and femur were lower in CLD than in general population (GP) (P<0.001 in spine, and P=0.003 in femur). The prevalence of osteoporosis in CLD was higher than GP (25.0 % vs. 6.2%, P<0.001). FRAX were 4.21±3.69% in CLD and 3.27±1.53% in GP (P=0.004). In multivariate analysis, CLD and low BMI were the significant factors for the osteoporosis (P<0.001, OR=5.10, 95% CI=2.77-9.42 and P=0.019, OR=0.89, 95% CI=0.81-0.98, respectively). In subgroup analysis according to CLD status (chronic hepatitis (CH) vs. liver cirrhosis (LC)), BMD of spine in LC group showed significantly lower than those in CH group (-1.58±1.57 vs. -0.72±1.76, P=0.003). The prevalence of osteoporosis in LC was higher than CH (38.6 % vs. 16.5%, P=0.002). In multivariate analysis of osteoporosis, older age (>55 years) and LC were the significant factors (OR=1.07, 95% CI=1.03-1.12, P=0.003, and OR=2.90, 95% CI=1.29-6.49, P=0.010, respectively). LC group showed higher 10 year fracture risk compared with CH group (5.01±4.66% vs. 3.71±2.85%, respectively) (P=0.041).

**Conclusions:** This study demonstrates the progression of CLD may influence bone metabolism and develop osteoporosis. This may imply the 10 year fracture risk in CLD patients rises as the disease aggravates from CH to LC. Therefore, surveillance of BMD may be useful when managing CLD, especially in LC patients with age over 55. Further prospective study with large number of patients is needed.

**Keywords:** Liver cirrhosis, Bone mineral density, Osteoporosis, Liver disease

#### Table 1. Baseline characteristics of patients

	Normal	CLD	<b>D</b> valuo	
	(n = 292)	(n = 148)	P value	
Age	54.81 ± 9.86	54.63 ± 9.48	0.852	
Sex (male)	152 (52.1)	78 (52.7)	0.900	
BMI	23.74 ± 2.79	23.84 ± 3.96	0.796	
Diabetes	16 (5.5)	17 (11.5)	0.024	
High blood pressure	59 (20.2)	38 (25.7)	0.191	
Drinking	62 (21.2)	23 (15.5)	0.153	
Smoking	61 (20.9)	21 (14.2)	0.088	
Steroid	0 (0.0)	6 (4.1)	0.001	
Spine BMD	-0.46 ± 1.45	-1.05 ± 1.74	<.001	
Femur BMD	-0.35 ± 1.13	-0.78 ± 1.32	0.003	
FRAX	3.27 ± 1.53	4.21 ± 3.69	0.004	
Osteoporotic status			<.001	
Normal	147 (50.3)	63 (42.6)		
Osteopenia	127 (43.5)	48 (32.4)		
Osteoporosis	18 (6.2)	37 (25.0)		

Dataset are composed of matching by age and sex (2:1).

NAFLD, Clinical

# PE-186

Nonalcoholic Fatty Liver Disease is Associated with Coronary Artery Calcification in Asymptomatic Individuals

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is related closely to risk factors for coronary artery disease (CAD), but it is unclear whether NAFLD independently contributes to asymptomatic individuals. Coronary artery calcium (CAC) scanning is the predictor of coronary events. We investigated the association of coronary artery calcification with NAFLD in asymptomatic adults.

**Methods:** This is the cross-sectional study performed in Hansol Hospital Healthcare Center. NAFLD was defined as cases with the typical ultrasonographic findings without excessive alcohol consumption, medications causing hepatic steatosis or other chronic liver diseases. CAC was evaluated using the Agatston method.

**Results:** We enrolled 312 subjects (mean age,  $46.8 \pm 8.7$  years; 60.7% males) without known liver disease or a history of ischemic heart disease. NAFLD was found in 27% of the enrolled 312 subjects and CAC > 100 with moderate-high risk of CAD was found in 10.3% of subjects. Male gender (odds ratios (OR), 2.857; 95% confidence intervals (CI), 1.169-6.147), diabetes mellitus (OR, 2.739; 95% CI, 1.092-5.638), increased age (OR, 1.208; 95% CI, 1.071-1.316), and NAFLD (OR, 1.862; 95% CI, 1.065-3.592) were the independent factors that increased the risk of CAC > 100 in binary logistic regression.

**Conclusions:** NAFLD is associated with increased coronary artery calcification independent of traditional risk factors. The assessment of CAC may be useful in identifying NAFLD patients at risk of future cardiovascular events even in asymptomatic individuals.

Keywords: NAFLD, Coronary artery calcification

# PE-187

Comparison of Clinical Outcomes Following Hepatic Resection in NAFLD-related Hepatocellular Carcinoma and HBV-related Hepatocellular Carcinoma : Propensity Score-Matched Analysis

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<sup>1</sup>Departments of General Surgery, Yonsei University College of Medicine, Seoul, Korea; <sup>2</sup>Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; <sup>3</sup>Department of Pathology, Yonsei University College of Medicine, Seoul, Korea **Aims:** Since it was first reported in 1990, NAFLD-related HCC has increased with the increase in metabolic syndrome. In the prior study, the prognosis for NAFLD-related HCC is controversial, and a comparison with HBV-HCC is insufficient. Clinical characteristics of HCC caused by NAFLD or HBV were compared in a retrospective analysis.

**Methods:** A total of 338 patients underwent hepatic resection for HCC in Severance Hospital between 2005 and 2015 were retrospectively reviewed. Metabolic syndrome is defined according to the NCEP-ATP III report. Occult HBV infection was identified by nested PCR analysis using known primers. Propensity analysis was carried out using logistic regression in order to minimize lead-time bias caused by lack of surveillance in NAFLD patients. Surgical and oncologic outcomes were compared between two groups.

**Results:** Among 338 patients underwent hepatectomy for HCC, 23(6.9%) had NAFLD-HCC. Before matched analysis, cirrhosis was more detected in HBV-HCC patient. (30.4 vs 61.3%, P=0.004). Surgical outcomes were similar between the two groups, especially in morbidity rates (22.0 vs 26.1%, P=0.795), in hospital stay (12.0 vs 13.4 days, P=0.379) and in intraoperative bleeding (495 vs 442mL, P=0.659). Tumor size is larger in the NALFD group than in the HBV group (4.6 vs 3.3cm, P=0.004). After a median follow-up of 63.0 months (range 0-139 months), although not statistically significant, the survival analyses after propensity score-matching showed similar 5-year overall survival (44.3 vs 44.3%, P=0.317) and recurrent-free survival rates (67.4 vs 65.1%, P=0.483) between the two groups.



Fig.1. Survival analysis after hepatectomy for HCC in the HBV and NAFLD group : (A) Disease-free survival (5YR DFS 53.7 vs 44.3%, p=0.651) and overall survival (5YR survival 84.7 vs 65.1%, p=0.108) before matched analysis: (B) Disease-free survival (5YR DFS 44.3 vs 44.3%, p=0.317) and overall survival (5YR survival 67.4 vs 65.1%, p=0.483) after matched analysis.

**Conclusions:** In NAFLD group, the tumor size is larger than HBV group at the time of diagnosis, but there were no statistically significant differences in the long-term outcomes between the two groups after matched analysis for tumor size. These results

might result from a delayed diagnosis in patients with a more advanced tumor stage rather than to a more aggressive biology of tumor.

Keywords: NAFLD, NASH, Metabolic syndrome, HCC

#### **PE-188**

#### Weight Loss Significantly Reduces the Risk of Chronic Kidney Disease Development in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** Weight loss is regarded as a pivotal treatment strategy in non-alcoholic fatty liver disease (NAFLD). However, there is a lack of data evaluating whether weight loss affects long-term kidney function in this population. Therefore, we investigated the impact of weight changes on adverse kidney outcomes in NAFLD patients using a community-based, prospective cohort with a 12-year follow-up.

**Methods:** Among 10,030 participants from the Korean Genome Epidemiology Study, 1,774 NAFLD patients were included in this study. Patients were categorized into four groups according to the quartiles of time-averaged percent weight change (TA-%weight change). Study outcomes were development of chronic kidney disease (CKD) and rapid decline of kidney function. The median value of TA-%weight change was –1.3% (interquartile range, –4.2 to 1.1).

**Results:** Patients in the first quartile (TA-%weight change < -4.2%) had a significantly lower risk of CKD development (hazard ratio [HR]=0.531, 95% confidence interval [CI]=0.409-0.690) and rapid decline of kidney function (HR=0.598, 95% CI=0.458-0.782), compared with patients with minimal changes. Decreased risk of CKD development in patients of the first quartile remained significant in the overweight (HR=0.528, 95% CI=0.372-0.751) and obese (HR=0.482, 95% CI=0.307-0.755) groups.

**Conclusions:** In conclusion, this study is the first to demonstrate that weight loss, above an average of 4.2%, was associated with significant risk reduction of CKD development and rapid decline in kidney function. It suggests that significant and sustained weight loss may improve long-term kidney outcomes in patients with NAFLD.

**Keywords:** Body weight, Chronic kidney disease, Non-alcoholic fatty liver disease, Obesity

#### PE-189

# New Risk Prediction Model of Hepatocellular Carcinoma in Treatment-NaïVe

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**Aims:** The use of oral antiviral agent was known to effectively decrease the development of hepatocellular carcinoma (HCC). However, despite the use of antiviral agents, a risk of HCC development still remained in these patients. Therefore, the aim of this study is to identify the risk factor of HCC development and to develop the reliable risk prediction model in chronic hepatitis B patients receiving highly potent antiviral agents such as entecavir (ETV) or tenoforvir (TDF).

**Methods:** From 2007 to 2012, 1470 patients with chronic HBV infection initially treated with ETV or TDF in 4 hospitals were recruited, and those with a history of HCC or short follow-up duration less than 12 months after antiviral therapy were excluded. A new HCC risk model was developed with based on multivariable Cox regression model in the derivation dataset (2center, n=944), and was validated using validation dataset (2 other center, n=298).

Results: The 3 and 5-year cumulative incidence rates of HCC were 3.9% and 13.9%, respectively, in the derivation dataset, and 4.2% and 18.1%, respectively, in the validation dataset, respectively (P=0.08). In the derivation dataset, four significant predictors associated with HCC development, such as age, albumin, sex, and liver cirrhosis (LC) at the time of antiviral therapy were identified by multivariate analysis and bootstrapping analysis. The AASL (Age, Albumin, Sex, and LC) - HCC score was developed based on these factors, and simplified to an integer scoring system. When AASL-HCC score was divided into  $\leq$ 5, 6-14, and  $\geq$ 15 (low, intermediate, and high risk group), the 5-year cumulative incidence rate of HCC were 0%, 4.5%, 17.6%, respectively, in the derivation dataset, and 0%, 8.4%, 30.9%, respectively, in the validation dataset (P>0.05). Furthermore, AASL-HCC score showed the reliable AUROC for the prediction of HCC development in the derivation dataset (0.813, CI 0.772-0.854), compared with CU-HCC (0.758, CI 0.705-0.811), GAG-HCC (0.810, CI 0.764-0.856), REACH-B (0.640, CI 0.561-0.719), and PAGE-B (0.719, CI 0.656-0.782), respectively.

**Conclusions:** HCC risk after highly active antiviral therapy has remained in CHB patients. A simple HCC prediction model using AASL-HCC score based on age, albumin, sex, and LC in treatment-naïve CHB patient treated with ETV or TDF showed reliable prediction performance. We expect that this model helps to predict the occurrence of HCC in these patients.

**Keywords:** Chronic hepatitis B, Hepatocellular carcinoma, Entecavir, Tenofovir

# PE-190

#### Subclinical Hypothyroidism and Low-Normal Thyroid Function Are Associated With Nonalcoholic Steatohepatitis and Fibrosis

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Aims: Variations in level of thyroid-stimulating hormone (TSH) within the reference range of thyroid hormone could have negative health effects. We evaluated the effect of plasma TSH levels within the euthyroid range on the severity of histological damage associated with nonalcoholic fatty liver disease (NAFLD). Methods: We performed a cross-sectional study of 425 subjects with biopsy-proven NAFLD (mean age, 53 years; 52% male) who participated in the Boramae NAFLD study from January 2013 to January 2017. Each subject underwent an anthropometric assessment and laboratory and clinical evaluations. Of the subjects, 282 were assigned to a strict-normal thyroid function group (plasma level of TSH, 0.4 to 2.5 mIU/L). Patients with low thyroid function were assigned to groups of subclinical hypothyroidism (plasma level of TSH above 4.5 mIU/L with a normal thyroid hormone level; n [ 59) or low-normal thyroid function (higher plasma TSH level [2.5 to 4.5 mIU/L] with a normal thyroid hormone level; n [ 84). Multivariate logistic regression analysis was used to identify factors independently associated with nonalcoholic steatohepatitis (NASH) and advanced fibrosis. Results: NASH and advanced fibrosis were found in higher percentages of subjects with low thyroid function vs strict-normal thyroid function (52.4% vs 37.2% for NASH and 21.0% vs 10.6% for advanced fibrosis; P<.01). Among subjects with low thyroid function, a higher proportion of patients with subclinical hypothyroidism had NASH and associated advanced fibrosis vs patients with low-normal thyroid function (57.6% vs 48.8% for NASH and 25.4% vs 17.9% for advanced fibrosis; P<.01). Subjects with low thyroid function had more extensive hepatic steatosis with greater severity of balloon degeneration and fibrosis. In multivariate analyses, low thyroid function was significantly associated with NASH (odds ratio, 1.61; 95% CI, 1.04–2.50; P [ .035) and advanced fibrosis (odds ratio, 2.23; 95% CI, 1.18-4.23; P [ .014). Risks of NASH and advanced fibrosis increased significantly with plasma concentration of TSH (Ptrend <.05 for each).

Conclusions: Subclinical hypothyroidism and low-normal

thyroid function are independent predictors of NASH and advanced fibrosis, confirming the relationship between these diseases. ClinicalTrials. gov, Number: NCT02206841.

Keywords: Hepatic Steatosis, Thyroid Dysfunction, Thyroxine

# PE-191

#### Moderate Alcohol Drinking in Nonalcoholic Fatty Liver Disease: Friends or Foes?

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**Aims:** Whether moderate alcohol intake is beneficial or not remains an unsolved issue. Recent studies suggested that moderate alcohol consumption is associated with beneficial effects related to the prevention of cardiovascular diseases. Moderate alcohol consumption leads to a higher risk of hepatocellular carcinoma in patients with chronic viral liver diseases. However, the effects of moderate alcohol intake in patients with nonalcoholic fatty liver disease are unclear. In this review, we analyzed, from various perspectives, the effect of moderate alcohol consumption in patients with nonalcoholic fatty liver disease.

**Methods:** We reviewed three cohort studies and five cross-sectional studies.

**Results:** The results showed that moderate alcohol consumption was negatively related with the incidence of nonalcoholic steatohepatitis, liver fibrosis, and homeostasis model assessment of insulin resistance. However, moderate alcohol consumption was positively related with the incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease. The results of the analysis of the relationship between moderate alcohol consumption and the levels of triglycerides, total cholesterol, high-density lipoprotein, and hypertension were diverse. More clinical data are needed to draw a conclusion about the effects of moderate alcohol consumption in patients with nonalcoholic fatty liver disease.

**Conclusions:** Clinical data are still lacking and conclusions cannot be drawn on how much alcohol is : ppropriate for each individual patient. Additional studies should be undertaken on the analysis of adequate alcohol intake, patterns of intake, and positive and negative effects.

Keywords: Nonalcoholic fatty liver, Alcohol, Moderate drinking

# PE-192

# Serum Paraoxonase 1 (PON1) Activity and Oxidative Stress in Young Children with Non-Alcoholic Fatty Liver Disease

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**Aims:** The aim of this study was to determine the level of serum paraoxonase 1 (PON1) in young children with Non-Al-coholic Fatty Liver Disease compared to healthy controls, and to examine the association of biochemical and hematological parameters with oxidative stress.

**Methods:** Anthropometric measurements, blood pressure, biochemical and hematological parameters, abdominal ultrasonography (USG) and clinical examinations were assessed in all subjects to diagnose NAFLD. Forty seven young children diagnosed Non-Alcoholic Fatty Liver Disease and Forty seven age and gender matched healthy controls were enrolled and Serum PON1 levels, total antioxidant status (TAS), total oxidant status (TOS) were measured. Oxidative stress index (OSI) was calculated to indicate the degree of oxidative stress.

**Results:** A total of ninety four children (51 boys, 43 girls) were included in this study, with 33 children age  $\leq$  10 years and 61 adolescents. Serum PON1 activity is significantly reduce in NAFLD children than control (110.81±7.43 Vs 152.73±12.72, *P*=0.003). In children with NAFLD, TAS level is significantly lower than control (1.19±0.22 Vs 1.37±0.41, *P*=0.03), whereas TOS is increased significantly (0.24±0.05 Vs 0.17±0.03, *P*=0.05). Our results show that OSI is significantly higher in NA-FLD group in comparison to the control groups (0.20±0.08 Vs 0.12±0.06, *P*<0.05).

**Conclusions:** Our results suggest that NAFLD are associated with decreased PON1 activity and increased oxidative stress. Thus, in NAFLD patients, low level serum PON1activity may contribute in pathogenesis of carotid atherosclerosis from the childhood.

Keywords: NAFLD, PON1, TAS, OSI

# PE-193

#### Association between Non-Alcoholic Fatty Liver Disease Incidence and Colorectal Cancer

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases(CLD) globally(prevalence of 25.2%). Recently, It is stipulated that NAFLD may be an independent risk factor for developing colorectal cancer(CRC). We analyzed the prevalence of NAFLD in patients with CRC and the effect of NAFLD on the prognosis of CRC.

**Methods:** Total 293 patients with CRC were enrolled from March 2003 to April 2018. Patients who had other CLD including chronic viral hepatitis B/C, autoimmune hepatitis, and primary biliary cholangitis and significant alcohol abuse (more than 140 g/week in women and 210 g/week in men) were excluded. Hepatic steatosis was evaluated by non-enhanced computed tomography (CT) scan. We measured values of regions of interest (ROI) for 3 times in liver and spleen, respectively. We diagnosed NAFLD when the average ROI of liver 10 less than it of spleen. 123 healthy controls who took non-enhanced CT scan were also analyzed.

**Results:** The median age was 65.0(interquartile range[IQR] 54.0-73.0 years), and median Body mass index(BMI) was 24.02 (IQR 21.4-26.1). The median BMI of CRC patients without NA-FLD was 23.75(IQR 21.3-25.7), and CRC patients with NAFLD was 25.16(IQR 21.8-27.0). The prevalence of Hypertension was 49.8%(146/293) in CRC group, and 35.77%(4/123) in control group (P=0.009). The prevalence of Diabetes Mellitus was 32.08% (94/293) in CRC group, and 16.26%(20/123) in control group(P=0.001). The prevalence of NAFLD was significantly higher in CRC group(24.57%, 72/293) than in the healthy group. (13%, 16/123) (P=0.008). Overall survival did not showed significant difference between NAFLD group and non-NAFLD group (P=0.706 by log-rank test).

**Conclusions:** The prevalence of NAFLD in patients with CRC is significantly higher than control group. But the overall survival didn't show singnificant difference. Further studies are needed to specify the effect of NAFLD on CRC prognosis in terms of recurrence and progression.

Keywords: NAFLD, Colorectal cancer

#### PE-194

# Improvement of Hepatic Fat Fraction with Carnitine-Orotate Complex in Chronic Liver Disease: A Randomized Controlled Trial

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**Aims:** Carnitine has been shown to beneficial effects on hepatic fat content using semi-quantitative computed tomography. We investigated the effects of carnitine complex on intrahepatic fat in patients with chronic liver disease using MRI PDFF.

**Methods:** The purpose of this study was to compare the changes in intrahepatic fat measured by MRI-PDFF after randomization for 12 weeks with carnitine complex and placebo in 58 chronic liver disease patients. Also we evaluated that changes in Fibroscan, biochemical test (liver function test, lipid profiles, glucose, Hemoglobin A1C), psychometric hepatic encephalopathy score and quality of life were compared.

**Results:** The mean age of the patients was 44.6 years in the test group and 50.0 years in the control group. The mean in-

trahepatic fat fraction performed with MRI-PDFF was 17.2% and 14.7% in the test and control groups, CAP using Fibroscan was 323.6 and 309.5, and Liver stiffness was 10.0 and 6.6, respectively. Intrahepatic fat measured by MRI-PDFF decreased significantly after 12 weeks in carnitine treatment (17.2  $\pm$  8.7 vs. 15.2 ± 7.7, P<0.001). But intrahepatic fat increased significantly (14.7 ± 8.4 vs. 15.2 ± 9.4, P<0.001) in the control group. Also, the rate of change (%) of intrahepatic fat measured by MRI-PDFF was statistically significantly between the two groups,  $10.4 \pm 26.7$  in the test group and  $-4.4 \pm 32.0$  in the control group. (p value 0.45) There was no statistically significant difference between the two groups in the proportion of normal subjects with ALT at 12 weeks (14.29% in the test group and 3.11% in the control group) questionnaire), the total score of all items was  $0.3 \pm 0.4$  and  $0.1 \pm 0.3$  at 12 weeks, respectively, and there was no statistically significant difference between the two groups (P=0.1113). However, in the CLDQ sub-items, the test group showed a statistically significant improvement at 12 weeks (0.3 ± 0.6 vs -0.1 ± 0.5, P=0.0107) (0.3 ± 0.5 vs -0.1 ± 0.5, P=0.0025) in the test group at 12 weeks than the control aroup.

**Conclusions:** The 12-week administration of carnitine complex reduced intrahepatic fat in patients with chronic liver disease.

**Keywords:** Chronic liver disease, Carnitine, Hepatic steatosis, Magnetic resonance image

# PE-195

#### Altered Biochemical and Hematological Profile of Fatty Liver Disease Patients in Western Nepal

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**Aims:** Fatty liver disease (FLD) is one the most common liver disease in the world, however, there are limited studies on biochemical and hematological features of fatty liver disease. Different laboratory tests are extremely useful in better understanding of diseases, and thereby, confirm clinical diagnosis for the better management of disease. The aim of the present study was to demonstrate the significant changes in biochemical and hematological parameters in FLD patients of western Nepal compared with control group.

**Methods:** About 49 patients with FLD and 27 healthy control subjects from the outpatient clinic of the Internal Medicine Department, Fishtail Hospital and Research Centre Pokhara, Nepal were enrolled in the study. Hepatosteatosis is studied by abdominal ultrasonography to confirm the diagnosis of FLD. The anthropometric parameters: height, weight, waist and hip circumferences, blood pressure were measured, and body mass index (BMI) and waist/hip ratio (WHR) were calculated. Overnight fasting blood samples were collected from the patients and controls to analyze biochemical tests: lipid profile, liver function tests, renal function tests, blood sugar, HbA1c, and hematological tests: hemoglobin, WBC and platelet counts.

**Results:** With the increased level of serum triglyceride in the patients with FLD, total cholesterol, LDL-cholesterol had a significantly increasing trend (P<0.05); whereas HDL-cholesterol was found significantly decreased in comparison to control group. The levels of alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and Gamma-GT were noticed significantly difference in the cases as compared to those in the controls (P<0.05). Other biochemical and hematological parameters also noticed significant difference.

**Conclusions:** Most of the patients with FLD were found asymptomatic. The study revealed that fatty liver patients have dyslipidemias, abnormal liver function tests, increased trend of blood sugar and HbA1c, and hematological test parameters were significantly different compared to control group.

# PE-196

#### Association Between Vitamin D Deficiency and Suspected Nonalcoholic Fatty Liver Disease in an Adolescent Population

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**Aims:** Recent studies have shown that vitamin D deficiency is associated with obesity and metabolic syndrome. The purpose of the study is to examine the relationship between vitamin D deficiency and nonalcoholic fatty liver disease (NAFLD) in adolescents.

**Methods:** Data were obtained from the Korean National Health and Nutrition Examination Survey 2008-2014. A total of 3,878 adolescents were included. Vitamin D deficiency was defined as a 25-hydroxyvitamin D concentration < 20 ng/mL, and suspected NAFLD was defined as a alanine transaminase concentration > 30 U/L.

**Results:** Vitamin D deficiency was noted in 78.9%. Age, body mass indexes, waist circumferences, and blood pressure levels, as well as glucose, cholesterol and triglyceride levels were significantly higher in adolescents with suspected NAFLD than in adolescents without suspected NAFLD, while the mean vitamin D level was significantly lower in adolescents with suspected NAFLD. The multivariate-adjusted odds of suspected NAFLD were higher with increased age, male gender, obesity, and metabolic syndrome. Vitamin D deficiency was at higher risk for suspected NAFLD (odds ratio 1.76, 95% confidence interval 1.05-2.94) after adjustment for age, gender, obesity and metabolic syndrome.

**Conclusions:** Vitamin D deficiency is associated with suspected NAFLD independently of obesity and metabolic syndrome in adolescents.

**Keywords:** Vitamin D deficiency, Non-alcoholic fatty liver disease, Adolescent, Obesity

# PE-197

#### Impact of Tamoxifen on Development of NAFLD

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**Aims:** Tamoxifen and aromatase inhibitors (AI) suppress the action of estrogen and are used in the adjuvant therapy of breast cancer patients. Recently, the use of these drugs is increasing, there are still few studies between the incidences of nonal-coholic fatty liver disease (NAFLD) and these drugs. The aim of this study was to investigate the incidence of NAFLD after tamoxifen and AI use and the high risk patients.

**Methods:** This retrospective study included consecutive 702 patients taking tamoxifen or AI more than 2 years between 2007 to 2017 in a tertiary hospital. The occurrence of NAFLD was determined by ultrasound or pre-contrast CT. The primary outcome was the incidence of *de nov*o NAFLD increase of fatty liver grade in ultrasound.

**Results:** Mean age of the patients was  $50.4 \pm 10.3$  years and 466 (66.4%) received tamoxifen, and 236 (33.6%) received AI. The incidence or worsening of NAFLD was 35.0 % during the median 37 months observational period, which was significantly higher in tamoxifen group than AI group (40.8% vs. 23.7%, P=0.039). In multivariate analysis, tamoxifen increased the risk or severity of NAFLD 1.50 times than AI [hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.11-2.03, P=0.009] as well as body mass index (HR 1.07, 95% CI 1.03-1.11, P<0.001). However, when analyzed for diabetic patients, tamoxifen did not significantly exacerbate NAFLD compared to AI.

**Conclusions:** TMX significantly increases the incidence of de-novo NAFLD or severity of NAFLD, especially in non-diabetic breast cancer patients. Therefore, when tamoxifen is used for a long-term period, it is necessary to investigate and careful consideration the above side effects.

**Keywords:** Nonalcoholic fatty liver disease, Tamoxifen, Aromatase inhibitor

# PE-198

#### Critical Appraisal for Low-Carbohydrate Diet in Nonalcoholic Fatty Liver Disease

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**Aims:** The lifestyle modification is cornerstone for NAFLD. Low carbohydrate diet has showed favorable effects for body weight as well as hepatic fat in several reports. In this study, we investigated the efficacy and safety of the low-carbohydrate high-fat diet in patients with NAFLD.

**Methods:** In this study, we searched MEDLINE, and EMBASE (January 1, 2000 to May 30, 2017) with English publication. All clinical trials which primary endpoint was changes of hepatic steatosis or aminotransferase activity using low carbohydrate diet program were include. A total of 11 intervention studies have been conducted on the effects of a low-carbohydrate diet in NAFLD.

**Results:** In the literature on the low-carbohydrate high-fat diet in patients with NAFLD, the number of subjects was small, the study period was <6 months, and the criteria for carbohydrate intake were variable. Moreover, no RCT used liver biopsy. Therefore, there remains little evidence supporting that the low-carbohydrate diet is superior to the low-fat diet in the management of fatty liver disease. The low-carbohydrate diet seems to increase the protein intake ratios and satiety, and leads to a decrease in total caloric intake. Nevertheless, long-term clinical data of >2 years maintenance of a very low-carbohydrate highfat diet are insufficient.

**Conclusions:** In conclusion, to present the evidence of low-carbohydrate diet as a treatment of NAFLD is still lack, additional investigations and evidence-based studies should be conducted to evaluate its long-term stability. Most current studies focused on the efficacy of the very-low-carbohydrate diet; however, long-term feasibility and safety data of the very-low-carbohydrate diet are needed.

**Keywords:** Low carbohydrate diet, Non-alcoholic fatty liver disease, Intrahepatic fat

# PE-199

## Appropriateness of Liver Biopsy for Nonalcoholic Fatty Liver Disease in Obese Patients during Laparoscopic Cholecystectomy for Gallstone Disease

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**Aims:** Obesity is well known as a risk factor for gallstone disease and is also a risk factor for fatty liver. Before laparoscopic cholecystectomy, it is not easy to detect fatty liver, except for the cases of severe fatty liver by blood chemistry and imaging diagnostic tools. However liver biopsy is particularly useful in patients without definite clinical manifestations. Liver biopsy is invasive and is not recommended except in special cases, but hepatic biopsy is not a relatively risky procedure during laparo-

scopic cholecystectomy. Therefore, we investigated the clinical characteristics in biopsy proven non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in obese patients during laparoscopic cholecystectomy for gallstone disease.

**Methods:** We retrospectively reviewed medical records in obese patients with gallstone disease who underwent laparoscopic cholecystectomy with liver biopsy. The definition of obesity was based on the Asian obesity criteria. (overweight :23~24.9, obese class I :>25, & obese class II >30). Total 74 patients were included, and 30 patients were diagnosed as fatty liver(A) and compared with patients without fatty liver disease(B) using various parameters.

**Results:** There were 9 male and 21 female in fatty liver group and 18 male and 26 female without fatty liver. In the fatty liver group, 6 overweight, 19 obese class I, & 5 obese class II, but in the group without fatty liver, 21 overweight, 19 obese class I, & 4 obese class II. The degree of obesity in the fatty liver group was more severe(P=.022). Except level of aminotransferase, all biochemical parameters were not different between two groups.

**Conclusions:** The liver biopsy could be recommended in obese I & II patients with abnormal levels of aminotransferase.

**Keywords:** Nonalcoholic fatty liver disease, Gallstone disease, Liver biopsy, Lapacoscopic cholecystitis

# **PE-200**

# Additive Effects of PNPLA3 and TM6SF2 on the Histological Severity of Non-Alcoholic Fatty Liver Disease

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**Aims:** We investigated the effects of *PNPLA3* rs738409, *TM6SF2* rs58542926, and *MBOAT7-TMC4* rs641738 variants on metabolic phenotypes and their combined effects on the histological severity of non-alcoholic fatty liver disease (NAFLD). **Methods:** We genotyped rs738409, rs58542926, and rs641738 in biopsy-proven NAFLD patients (n = 416) and healthy controls (n = 109). Homeostasis model assessment of insulin resistance and adipose tissue insulin resistance were calculated.

**Results:** The rs738409 and rs58542926 variants, but not rs641738, were associated not only with non-alcoholic steatohepatitis (NASH) (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.46–2.73 and OR, 1.91; 95% CI, 1.04–3.51) but also with significant fibrosis (= F2) (OR, 1.53; 95% CI, 1.11–2.11 and OR, 1.88; 95% CI, 1.02–3.46) in NAFLD, even after adjustment for metabolic risk factors. Of both variants, only rs738409 was associated with homeostasis model assessment of insulin resistance and adipose tissue insulin resistance even in healthy controls (P=0.046 and 0.002, respectively) as well as in the entire study cohort (P=0.016 and 0.048, respectively). *PNP-LA3* and *TM6SF2* risk variants additively increased the risk of NASH and significant fibrosis (OR per risk allele, 2.03; 95% CI, 1.50–2.73 and 1.61; 95% CI, 1.19–2.17). Even in subjects with low insulin resistance, the risk of NASH or significant fibrosis increased as the number of risk alleles increased (*P*=0.008 and 0.020, respectively).

**Conclusions:** *PNPLA3* and *TM6SF2* determine the risk of NASH and significant fibrosis, even after adjustment for insulin resistance, and exert an additive effect on NASH and significant fibrosis.

**Keywords:** Insulin resistance, Non-alcoholic fatty liver disease, PNPLA3, TM6SF2

# PE-201

# Clinical Characteristics of Non-Alcoholic Fatty Liver Disease in Korea

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**Aims:** Recently, in South Korea, the prevalence of non-alcoholic fatty liver disease (NAFLD) has been gradually increasing along with westernized lifestyle and aging society. This study investigated the characteristics and lifestyle of NAFLD patients and identified the modifiable factors.

**Methods:** Patients with NAFLD who visited Severance Hospital between 2015 and 2017 were prospectively enrolled. All patients underwent ultrasonography, transient elastography, bioelectrical impedance analysis, and laboratory tests and answered the questionnaire concerning their lifestyle. NAFLD was diagnosed based on history, ultrasonography and transient elastography.

Results: A total of 225 patients were finally analyzed. Mean age was 45 years, with female predominance (64%) and mean body mass index (BMI) was 27.9 kg/m2. Obese patients (BMI=25kg/m<sup>2</sup>, 79.1%) showed significantly higher waist circumference, hip circumference, higher risk of liver damage, higher liver stiffness values, controlled attenuation parameter (CAP), body fat percentage and less appendicular skeletal muscle (ASM)/height2, compared to non-obese patients (20.9%). (P<0.05). Compared to male NAFLD patients, females showed older age (52.9 years vs. 40.5 years, P<0.001), higher proportion of diabetes mellitus (32.1% vs. 16.7, P=0.008), and less muscle power exercise (9.9% vs. 20.1%, P=0.046). Patients with metabolic syndrome (MS) (n=126, 56%) tended to have higher abdominal fat ratio (1.0 vs. 0.9 P=0.003), waist circumference (99cm vs. 92cm, P=0.005), do less aerobic exercise (30.2% vs. 40.4%, P=0.109) and muscle power exercise (15.1% vs. 18.2%, P=0.533) than those without. There was no significant difference in liver enzyme and CAP score according to the presence or absence of MS. Total skeletal mass was also similar between two groups, but the muscle mass of the upper was

significantly less in those without MS.

**Conclusions:** Based on our data, female patients with NA-FLD showed older age and more diabetes mellitus and less tendency of exercise.

Keywords: NAFLD, Metabolic syndrome, Obesity, Lifestyle

# **PE-202**

#### Liver Stiffness in Non-Alcoholic Fatty Liver Disease : A Comparison of ARFI (Acoustic Radiation Force Impulse) and Scoring System with Liver Biopsy

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**Aims:** Abdominal ultrasonography is used in diagnosis of nonalcoholic fatty liver disease. However, it is impossible to differentiate between simple steatosis and NASH. Sometimes, even NAFLD progressed to cirrhosis, US might show only fatty change. The aim of the present study was to evaluate the diagnostic efficacy of ARFI and scoring system in detecting advanced fibrosis in NAFLD patients.

**Methods:** We prospectively enrolled consecutive patients with NAFLD from November 2017 to April 2018. Twenty-nine patients had undergone liver biopsy. We evaluated the BMI, liver enzymes, lipid profile, HOMA-IR, fasting glucose levels and ARFI in 29 patients.

**Results:** Mean age was 51.6 years and 15 were males (52%). Mean BMI was 28.7 kg/m<sup>2</sup>. At histologic finding, 13 patients (44.8%) had a fibrosis stage F0, 7 (24.1%) had F1, 2 (6.9%) had F2, 3 (10.3%) had F3, and 4 (13.8%) had F4. Seven patients (24.1%) were compatible with advanced fibrosis. The AUROC values for advanced fibrosis were 0.786 for NAFLD fibrosis score, 0.922 for FIB-4 score, 0.903 for APRI, and 0.899 for ARFI.



**Conclusions:** FIB4, APRI and ARFI are useful noninvasive tools for estimating the severity of fibrosis in NAFLD patients. However, we analyzed the data in small patients and we are continuing our research.

Keywords: ARFI, FIB4, NAFLD, Fibrosis

# NAFLD, Basic

#### PE-203

#### Molecular Genetic Analysis of Marker rs738409 Gene PNPLA3 in the Yakut Population

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) is an emerging health concern, with increasing prevalence worldwide. Recently, a non-synonymous genetic variation (rs738409) in the human patatin-like phospholipase domain-containing 3 gene (*PNPLA3*), was found to be associated with NAFLD among Hispanics, African Americans, and European Americans. Studies have shown that the G allele (risk allele) of rs738409 in *PNP-LA3* gene was associated with increased propensity of steatosis and severe fibrosis. In this study, we investigated the distribution of *PNPLA3* genetic variation among various ethnic populations could provide useful information for the improvement of care of patients at risk for developing hepatic steatosis and advanced liver damage.

**Methods:** 179 samples, a population cohort of the Yakuts, were analyzed. Study participants were enrolled from YSC CMP hospital-Yakutsk City. The study was approved by YSC CMP Ethics Committee. All study participants gave written informed consent. Мы определили варианты SNP (rs738409) в гене *PNPLA3*.

**Results:** As a result of genotyping of the population sample of the Yakuts for the *PNPLA3* gene, the prevalence of the GG genotype (61.5%) was revealed. The allele G frequency was 76.8%. The distribution of genotypes of polymorphism rs738409 was in the Hardy-Weinberg equilibrium in the sample studied (*P*> 0.05).

**Conclusions:** The high frequency of G allele in Yakuts (76.8%) is probably associated with a high incidence of liver disease and severity (severe fibrosis) among the Yakuts. It is necessary to further study the *PNPLA3* gene in the Yakuts with NAFLD. **Keywords:** NAFLD, PNPLA3, rs738409, Yakut

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# **PE-204**

# Expression of the Long Noncoding RNA GAS5 Correlates with Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** To evaluated the both liver and plasma lncRNA GAS5 in patients with non-alcoholic fatty liver disease (NAFLD)

**Methods:** We analyzed 51 patients with NAFLD, the diagnosis of which was confirmed by the examination of percutaneous liver biopsy specimens by a single pathologist. Expression of GAS5 in both the liver and plasma of the patients was analyzed using quantitative real-time polymerase chain reaction according to fibrosis stage.



**Results:** GAS5 expression was significantly higher in patients with advanced fibrosis than in those without (liver:  $4.5 \pm 1.6$  vs.  $6.3 \pm 2.8$ , *P*=0.026; plasma:  $8.7 \pm 4.9$  vs.  $17.1 \pm 6.0$ , *p* = 0.001). As fibrosis progressed, GAS5 expression in both the liver and plasma increased, with the exception of cirrhotic livers (liver: *r* = 0.305, *P*=0.042; plasma: *r* = 0.452, *P*=0.002). Plasma levels of GAS5 were lower in patients with cirrhosis than in those with advanced fibrosis ( $8.8 \pm 5.9$  vs  $17.1 \pm 6.0$ , *P*=0.036).

**Conclusions:** Both liver and circulating levels of the lncRNA GAS5 correlate with liver fibrosis stage prior to the development of cirrhosis.

**Keywords:** LncRNA GAS5, Non-alcoholic fatty liver disease, Liver fibrosis

# PE-205

# Dipeptidyl Peptidase-IV Inhibitor and Antioxidant Properties from Alkaloid Rich Fraction of Withania Somnifera Improve Liver Dysfunction in Type 2 Diabetic Mellitus

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**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 haemolysis was performed.

**Results:** DPP-IV inhibitor reduced the level of aminotransferases i.e SGOT & SGPT and alkaline phosphatase with increasing the level of insulin and decrease HbA1c. Triglyceride and cholesterol level also significantly in the normal range as compared to control group.WS plant extract has shown a better antioxidant capacity to protect lipid peroxidation and reduced erythrocytes haemolysis of RBC. The histoarchitectural of liver also relevant good result after treatment of DPP-IV inhibitor.

**Conclusions:** DPP-IV inhibitors improve insulin sensitivity and help to improve the liver dysfunction in T2DM. Additionally, plant isolated DPP-IV inhibitors with its antioxidant properties reduced the toxic effect by scavenging the free radicals

**Keywords:** Dipeptidyl peptidase-iv, Antioxidant, Diabetic mellitus, Incretin hormons

# PE-206

# Hydrogen Water - A Preliminary Therapeutic for Non-Alcoholic SteatoHepatitis (NASH)

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is characterized by a wide spectrum of liver damages spanning from steatosis, nonalcoholic steatohepatitis (NASH), cryptogenic liver cirrhosis, even to hepatocellular carcinoma. Oxidative stress is a strong contributor to the progression from simple fatty liver to nonalcoholic steatohepatitis (NASH). Our aim was to investigate the effects of hydrogen water on liver NASH and the mechanism underling these effects.

Methods: A methionine choline deficient diet (MCD) was pre-

pared for the mouse models. In our investigation we made two experimental groups as follows: (1) MCD diet + normal water group(n=12); (2) MCD diet + hydrogen water group(n=12). Both groups were fed for three different periods, which are 8 weeks, 12 weeks, and 16 weeks.

**Results:** The control group and hydrogen water group average concentration of ROS at 8 weeks (588±24 FORT units vs 164±8; P=0.029), at 12 weeks (587±26 FORT units vs 163±5; P=0.029) and at 16 weeks (439±176 FORT units vs 160±0; P=0.029). From H&E staining the inflammation was vicissitudinous in control group at 8, 12, and 16 weeks (control group C:151.50 vs HW group HW:123.25; P=0.289)(control group C:104.33 vs HW group HW:84.75; P=0.077)(control group C:147.00 vs HW group HW:104.00; P=0.157).

**Conclusions:** Daily consumption of hydrogen water reduces nonalcoholic fatty liver disease and may be an effective treatment for NASH by reducing hepatic oxidative stress, apoptosis, and inflammation.

#### PE-207

# Circulating Long Non-Coding RNA TCONS\_00016452 Is Inversely Correlated with Liver Steatosis in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** To evaluate the circulating lncRNA TCONS\_00016452 in patients with non-alcoholic fatty liver disease (NAFLD)

**Methods:** We analyzed a total of fifty patients who underwent percutaneous liver biopsy to confirm NASH, which is reviewed by one pathologist. Expression of circulating lncRNA TCONS\_00016452 in plasma was compared using quantitative real-time polymerase chain reaction according to pathologic results. **Results:** Expression of circulating lncRNA TCONS\_00016452 was significantly decreased in patients with severe steatosis compared to patients with minimal to moderate steatosis (13.9±16.0 vs 7.4±5.3, *P*=0.039. As the grade of steatosis was advanced, circulating lncRNA TCONS\_00016452 was decreased (*r*-value=-0.29, *P*=0.004). However, circulating lncRNA TCONS\_00016452 was decreased in patients with significant

fibrosis compare to without significant fibrosis (8.3 $\pm$ 5.1 vs 17.2 $\pm$ 19.6, *P*=0.040).



**Conclusions:** Circulating IncRNA TCONS\_00016452 is inversely correlated with grade of liver steatosis in patients with NAFLD. **Keywords:** LncRNA lexis, Non-alcoholic fatty liver disease, Liver steatosis

#### PE-208

#### Differential DNA Methylation as a Potential Biomarker for Stratification of Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) can progress to advanced liver disease, but only in a minority of patients. Differential liver DNA methylation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) gene promoter has been shown to distinguish patients in terms of fibrosis severity in NAFLD. However, a study of methylation of PPAR $\gamma$  gene promoter in human with a sufficient number of patients is still scarce. We therefore determined the prognostic significance of DNA methylation of PPAR $\gamma$  gene promoter in patients with NAFLD.

**Methods:** This study enrolled 54 biopsy proven NAFLD patients and 18 healthy controls who attended Kyungpook National University Hospital, Republic of Korea between March 2015 and October 2016. We extracted genomic DNA from liver tissue of enrolled patients. Bisulfite modification of genomic DNA was performed and PPARy methylation level was confirmed with pyrosequencing. **Results:** The average of 4CpG methylation of PPARy promoter had significantly lower in the NAFLD group (15.03% DNA methylation) when compared to the healthy controls (19.55%) (P=0.001). Quantitative DNA methylation of PPARy stratified patients into mild (Kleiner 0-2) and severe (Kleiner 3-4) fibrosis (14.21% vs 17.87%, P=0.007). Moreover, hypermethylation at the PPARy promoter of liver was also associated with higher age, the presence of DM, NAFLD fibrosis score, the degree of steatosis and fibrosis (P=0.015, 0.024, 0.012, 0.027, 0.009, respectively). However, they were not associated with presence and degree of inflammation, ballooning, NAFLD activity score, the presence of NASH, and other liver function test. Patients with advanced fibrosis exhibited significantly higher NAFLD fibrosis score, FIB-4, and PPARy DNA methylation (all P<0.05) and showed borderline significance with transient elastography (P=0.084). These markers, including NAFLD fibrosis score, FIB-4, and PPARy DNA methylation, had an area under the receiver operating curve (AUROC) of 0.855, 0.778, 0.75, respectively for predicting advanced fibrosis. PPARy mRNA was also related to the fibrosis and steatosis severity (P<0.05). This showed negative regulation with DNA methylation level (P=0.001).

**Conclusions:** DNA methylation level of PPARγ may be useful in NAFLD patients for stratification and prediction of progressive liver fibrosis, which is a very important factor of NAFLD patients that is currently impossible to predict. It may be possible to generate an algorithm that can predict more precisely which patients are likely to progress on to a severe fibrosis in patients with NAFLD using DNA methylation and other markers related to liver fibrosis.



**Keywords:** Non-alcoholic fatty liver disease, DNA methylation, Peroxisome proliferator-activated receptor gamma

#### PE-209

#### Body Weight Gain Is Exaggerated by Diet Type on ad Libitum Feeding

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**Aims:** Obesity raises the risk of morbidity from metabolic syndrome including dyslipidemia, diabetes mellitus and fatty liver disease. Weight loss is associated with lowering the risk of metabolic syndrome. To lose body weight, reduced-calorie diet and increased physical activity are required. We report *foz/foz* (11-bp truncating deletion in exon 8 of *Alms1* gene) mice which has disordered appetite regulation fed with western diet, high fat diet and normal chow *ad liblitum* showed exaggerated body weight gain according to diet pattern.

**Methods:** 4~5 weeks old *foz/foz* mice and wild type (WT) littermates were fed with western diet, choline-deficient high fat diet(CD-HFD) and normal chow for 12 weeks, *ad liblitum*. Every week, food intake and body weight were measured and after 12 weeks, metabolic indices were assessed by evaluating body weight, liver weight, the level of fasting glucose and aminotransferase.

**Results:** Total amount of food intake showed no significant difference among western diet, choline-deficient high fat diet and normal chow in spite of different flavor and taste. Average calorie intake was 35% higher in WD and CD-HFD compared with normal chow. However, body weight gain was 75% higher in WD and 49% higher in CD-HFD. AST was 10 times higher in WD and CD-HFD compared with normal chow. All three groups showed glucose intolerance.

**Conclusions:** To reduce the risk of metabolic syndrome associated with obesity, reduced calorie intake and increased physical activity is mandatory. However, to keep reduced calorie intake is challeged while restriction of food intake only. This finding showed that western diet induced most exaggerated body weight gain and body weight gain is influenced more by diet pattern rather than calori itself. Finally, changing behavioral eating pattern is recommended to keep the reduced body weight and improve NASH.

Keywords: Western diet, NASH, Foz mouse, Obesity

**Liver Transplantation** 

#### PE-210

# Singel Agent DAA in HCV PCR Positive Liver Transplant Patients, Experience from a Developing Country

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**Aims:** Chronic hepatitis C (CHC) is the leading cause of decompensated liver disease and liver transplant indication in Pakistan, which is the second most prevalent country with a prevalence of 3.5% to 5.2%. Being the seventh most populous country in

the world, lacking significantly on medical grounds reflected by only one liver transplant centre for more than 10 million chronically affected liver disease patients. Before the era of directly acting antiviral agents (DAAs) most common problem faced in the post liver transplant period was recurrence of HCV and most of the patients were non responders to interferon therapy well before transplantation of liver graft. Aim of this study is to see the outcomes of single agent DAA in HCV PCR positive liver transplant patients.

**Methods:** This cross sectional analysis was carried out in CHC infected post liver transplant patients with high viremia. The effect of DAAs were noted in the form of eradication of virus and achievement of sustained virological response (SVR). DAAs used, were also recored. Also to note the interaction with immunosuppresants and development of side effects notably derangement of liver function test or failure of graft and anemia. And to note the development of acute kidney injury or any other untoward effect.

**Results:** During study period of 24 months, from January 2015 to December 2016, 51 HCV positive liver transplant patients were enrolled in the study. 26 (52%) out of 51 found to have active viral replication with positive PCR. All 26 received combination of Sofosbuvir (only DAA availabe till December 2016 in Pakistan) and Ribavirin. Achievement of viral eradication was 100% so was for SVR. There was no interaction with immunosuppressants. Most commonly reported side effect was fatigue and a feeling of nausea. Kidney and liver function tests remained normal. Contrary to recent data, there was no recurrence of hepatocellular carcinoma (HCC) in patients who recieved liver graft for HCC on background of CHC cirrhosis.

**Conclusions:** Directly acting antiviral therapy has revolutionized outcomes of HCV infected post liver transplant patients in a country lacking modern and advanced health care system. Even the single agent therapy has done wonders for the economically less privileged.

**Keywords:** Single agent DAA, HCV PCR positive, Liver transplant patient

#### PE-211

#### No Touch Isolation Technique for the Prevention of Postoperative Recurrence of Hepatoceullar Carcinoma after Liver Transplantation-Combined with Trans-Arterial Radioembolization

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**Aims:** Recently, trans-arterial radioembolization (TARE) was done in the patients who had advance stage hepatocellular carcinoma. Sometimes totally necrosis of tumor was reported after operation. No touch isolation technique is concept of preventing tumor spread during tumor operation. We expected

that if we can use these technique and control all viable tumors before transplantation. We could get better outcomes in the hepatocellular patients.

**Methods:** 36-year old female patient had liver cirrhosis with hepatitis B virus infection and multiple hepatocellular carcinoma in both lobe. Alpha-feto protein level was 850,000 PIVKA 136,000. At first, there were high change of recurrence, we did not consider liver transplantation. Hepatologist decided to do TARE and additional conventional TACE. After that treatment, AFP and PIVKA level were dramatically decreased, and there was no viable tumor in follow up CT after 3 weeks. We performed living donor liver transplantation using no touch isolation technique in the patients who had multinodular hepatocellular carcinoma and high AFP, PIVKA level after TARE and conventional TACE.

**Results:** Living donor liver transplantation wad done, donor was 32 year old her sister, there was no variation in the donor side. Total operative time was 4 hour 30 min and blood loss was 100cc. We did recipient hepatectomy using no touch isolation technique, suprahepatic and infrahepatic IVC were isolated and clamped. Then we clamped hilum and resected using high hilar dissection technique. Immediate postoperative period there was no acute complication, patients transferred to general ward at postoperative 4 days then discharged postoperative 14 days. Postoperative 4 months, patients is alive, there is no recurrence, and AFP level is 11.5 and PIVKA level is 33.

**Conclusions:** TARE(trans-arterial radioemblization) is good modality for pre-transplant treatment for far advanced stage case of hepatocellular carcinoma. No touch isolation technique during recipient hepatectomy might be helpful in advanced stage hepatocellular carcinoma patients.

**Keywords:** Livertransplantaiton, No touch isolation, Transarterial Radioembolization, Hepatocellular carcinoma

#### PE-212

Clinical Efficacy of Pretransplant Vaccination for Preventing Herpes Zoster after Living Donor Liver Transplantation in Recipients Aged 50 years and Older

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**Aims:** There have been no reports concerning the efficacy of pretransplant herpes zoster (HZ) vaccination following living donor liver transplantation (LDLT). From January 2013 to May 2016, 24 patients aged 50 years and older received vaccination of HZ prior to transplantation and underwent LDLT at a single institution.

**Methods:** We compared this to the one-year HZ incidence of unvaccinated recipients (N=180) who underwent LDLT in the same time frame.

**Results:** For general characteristics, the MELD scores (P<0.001) and CTP grades (P=0.007) of the vaccinated group were significantly lower than those of unvaccinated group. In Kaplan-Meier analysis, the one- year HZ incidence rates of the vaccinated and unvaccinated groups were two (8.7%) and 16 (9.9%) cases, respectively (P=0.883). In the subgroup aged 50 through 59 years, two vaccinated recipients had HZ after LDLT. However, in the subgroup aged 60 years and older, no vaccinated recipients had HZ after LDLT. Multivariate analysis showed the independent risk factor for HZ after LDLT was use of mycophenolate mofetil (MMF; hazard ratio [HR] = 3.00; P=0.041).



**Conclusions:** The efficacy of pretransplant vaccination for preventing HZ was not apparent in our study. A large prospective study is needed to determine the indications for pretransplant HZ vaccination according to age group and to evaluate the efficacy of HZ vaccination after LDLT.

Keywords: Liver transplantation, Herpes zoster, Vaccination

# PE-213

#### Pediatric Liver Transplantation Program in Kazakhstan

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CF "UMC" National Scientific Center for Mother and Child Health

**Aims:** Living donor liver transplantation has become a cornerstone for the treatment of children with end-stage hepatic dysfunction, especially in Kazakhstan with low rates of organ from deceased donors. In our center, 8 pediatric living donor liver transplantations we carried out since 2014. Patients between the ages of 0 to 5 years. The indications for liver transplantation in our patients were biliary atresia.

**Methods:** The mean hospitalization time of our patients was 25 days and the mean stay in the intensive care unit was 8 days. The Child-Pugh score was C in 2 of our patients, B in 5 patients, and A in 1 patient. The donor age ranged from 27 to 41 years, and the weight ranged from 62 to 78 kg, mothers being the donors in a majority of these. As most children require only a left lateral segment graft, the morbidity and risks to the donor are much less than those donating their right lobes. Living donor transplants are ideally suited to children as it allows for a planned procedure, allows for a near optimal size graft for the child, reduces the risk for the donor, and the incidence of rejection is reduced.

**Results:** The main complications after pediatric liver transplantation were infections and surgical complications including (biliary complications). We encountered biliary complications in 2 of the 8 patients and we performed surgical revision due to anastomosis leakage in 1 patient. Our immune suppression protocol is based on a combination of steroid and tacrolimus. MMF is also used as a second maintenance agent in addition to tacrolimus in children who have had a documented rejection episode.

**Conclusions:** Infections and biliary complications were the most common outcome occurring in children after LT. Advances in post-transplant care and monitoring of the recipients, technical refinements enable the better results.

Keywords: Pediatric, Liver, Transplantation, Biliary atresia

# PE-214

#### Idiopathic Hyperammonemia after DDLT: Case Report

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**Aims:** Idiopathic hyperammonemia (IHA) is an extremely rare complication after liver transplantation (LT). Ornitine transcarbamylase deficiency or hepatic glutamine synthetase deficiency is suggested as a possible cause of IHA after LT.

**Methods:** We present a case of a 54-year-old female patient with HBV and HCV-related liver cirrhosis who developed fatal IHA after cadaveric LT. The postoperative course was uneventful until the postoperative day 9. She presented sudden mental deterioration and respiratory failure with hyperammonemia (> 700 umol/L). Management to reduce serum ammonemia started

**Results:** However, hyperammonemia was sustained without graft dysfunction. On the postoperative day 10, generalized seizure developed. EEG revealed brain death and the patient expired on the postoperative day 15 day with nearly normalized liver enzymes.

**Conclusions:** Although idiopathic hyperammonemia is extrely rare complication after liver transplatation, this condition should be suspected as a cause of death.

Keywords: Transplantation, Complication

# PE-215

# Large-For-Size Syndrome after Deceased Donor Liver Transplantation: A Case Report

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**Background:** Large-for-size (LFS) is a serious problem that can develop during liver transplantation (LT) and is related to morbidities such as insufficient blood supply causing graft dysfunction or impractical closure of the abdominal wall leading to graft compression. LFS is usually discussed in pediatric LT and is often managed by reducing the size of the graft before implantation. In contrast, only a few cases about managing unexpected LFS during adult LT have been reported.

Case: The female patient of 44 years of age was admitted to the Incheon St. Mary's Hospital with drug-induced acute hepatitis and managed conservatively. However, the patient underwent deceased donor liver transplantation (DDLT) due to persistent liver deterioration. Donor was a 51 year old male, weighing 60.0 kg and matched because the patient weighed 58.4 kg. Donor had a history of eating one bottle of Soju daily for 30 years, but the liver biopsy showed no fatty change at 0 %, but the liver size was shown larger than normal. The weight of donor liver was 2040 g, which was much heavier than normal but the liver transplantation was performed uneventfully. However, left lateral sectionectomy was performed because the abdomen was not be closed. On the next day, the liver function was deteriorated and blood pressure was dropped. Immediately, we took computed tomography (CT) scan and were able to observe the narrowing of the inferior vena cava (IVC) by the liver. Venogram showed significant stenosis at IVC suprahepatic portion, so IVC stent placement was performed using 24 x 80 mm Hercules stent graft (MicroPort Scientific Corporation, Shanghai, China). After stenting, blood pressure was stabilized but liver function was deteriorated more and renal replacement therapy was performed because of impaired renal function. However, liver and renal function gradually improved and discharged without any complication.

**Discussion & Conclusion:** LFS can cause serious complication, but can be solved by various treatment modality.

Keywords: Liver transplantation, Large for size, Hepatic failure

#### **PE-216**

#### Stent Insertion and Balloon Angioplasty for Portal Vein Stenosis after Liver Transplantation: Long-Term Follow-Up Results

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**Aims:** This study aimed to conduct a long-term retrospective study of transhepatic percutaneous intervention and to find a method to reduce the need for additional procedures.

**Methods:** Between January 2001 and December 2015, 283 patients underwent deceased donor liver transplantation (DDLT), and 1086 patients underwent living donor liver transplantation (LDLT). Seven (2.4%) of the 283 DDLT patients and 24 (2.2%) of the 1086 LDLT patients were diagnosed with portal vein stenosis. We evaluated technical and clinical success and long term results.

**Results:** Technical success was achieved in 100% of balloon angioplasties and stent insertions, and clinical success was achieved in 78% of balloon angioplasties and in 100% of primary stent insertions. At 1, 5, and 10 years after balloon angioplasty, the rates of primary patency were 87%, 82%,

and 68%, respectively, and the rates of primary stent patency were all 100%. The portal vein size in non-recurrence patients and recurrence patients was  $19 \pm 4.2$  mm and  $19 \pm 3.0$  mm (*P*=0.956), respectively. The balloon size of the non-recurrence patients and recurrence patients was  $14 \pm 1.66$  and  $11 \pm 1.95$ , respectively (*P*=0.013), when balloon angioplasty was performed after a diagnosis of stenosis.

**Conclusions:** Balloon angioplasty showed lower risk of anastomotic rupture than we are concerned and may be safe and effective at an early portal vein stenosis(PVS). Also, primary stent insertion should be considered when fibrotic change is expected due to reoccurring inflammation and when the balloon size to be used is small.

**Keywords:** Portal vein stenosis, Stent, Balloon angioplasty, Complication

#### PE-217

#### Guideline for Optimal Port System in Pure 3D Laparoscopic Donor Right Hemihepatectomy

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**Aims:** The position of the port is important in laparoscopic hepatectomy. The method of choosing the proper port location for will be the first step needed for those who initiate laparoscopic hepatectomy. However, direction of surgical plane is diverse and the positions per person are slightly different, It is necessary to standardize of port location and to make the appropriate guidelines. Standardization is not easy. Pure 3D Laparoscopic donor Rt. hemihepatecotmy is more standardized procedure than other laparoscopic liver resection.

**Methods:** From December 2015 to December 2017. 158 donors were underwent pure 3d laparoscopic Rt. hemihepatecotmy. We described advantage and disadvantage depending on the role and location of each port through experience of surgery in the past year.

**Results:** Our institute is the only center in the world that has performed pure laparoscopic donor surgery over 100 cases. Making a good guidelines provides experience of experienced surgeon to initiate laparoscopic surgery and is very important for proper training. It is not appropriate to describe fixed anatomical landmark like a mid-clavicular line or below a few centimeters from rib. It is necessary to determine the position of the port step by step after confirming that role of each port and 1st assistant in the surgical procedure and role of the hand of the surgeon are taken into consideration.

**Conclusions:** Making optimal port system for pure 3D laparoscopic donor Rt. hemihepatecotmy is the first step. By sharing our experience, we believe that it will be useful for the center to enforce future pure laparoscopic donor Rt. hemihepatectomy



**Keywords:** Livertransplantaiton, Pure laparoscopic donor hepatectomy, Guideline

# PE-218

Identification of Unknown Bile Duct Injury in the Right Liver Graft and Adequate Anastomosis Method to Overcome Delayed Biliary Complication: A Case Report

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Different anatomical variations of the intrahepatic bile ducts, and in particular its right half, is one of the important risk factors for billiary complication in recipients undergoing living-donor liver transplantation (LDLT). The authors already reported high risk group of biliary injury during living donor hepatecotmy according to the anatomy of the right posterior bile duct (RPBD). We experienced a case with the bile duct injury in the graft which was unnoticed during living donor hepatectomy. 26 years old male underwent right liver hepatectomy for donation to his father 55 years old. The preoperative MRCP showed long caudal segment of RPBD, which has been reported as high risk for biliary complication in the recipient. There was no problem during donor hepatectomy and bench surgery. However, we found that RPBD was not easily identified and RPBD was partially ligated when probing was tried just before biliary anastomosis. We opened ligated RPBD. But the wall was thin. We opened damaged wall of RPBD and duct-to-duct anastomosis was done without stent. According to this case, we learned several lessons: 1) Understanding of the preoperative risk of bile duct injury during hepatectomy based on preoperative MRCP is important, 2) different bile duct division method in the high risk patient should be applied, 3) comparison of the biliary anatomy by probing the graft during bench with that of preoperative MRCP is necessary to detect unknown bile duct injury, 4) injured wall should be opened and anastomosed using healthy duct is important to reduce delayed biliary complications.

Keywords: Bile duct, Liver transplantation, Posterior bile duct

# PE-219

## The Impact of Pathologic Diagnosed Early Hepatocellular Carcinoma on Clinical Outcomes in Liver Transplantation for Hepatocellular Carcinoma

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**Aims:** Early hepatocellular carcinoma(HCC) is characterized by vaguely nodular appearance, well-differentiated with stromal invasion. Although clinical course of early HCC is not well known, it is a part of multistep carcinogenesis for HCC that distinguishes it from the dysplastic nodule. In this study, clinical impact of early HCC will be discussed in patients who underwent liver transplantation for HCC.

**Methods:** A total of 364 patients underwent liver transplantation for HCC in Severance Hospital between 2005 and 2017 were retrospectively reviewed. The patients were divided into two groups according to the presence of early HCC. Initial tumor staging was performed according to mUICC staging system based on pathologic findings from explant liver. After subtracting data of early HCC from initial staging and re-staging was performed. A survival analysis was performed between restaged group with early HCC and initial-staged group without early HCC.

**Results:** Among 364 patients underwent liver transplantation for HCC, 129(35.4%) had early HCC. The presence of early HCC did not affect the overall survival (HR : 0.653, 95% CI 0.407-1.407, P=0.077) or disease-free survival (HR 1.141, 95% CI 0.690-1.884, P=0.607). A total of 80 patients with early HCC were downstaged after re-staging. In the Kaplan-meier estimate perfomed on each stage after re-staging, no significant differences between the groups were observed in the overall survival (5 years; Stage I 80.4 vs 76.6%, P=0.552; Stage II 88.4 vs 76.2%, P=0.120; Stage III 77.8 vs 63.3%; Stage IVA 17.6 vs 64.8%, *P*=0.398) and disease-free survival (5 years; Stage I 88.7 vs 86.5%, *P*=0.962; Stage II 92.6 vs 92.0%, *P*=0.448; Stage III 66.7 vs 63.6%, *P*=0.520; Stage IVA 30.8 vs 29.2%, *P*=0.463).



**Conclusions:** Although it is not clear about the biologic behavior of early HCC, its effects on the long-term outcomes after liver transplantation for HCC are expected to be not significant. **Keywords:** Liver transplantation, Early hepatocellular carcinoma, Hepatocellular carcinoma

#### **PE-220**

#### First Expiriens of Living Donor Liver Transplantation

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**Aims:** Presents to analyze of first experience of Living Donor LiverTransplantation (LDLT) at Aktobe Medical Center, in the two-year period. LDLT were performed with the participation of specialists from Korea.

**Methods:** LDLT were done after the candidates (living donor and recipient) were : valuated following our practices guidelines. After donor right hepatectomies TNK solution with heparine was used for graft perfusion. "Middle hepatic vein" reconstruction performed by synthetic vascular graft. During recipient hepatectomy used "High Hillary Dissection" method. Right liver graft implantation made as standard technique. Before portal reperfusion, liver graft washed by 5% Albumine solution. Immunosupressive therapy in all patients included three components (CNI + MMF + Steroid) with introduction of Basiliximab (first and fourth postoperative day).

**Results:** In our Center during 2016-2017 years performed 9 living donor liver transplantation. Our donors age were between 22 and 54 years. In all cases removed right lobe. From 3 donors we used 3D-laparoscopic right hepatectomy. All donors discharged at 7<sup>th</sup>-9<sup>th</sup> day after operation. Recipient's characteristics shown in Tab.1.

Died 2 recipient in late postoperative period: after infection complications (cholangiogenic abscess with sepsis and chronic rejection).

Table	1.	Reci	pients
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Case	Cause	Gender	Age	Donor	Complications	Outcomes
#1	AIH	F	39	Sister	Chronic rejection	Died, after
						2 year
#2	PBC	F	34	Brother	Cholangiogenic	Died, after
					abscess, sepsis	6 month
#3	PBC	М	48	Son	No	Discharge
#4	HBV	М	50	Brother	No	Discharge
#5	HBV+HCV	М	36	Brother	No	Discharge
#6	HBV	М	53	Son	No	Discharge
#7	HBV	F	48	Daughter	No	Discharge
#8	PBC	F	56	Brother	No	Discharge
#9	HBV	F	54	Sister	Bleeding POD#1	Discharge

**Conclusions:** LDLT gives a big chance to survive for patients : ith end-stage liver disease in Kazakhstan. Our transplant program needs to be gain experience, particularly with respect to donor selection, recipient preoperative preparing.

Keywords: Liver, Transplantation, Living donor

#### PE-221

#### Kidney Dysfunction after Liver Transplantation: Calcineurin Inhibitor Nephrotoxicity

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**Aims:** Show the effect of calcineurin inhibitor nephrotoxicity. as a cause of kidney dysfunction after liver transplantation

**Methods:** In our medical center from 2013 to 2017 were performed total 44 liver transplantations. Of these, 31 were from a living donor, the remaining 9 from a cadaver donor. All patients after liver transplantation as basic immunosuppressive therapy received a three-component therapy: tacrolimus, mycophenolic acid and steroid. For induction therapy, Basiliximab was used on days 0 and 4 after surgery at a dose of 20 mg i.v. Tacrolimus was administered on the first day after liver transplantation at a dose of 0.01 mg/kg per day orally. Further, the dose of tacrolimus was increased to 0.05 mg/kg under the control of tacrolimus concentration in the serum. Steroids were administered on the day of the operation i.v., followed by a transfer of the drug per os. Mycophenolic acid preparations were administered on the third day after the operation in a standard dose.

**Conclusions:** Thus, high doses of tacrolimus contribute to impaired renal function, leading to uremia and aggravation of the patient's condition. Decreased doses of tacrolimus restore the function of the kidneys and, accordingly, normalize the indices of creatinine and urea in the serum of the patient

**Keywords:** Liver transplantation, Nephrotoxitity, Kidney dysfunction, Uremia

# PE-222

#### Donor Biliary Complications in High-Volume Living-Donor Liver Transplantation Center in Korea

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**Aims:** Donor safety is the most important Living donor liver transplantation. Biliary complication is common complications in donor hepatectomy. This study intended to analyze the incidence and outcomes of donor biliary complications in a Korean high-volume LT center.

**Methods:** Institutional LT database was searched from 2006.01.01 to 2011.05.31. Their medical records and imaging studies were reviewed. All of them did AMC technique for BD division.

Results: Between 2006.01.01-2011.5.31, total 1658 donors did hepatectomy in AMC center. Among them, 1099 were male and 559 were female. Graft types were Right liver graft in 1302 (78.5%), Left liver graft in 274 (16.5%), Left lateral section graft in 72 (4.3%) and Right posterior section graft in 10 (0.6%). Mean age of total donor was 29 years and Mean steatosis of liver was 5.7%. Mean hospital days was 12days and Mean follow-up period were 17.5 month. Among 1658 donors, the biliary complications occurred in 47 donors (2.7%). Most of them were bile leak, only 2 case were bile duct stenosis. All of the biliary complication occurred in early period (< 1 month). In the biliary complication(BC) group, the 10 donors did percutaneous drainage(21.3%) and the 12 donors did ERCP(25.5%) and the only one donor was re-operated. Mean hospital days in BC group was 22 days and mean duration of treatment was 1.8 month. Hospital days in BC group was more longer than non-BC group but, there is no significant difference.

**Conclusions:** Very low incidence of BC in donor by using AMC technique for BD division. The incidence of late BC in LD hepatectomy is neglisible.

**Keywords:** Living liver transplantation donor, Biliary complication

# PE-223

#### The Effects of Various Immunosuppressants to Epithelial–Mesenchymal Transition on HCC Cell Line

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**Aims:** The purpose of this study was to elucidate the effect of various immunosuppressants to epithelial–mesenchymal transition (EMT), which strongly correlated with tumor growth and

#### metastasis of HCC.

**Methods:** The effect of various immunosuppressive drugs will investigate on tumor growth and lymph node metastasis in a Balb/c nude mice model of HCC. Cell proliferation and invasion were monitored *in vitro* using the CCK8 and Matrigel Invasion Chambers, respectively. Levels of expression specific markers of EMT were measured using Western blots analysis.

**Results:** Various immunosuppresses showed differing results to the proliferation of HCC in vitro study. Treatment with high and low doses of Tacrolimus and Cyclosporine A in high doses resulted in increase in the invasive potential of SK-Hep1 cells by enhancing EMT in vitro and there was no significant effect of Sirolimus and MMF on cell migration and invasion. The Western blotting analysis revealed that Tacrolimus increased the levels of expression of TGF-B, N-Cadherin, ZEB1, Slug in the HCC tumor cells, while Cyclosporine A, Sirolimus and MMF did not have a significant effect on the expression of these proteins. The increase in expression level was especially pronounced in TGF-B, N-Cadherin, ZEB1 proteins when using high doses of Tacrolimus (100ng/ml) and moderately expressed, however, higher than other immunosuppressors using a low dose (5ng/ml) of the drug. The use of other immunosuppressors in different doses did not significantly affect the expression of all proteins.

**Conclusions:** Tacrolimus and high doses Cyclosporine A increased the invasive potential of HCC cells in our *in vitro* study.

# PE-224

# Successful Bypass Operation in Liver Transplant Recipient with Budd-Chiari Syndrome: A Case report

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**Aims:** Budd-Chiari syndrome (BCS) is a rare disease caused by the interruption of hepatic venous drainage in the hepatic vein, inferior vein or right atrium. Resection and replacement of the inferior vena cava (IVC) are standard procedures fro deceased donor liver transplantation (DDLT) for patients with BCS. However, there is no definite method for resolving liver cirrhosis that recur IVC occlusion due to BCS. We report a case of successful bypass surgery in a patient with BCS after liver transplantation (LT).

**Methods:** The patient was a 61-year-old male who underwent DDLT at an outside hospital in 2008 due to liver cirrhosis caused by BCS. At the liver transplant time in an outside hospital, the patient's condition was so severe that replacement of IVC was not performed. The patient's condition improved after LT. However, the cirrhosis of the transplanted liver have progressed due to the occlusion of the IVC, which has not been resolved over time. The patient was referred to the our transplantation center for a second opinion. At the time of our first visit, the patient's condition was not in a state of needing immediate surgical treatment. During outpatient follow-up, patient's liver

function was not bad, but liver cirrhosis were further intensified and decide to perform IVC bypass operation. CT scan shows obliteration of intrahepatic IVC, splenomegaly, increased extent of multiple collateral vessel, and liver cirrhosis due to BCS.

**Results:** The operation time was 415 min and estimated blood loss was 900 ml. The operation was performed under biopump applied to lower the pressure. The distal stump was confirmed in the renal vein. We opened the diaphragm to secure the proximal site and clamped the proximal IVC. We used the Dacron 20 mm graft for bypass surgery. After the operation, blood flow through graft was very good. The patient should be on anti-coagulation treatment to prevent obstruction of graft.

**Conclusions:** Bypass surgery using an artificial graft can be a safe and good treatment option in patients with cirrhosis caused by IVC occlusion after LT.

**Keywords:** Liver transplantation, Budd-Chiari syndrome, Bypass, Liver cirrhosis

#### PE-225

#### In Situ Split Liver Transplantation for 2 Adult Recipients: Report of Initial Experience

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**Aims:** To expand donor pool, split liver transplantation has been conventionally performed for one adult and one pediatric patient. Application of this technique for two adult recipients under proper donor and recipient selection can produce remarkable impact on the waiting list.

**Methods:** Donor was 40 years old without any underlying disease and an estimated liver size was over 2000g without fatty change. One recipient was 50 years old with acute on chronic hepatitis B, model for end stage liver disease (MELD) score was 46 and a weight was 63kg. The other recipient was 54 years old with non-alcoholic steatohepatitis related liver cirrhosis and recurrent esophageal varix bleeding, MELD score was 15 and a weight was 47kg. We performed in situ splitting of the whole liver using LDLT technique. Parenchymal transaction was performed on middle hepatic vein line and modified right lobe graft and whole left lobe graft was generated.

**Results:** Graft-recipient weight ratio was 2.26 and 1.40, respectively. The cold ischemic time was 59 minutes and 178 minutes. Total operation time was 324 and 245 minutes. No vascular and biliary complications were occurred. One patient was discharged at 18 days after operation without any problem and the other patient was discharged at 40 days after operation because of ascites control and gastric ulcer bleeding. Both of the recipient are doing well with good liver function.

**Conclusions:** In situ split liver transplantation for 2 adult recipient using LDLT technique is feasible and a considerable options to expand donor pools under proper donor and recipient selection.

# PE-226

# Failing Transplanted Liver from an Unrecognized Recently Discovered Autoimmunity

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**Aims:** Unfortunately, recurrent HCV infection of engraftment is inevitable if the virus was not eradicated in recipients. Because of immunosuppression, if left untreated, HCV infection progresses to cirrhosis quickly. The era of direct antiviral agents (DAAs) has greatly improved the SVR (sustained virological response) to 90%, and safety concerns were minimal. Despite advancements there remain a gray zone of mixed involvement in the form of viral hepatitis with autoimmunity. Here we are reporting a case of a patient whose graft showed features of deterioration despite achievement of SVR and ultimately, the question was answered by liver biopsy.

**Methods:** 47years old man with living donor liver transplantation in October 2012 for HCV-CLD., remained uneventful on mycophenolate mofetil and tacrolimus & achieved SVR on Sofosbovir and Ribavirin therapy which was completed in December 2015. After 8 months of DAAs therapy he developed itching and fatigue, and on follow up he was found to have deranged LFTs in December 2016. Although, HCV PCR was negative and so was MRCP.

**Results:** His liver biopsy revealed chronic ductopenic rejection with granuloma formation and features of autoimmune hepatitis. His ANA profile was found to be significantly positive. Despite steroids and further immunosuppression he could not manage to recover. He was sent to liver transplant centre for second liver transplant but concerns were reappearance of autoimmune flare and graft failure which limited his liver retransplant.

**Conclusions:** This case is an eye opener for the transplan team as autoimmunity remains to be a difficult scenario to cope with in transplant setting.

# PE-227

#### Transsplenic Endovascular Recanalization, Stenting and Surgical Reconstruction of (Grade 4) Portal Vein Thrombosis in Living Donor Liver Transplantation

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**Aims:** Complete occluded portal vein thrombosis (PVT) is not any more contraindication of liver transplantation since many innovative surgical techniques have been introduced, such as surgical or endovascular thrombectomy, vascular stenting, portal vein patch, venous jump grafts, cavoportal hemitransposition. When PVT has reached to (grade 4) which is the thrombosis involving the proximal superior mesenteric vein (SMV), splenic vein (SV) and the main portal vein (MPV). It's making more difficulty to reconstruct the donor and recipient PV.

**Methods:** We are describing our experience on the LDLT surgical approach for a patients suffered from uncompensated liver cirrhosis with portal hypertension complicated by difficult controllable bleeding of esophageal varices due to chronically progressive and extensive thrombosis causing complete occluded of the portal vein (grade 4), which successfully managed with transsplenic endovascular access (4 French) for PV recanalization, thromectomy, stent-angioplasty and then portal patch using either native recipient portal vein or cryopreserved cadaveric vessels to ensure a proper portal alignment and flow with graft PV. Also, we are doing an intra-operative portography (IOP) to interrupt any sizable collaterals. The postoperative follow up showed good portal flow to the graft.

**Conclusions:** LDLT for completely occluded PVT is adding a more challenging and morbidity in the recipient and need special surgical approach to overcome the difficulty for restoring the anatomical flow of PV. High volume transplant center and multidisciplinary approaches including surgical correction of PVT, intra-operative portography (IOP), and interruption of sizable collaterals are necessary to decreased PVT-related complications and showed acceptable results despite the severity of PVT.

# **PE-228**

# Outcomes of Direct Acting Antiviral Agents (DAAS) in HCV LT Patients

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**Aims:** HCV infection is not only a risk factor for HCC, but also closely related to recurrence after HCC treatment. Currently, worldwide treatment of HCV infection is being developed, among which DAA has become a more effective treatment than conventional interferon + ribavirin therapy. Because of the importance of HCV therapy in patients who undergo liver transplantation, this study aims to evaluate the efficacy of DAA in liver transplant recipients due to HCV related HCC.

**Methods:** In this study, 42 patients were enrolled who received liver transplantation at Seoul National University Hospital and treated with DAA for chronic HCV infection from July 2015 to August 2017. We retrospectively analyzed the results of the study and found that the sustained viral response (SVR), which was not associated with the re - proliferation of the virus for 24 weeks after treatment, was considered to be effective.

**Results:** Of the 42 subjects included in the study, 39 had achieved SVR, or remained unresponsive to the virus until August 2017. One of the patients who had experienced reactivation of the virus after the treatment was found to have recurrence of HCC 12 weeks after the start of treatment. Virus regrowth was

observed 4 weeks after the end of treatment. HCV. **Conclusions:** If possible, it is advisable to perform HCV treatment before receiving a liver transplantation. **Keywords:** Liver transplantation, Antiviral, HCV, DAA

# PE-229

#### De Novo Malignancy within One Year after LDLT: Case Report

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**Aims:** Biliary obstruction is a common morbidity after liver transplantation. The anastomotic failure of biliary reconstruction is the leading cause. When the patient with hepatocellular carcinoma (HCC) underwent liver trasplantation and developed a jaundice, the recurrence of HCC is suggested as the main cause.

Methods: Here we describes a case of biliary obstruction due to pancreatic head cancer at 11 months after LDLT. The patient was a 54-year-old male with HBV related cirrhosis and hepatocellula carcinoma (HCC) within Milan criteria. Our patient previously underwent liver resection for HCC two times in 1998 and 2002. Recurrence of HCC revealed and LDLT using the right lobe from his 23-year-old daughter was performed in December 2008. Immnosuppressive treatment was administered with basiliximab, tacrolimus, corticosteroids and mycophenolate mofetil. He discharged on postoperative 28th day with uncomplicated course. **Results:** At eleven months after operation, the patient showed icterus. Ampullary stricture below the anastomosis site was found by MRCP and finally diagnosed in adenocarcinoma with endoscopic biopsy. Pylorus-preserving pancreaticoduodenectomy (PPPD) was performed for complete resection of pancreatic head cancer on 14 months after LDLT. The patient revealed favorable outcomes except for superior mesenteric arterial (SMA) pseudoaneurysmal bleeding controlled by endovascular graft postoperatively. However, the patient died from recurred pancreatic head cancer two year after LDLT.

**Conclusions:** Our experience suggest that high suspicion of de novo malignancy is needed for the patient with HCC who has undergone liver transplantation.

# PE-230

# Liver Transplant M & M, from a Non Transplant University Hospital

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**Aims:** Liver transplant is the only curative therapy for decompensated cirrhosis, but there remained several regions throughout the globe where this important and lifesaving modality is non-existent or in the phase of early development. Pakistan ranks third among countries with highest burden of
chronic hepatitis C, with a prevalence of >4.8%. For decompensated cirrhotics, only one liver transplant center is available. Post-transplant care remains a challenging domain for the hepatologists in the country

**Methods:** This cross-sectional analysis was done for the post-transplant care and follow up of liver transplant patients in a facility devoid of transplantation. Apart from demographic information, data were collected for indications of liver transplant, post-transplant complications- immediate or within 4 weeks, delayed within one year and then during follow up periods, along with therapeutic modality for treatment of complication. Adverse effect, rejection episodes, their cause and management were recorded.

**Results:** 41 transplant recipients were enrolled between 2016 and 2017. 80% were male. 39 were living donor liver transplant. Most common indication of transplant was HCV in 25 (61%), 13 were PCR positive and given directly acting antivirals (DAAs) with 100% eradication. 2 patients developed diabetes after 6 months of transplant, both were on tacrolimus. Thirteen patients developed biliary anastomotic strictures and went through successful therapeutic ERCP. 21 patients extensively worked up for deranged liver function test and there biopsy showed chronic rejection. Hepatoma recurrence was not seen.

**Conclusions:** Pakistan is in a desperate need of liver transplant facilities and transplant hepatologists. Collaborative work is needed with expert centers.

#### **PE-231**

# A Review of Discarded Organs from Deceased Donors in South Korea

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**Aims:** Despite a steady increase in the number of organ transplantations performed each year throughout the world, the shortage of available organs for transplantation is worsening. This study aims to analyze the current status of discarded organs (Harvested, but not be transplanted organ) from deceased donors in Korea.

**Methods:** We used KODA (Korea Organ Donation Agency) and KONOS (Korean Network for Organ Sharing) database to search for deceased donor organ transplantations (DDOTs) performed between 2013 and 2016. Based on the data, we analyzed the incidence and causes of discarded organs according to organs.

**Results:** In South Korea, 6315 DDOTs were performed between 2013 and 2016. A total of 63 discarded organs were procured. The most common organ was the kidney (n=24) followed by islet cell (n=23), lung (n=9), liver (n=6) and pancreas (n=1). There were no discarded hearts. Except for islet cells, the most common reasons for organs to be discarded were organ dysfunction and vascular defects. All of discarded islet cells (n=23) were caused by

separation failure or shortage of proper cell number. We also analyzed cases of discontinuation of harvesting operations for past 4 years. Out of 39 total cases, donor's poor organ condition (n=27) was the most prevalent reason for discontinuation.

**Conclusions:** It is obvious that the shortage of organ donors will continue to get worse. To prevent and reduce unnecessary procurement and discard rate, we should more carefully perform preoperative evaluations and intraoperative inspection. Also, it would be necessary to implement a better control system.

### PE-232

# The Experience of Management for Biliary Complication after Liver Transplant in Local Tertiary Center

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**Aims:** Biliary complications have still remained as major problem after liver transplant (LT) and accepted as Achilles' heel. Herein, we introduce our experience of biliary complications after LT in small volume center.

**Methods:** From November 2002 to July 2017, 100 patients underwent LT at Dongsan Medical center, Daegu, Korea. Among these patients, 60 patients underwent deceased donor liver transplant (DDLT) and 40 patients underwent living donor liver transplant (LDLT). Medical records of these patients were reviewed retrospectively

**Results:** Among these patients, biliary complications (bile leakage in 10 patients and bile duct stricture in 26 patients) were developed in 28 patients (28%). For the management of biliary complications, reoperation was performed in 2 patients for bile leakage, percutaneous transhepatic biliary drainage (PTBD) in 11 patients and endoscopic retrograde biliary drainage (ERBD) in 22 patients for bile leakage and biliary stricture. All patients were improved after treatment and followed up without biliary problem until now.

**Conclusions:** The rate of biliary complications in our center was comparable with that of other centers reported previously and the outcome of treatment was acceptable. Co-operation with interventionist and gastroenterologist is important to overcome biliary complications after liver transplant.

### PE-233

### Clinical Course of Hepatic Artery Thrombosis after Living Donor Liver Transplantation Using the Right Lobe

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Aims: Hepatic artery thrombosis (HAT) can result in biliary tree

necrosis and graft loss necessitating re-transplantation. This study was performed to review the outcomes of HAT after living donor liver transplantation (LDLT), and to clarify the feasibility of different strategies.

**Methods:** From May 1996 to August 2017, LDLT using the right lobe was performed in 827 adult patients in our center. Diagnosis of HAT was performed using Doppler sonography and computed tomography (CT) angiography. HAT was initially treated with surgical or endovascular according to the graft condition.

**Results:** Among the 827 cases of LDLT using the right lobe, HAT occurred in 16 (1.9%) cases within 1 month after transplantation. Seven of these HAT cases occurred within the first week (early HAT), while the remaining nine cases occurred between the first week and 1 month (late HAT). The incidence of graft failure was high in early HAT (42.9%), and the frequency of biliary complications was high in late HAT (77.8%). The success rate of HA recanalization was 62.5%: 100% (5/5) after reoperation and 45.5% (5/11) after endovascular procedure. Of the five patients in whom treatment failed in late HAT, four underwent neovascularization during observation. Mortality occurred in three patients, including one in the surgical group and two in the endovascular group.

**Conclusions:** Early diagnosis and aggressive treatment of HAT are necessary to avoid graft failure, and the choice of treatment depends on various factors. Although further studies are required, early HAT requires preparation for graft failure, while late HAT requires treatment for biliary complications.

## PE-234

# Successful LDLT in a Case of Mean Pulmonary Arterial Pressure of 52 mmHg

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**Aims:** Pulmonary hypertension (PH) is defined as an elevated mean pulmonary arterial pressure (mPAP) =25 mmHg at rest. Krowka reported that mPAP of 50 mmHg or greater was associated with 100% cardiopulmonary mortality in liver transplantation (LT) setting.

**Methods:** A 45 years old male patient underwent LDLT for HBV + alcoholic cirrhosis and HCC. MELD score was 28. Echocardiography showed right ventricular systolic pressure (RVSP) 62 mmHg, suggesting moderate resting PH. During anesthetic induction, mPAP was measured as 52mmHg. With infusion of Isosorbide, mPAP decreased to 40. Vital signs were stable and PaO2 level was 223 mmHg. So we decided to proceed with surgery despite of moderate PH.

**Results:** The LDLT procedure was done with modified right lobe graft. mPAP was in the range of 46~31. Alprostadil was started after finishing arterial anastomosis and was infused for 7 days

thereafter. The day after LT, RVSP was 96 mmHg. And 5 days after LT, he complained of dyspnea and Beraprost (prostacyclin pathway agonist) was given orally. The patient was discharged 19 days after LT. 6 weeks after LT RVSP was measured as 84 mmHg. mPAP was 63 mmHg on right heart catheterization. On CT scan, there was marked hepatic congestion resulting from PH. Endothelin receptor antagonist Ambrisentan was given orally. The patient's breathing difficulty almost disappeared soon. Now, 5 months after the operation, he returned to work. **Conclusions:** When encountered a case of moderate to severe pulmonary hypertension during LT, initial response to anesthetic management might dictate whether to proceed with LT or not.

## PE-235

### The Course of Renal Disease Liver Transplant Recipient who Requiring Perioperative Dialysis in Liver Transplantation

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**Aims:** The development of renal dysfunction before and after liver transplantation is a complicated, mulifactered, and critical issue that affect recovery after liver transplantation. The aim of this study is to review the courses of LT recipients who needed dialysis pre and post LT at our center.

**Methods:** We reviewed the medical records of 21 LT recipient from May 2015 to September 2017 at our center. We compared their clinical demographic, morbidity, and motality between dialysis pre and post LT patients and those not needed.

**Results:** We have performed 21 liver transplants from May 2015 to August 2017. Among them, 8 patients had peri-transplant dialysis and 13 patients did not. Patients who underwent dialysis had more frequent acute renal injury pretransplantly, a higher preoperative MELD (41.5 vs 12, P<0.001) and longer post LT hospital stay (32 vs 22 days). However, there was no significant difference between the two groups in terms of serum creatinine (1.06 vs 0.89 mg/dl, P=0.256) for first week, (0.80 vs 0.70 mg/dl, P=0.427) for first month (1.12 vs 0.89 mg/dl P=0.256) for third months. One patient in the dialysis group died of graft failure due to HAT for 26th days postoperatively, but there was no significant difference in mortality between the two groups (P=0.400).

**Conclusions:** In most cases, kidney function is recovering within a few weeks of transplantation. However, long-term follow-up is required for more patients for more concrete conclusions.

### PE-236

### Long-Term Survival with Multidisciplinary Therapy for a Patient with Multiple Liver Metastases from Rectal Cancer: A Case Report

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**Aims:** Multidisciplinary therapy is necessary to prevent recurrence of advanced rectal cancer and advanced cancer with metastases.

**Methods:** Here we report a case of long-term survival of a patient with advanced rectal cancer with multiple liver metastases metachronously.

**Results:** A 55 year-old man had previously undergone anterior resection. A year after chemotherapy, a CT scan revealed multiple liver metastases. Thus, we performed partial liver resection such as right hemihepatectomy and wedge resection in segment 3. After another round of chemotherapy, a CT scan showed another liver metastasis in segment 2 and 4. We performed partial resection of liver after chemoradiation.

**Conclusions:** These procedures were conducted 12 year after his first operation. He has still survived until now with no evidence of disease recurrence.

### **PE-237**

# Pure Laparoscopic Left Lateral Sectionectomy for Living Donor with Anatomic Variation

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**Aims:** In adult-to-child living donor liver transplantation (LDLT), a pure laparoscopic donor left lateral sectionectomy could be considered as a standard practice with emerging evidences supporting its feasibility and safety. The pure laparoscopic left lateral sectionectomy for living donor with anatomic variations in hepatic artery and bile duct is presented.

**Methods:** After intraoperative frozen biopsy of the liver and cholecystectomy, mobilization of left side of liver was done through division of falciform ligament, followed by left coronary ligament and triangular ligament division. Thereafter during the division of gastrohepatic ligament, aberrant left hepatic artery originating from left gastric artery was identified and taped with vessel loop. Hilar dissection with identification of middle hepatic artery and left portal vein was performed. Parenchymal division was performed using a combination of CUSA and energy device on the right side of falciform ligament

and umbilical fissure. Three times of vascular clamping were used during parenchymal transection. As division of the hepatic parenchyme was completed, left bile duct transection was performed after confirming aberrant right posterior hepatic duct drainage into left hepatic duct through intraoperative cholangiography with fluoroscopy. Procurement of left lateral section graft was performed followed by retrieval through suprapubic transverse incision.

**Results:** Donor recovery was not eventful and discharged 8 days after the operation. Follow-up CT and hepatobiliary scan after the operation showed no abnormal findings.

**Conclusions:** Pure laparoscopic living donor left lateral sectionectomy with complicated anatomic variations could be safely performed and feasible option for living liver donors even with these kinds of aberrant anatomy.

## PE-238

### Efficacy and Superiority between ERCP and PTBD as First Line Intervention of Biliary Complication after Liver Transplantation

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**Aims:** Biliary complications after liver transplantation(LT) are most common complications and associated with morbidity and mortality. Currently, the generally applied first intervention for post-LT biliary complications is Endoscopic retrograde cholangiopancreatography(ERCP) because of less invasiveness and patient convenience. However, there has not been a uniform conclusion published on superiority of the two types of intervention as first trial. Therefore, we compared the efficacy of ERCP and percutaneous transhepatic biliary drainage(PTBD) as a first line treatment of post-LT biliary problems.

**Methods:** From January 2013 to December 2016, 565 patients underwent LT in Seoul National University Hospital(SNUH). Medical records of LT recipients with biliary complications retrospectively reviewed. Long-term follow-up was evaluated using cholangiogram, computed tomography(CT) scan and laboratory parameters.

**Results:** Among 565 LT patients, 85 patients(15.0%) were treated by intervention including ERCP and PTBD with diagnosis of biliary complications. Successful intervention on the first attempt was achieved in 36 of 60 patients(60.0%) with ERCP, and 19 of 25 patients(76.0%) with PTBD, respectively(P=0.16). We also classified the groups based on the location of the biliary complications and compared the success rate; one with anterior bile duct problems (a-BD, n=29) and another with posterior bile duct (p-BD, n=14). In a-BD, there was no difference in the intervention success rate of PTBD and ERCP(25% vs.24%, P=0.692). However, in p-BD, PTBD success rate was significant-

ly better than ERCP(75% vs.18%, P=0.002).

**Conclusions:** PTBD could be considered as more effective procedure for termination of treatment in patients with post-LT biliary complications, especially posterior duct problems.

### PE-239

### Pegylated Interferon versus Direct-Acting Antiviral Agents Pre-emptive Treatment of HCV after Living Donor Liver Transplantation

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**Aims:** HCV universally recurs after liver transplantation. Although the introduction of direct-acting antiviral agents (DAAs) has revolutionized the treatment of HCV infection, no optimal treatment for HCV recurrence after liver transplantation has been developed.

**Methods:** This study retrospectively evaluated the efficacy of DAAs as a pre-emptive treatment for recurrent HCV infection after living donor liver transplantation (LDLT). From January 2010 to December 2016, 105 patients received LDLT followed by either pegylated interferon (PegIFN) or a DAA-based regimen to treat recurrent HCV. All antiviral treatments were pre-emptive.

**Results:** After LDLT, 70 patients received PegIFN and 35 received a DAA. Genotype 1b was the most common HCV type (61.9%), followed by 2a (27.6%). Twenty-two recipients in the DAA group were treated with ledipasvir/sofosbuvir, nine received daclatasvir plus asunaprevir, three received sofosbuvir, and one received sofosbuvir plus daclatasvir. All 35 patients (100%) in the DAA group achieved a sustained virologic response (SVR), a percentage significantly higher than that (71.4%) in the PegIFN group (P<0.001). Recipients in the DAA group also showed a significantly stronger early virologic response (EVR) and an end-of-treatment virologic response (EVR). In the PegIFN group, the 1, 3, and 5 year graft survival rates after LDLT were 85.7%, 73.9%, and 70.7%, respectively, whereas those in the DAA group were significantly higher, at 100%, 100%, and 100%, respectively (P=0.008).

**Conclusions:** DAA-based regimens are an effective treatment for HCV recurrence after LDLT, resulting in an improved SVR and better graft survival than PegIFN-based treatments. **Drug and Toxic Injury** 

## PE-240

### Hepatotoxicity and Related Risk Factors of Severe Hepatotoxicity among HIV-1 Infected Individuals Initiated on Highly Active Antiretroviral Therapy (HAART) in Cameroon

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**Aims:** Hepatotoxicity due to highly active antiretroviral therapy (HAART) has gained prominent attention since it can be affected by many factors. The aim of this study was to determine the prevalence of hepatotoxicity and related risk factors of severe hepatotoxicity following HAART initiation.

**Methods:** One hundred naive HIV-1 patients were recruited and followed up for 24 weeks. They were placed on either Tenofovir (TDF)+Lamivudine (3TC)+Efavirenz (EFV) or Zidovudine (AZT)+Lamivudine+Nevirapine (NVP) or Zidovudine+Lamivudine+Efavirenz regimen. Venous blood samples were collected to measure transaminotransferases (ALT and AST) and alkaline phosphatase (ALP), using colometric enzymatic reaction which were used to classified hepatotoxicity based on age and sex.

**Results:** A total of 38(38%) and 55(55%) patients presented with hepatotoxicity while 15% and 28% of patients of them had severe hepatotoxicity at 4 and 24 weeks respectively. Serum levels of all enzymes increased significantly (*P*<0.05) with increased treatment duration. Univariate analysis revealed that the risk factor of developing severe hepatotoxicity was significantly (*P*<0.05) greater in patients <30years, males, low BMI, low monthly income earners and patient on AZT+3TC+NVP regimen. While multivariate analysis showed that age <30 years, Low BMI, low monthly income and the use of AZ-T+3TC+NVP was an independent risk factors.

**Conclusions:** Low BMI, <30years, low monthly income and the use of AZT+3TC+NVP regimen were identifiable risk factors for the development of severe hepatotoxicity. As such these factors should be considered as an important strategy by clinicians in preventing the hepatotoxicity.

Keywords: HAART, Hepatotoxicity, HIV, Risk factor

### PE-241

# Current Status of Severe Drug-induced Liver Injury: A Single-Center Experience in South Korea

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**Aims:** Drug induced liver injury (DILI) is a common cause of severe liver injury in Korea. We investigated the causative agents and clinical manifestations of DILI in a single health care center. **Methods:** A retrospective analysis examined the medical records of patients with severe DILI requiring admission from January 2011 to December 2017. A total of 46 cases that have causal relationship to agents were included.

Results: The mean age was 54 years and female patients were predominant (78%). The causative agents included "herb or herbal medications" (N=21, 45.7%), "general pharmaceuticals or prescription-based medicines" (N=14, 30.4%), "folk medicines" (N=11, 23.9%). As a single causative agent, kudzu (Pueraria spp.) root extract (N=5) and fimasartan (anti-hypertensive agent) (N=4) were common. The frequencies of hepatocellular, cholestatic, and mixed types were 84.8%, 6.5%, and 8.7 %, respectively. Median serum values of peak total bilirubin, aspartate aminotransferase and alanine aminotransferase were 5.4 mg/dl (Interguartile range [IQR], 2.9–15.9), 911 U/L (IQR, 495-1470), 1138 U/L (IQR 350-1573), respectively. The average duration of hospital stay was 10 days (range 3-36). Most patients (96%) recovered clinically. Two patients (4%) caused by kudzu root extract and mushroom (Fomes fomentarius) extract progressed to fulminant hepatic failure and expired at 5 and 10 days of hospitalization waiting liver transplantation, respectively.

**Conclusions:** The causative agents of DILI were very diverse. Herbal medications or herbs were still common causes of DILI. Especially, kudzu (*Pueraria spp.*) root extract and fimasartan were frequently related with DILI.

Keywords: Chemical and Drug Induced Liver Injury, Fimasartan, Herbal Medicine, Pueraria

### PE-242

### Evaluation of Cucurbita ficifolia Juice as a Hepatoprotective Drug in Human Type 2 Diabetes

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**Aims:** The present study has been undertaken to analyze the hepatoprotective potential of *Cucurbita ficifolia* juice in type 2 diabetic subjects.

**Methods:** A total 34 subjects were selected for the study out of which 14 subjects were with type 2 diabetes mellitus, 10 subjects were selected as a normal control group and 10 subjects were selected as a normal treated group. The patients had type 2 diabetes for more than 2 years, their mean age was less than 45 years, and subjects were then asked to start the *Cucurbita ficifolia* juice therapy starting at day 0 and continuing up to 40 day both for diabetic and normal subjects. Liver enzymes such as. *serum glutamic-oxaloacetic transaminase* (SGOT), serum glutamic-pyruvic transaminase (SGPT), and bilirubin were measured.

**Results:** After 40 days of *Cucurbita ficifolia* juice therapy, there was a decrease of 9.45% and 27.85% (*P*<0.01) for SGPT and total serum bilirubin, while the SGOT levels increased by 2.02% in the case of diabetic treated subjects that was not found to be significant.

**Conclusions:** The liver enzymes measured in our study ameliorated in type 2 diabetic patients. The results suggest that the *Cucurbita ficifolia* juice therapy could be used as a hepatoprotective drug in type 2 diabetes.

**Keywords:** Cucurbita ficifolia, Type 2 diabetes, Liver enzymes, Human subjects

## PE-243

# Effect of Herbal Medicines on Liver Function Markers in Type II Diabetic Subjects

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**Aims:** Herbal medicines have been used in the treatment of liver diseases and other problem for a long time in folk system. However there are some reports in general state that, herbal medicine has hepatotoxicity. Hence in the present study we evaluate some anti-diabetic herbal medicines effect in liver function markers

**Methods:** Total of 100 subjects those who have T2DM were randomly selected from the week end diabetic clinic of Centre for Translation Research, 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 and Regimen IV diabegon kwath (polyherbal formulation) for 3 - 4 months. Fasting and PP blood glucose and glycosylated hemoglobin, 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. 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 P<0.05) and the antioxidant markers were also improved significantly (P<0.05).

**Conclusions:** Herbal medicines for the treatment of human type II diabetes mellitus show the significant improvement in glycemic control. The liver functions remained normal and in fact improved in many subjects. It may be the due to the anti-oxidant property of the herbal formultions.Hence the studied herbal formulations not have hepatotoxicity in the subjects.

**Keywords:** Herbal medicine, Liver enzymes, Hepotoxity, Type II diabetes

## PE-244

## Is Liver Function Tests Necessary for Acute Organophosphorus Poisoning Subjects Attending Emergency Room?

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**Aims:** Acute organophosphorus poisoning (OP) is a major problem worldwide causing thousands of deaths annually. Self ingestion of these organophosphorus poisoning and deaths taking place in low income countries is very high. And the major causes of this self ingestion of OP are mainly domestic violence, poverty, illiteracy, mental disorder etc. The main aim of this study is to explore the association of liver function test in OP poisoning subjects which is commonly requested from emergency department.

**Methods:** It is a hospital based observational study where 103 (79 females and 24 males) patients seen in emergency room of University Hospital in the duration of two year. Pre-structured sociodemographic questionnaire along with selected biochemical parameters for OP ingested patients were analyzed where random blood sugar, electrolytes, renal function test, liver function test and cholinesterase was performed in fully automated chemistry analyzers. According to patients relatives, known case of chronic alcohol consumer, liver disease, diabetes, hypertension, and renal failure were excluded. Descriptive analysis was done to explore the association of these biochemical parameters among OP ingested patients.

**Results:** Dyselectrolytemia and low level of cholinesterase is very common observation among OP subject but there was no statistical significant association was found in liver function test of these subjects except Aspartate transaminase enzyme which was slightly increased only in 32% and mild hypoalbunemia was found in 22.3% subjects.

**Conclusions:** This study suggested that requesting liver function test for acute OP patients from emergency department may be financial burden for family of OP subjects rather than clinical benefits, however large sample sized multicenter study is essential.

**Keywords:** Organophosphorus, Cholinesterase, Liver function tests

## PE-245

### Assessment of Methotrexate Hepatotoxicity in Psoriasis Patients from Nepal

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**Aims:** Methotrexate (MTX) has been used to treat a wide spectrum of skin conditions including psoriasis. Hepatotoxicity is a major side effect of MTX which can range from simple elevation of liver enzymes to fatty liver, fibrosis, and liver cirrhosis. Current literatures suggest that MTX has less hepatotoxicity than previously assumed. However, MTX induced hepatotoxicity in Nepalese psoriatic patients has never been assessed. Herein, we evaluated the development of MTX induced liver damage among psoriasis patients from Nepal.

**Methods:** Liver function test was done in patients prior to and at 6 months of oral *MTX* (15 mg/week) administration. Liver enzymes SGPT and SGOT were measured using UV-kinetic method. Serum albumin was determined by bromocresol green dye-binding technique. Patients consuming alcohol during the treatment period were excluded.

**Results:** Out of 471 patients diagonosed of psoriasis, 24 were treated with MTX oral dose of 15 mg/week. Seven patients (29.16) developed deranged liver function, with five (31.25%) being male and two (25%) being female. Interestingly, SGPT is markedly elevated (267.22  $\pm$  35.50) than SGOT (150.20  $\pm$  30.14). However, the MTX therapy did not altered albumin level (4.1 compared to 4.03).

**Conclusions:** Abnormal serum SGOT/SGPT level developed in less than one-third of psoriatic patients under MTX therapy; prompting drop in the therapy. Although, the associated risk factors, except alcohol consumption, are not studied, the use of MTX is relatively safe considering patient's quality of life which is severely affected by psoriasis. Additionally, continuous monitoring of the liver function is warranted in patients undergoing MTX therapy.

Keywords: Methotrexate, Hepatotoxicity, Psoriasis, Nepal

### PE-246

# Drug Induced Liver Injury Caused by Isopropylantipyrine in South Korea: Case Report

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**Aims:** Drugs and herbs are major causes of severe liver injury in Korea. Isopropylantipyrine (IPA, or propyphenazone), a derivative of nonsteroidal anti-inflammatory drug, has been widely used as an over-the-counter preparation (Geworin®) for long time in Korea, while it has now been restricted in the most countries.

Despite popular use of this drug, IPA-related liver injury has not been reported in the country. Herein, we report severe liver injury following long-term use of IPA for the first time in Korea.

Results: Case: A 49-year-old, icteric and acutely ill-looking male visited emergency department for 2 weeks of severe fatigue and generalized weakness. Initial serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was 1,593 U/L and 1,582 U/L. Total bilirubin was 15.6 mg/dL and prothrombin time (INR) was 1.2. Viral serology including hepatitis A, B, and C virus were all negative and abdominal CT didn't show any structural abnormality of liver and biliary system. Further serologic work-up including HEV, CMV, AMA and ANA was also negative. Thorough interview about patient's previous medical and social history revealed that he was a social drinker. Notably, he admitted that he took 2 tablets of Geworin® everyday for 3 months to relieve his headache. Neither medications other than Geworin® nor herbs, he didn't take previous 3 months. Liver biopsy showed lobular and portal distortion with heavy lymphocyte accumulation. After stopping the culprit drug, he was discharged with improved clinical conditions at day 17. Following blood liver tests were all normalized at 2 weeks after the discharge. Considering his clinical course, calculated RUCAM score was 9 (highly probable cause of liver injury). Rechallenge test was not performed.

**Keywords:** Chemical and Drug Induced Liver Injury, Nonprescription drugs, Propyphenazone

### **PE-247**

### Evaluation of Hepatoprotective Effect of Secondary Metabolites of Chickpea (Cicer arietinum L.)

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**Aims:** To evaluate the hepatoprotective effect of secondary metabolites of chickpea on paracetamol induced liver toxicity in rats. **Methods:** Twenty four chickpea genotypes were collected from College of Agriculture, Sehore, Madhya Pradesh. Seed coat were removed and crushed into fine powder. Phytochemicals were isolated using soxhlet apparatus with various solvents. Extract was investigated to find active constituents of the seed extracts by the different phytochemical tests. Among all cultivars tested JAKI 9218 variety showed highest concentration of phytochemical such as flavonoids, phenolics and tannins. The hepatoprotective activity of the crude extract of JAKI 9218 was assessed in paracetamol induced hepatotoxic in rats. Alteration in the levels of biochemical markers of hepatic damage like ALT, AST, ALP, total protein and total bilirubin were tested in both paracetamol treated and untreated groups.

**Results:** Paracetamol (3 g/kg) prepared in 40% sucrose solution has enhanced the ALT, AST, ALP, total protein and total bilirubin in liver. Treatment of crude extract of *Cicer arietinum* L. (200 mg/kg) of seven days have brought back the altered levels of biochemical markers to the near normal levels in the dose dependent manner which is compared with standard silymarin

#### (100 mg/kg).

S. No	Group (n)	Dose (mg/kg)	ALT (U/L)	AST (U/L)	ALP (U/L)	Total protein (mg/dl)	Total bilirubin (mol/L)
1.	Control	5ml/kg b.w.	37.2±1.6	50.6±2.4	67.39±3.48	7.75±0.76	0.65±1.82
2.	Paraceta- mol	(3 g/kg)	287.53±12.76	378.55±2.85	113.85±3.69	9.44±8.63	6.38±0.5
3.	Silymarin	100 mg/kg	39.26±5.8	56.76±5.79	59.67±4.6	7.07±0.5	0.79±1.73
4.	Crude extract	200 mg/kg	83.27±0.8	68.64±1.8	88.31±0.5	8.17±2.9	1.33±0.5

Values are expressed as Mean SEM, n =3 rats in each group. (P<0.05).

**Conclusions:** The result concludes that *Cicer arietinum* L. possesses the hepatoprotective effect against paracetamol induced liver toxicity in rats.

**Keywords:** Secondary metabolites, Hepatoprotective, Flavonoides, Phenolics

### **PE-248**

### Protective Effects of Kolaviron on Diclofenac-Induced Hepatotoxicity in Rats

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**Aims:** The present study was carried out to evaluate the protective effects of kolaviron (KV), a biflavonoid from Garcinia kola seeds on diclofenac-induced hepatic injury in Wistar rats.

**Methods:** Twenty-five male Wistar rats were divided into 5 groups of 5 animals each. Group 1 (control) received propylene glycol at 2 ml/kg orally for 28 days. Group 2 received 10 mg/kg of diclofenac (DCLF) (i.m) for 7 days. Groups 3 and 4 received KV orally at 100 and 200 mg/kg respectively for 28 days and subsequently treated with DCLF for 7 days. Group 5 received Livolin Forte (a reference drug) orally at 5.2 mg/kg for 28 days and DCLF for 7 days. At the end of the study, all the rats were sacrificed under ketamine anesthetic, 24 hours after treatment. Pro-inflammatory cytokines level, markers of liver function, oxidative stress and histopathological alterations were evaluated.

**Results:** DCLF caused significant increase in the plasma activities of liver enzymes, including bilirubin level, pro-inflammatory cytokine and NF-kB when compared with the control (P<0.05). It also caused significant alteration in antioxidant status of the rats. It caused distortion of the liver histoarchitecture of the rats. However, kolaviron significantly prevented or reduced (P<0.05) the alterations caused by DCLF in the plasma and liver of the rats pre-treated with KV before DCLF administration.

**Conclusions:** KV exhibited a protective properties against DCLF-induced hepatotoxicity, due to its antioxidant and anti-in-flammatory effects. It appears to be as effective as Livolin Forte in attenuating DCLF-induced hepatotoxicity in rats.

## Cell Biology/Molecular Biology

### PE-249

### Neurotropin Treatment Can Lead to Autophagy in Liver by AMPK Phosphorylation

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**Aims:** Autophagy has two main function: to eliminate potentially hazardous or dysfunctional organelles or proteins, and to obtain energy and new building blocks for protein synthesis. Neurotropin is a drug derived from a non-protein fraction extracted from the inflamed skin of rabbits after the administration of vaccina virus. We aimed to investigate whether neurotropin can induce autophagy in liver.

**Methods:** We treated HepG2 cell line with neurotropin 0.2 NU/ ml and 0.4 NU/ml. As a positive control metformin 2mM was used. Samples were collected at baseline, 3 hours, 6 hours, 9 hours and overnight after treatment. Western blot was performed with Phospho-AMPK(p-AMPK), AMPK, LC3B and SQST-M1(p62) monoclonal antibodies as primary antibody.

**Results:** Western blot showed enhanced expression of p-AMPK and LC3B II protein after neurotropin treatment. AMPK and p62 expressions were not different from baseline.

**Conclusions:** Neurotropin treatment has possibility to induce autophagy in liver disease by AMPK phosphorylation. Further investigation including *in vivo* experiment is warranted. **Keywords:** Autophagy, Neurotropin, Liver

### PE-250

### Modulation of Bone Marrow Mesenchymal Stem Cells Using WT1 and EGR1 during Hepatocyte-Like Cells Differentiation Process

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**Aims:** Human bone marrow-derived mesenchymal stem cells (hBM-MSCs) have been known to differentiate into multi-lineage cell types and used for differentiated hepatocyte-like cells.

The mesenchymal-epithelial transition (MET) plays as a key of cellular transdifferentiation programs, including wound healing and tissue regeneration. The purpose of this study is to clarify underlying differentiation mechanism and function of Wilms' tumor suppressor gene (WT1) and early growth response 1 (EGR1) by screening the key factors in hepatic differentiation stem cells.

**Methods:** To detect the regulatory genes of hBM-MSC into functional hepatocytes, protein/DNA array was performed in hBM-MSCs before and after differentiation. To determine the effects WT1 and EGR1, knockdown and overexpression were obtained respectively by the use of siRNA and pcDNA3.1 (-)-mWT1 (B) or pcDNA3-mEGR1. The role of WT1 and EGR1 were identified through the change of liver-specific genes and MET markers using RT-PCR and western blotting.

**Results:** We demonstrate that WT1 and EGR1 increase during hepatic differentiation of hBM-MSCs. Hepatic differentiated hBM-MSCs increased the expressions of epithelial markers but decreased the expressions of mesenchymal markers. However, downregulation of WT1 or EGR1 reduced hepatic differentiation and didn't change in morphology, looked spindle or fusiform shape as compared control during hepatic differentiation of hBM-MSCs. Furthermore, the expression of mesenchymal markers was increased, while the expression of epithelial markers, the expression of epithelial markers decreased in WT1 or EGR1 knockdown hBM-MSCs. In contrast, the expression of mesenchymal markers decreased in WT1 or EGR1 overexpression hBM-MSCs. In addition, overexpressing of WT1 or EGR1 induced rapid maturation of hepatic differentiation.

**Conclusions:** In this study, we identified novel factors in the process of hepatic differentiation by MET. Our results demonstrate that hBM-MSCs may be a source of cells for liver regeneration and provide the mechanism of liver regeneration through MET process by the WT1 and EGR1.

**Keywords:** Wilms' tumor suppressor gene (WT1), Early growth response 1 (EGR1), Human bone marrow-derived mesenchymal stem cells (hBM-MSCs), Mesenchymal-epithelial transition (MET), Hepatic differentiation

## PE-251

### Exosomes by Placenta-Derived Mesenchymal Stem Cells Is Involved in Liver Regeneration in a Rat Model with Hepatic Failure

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**Aims:** Placenta-derived mesenchymal stem cells (PD-MSCs) as an alternative MSC source have several advantages such as abundant cell numbers, multi-potential and strong immu-

no-suppressive properties. Although we reported that hepatic regeneration in a CCl4-injured rat model was enhanced by PD-MSCs transplantation through anti-fibrotic effect and increased proliferation of hepatocytes, their therapeutic mechanism and information for effective molecules are still unclear. Recently, it has been known that exosomes secreted from stem cells have therapeutic potential. Therefore, the objectives of this study are to analyze exosome profiling in a rat model with bile duct ligation (BDL) and demonstrate selected effective molecules in exosomes according to PD-MSCs transplantation (TTx). Finally, we evaluate their correlation between effective molecules and hepatic regeneration.

**Methods:** Exosome profiling was analyzed in serum of a rat model according to PD-MSCs transplantation through LC-MS analysis. Also, candidate factors were demonstrated by real-time PCR, Western blot in the liver tissues of a rat model. Also, their functions were evaluated by co-culture system.

**Results:** In exosome profiling, C-reactive protein (CRP), which known as inflammatory factor, was decreased in the rat serum of TTx group. Otherwise, their expression was significantly increased in a rat liver tissues of TTx group (*P*<0.05). Interestingly, the correlation between CRP expression and angiogenesis via Wnt signaling was observed in the liver tissues of a rat model with TTx. Furthermore, increased CRP by PD-MSCs co-cultivation activated Wnt signaling in HUVECs with rat hepatocytes.

**Conclusions:** Our findings suggested that the increased exosomes containing CRP by PD-MSCs induce vascular remodeling through activation of Wnt signaling in the liver tissues damaged by BDL, thereby promoting regeneration of damaged liver tissues. Therefore, these results suggest that exosomes containing CRP by PD-MSCs can be used as a therapeutic source as well as helpful to understanding therapeutic mechanism in a chronic hepatic disease.

Keywords: Liver cirrhosis, Exosome, C-reactive protein, Angiogenesis

## Liver, Infectious Disease

#### PE-252

Liver Stiffness Decrease Post Ledipasvir/Sofosbuvir Combination Treatment in Mongolian Patients with Chronic Hepatitis C

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Aims: The prevalence of liver cancer in Mongolia is 7 times

higher than that of world average, generally caused by HBV and HCV. The most prevalent cause of HCC in Mongolia, HCV, accompanied with liver stiffness and cirrhosis, is an emerging public health issue. Mongolia is one of the first countries that registered Ledipasvir/Sofosbuvir (LDV/SOF) regimen from developing countries. By the support of Access program run by Gilead Sciences, USA, we started HCV treatment program from January 2016.

**Methods:** We followed and evaluated treatment outcome of patients with HCV infection using combination of 90 mg ledispavir/400 mg sofosbuvir (manufactured by Gilead Science) in 298 treatment naïve patients. All patients were treated with LDV/SOF for 12 weeks and, their treatment was evaluated by quantitative HCV-RNA assays prior and W (week) 4 and W12 of treatment. Sustained virological response (SVR) after 12 weeks treatment was assessed. Virus genotype analysis using cDNA microarray, liver enzymes, CBC and drug related adverse events were assessed in every patient. The laboratory tests were conducted at National Center of Communicable Diseases and Happy Veritas Laboratories.

Results: Out of 298 patients underwent treatment, 138 patients were examined for pre-treatment liver stiffness using Fibroscan. When patients were examined by Fibroscan test, 25% (n = 35) of assessed patients were F0 stage; 13.57% (n = 19)were F1 stage; 10% (n = 14) were F2 stage; 20.71% (n = 29) were F3 stage; and 30.72% (n = 43) were F4 stage. Patients (n = 35) with fibrosis stage F0 were omitted from post-treatment control examinations. The one hundred three patients were selected for further post-treatment fibrosis staging. The twenty three patients were successfully contacted and complied posttreatment Fibroscan scanning. 23/23 (100%) patients achieved SVR12. W, were all genotype 1b. Median ALT level significantly dropped during treatment from 121.19  $\pm$  98.3 IU/L to 33.2  $\pm$ 14.7 IU/L and slightly increased by the end of treatment 41.4  $\pm$ 18.8 IU/L. The ninety one percent of the patients had improved in liver stiffness while remaining patients were observed increased stiffness.

**Conclusions:** After treatment, 30.43% (n = 7) of patients moved to the F0 stage from liver stiffness. There are many studies that assess liver fibrosis after cure of HCV, but varying numbers were observed. We assess liver stiffness after treatment of HCV in Mongolian population for the first time. Though study population was small, we had 91% of

Keywords: Ledipasvir, Sofosbuvir, Treatment

## PE-253

#### Experience of Managment of Large Liver Hemangiomas

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**Aims:** Hepatic hemangiomas are benign tumors, and they are usually asymptomatic with normal liver function. The aim of

this study was to find applicable solutions for patients with large hepatic hemangiomas due to detailed observation of tumor diameter and liver function.

**Methods:** In our study we retrospectively reviewed the patient charts of 21 patients with large hepatic hemangiomas treated with several methods at National Scientific Medical Research Center, Astana.

Clinical Features:

- The commonest liver tumor
- 5% of autopsies
- Usually single small
- Well demarcated capsule
- Usually asymptomatic

**Results:** The median age was 41 years (37-51) and 85% were female. The median hemangioma size was 6.5 cm (6-12.1). Abdominal ultrasound was conclusive in 66.7% (13/21) and four-phase computed tomography (CT) in 82.6% (17/21) of patients. The indication for treatment was progressive abdominal pain in 78.6% (18/21). All patients were observed and showed no complications related to the liver hemangioma during follow-up. A large hemangioma resection – 3 cases – safely performed at highly specialized surgeon. The main indication for surgical procedures remains abdominal pain symptoms. Both surgical resection, enucleation and TAE are safe and are well admitted by patients.

**Conclusions:** Surgical resection and surgical enucleating are the treatments of choice in the management of hepatic hemangiomas. In recent period transcatheter arterial embolization (TAE) has become as routine method to manage tumor growth. However, we use definition as large hemangiomas when hepatic tumors reach 4 cm.

Keywords: Liver, Lesion, Surgery

## PE-254

# Practice of Ethnobotanical Plants for the Treatment of Jaundice among Tharu Tribe of Far Western Nepal

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**Aims:** Ethnomedicine is a system of therapy using natural agents and their derivatives to treat ailments by the ethnic communities. This study was aimed to analyze and record the knowledge of ethnomedicinal plants for treating liver disorders among tharu tribe of far western Nepal.

**Methods:** A descriptive cross sectional observational study was conducted in ten Tharu Tribe inhabited villages of Kanchanpur district of Far West Nepal. Rapid Rural Appraisal (RRA), 'Semi-structured interviews and focus group discussions were employed to collect data from four *Guruwas*, the main traditional healer, as key informants, some knowledgeable persons, (but not *Guruwas*) as informants and some youths in Tharu tribes, categorizing them into three groups. The information shared was further discussed among all three groups.

**Results:** This study enumerated an encouraging data of 39 plant species being used for the treatment of liver and related diseases by tharu community. Out of these, 9 plant species (8 families) were solely used for jaundice and biliary ailments.33 other plant species were also recorded for being used to cure digestive system related disorders which might be related to liver diseases.Fresh plants and their parts including leaves (maximum used), barks, fruits, flowers, roots, rhizome and latex in the form of juice, powder, decoction, and paste and pulverized were used and administered by oral route. Some dietary restrictions (no alcohol, less oil etc.) were also made during medication. Consult the Guruwas for traditional healing was found to be the first choice for jaundice in the selected community. Around 43% jaundiced get well with traditional treatment while rest of the patients visited hospitals.

**Conclusions:** A proper documentation and further elaborated research for ethnomedicinal plant being used by this tribal people is essential to understand the mechanism of action of these plants for jaundice and other liver diseases.

**Keywords:** Tharu tribe, Ethnomedicine, Traditional healers, Jaundice

## PE-255

### Laparoscopic Liver Echinococcectomy

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**Aims:** Improvement of the results of surgical treatment of patients with liver echinococcosis by reducing the traumatism of operations, the frequency of postoperative complications, relapses and the duration of rehabilitation of patients.

Methods: In the Surgery department of the Kyzylorda Regional Medical Center between 2013-2018 performed 68 laparoscopic surgery in patients with liver echinococcosis. Among them were 24 men and 9 women aged 15 to 58. We use 3 trocars: 10 mm paraumbilical trocar for camera, two additional trocars on right subcostal area (point depend from cysts topography). Around cyst put gauzes with a solution of povidone. Then, we puncture the cyst and aspirate it contents. Then through this needle (without removing it from the cyst) were introduced into the cavity 1% Povidone solution. This procedure was repeated twice. Then cut the cyst wall in the most thinning place. Excised the fibrous capsule - perycystectomy. Chitinous membrane and excised fibrous capsule of echinococcus cysts removed from the abdomen by endobag. In the presence of biliary fistulas, using argon plasma coagulation or they are sutured by 6/0 suture. The residual cavity walls treated with a 1% povidone solution again. The cavity is drained, sometime draining subphrenic or subliver area.

**Results:** Laparoscopic echinococcectomy from the liver was possible in all 33 patients. No case of conversions to laparot-

omy. The average duration of the operation was  $43,5\pm3,4$  minutes (30 to 55 minutes). The drains was removed on postoperative  $3^{rd}-4^{th}$  days after ultrasonic control. The average stay in the hospital was from 5 to 8 days. No complications and no mortality after surgery.

**Conclusions:** Laparoscopic echinococcectomy can be successfully used in the treatment of liver echinococcosis with shortening the terms of patients rehabilitation.

Keywords: Laparoscopic, Liver, Echinococcectomy

#### PE-256

### Seroprevalence of Hepatitis B Virus and Hepatitis C Virus Among Patients Visiting Tertiary Care Hospital of Western Nepal

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**Aims:** Hepatitis viruses including hepatitis B and hepatitis C are major public health problems and significant cause of mortality and morbidity especially in developing countries like Nepal. Patients with hepatitis B and hepatitis C virus infections are important sources for spread of infection to close contact population. This study was aimed to determine the sero-prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection among the patients visiting Manipal Teaching hospital, Pokhara, Nepal. Co infection among Human Immunodeficiency Virus (HIV) infected patients was also studied.

**Methods:** This retrospective study was conducted over a period of four years from 2014 to 2018. A total of 32410 serum samples were tested. Screening of HBV, HCV and HIV was carried out by rapid diagnostic test kits and confirmed by Enzyme Linked Immunosorbent Assay (ELISA).

**Results:** The overall sero-prevalence of HBV and HCV was 0.96% (314/32410) and 0.29% (96/32410) respectively. Infection of both hepatitis B and hepatitis C virus was detected in 9 patients. Hepatitis B and hepatitis C co-infection among HIV positive cases was found in 8 patients. Prevalence of hepatitis B and Hepatitis C was found higher among male patients as compared to females, however differences were statistically insignificant. Most of the cases of HBV and HCV were detected among the age group of 25 to 35 years.

**Conclusions:** Despite availability of effective vaccines, HBsAg carrier rate was found high as compared to HCV. Regular screening of patients for HBV and HCV would minimize the transmission among close contact group and healthcare workers. Effective vaccination program at national level would be effective to reduce the consequences.

Keywords: Hepatitis, HBV, HCV, HIV

### PE-257

# Epidemiology and Prevalence of Hepatitis B and C Virus Infections among Nurses in Mongolia

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**Aims:** M.Colombo, W.Lange studies showed that 30-40% of people become chronic after suffering from-Hepatitis B and C virus, about 50% chronic cases transformed into primary liver cancer. There are a few studies in our country were conducted on hepatitis among health care professionals, particular nursing personnel. The study was conducted to identify of hepatitis B and C virus among nurses and make recommendations to prevent and control of hepatitis B and C virus infections.

**Methods:** We carried out cross-sectional study among selected nurses to determine surface antigen of hepatitis B virus and antibodies to hepatitis C virus. For identification of these antibody and antigen and validation of results ELISA tests from CTK, Biotech company (USA) and simplifying diagnostics were used.

**Results:** There were 598 nurses from the First Central hospital, the Second Central hospital, the Third central hospital, Railway Central hospital, Hospital Ministry of Justice and Internal Affairs and National Center of Maternal and Child Health who participated in the study. From 5 hospitals 598 nurses surveyed and revealed the hepatitis B virus surface antigen positive 18.9%, hepatitis C virus antibodies in 23.1%, co-infection of hepatitis B and C were detected 1.2%. There is an urgent need to provide knowledge to medical personnel regarding standards during the procedures, concerning hepatitis infections monitoring and improve technology used during procedures.

**Conclusions:** The study identified that 43.2% of nurses surveyed on hepatitis B and C viruses were detected . It shows a high prevalence among the nurses in Mongolia.

Keywords: Nurse, Prevalence, HBV, HCV

#### PE-258

Campylobacter Fetus Bacteremia after Ingestion of Cow's Omasum in Patient with Alcoholic Liver Cirrhosis

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**Aims:** Campylobacter fetus Bacteremia is rare and occurs primarily in patients with immune problems. Its symptoms range from mild diarrhea to systemic symptoms. In Korea, it is known that sometimes patients are infected by eating raw liver of cow or sheep. We present a case of *Campylobacter fetus* bacteremia after ingestion of cow's omasum in patient with alcoholic liver cirrhosis.



			Inform	ation					
mer Informati	on								
Sequencing	Primer Name Primer	Sequences			PCR Prin	ner Nar	ne Primei	r Sequences	
785F 5' (GGA TTA GAT ACC CTG GTA) 3'				27F 5' (AGA GTT TGA TCM TGG CTC AG) 3					
907R 5' (CC	G TCA ATT CMT TTF	R AGT TT) 3		1492	2R 5' (TAC	GGY T	AC CTT G	GTT ACG ACT	T) 3'
	Subje	ect				S	core	Identities	
CP006833.1	Campylobacter fetus	177548 0	13905 4	14055 0	0	2687	0.0	1485/1499	99
Kingdom	Family			G	enus			Species	
Bacteria	Campylobacte	Campylobacteraceae		Campylobacter		Can	Campylobacter fetus		
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**Results:** A 62-year-old man with cirrhosis (Child-Pugh score 9) was admitted due to anorexia, nausea, diarrhea for 7 days. On admission, BP was 100/60 mmHg, HR 102 beats/min, RR 20 breaths/min, BT 36.5°C. He has drunk more than two bottles of makgeolli (Korean rice liquor) every day for 40 years. What's unusual is that a week ago, he ate a cow's omasum. Laboratory findings revealed WBC 3,660/mm<sup>3</sup>, Hb 11.2 g/dL, PLT 27,000/ mm<sup>3</sup>, PT 17.1 sec, PT (INR) 1.55, AST 56 IU/L, ALT 13 IU/L, total bilirubin 3.98 mg/dL, albumin 3.0 g/dL, BUN 12 mg/dL, creatinine 1.13 mg/dL, CRP 0.38 mg/dl. Abdomen CT showed advanced liver cirrhosis with splenomegaly and small amount of ascites. We did blood gram stain & culture, finding Primers used for amplification and sequencing by 16S rRNA analysis

and MALDI (Matrix-assisted laser desorption/ionization) TOF (time-of-flight). We found *Campylobacter fetus* bacteremia and had no choice but to treat with empirical antibiotics, gentamicin evidenced by the Sanford guide to antimicrobial therapy because of no data about antimicrobial susceptibility test. Fortunately he was completely cured and left the hospital healthy.

**Conclusions:** In gastrointestinal infection of immunocompromised patient, *Campylobacter fetus* infection might be suspected. In this case, the cause of bacteremia was a characteristic food intake in Korea. We provide a case report of caused by *Campylobacter fetus*, which was identified using molecular biological techniques. *Since* we did not have antibiotic susceptibility results, we had to do empirical treatment and it was effective.

Keywords: Campylobacter fetus, Bacteremia, Cirrhosis

## PE-259

# Results of Surgical Treatment of Liver Alveococcosis with Main Vessels Budding

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**Aims:** To improve the results of surgical treatment of liver alveococcosis with the budding of the main vessels

Methods: We analyzed the results of surgical treatment of 77 patients diagnosed with liver alveococcosis with the budding of its main vessels: the inferior vena cava, portal vein and / or its branches, hepatic veins. All patients were hospitalized in the National Hospital under Ministry of Health of The Republic of Kyrgyzstan named after I.K Akhunbayev. The observation period was from 2009 to 2017. There were 27 men (35%), women - 50 (65%) out of 77 patients. The age range of the patients was from 15 to 65 years; the average age of the patients was  $34.8 \pm 1.4$  years. 73 (94.8%) patients were at the able-bodied age. All patients were divided into three groups depending on the vascular injury: the first group - patients with liver alveococcosis with injury of the vena cava inferior - 42 (54.5%), the second group - with injury of the portal vein and / or its branches -28 (36.3%), the third group - with injury of the hepatic veins -7 (9.2%).

**Results:** The resection of the liver was performed in 32 patients; there were marginal resection of the vena cava inferior in 7 cases, with resection and prothesis of the vena cava inferior and left hepatic vein in one cases. Surgical treatment had curative character in 8 cases, which was 19%. The were 24 cases of liver resection in the second group including marginal resection of portal vein in 2 cases and circular resection of the portal vein with the imposition of the porto-porto anastomosis "end-to-end" in 3 cases. Surgical treatment had curative character in 19 cases, which was 70%. There were 1 case with resection of the left and middle hepatic veins, 2 case with resection of the mouth

of the right hepatic vein included in the third group of patients with injury of the proper hepatic veins. Surgical treatment had curative character in 6 cases which was 86%



A picture of MSCT: sprouting of the vena cava inferior with alveococcosis and narrowing (yellow arrows) the lumen of the vena cava inferior.



Intraoperative photo. Resection and prosthetics of the inferior vena cava (2) and the estuary of the left hepatic vein (1). The Roman numerals are the decrees corresponding to the segments..



Phono of the removed macro preparation, the alveococcoss germination of the inferior vena cava along and the month of the right and middle hepatic vens. Alveococcus tissue narrows the lumen of the inferior vena cava. Roman numerals indicate the corresponding segments.

**Conclusions:** It is possible to perform a radical operation due to combined intervention on vessels and / or inferior vena cava in 48.1% of patients despite the growth of LIP and portal vein. Liver recovery with resection and / or reconstruction of the main vessels is an alternative to liver transplantation.

**Keywords:** Liver alveococcosis, Liver resection, germination of the main vessels, VCI, VP

### PE-260

#### Surgical Aspects of the Treatment of Liver Alveococcosis

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**Aims:** Generalized alveolar disease - alveolar or multi-helminthiasis, caused by larvae of Echinococcus multilocularis, is characterized by the formation of parasitic nodules in the liver.

**Methods:** In total, 54 patients with liver alveococcosis were treated in the period : rom 2007 to 2017 under the conditions of Aktobe medical center and the regional medical center of Kyzylorda, including 34 men and 20 women. The disease was found mainly in young and middle-aged people (mean age was  $35\pm3$ ,6 years). The right proportion of the liver was affected in 32 patients (60.0%), the left – in 13 patients (25.5%), the defeat of both shares was noted in 9 (14.5%) patients.

**Results:** A total of 58 surgical interventions were performed, with one patient having 2 for one hospitalization, the first - lumping of the tumor, and the second – liver transplantation. Right-sided hemihepatectomy-12, left-sided hemagepatectomy-8, trisegmentectomy-6, bisegmentectomy-6, segmentectomy-2, palliative surgery-22, liver transplantation-2.

**Conclusions:** Liver Alveococcosis is a relatively rare but insidious disease with severe complications, especially in epidemic foci, and requires unification of diagnostic and therapeutic measures. Radical method of treatment for alveococcosis is liver resection of different volumes. Surgical carbon dioxide laser providing reliable hemostasis has shown high efficiency in performing surgical intervention, which reduces the risk of parenchymal bleeding in the postoperative period. With alveococcosis, when there is a defeat of both liver lobes, or parasitic node is localized in the liver, or there is a germination of the parasite of the inferior Vena cava, liver transplantation is possible. **Keywords:** Liver, Alveococ, Treatment

## PE-261

### Seroprevalence and Risk Perception of TransfusionTransmissible Hepatitis among Voluntary Blood Donors in Western Nepal

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**Aims:** The study aimed to assess the seroprevalence and risk perception of hepatitis B virus (HBV) and hepatitis C virus (HCV) among voluntary blood donors in the Western Region of Nepal. **Methods:** A total of 13,079 voluntary blood donors aged 18-60 years attending from July, 2016 to June, 2017 were enrolled in the study. Perceived risk of HBV and HCV was measured by Likert-type scale: 'no risk', 'little', 'moderate', 'high' and 'very high' risk, ranging from 1 to 5. Blood samples were analyzed for the presence of HBsAg and HCV antibodies by ELISA at Western Regional Blood Transfusion Service Center. Proportion, mean, chi-square test and independent samples t-test were applied for statistical analysis.

Results: Of the total, 83.8% participants were males; 88.2% were married; and mean age of the participants was 30.0 years. Seroprevalece of HBV was 0.3% in the total samples; 0.3% among males and 0.2% among females; and 0.5% among unmarried donors. Seroprevalece of HCV was 0.1% in the total; 0.1% among males and one case among females; 0.2% among unmarried; and 0.2% among those who ever pierced tattoo. No significant difference was observed in the seroprevalence of HBV and HCV among those who reported having multiple sexual partners and single sexual partner; and among Tattoo piercing and non-piercing respondents (P>0.05). Mean risk perception of HBV was slightly greater ( $x^{-}$ , 2.75; SD,  $\pm 1.24$ ) than that of HCV (x<sup>-</sup>, 2.68; SD,  $\pm 1.22$ ). The mean risk perception of both types did not differ significantly across gender, age, marital status; and having multiple sexual partners and tattoo piercing practices (P>0.05).

**Conclusions:** The study revealed low seroprevalence and low risk perception of HBV and HCV among voluntary blood donors in Western Nepal. Although the seroprevalence is low among voluntary blood donors, there might be higher prevalence of HBV and HCV in the community.

**Keywords:** Seroprevalence, Transfusion Transmissible Hepatitis, Risk Perception, Blood Donors, Nepal

### PE-262

### Phosphate Is Associated with the Severity of Acute Hepatitis A

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**Aims:** Acute hepatitis A (AH-A) is one of the most common forms of viral hepatitis, and distinct clinical features are asso-

ciated with the prodromal, icteric, and recovery phases. This study was designed to investigate the correlations of various clinical parameters with severity in AH-A patients in each of these 3 phases.

**Methods:** The medical records of 455 patients diagnosed with AH-A were retrospectively reviewed. The prodromal, icteric, and recovery phases were defined by the patterns of changes observed after admission in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels. Clinical parameters, including phosphate levels, were analyzed to identify their associations with the peak levels of AST, ALT, and bilirubin.



**Results:** Of the patients, 129 (28.4%) were admitted in the prodromal phase, 187 (41.1%) in the icteric phase, and 139

(30.5%) in the recovery phase. Phosphate levels showed an inverse relationship with the peak AST and ALT levels in the prodromal phase (P=0.011 and P=0.005, respectively). Prothrombin time (PT, %) showed a negative relationship with peak AST levels throughout the prodromal, icteric, and recovery phases (P=0.039, P=0.028, and P=0.001, respectively), the peak ALT level in the prodromal phases (P=0.038) and the peak bilirubin level in the icteric phase (P=0.029).

**Conclusions:** In conclusion, the baseline phosphate, AST, and ALT levels, as well as PT and the platelet count, were correlated with the peak levels of AST, ALT, and bilirubin in patients with AH-A.

Keywords: Acute hepatitis A, Phosphate, Prognosis, AST, ALT

## PE-263

Clinical Characteristics of Pyogenic Liver Abscess; Focusing on Comparison of Primary Pathogens between Escherichia coli and Klebsiella pneumonia

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**Aims:** Pyogenic liver abscess (PLA) is a common intra-abdominal infection in adults. However, the clinical influence of primary pathogens of liver abscess on patients has not yet been fully elucidated. We aimed to investigate the clinical features of PLA patients according to the pathogens, such as, *Escherichia coli* (PLA-EC) or *Klebsiella pneumoniae* (PLA-KP).

**Methods:** A retrospective review was performed for consecutive 255 PLA patients who admitted to our institute from January 2007 to December 2017. Of these 255 patients, 100 patients were excluded due to definite pathogen (n=63) and the other pathogen rather than *Escherichia. coli* or *Klebsiella pneumonia* (n=37). Culture was defined as positive when pathogen was confirmed by blood or aspiration culture. The remaining 155 patients were enrolled in this study, and were dichotomized as two groups of PLA-EC (n=34, 21.9%) and PLA-KP (n=121, 78.1%).

**Results:** The mean age of PLA-EC patients was higher than that of PLA-KP patients ( $66.5\pm13.7 \text{ vs} 60.2\pm13.2$ , P=0.016). Gastrointestinal cancer including stomach, liver, or biliary tract was more common in PLA-EC group than PLA-KP group (50.0 vs 18.2 %, P<0.001). Chronic alcoholics (0.0 vs 9.1 %, P=0.068) and diabetes (88.2 vs. 11.28 %, P=0.073) tended to be more frequent in PLA-KP group than PLA-EC group. Anemia (29.4 vs 9.1 %, P=0.002) and hyperbilirubinemia (58.8 vs . 36.4 %, P=0.019) were found more frequently in PLA-EC than in PLA-KP. The abscess-related mortality in PLA-EC patients was significantly higher than that in PLA-KP patients (7/27, 20.6% vs . 7/114, 5.8%) (P=0.008).

**Conclusions:** Gastrointestinal cancer of stomach, liver, or biliary tract may be associated with PLA-EC. Therefore, these patients require work-up and careful managements, especially in PLA patients who are combined with anemia or jaundice.

**Keywords:** Liver abscess, Escherichia coli, Klebsiella pneumoniae, Gastrointestinal neoplasms

### PE-264

### Value of Blood Culture for the Ascetic Fluid in the Diagnosis of Spontaneous Bacterial Peritonitis

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**Aims:** Liver cirrhosis is the end result of hepatocellular injury that leads to both fibrosis and nodular regeneration. Usual presentations are upper gastrointestinal bleed, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, hepatocellular carcinoma and hepatorenal syndrome. Inoculation of the ascetic fluid into blood culture bottles at the patient's bedside resulted in more rapid detection of bacterial growth, and it is superior to inoculation of the ascetic fluid into conventional culture. We aim to compare the diagnostic accuracy of ascetic fluid inoculation into blood culture versus the conventional culture method in the diagnosis of SBP in patients attending Sohag university Hospital at Upper Egypt.

**Methods:** One hundred consecutive cirrhotic patients (54 males; mean age: 62.02±years) were included, and a total of 100 paracenteses were performed. All ascetic fluid samples were analyzed using the cytology, neutrophils, lymphocyte count and culturing. The Culturing was done using both Conventional and Blood cultures technique.

**Results:** In our study 47 patients of 100 cirrhotic patients had spontaneous bacterial peritonitis of them 32 of the inoculated sets demonstrated growth ; of which were 11(23,4%) set demonstrated growth by both conventional and blood culture bottles, and 21 set demonstrated growth by culturing in blood culture bottles alone.

**Conclusions:** Ascetic fluid culture has an important role in the diagnosis and management of SBP, the ascetic fluid inoculation into blood culture bottles at the patient's bedside resulted in more rapid detection of bacterial growth and it is superior to inoculation of the ascetic fluid into conventional culture.

### PE-265

### Clinical Outcomes of Laparoscopic Partial Cystectomy and Conventional Partial Cystectomy for the Treatment of Hepatic Hydatid Cyst

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**Aims:** The aim of this study was to compare the mid-term outcomes of open and laparoscopic partial cystectomy (LPC).

**Methods:** The medical records of patients who underwent conventional partial cystectomy (CPC) and LPC for liver hydatid cyst from March 2009 to January 2016 were retrospectively reviewed. Operative time, blood loss, length of hospital stay, postoperative morbidity, mortality, and follow up outcomes were evaluated.

**Results:** Among 162 patients, 59 of patients were underwent LPC and 103 underwent CPC. Blood loss, postoperative complications were similar in both groups. The mean operative time in the LPC and the CPC groups was respectively 91.4±11.5 and 61.5±18.1 minutes, which showed a significant difference between the both groups. The mean length of hospital stay in CPC group was significantly longer when compared the LPC group. The mean diameter of cyst in LPC group was 6.1±1.1 cm, and 7.8±2.1 cm in CPC group with significant difference. The overall complication rates were 15.2 % in LPC group and 16.5 % in CPC group without significant difference. The most common complication was biliary leakage and surgical site infection.

**Conclusions:** In the hands of experienced laparoscopic surgeons with appropriate technical tools; Laparoscopic drainage and partial cystectomy seem to be safe and effective techniques in carefully selected patients in the surgical treatment of liver hydatid cysts. Technical devices such as grinder aspirator and laparoscopic ultrasonography may expand the indication for laparoscopy.

### PE-266

# Viral Hepatitis among the Emigrants Population of Nepal

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**Aims:** Viral hepatitis is inflammation of the liver due to a viral infection. It may present in acute or chronic forms. Viruses that primarily attacks the liver is called hepatitis viruses. There are several types of hepatitis viruses including types A, B, C, D, E, and possibly G. Types A, B, and C are the most common. Viral hepatitis is the significant health problem in Nepal. The emigrants going abroad for job are found infected with viral hepatitis during domestic medical examination. Some people return to domestic country after they are diagnosed with the disease in foreign country which creates the great financial as well as social problem. The aim of this study is to find out the seroprevalance of viral Hepatitis B and Hepatitis C in nepalese emigrants.

**Methods:** The descriptive cross-sectional study was conducted in the domestic medical eamination centre within a period of six months from Jan -July 2017. The study included 800 people who visited the center for medical check up. Serum samples from these people were screened for HBV and HCV by ELISA method and reactive samples were counter checked by immunochromatographic method.

**Results:** Of the 800 emigrants screened, 0.6 % was infected with Hepatitis B whereas 0.3% was infected with hepatitis C. Among the infected cases, 0.77% of the (15-25) age group was infected with hepatitis B. Also, 0.65% and 0.3% of (26-35) age group were infected with HBV and HCV respectively. Similarly, 1.0% of (36-45) age group was only infected with Hepatitis C. Also, 0.9% and 0.3% of the emigrants were infected with syphilis and HIV respectively during the serological screening.

**Conclusions:** Viral hepatitis is in increasing trend among immigrants' people and indicates the need for Nepalese healthcare authorities to enhance their support for providing screening, HBV vaccination, treatment, and educational programs for this populations.

**Table 1.** Frequency of HBV and HCV Positive Test Results in Napelese emigrants in domestic medical check up

Ago group	HBsAg-	HBsAg-	Anti-HCV-	Anti-HCV-	
Age group	positive/total	positive/total	positive/total	positive/total	
(115)	males(No.)	females(No.)	males (No.)	females(No.)	
15- 25	3/378	0/13	0/378	0/13	
26-35	2/295	0/14	1/295	0/14	
36-45	0/95	0/2	1/90	0/2	
45-55	0/7	0/1	0/7	0/1	

HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

**Keywords:** Viral hepatitis, Hepatitis B virus, Hepatitis C virus, Emigrants

## PE-267

## Clinical Features of Cases Initially Presenting as Liver Abscess with Final Diagnosis as Intrahepatic Cholangiocarcinoma

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**Aims:** It is clinically challenging if intrahepatic cholangiocarcinoma (ICC) presents as a liver abscess in an initial imaging study. In these cases, clinical manifestations such as persistent fever may delay the proper diagnosis of ICC and worsen the prognosis of the patients. The purpose of this study was to compare clinical features of ICC masquerading as liver abscess with true liver abscess.

**Methods:** A total of 287 patients initially diagnosed with liver abscess at first hospitalization, between 2001 and 2017 at a single center, were included. All patients were classified into two groups depending on whether the final diagnosis was ICC (n=21) or liver abscess (n=266). CT findings and laboratory findings of all patients with ICC and liver abscess were analyzed.

**Results:** The most common clinical feature of the ICC group was right upper quadrant pain (71.4%), followed by fever (42.9%) and unintended weight loss (23.8%). In contrast, in the liver abscess group, fever was most common at a frequency

of 80.5%, followed by right upper quadrant pain (56.0%). CT findings of capsular retraction, lymph node enlargement and focal bile duct dilatation were significantly more frequently observed. (all *P* values < 0.01). Findings of round outer margins, cystic components, multilayered enhancement and transient hepatic attenuation differences were significantly higher in the liver abscess group. No significantly difference was observed in proportion of alkaline phosphatase (ALP) elevation between the two groups. (ICC vs. Liver abscess: 33.3% vs. 48.9%, *P* = 0.183). However, elevated carbohydrate antigen (CA) 19-9 levels was more frequently observed in the ICC group than the liver abscess group. (52.4% vs 18.0, *P* < 0.01).

**Conclusions:** Although there can occur difficulty distinguishing ICC from liver abscess in clinical practice, specific CT findings of ICC and abnormal CA 19-9 levels could facilitate differential diagnosis between two disease categories.

**Keywords:** Liver abscess, Cholangiocarcinoma, Carbohydrate antigen, Computed tomography

### PE-268

### Risk Predictors of Infectious Complications after Liver Surgery

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**Introduction:** Serious infectious complications such as bloodstream infection pose a life-threatening condition in patients after liver surgery. Despite the development of modern medicine, infection remains one of the main problems in hepatic surgery that affects survival of patients. In recent studies researchers focused on immunological changes in patients with liver diseases which could be the important factors influencing the mortality associated with liver surgery.

**Materials and methods:** Twenty-six patients who had undergone the liver surgery and had severe infectious complications at National Scientific Medical Research Center between January 2011 and December 2017 were enrolled in this study. We included cases in which the infections had developed within 30 days after surgery where the immunostatus and blood culture tests were observed. All patients who underwent a segmental resection, left hepatectomy or trisectionectomy were included.

**Results:** Rates of infectious complications varied significantly across primary procedures and ranged from 6.5% in segmental resection patients to 23% in trisectionectomy patients. No statistically significant differences in any preoperative characteristics between patients with or without infectious complications were observed. There was no correlation between intraoperative factors and infection episodes. The association between the changes in immunological components and infectious complications were found in this study.

**Conclusion:** These results can help identify the patients at risk of developing infectious complications and advance strategies to reduce the incidence of infections.

## Surgery, Technical Issues

### PE-269

### Central-Located Massive Tumor With Inflow And Outflow Reconstruction For Massive Hepatectomy - A Case Report

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**Aims:** Right trisectionectomy was the most effective curative treatment with massive tumor located in the right lobe especially central location of liver. Due to the compressing or even invasion from huge tumor to main branches of portal vein, hepatic vein and bile duct, adequate consideration of inflow and outflow reconstruction during surgery was needed and vessels acquired from cadaveric donor or artificial should be prepared preoperatively.

**Methods:** We present the case of a 59-year-old man who found a 10 cm malignant mass in the right lobe with the invasion of right anterior portal vein, right hepatic vein and middle hepatic vein. By performing right portal vein embolization, left lateral section volume was increased from 26.5% to 37.3%, satisfy the condition of right trisectionectomy. Outflow reconstruction was performed using pericardium, which was acquired from previous cadaveric donor.

**Results:** The recovery process was smooth, patient was discharged in POD 58 without any complication,

**Conclusions:** Preoperatively, sufficient consideration of using allograft to perform inflow or outflow reconstruction is needed in patient with vascular invasion. Postoperatively, regular hepatic mesenteric doppler F/U is needed. Usage of allograft is limited in the hospital where cadaveric donor liver transplantation is feasible. Thus, artificial graft should be prepared in the vascular invasion cases.

**Keywords:** Massive tumor, Vascular invasion, Inflow and outflow reconstruction, Allograft

### PE-270

Long-Term Results of Laparoscopic Liver Resection for the Primary Treatment of Hepatocellular Carcinoma: Role of the Surgeon in Anatomical Resection

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Aims: Liver resection is a potentially curative therapy for hepa-

tocellular carcinoma (HCC). LLR is a newly developed and safe technique associated with shorter hospital stay, less pain, better cosmetic outcomes, and similar complication rates as open surgery; however, data on its long-term outcomes remain scarce.

Methods: We retrospectively examined the clinical and follow-up data of 234 patients who underwent LLR (performed by a single surgeon in all cases) for the primary treatment of HCC between July 2007 and December 2015 at Asan Medical Center. Results: The mean patient age was 55.63 (range, 31–76) years; 167 were men. The median follow-up duration was 38 (range, 6-116) months. A total of 227 patients (97.0%) had Child-Turcotte-Pugh grade A disease. Of them, 167 (71.4%) underwent anatomical resections and 63 (28.6%) underwent nonanatomical partial hepatectomies. Overall survival rates were 98.3%, 91.7%, and 87.1%, and recurrence-free survival rates were 82.1%, 67.5%, and 55.3% at 1, 3, and 5 years, respectively. In Cox regression analysis, anatomical resection was a risk factor for recurrence (univariate analysis: hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.31–0.75; P=0.001; multivariate analysis: HR, 0.59; 95% CI, 0.38-0.94; P=0.025).

**Conclusions:** LLR is an acceptable primary treatment for patients with HCC with good hepatic function and with an appropriate anatomical structure, and is associated with improved prognosis. LLR can achieve lower recurrence rates through anatomical resection.

**Keywords:** Laparoscope, Hepatectomy, Hepatocellular carcinoma, Anatomical resection

## PE-271

### Rare Cases of Variability of Hepatic Arteries by the Results of Computed Tomography

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**Background:** Modern technological progress and the successes of anatomical science have found their application in clinical medicine, which led to a revision of the strategy and tactics of treating patients. The study of variant anatomy of the hepatic arteries remains relevant and in hepatobiliary surgery is of great practical importance.

**Aim:** To search for and study of the new anatomical variants of Hepatic arteries based on the results of computed tomography. **Methods:** On the basis of the Radiology Department of the Aktobe Medical Center, 350 CT scans with contrasting of hepatic arteries of patients aged between 23 and 88 years were studied.

**Results:** The data obtained by us have shown rare combined variations of the hepatic artery deviation: the Left hepatic artery from the Superior Mesenteric artery + Right hepatic artery from

the abdominal part of the aorta; divergence of the left hepatic artery from the left gastric + right hepatic artery from the gastroduodenal artery; left hepatic artery from the left gastric + right hepatic artery from the superior mesenteric and other isolated variations.

**Conclusions:** The analysis of the results confirms the multivariance of extrahepatic parts of Hepatic arteries: the presence of combined variants replacing and accessorial arteries, their origin from previously undescribed sources. Accurate identification of one or another variant of the structure of the trunks studied by us will help to avoid damage to them, as well as safe grafting of the transplant and proper application of arterial anastomoses to prevent ischemic manifestations in the liver.

Keywords: Hepatic artery, Liver, CT csan

## PE-272

### Factors Responsible and Long Term Outcomes of Hepatic Resections in Post Cholecystectomy Benign Biliary Strictures

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**Aims:** Post cholecystectomy biliary strictures can lead to secondary biliary cirrhosis and portal hypertension and present a difficult proposition for management with poorer outcomes. These patients require a major hepatic resection (HR) in certain cases. This study was done to find the factors leading to HR in benign biliary strictures (BBS), the challenges faced and their long-term outcomes.

**Methods:** Analysis of prospectively maintained BBS database of our department from February 1989 to March 2014 done to identify patients who underwent HR. Type of cholecystectomy, bile duct injury (BDI) and BBS, indications for HR, any previous repair, intraoperative parameters and postoperative morbidity were noted. Outcomes classified according to McDonald classification.

**Results:** 648 patients of BBS were included in the study. Out of these 10 patients underwent HR (1.53%). 9 patients had high BBS (type IV and V) while 1 patient was of type III with strictured hepaticojejunostomy (HJ). Laparoscopic cholecystectomy was the primary surgery in 80%(8/10) patients. Median time from cholecystectomy to HR was 545 (226-1566) days. Proximal BBS (type IV and V, *P*<0.001) and Atrophy-hypertrophy complex (AHC) (*P*=0.004, OR = 15.4, CI: 2.94-80.99) were predictive factors for HR. Failed previous repair was also associated with HR (20%). Postoperative morbidity was 40%. Perioperative mortality occurred in 2 patients. Outcomes of HR with median follow up of 24 months were good with success rate of 80%.

**Conclusions:** Hepatic resections have distinct role in patients of proximal BBS (type IV and V) with AHC with good long-term results but require meticulous planning and execution. AHC and previous failed repair are strong predictors for need for HR in BBS.



Keywords: Hepatic resection, Cholecystectomy, Benign biliary stricture

## PE-273

### Results of Extensive Resections with Focal Liver Lesions

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**Aims:** To evaluate the results of extensive liver resections with focal lesions of the liver.

**Methods:** There were 445 patients with focal liver damage in the National Hospital named after Akhunbayev from April 2009 to December 2017. The main part of patients was patients with alveococcosis of the liver - 358 patients; metastases of colorectal cancer - 34 patients; hepatocellular carcinoma - 25 cases; hemangiomas - 23, cholangiocellular carcinoma - 3 cases of observations and 2 cases with fibronodular hyperplasia. 393 patients had surgical treatment from 445 totally, which was 88.3%. There were 193 patients with extensive liver resections, which was -49.1%. The men were 67 (34.7%), women 126 (65.3%). The age range of patients was from 14 to 73 years, the average age of patients was  $44 \pm 2.3$  years.

**Results:** Performed surgical resections: right hemihepatectomy was in 88 cases, which was 45.6%, resection of extrahepatic bile ducts in 3 cases, with portal vein resection in 3 cases and with resection of vena cava inferior in 7 cases. Left hemihepatectomy was performed in 37 cases, 2 patients with resection of extrahepatic ducts. Extra right hemihepatectomy was performed in 46 patients, resection of extrahepatic bile ducts in 4 cases, portal vein resection in 3 cases and vena cava inferior re-

section in 3 cases, Extra left hemihepatectomy was performed in 22 cases, resection of extrahepatic bile ducts in 2 cases. It should be emphasized that the expanded hemihepatectomies come up to 35.2%!







Extensive liver resection with resection of hepatitis choledochus and the imposition of Roux-en-Y Hepaticojejunostomy (n=10)



**Conclusions:** The main reason of development of massive bleeding at extensive liver resections is mainly due to damage of hepatic veins in the caval gates or inferior vena cava. It's preferred to perform extensive liver resection by a collar way, which allows reducing peroperative blood loss.

**Keywords:** Liver cancer, Liver alveococcosis, Extensiv liver resection, Hepatic hemangioma

### **PE-274**

### Surgical Treatment of Liver Echinococcosis

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**Aims:** One of the urgent problems at the present stage is the surgical treatment of liver ehinococcosis.

Methods: In the surgery department of the Kyzylorda Regional Medical Center between 2013-2017 various 108 operations to the patient in connection with echinococcosis liver. 73 patients (67,5%) were women, 35 (32,4%) were men aged 16 to 58. Location in the right lobe of the liver-64 (59.2%), in the left side-34 (31,4%), in both lobes of the liver-10 (9.2%). Hydatid cyst of the liver, recurrent 8(7,4%). The situation is complicated by fistulas, cystobiliary 17 (15,7%) of the patient. It was manufactured by the following operations: laparoscopic echinococcectomy - 22 (20,3%), bisegmentectomy-1 (0,9%), pericystectomy-8 (7,4%), echinococcectomy-77 (71.2%), including: marsupialisation-1 (0,9%), omentopexy-7 (6,4%), abdominal cysts-13 (12%), capitonnage of the residual cavity- 56 (51.8%). Results: In the postoperative period, 22 (20.3%) patients had complications. Of these, 13 (59%) in the form of exudative pleurisy, ended with a puncture of the pleural cavity. Suppuration of the residual cavity 7 (31,8%) patients, 2 (9%) patients, had relaparotomy drainage of abscess, 1 (4,5%) patients underwent laparoscopy, drainage of abscess, 4 patients (18,1%) performed puncture of the residual cavity under ultrasound control drainage and Pigtail type. Complications of the biliary tract in 2 (9%), a Pigtail catheter under ultrasound control. On 8 - 16 weeks after surgery, the bile fistula is closed, the catheter is removed. Hyperthermia in the postoperative period was in 20 (18.5%) patients, they were carried out antibacterial therapy and infusion therapy additionally prescribed fractional plasmapheresis. Postoperative hyperthermia occurred in patients who underwent omentopexy and cyst abomination. There was no mortality.

**Conclusions:** To prevent complications such as abscess of the residual cavity and hyperthermia, it is necessary to choose a radical operation. If it is impossible to perform a radical operation, then it is necessary to carry out capitonage of the residual cavity with adequate drainage.

Keywords: Liver, Echinococcos, Surgical

### PE-275

### Angiosurgery in the Treatment of Liver Hemangiomas

Aiya Bimurzayeva<sup>1</sup>, Nurbol Tursynbayev<sup>1</sup>, Batyr Aitmoldin<sup>1</sup>, Erlan Ashirbayev<sup>2</sup>

<sup>1</sup>Department of General Surgery, Astana City Hospital No2, Kazakhstan; <sup>2</sup>Department of Vascular Surgery, Astana City Hospital No2,

#### Kazakhstan

**Aims:** liver hemangioma is benign tumor and have a wide distribution throughout the world. The cause of hemangioma is not fully understood. The disease is very serious. It's one of the most pressing and socially significant problems of Kazakhstan's health, because leads to a reduction in the health of the population employed in manufacturing.

**Methods:** CT, MRI, x-ray equipment, assembly "ZORING", argon-plasmatic coagulator "Karl Stors". Morphological, microbiological research methods. During the period 2015-2017 we treated 11 patients with giant liver hemangioma. 7 (63.6%) of males and 4 (36.4%) females, 18-46 age old. 10 (90%) of the patients had the right lobe cyst, 1 (10%) in the left lobe. The size of the hemangiomas ranged from 5.0 to 10.0 cm.

**Results:** In the first step all patients underwent embolization of blood vessels of the liver segment with hemangioma. In the absence of blood flow there is a involution of hemangioma, size was a decrease. After 2-3 weeks patient will take the surgery treatment. Surgery: all patients were take liver resection

At the preoperative stage the patients were prepared in accordance with the clinical protocol management of patients with liver cysts and the recommendations of the clinical guideline. The postoperative period was uneventful.



Conclusions: Positive outcome of treatment depends on early

diagnosis, length of hospitalization, timely surgical treatment, also on adequacy of postoperative early and continued rehabilitation. The liver hemangioma needs surgery aimed to complete removal without opening the lumen. Active introduction in surgical practice of modern new technologies, computer assisted surgery methods of diagnostics and treatment allow us to successfully solve the problem of treatment of liver hemangioma. **Keywords:** Liver, Angiosurgery, X-ray, Hemangioma

## PE-276

### Acute Ischemic Cholecystitis after Transarterial Chemoembolization in Hepatocellular Carcinoma

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**Aims:** Conventional transarterial chemoembolization (TACE) has been accepted as an effective treatment mordality for unresectable hepatocellular carcinoma (HCC). However acute complications such as hepatic failure, liver abscess, liver rupture and acute cholecystitis can occur after the procedure. This study is to determine the incidence, risk factors and clinical outcome of acute ischemic cholecystitis after TACE of HCC.

**Methods:** From January 2000 to March 2018, retrospective reviewing of complications following conventional TACE therapy for patients with HCC. Patient demographics, clinical information, procedural data, and management of major complications following TACE therapy were gathered from patients' medical records.







Results: 519 patients with hepatocellular carcinoma underwent 1,274 sessions of TACE using adriamycin and lipiodol. According to the case, the practitioner did not perform embolization using gelfoam. Of the 519 patients who underwent TACE, 8 patients (1.5%) presented with radiological features indicative of acute cholecystitis, which developed within 15 days in 4 patients and within the first month after TACE in 4 patients. Review of the TACE procedures revealed that 4 cases had undergone lobar right hepatic embolization, 3 cases right and left hepatic artery embolization and 4 cases additional gelfoam embolization. 2 of 8 patients required laparoscopic cholecystectomy due to gangrenous cholecystitis and gallbladder perforation, 1 of 8 patients performed endoscopic ultrasonography (EUS) guided duodenocystostomy with stent insertion due to suppurative cholecystitis and remaining 5 patients were managed conservatively and none reguired surgical or interventional management. There was no death from the cholecystitis which was complication of TACE.

**Conclusions:** Acute ischemic cholecystitis after TACE occur in 1.5% in this study. As is known in other studies, cholecystitis is a complication of right lobe embolization in this study. Especially, the use of gelfoam embolization as well as right lobe embolization showed high risk of developing cholecystitis. Although most studies of cholecystitis after TACE have reported conservative management, urgent cholecystectomy or percutaneous cholecystostomy has been required occasionally. Furthermore, the EUS guided duodenocystostomy is performed recently as a choice of treatment for acute cholecystitis due to TACE.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Cholecystitis

### PE-277

# Robotic Distal Pancreatectomy with Celiac Axis Resection

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**Methods:** woman in her 70s found lesion in pancreatic neck by ordinary physical examination and denied abdominal discomfort, vomiting, nausea, fever or backache. undergone a robotic

distal pancreatectomy with celiac axis resection (Appleby). Surgeon: Rong Liu, Sai Chou

#### **Results:**

operation time94 mins blood loss: 50ml hospital stay: 5 days postoperative pathology: pancreatic adenocarcinoma R0 without lymph (-) No postoperative pancreas fistula

## PE-278

### Laparoscopic Right Posterior Sectionectomy Under Single Incision Plus One Port for Hemangioma

In Gun HYUN, YoungRok CHOI, Ho-Seong HAN, Yoo-Seok YOON, Jai Young CHO, Sungho KIM, Kil Hwan KIM

Department of Surgery, Seoul National University Bundang Hospital, Korea

**Aims:** Laparoscopic surgery for IHD stones is known to be difficult. With the development of surgical instruments, laparoscopic surgery has become a safe and effective procedure for IHD stones. The solo single surgery using a laparoscopic scope holder shows the highly cosmetic effect and we expect it to cause less pain. We described the solo single incision major hepatectomy for IHD stones.

**Methods:** A 3.0cm sized single incision through the umbilicus was made. A 10mm flexible laparoscopic camera was inserted through a glove port and fixed using a jaw of a camera holder. After the division of cystic duct and cystic artery, the gallbladder and round ligament were fixed to the abdominal wall using endo-grip. Left hepatic artery and portal vein were ligated, then demarcation line was drawn for the anterior approach. The left bile duct was dissected and ligated. During parenchymal dissection, the right anterior glissonean pedicle was dissected and transected using the Endo-stapler. After complete dissection of the left liver, the middle and left hepatic vein were ligated using the Endo-stapler.

**Results:** This operation took 220 minutes and the estimated blood loss was 150mL.

**Conclusions:** Laparoscopic surgery had become a safe and feasible procedure for IHD stones. The solo surgery under a single incision can be a new option in laparoscopic hepatectomy for IHD stones.

## PE-279

### A Comparative Study between the Use of Biliary Stent and T-Tube for Biliary Decompression after Laparoscopic Common Bile Duct Exploration

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Aims: Laparoscopic common bile duct exploration (LCBDE) and

cholecystectomy as a single-stage treatment of choledocholithiasis have been shown to be superior when compared to the two stage management. Decompression after supra-duodenal choledochotomy is common practice as it reduces the chance of bile leaks. We conducted a randomized comparative study to compare the feasibility and outcomes in patients undergoing biliary stent insertion versus T-tube drainage following LCBDE via choledochotomy.

**Methods:** The study involved 64 patients with choledocholithiasis, half of which underwent biliary decompression after LCB-DE using biliary stent and in the other half T-tube was used.

**Results:** Patients in the stent group had significantly shorter operative time, lesser post-operative complications, lesser hospital stay and earlier return to normal activity (*P*<0.001).

**Conclusions:** In our study, we found there is a significant reduction in length of hospital stay and morbidity for patients that have ante-grade biliary stent decompression of the CBD post laparoscopic choledochotomy when compared to T-Tube drainage. This implies that ante grade biliary stent insertion is likely to reduce costs and increase overall patient satisfaction.

## PE-280

### Combined Treatment of Liver Hemangioma

Aiya Bimurzayeva<sup>1</sup>, Batyr Aitmoldin<sup>1</sup>, Nurbol Tursynbayev<sup>1</sup>, Erlan Ashirbayev<sup>2</sup>

<sup>1</sup>General Surgery and Coloproctology, Astana City Hospital No2, Kazakhstan; <sup>2</sup>Cardiovascular surger, Astana City Hospital No2, Kazakhstan

**Aims:** Liver hemangioma is benign tumor and have a wide distribution throughout the world. The cause of hemangioma is not fully understood. The disease is very serious. It's one of the most pressing and socially significant problems of Kazakhstan's health, because leads to a reduction in the health of the population employed in manufacturing.

**Methods:** CT, MRI, x-ray equipment, argon-plasmatic coagulator "Karl Stors". Morphological, microbiological research methods. During the period 2015-2017 we treated 11 patients with giant parasitic liver cysts. 7 (63.6%) of males and 4 (36.4%) females, 18-46 age old. 10 (90%) of the patients had the right lobe cyst, 1 (10%) in the left lobe. The size of the cysts ranged from 5.0 to 10.0 cm.

**Results:** In the first step all patients underwent embolization of blood vessels of the liver segment with hemangioma. In the absence of blood flow there was a involution of hemangioma, size was a decrease. After 2-3 weeks patient will take the surgery treatment All patients were take liver resection. At the preoperative stage the patients were prepared in accordance with the clinical protocol management of patients with liver deseases. The postoperative period was uneventful.

**Conclusions:** Positive outcome of treatment depends on early diagnosis, length of hospitalization, timely surgical treatment, also on adequacy of postoperative early and continued rehabili-

tation. The liver hemangioma needs surgery aimed to complete removal. Active introduction in surgical practice of modern new technologies, computer assisted surgery methods of treatment allow us to successfully solve the problem of treatment of liver hemangioma.

## PE-281

### Post Fellowship Outcome of Major Liver Resections of Single Surgeon Working in T U Teaching Hospital, Kathmandu, Nepal

**Ramesh Singh Bhandari** 

Department of Surgery, T U Teaching Hospital, Kathmandu, Nepal

**Aims:** Major liver resections in high volume center around the world have become a safe procedure. With proper training and improved perioperative care, major liver resections are being safely performed even in low volume center of the underdeveloped country. Here, the author is presenting the outcome of major liver resections performed independently after completing two years of HPB training.

**Methods:** The presenting surgeon received two years of HPB training at high volume centers in Melbourne. The surgeon had received general surgical training in Nepal and had worked for few years prior to receiving HPB training. Retrospective review of the medical records of major liver resections performed by single surgeon following fellowship training were reviewed. Indications, extent of hepatectomy and perioperative outcomes were analyzed.

**Results:** Total 49 liver resections have been performed by the single surgeon out of which 30 were major liver resections (Three or more segments) over 6 years period. Out of them, total 14 were for malignant conditions, 14 benign and two were trauma hepatectomy. There were 13 Right hepatectomy, 7 left, 2 extended right, 6 non anatomical, 1 HPD and 1 ALPPS procedure. Two patients were operated following right portal vein ligation. There was 25% morbidity (Clavien Dindo Grade 1-3, SSI, Chest infection, UTI, Transfusion, bile leak). Post hepatectomy liver failure (PHLF) was 3% and mortality was 6.6% (1 Post AlPPS Sepsis, 1 PHLF).

**Conclusions:** With proper training and improved perioperative care, major liver resection can be performed safely with acceptable outcome even in low volume centers of developing nations. **Keywords:** Liver, Resections, Major, Outcome

### PE-282

### Single Purse-String Duct to Mucosa Pancreaticogastrostomy: A New Technique after Pancreaticoduodenectomy

Xu'an WANG<sup>1</sup>, Ping WANG<sup>2</sup>, Yingbin LIU<sup>1</sup>, Shuyou PENG<sup>3</sup>

<sup>1</sup>Department of General Surgery, Xinhua Hospital, Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; <sup>2</sup>Department of General Surgery, Hangzhou First People's Hospital, Hangzhou, China; <sup>3</sup> Department of General Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China **Aims:** We developed a new technique termed the single pursestring duct to mucosa Pancreaticogastrostomy, which reduced the risk of pancreatic stump bleeding caused by gastric acid corrosion and decreased the pancreatic fistula rate than Pancreaticojejunostomy.

Figure 1. (A) A 2- to 3cm diameter seromuscular layer was excised, around which a single parse-string suture (arrow) of 2-0 polydioxanone was placed. (B) Drawing.



Figure 2. (A) A small hole (2 to 5 mm) was made in the mucosa of the posterior gastric wall, through which the pancreatic duct with silicone stent was pulled into the gastric lumen. Arrow, silicone stent in the pancreatic duct. (B) Drawing.



Figure 3. (A) The gastric mucosa and pancreatic parenchyma beside the pancreatic duct were transfixed with 4 needles o each side. (B) Drawing.



Figure 4. (A) The pursestring suture was tied (arror to create a watertight closure. (B) Drawing.

Figure 5. The bleeding and pancreatic fistula prevention mechanism of single purse-string duct- to-mucosa pancreaticogastrostomy. (A) Pancreatic stump was covered with gastric mucosa (arrow). (B) Cross section of the anastomosis (arrow).

Figure 6. Gastric endoscopic investigation showed the pan creaticogastrostomy stoma (right arrow) and gastroenteric stoma (left arrow) 4 months after pancreaticoduodenectomy.





**Methods:** Data were collected prospectively on 75 consecutive patients (43 men and 32 women; mean age 65.3 years who underwent pancreaticoduodenectomy using the single-string duct to mucosa Pancreaticogastrostomy. The technique was performed by the same surgeon and the key point is that pancreatic stump was placed between gastric mucosa and

seromuscular layer.Pancreatic stump was covered with gastric mucosa and transfixed with it beside the pancreatic duct which was inserted with a silicone tube into the stomach lumen. finally, the gastric seromuscular layer was tied with the pancreas by a purse-string suture.

**Results:** Mean time for PG anastomosis was 19 minutes (range 17 to 32 minutes), and mean blood loss was 380 mL (range 210 to 800 mL). There was no perioperative death. Over- all morbidity rate was 34.7% (26 of 75).Two patients had PF (overall rate was 2.7%) ,No one demonstrated a grade B or C postoperative PF.Postoperative abdominal hemorrhage developed in 2 patients (2.7%), no pancreatic stump bleeding occurs.

**Conclusions:** These results suggest that our technique is effective. In addition to lower complication rates, this technique is easy to perform and mean time of the anastomosis was 19 minutes. This kind anastomosis is a reliable, safe, and easy to perform method. From our experiences, it appears to reduce the risk for pancreatic fistula and intragastric bleeding.

**Keywords:** Pancreaticogastrostomy, Duct to mucosa, Pancreaticojejunostomy, Pancreaticoduodenectomy

## PE-283

### Laparoscopic Removal of Residual Pancreatic Tissue after Distal Pancreatectomy

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Department of General Surgery, Soonchunhyang University Cheonan Hospital, Korea

**Aims:** Solid pseudopapillary neoplasm (SPT) of pancreas occurs predominantly in young woman with abdominal mass and discomfort.

**Methods:** Hear in, we described remnant pancreatic tissue masquerading of postoperative abscess after the distal pancreatectomy for SPT.

**Results:** Initially, A 21 year old female patient, with no prior medical history, was underwent distal pancreatectomy for huge SPT. She was discharged uneventfully POD#7. One month after the initial operation, she was readmitted for PCD drainage because of subphrenic abscess. After 3th readmission, we decided a reoperation.

**Conclusions:** The patient was placed in right lateral decubitus position and laparoscopic removal of residual tissue with abscess in subphrenic area. The histological analysis of specimen suggested remnant pancreas with splenic tissue. She was discharged on the 6th post-operative day with uneventfully.

### PE-284

VATH (Video Assisted Thoracoscopic Hepatectomy) for Overcome Posterior Superior Located Hepatic Malignancy Abutting Diaphragm in Patient with Marginal Liver Function

Samyoul YOON

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**Aims:** Laparoscopic hepatectomy has been widely performed by hepatobiliary surgeon for malignancy of liver and gained wide acceptance for various liver tumors, thanks to advances in surgical techniques and devices. But, there are some challenges for rt. side tumor in patients of cirrhotic liver. Especially, tumor located in rt. upper area is difficult for wedge resection in patients with marginal liver function, because trans-abdominal approach require normal parenchymal dissection. RFA is also difficult for such a lesion. So, we demonstrate unique technique of VATH (video assisted thoracoscopic hepatectomy) for overcome rt. upper side tumor abutting diaphragm.

**Methods:** Three patients underwent VATH. Four ports in rt. chest wall were created by chest surgeon. Diaphragm was open. Then traction of diaphragm was done by suture. After exposure of liver surface, tumor localization was done by ultrasound. The mass excision was done by harmonic scapel.

**Results:** Safety tumor resection margin (5-20 mm) could be achieved. The operation time was 145 min (120~170). Mean hospital stay was 7days without complication.

**Conclusions:** VATH is could be performed by experienced surgeon and chest surgeon for rt. upper liver malignancy abutting diaphragm in patient of marginal liver function.

## PE-285

### Laparoscopic Anatomical Right Inferior Bisegmentectomy Using the Glissonian Approach

Jin Woo LEE, Sung Hoon CHOI

Surgery, CHA Bundang Medical Center, CHA University, Korea

**Aims:** Anatomical parenchymal resection is theoretically effective treatment of hepatocellular carcinoma. We describe the laparoscopic approach of anatomical right inferior bisegmentectomy using the Glissonian approach.

Methods: Between March 2014 and December 2017, 8 patients who diagnosed hepatocellular carcinoma underwent this operation. The presenting patient was diagnosed with 1.3 cm and 1.1 cm sized two hepatocellular carcinomas on segment 5 and 6. There was mild liver cirrhosis without sign of clinical portal hypertension. The patient was placed in the reverse Trendelenburg position with right-side-up adjustment. Four ports (two 12-mm and two 5-mm ports) were used. After cholecystectomy, the right major, right posterior, and right anterior Glissonian pedicles were isolated and looped in order. The first resection plane between segment 5 and 4 was determined on ischemic discoloration clamping the right major Glissonian pedicle. Approaching to hilar level during the first parenchymal resection, the Glissonian pedicles of segment 5 and 6 were respectively identified and clamped. Then, the ischemic demarcation of segment 5 and 6 could be confirmed. Intermittent Pringle's maneuver was used.

**Results:** There was no open conversion. The mean operation time and mean estimated blood loss were 206.3 minutes (range, 150 to 350 min) and 331.3 mL (range, 80 to 800 mL). The mean postoperative hospital stay was 7.5 days (range, 5 to 10 days). All patients obtained negative resection margins. There was no postoperative mortality, but there was one morbidity of cerebral transient ischemic attack.

**Conclusions:** Laparoscopic anatomical right inferior bisegmentectomy is a feasible operative procedure.

### PE-286

# Pure Laparoscopic Central Bisectionectomy for HCC in S7 and S8

Hwui-Dong CHO, Ki-Hun KIM, Seok-Hwan KIM, Woo-Hyung KANG, Dong-Hwan JUNG, Gil-Chun PARK, Sung-Gyu LEE

Division of Hepatobiliary surgery and Liver transplantation, Department of Surgery, Ulsan University and Asan Medical Center, Korea

**Aims:** Laparoscopic major hepatectomy, especially laparoscopic right anterior sectionectomy or laparoscopic central bisectionectomy with two cut surface are the great challenge area.

Methods: The patient was 46 years old man and diagnosed with 5cm sized HCC between segment 7 and 8 and was performed TACE before surgery. Pringle maneuver was performed during the hepatic parenchymal transection using laparoscopic Bull-dog. During the hepatic transection, the Cavitron Ultrasonic Surgical Aspirator(CUSA) was used. Small hepatic vein branches and small glissonean pedicles were sealed and divided with a THUNDERBEAT™ (Olympus). iDriveTM Ultra Powered Stapling device (Medtronic) was used for division of major glissonean pedicle and large hepatic veins. The specimen was placed in endo-bag and extracted through Pfannestiel incision.

**Results:** There was no major bleeding during operation and no complication after surgery. The operation time was 338 min, and the estimated blood loss was less than 250 ml. On postoperative day 3, computed tomographic scan showed no pathological findings. The patient was discharged on postoperative day 5 without complications.

**Conclusions:** The authors suggest that the laparoscopic central bisectionectomy is safe and feasible for HCC.

### **PE-287**

### Robotic Hepatectomy: Initial Experience of a Single Institution

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**Aims:** Over recent years, minimally invasive hepatic resections have increasingly been reported in the literature. Even though hepatic surgery is still considered a challenge, the development and spread of robotic surgery have highlighted a new interest, which

has induced a rapid dissemination of robotic approaches. In this study, we report our initial experience with robotic hepatectomy.

**Methods:** A retrospective review of robotic hepatectomy cases performed from December 2017 to January 2018.

**Results:** Total cumulative cases are five; with a median age of 44 years (range 24–65). The first case was intrahepatic bile duct stone and left lateral sectionectomy was performed. The second case was metastatic neuroendocrine tumor from cervix located in segment 6 and segmentectomy was done. The third case was intrahepatic bile duct stone in the left lobe and left hemi-hepatectomy was done. The fourth case was hepatocellular carcinoma (HCC) located in segment 2 and Left lateral sectionectomy was performed with 297 min operation time. The last case was focal nodular hyperplasia with a symptom. Wedge resection was done and its operation time was 225 min. Median operative time was 329 min (range 188-490); median docking time was 15.4 min (range 10-17). There were no conversions to open or laparoscopic surgery. The median length of hospital stay was 12 days (range 11-14).

**Conclusions:** This initial series adds to existing data on the feasibility of robotic hepatectomy cases with inherent advantages of minimally invasive surgery, however with a limitation of availability and use of devices like CUSA and higher operative cost.

### PE-288

### Solo Single Incision Laparoscopic Extended Left Hemihepatectomy for Recurrent Pyogenic Cholangitis

In Gun HYUN, YoungRok CHOI, Ho-Seong HAN, Yoo-Seok YOON, Jai Young CHO, Sungho KIM, Kil Hwan KIM

Department of Surgery, Seoul National University Bundang Hospital, Korea

**Aims:** Laparoscopic surgery for IHD stones is known to be difficult. With the development of surgical instruments, laparoscopic surgery has become a safe and effective procedure for IHD stones. The solo single surgery using a laparoscopic scope holder shows the highly cosmetic effect and we expect it to cause less pain. We described the solo single incision major hepatectomy for IHD stones.

**Methods:** A 3.0cm sized single incision through the umbilicus was made. A 10mm flexible laparoscopic camera was inserted through a glove port and fixed using a jaw of a camera holder. After the division of cystic duct and cystic artery, the gallbladder and round ligament were fixed to the abdominal wall using endo-grip. Left hepatic artery and portal vein were ligated, then demarcation line was drawn for the anterior approach. The left bile duct was dissected and ligated. During parenchymal dissection, the right anterior glissonean pedicle was dissected and transected using the Endo-stapler. After complete dissection of the left liver, the middle and left hepatic vein were ligated using the Endo-stapler.

**Results:** This operation took 220 minutes and estimated blood loss was 150 ml. The patient was discharged 2 days after the operation with no postoperative complications.

**Conclusions:** Laparoscopic surgery had become a safe and feasible procedure for IHD stones. The solo surgery under a single incision can be a new option in laparoscopic hepatectomy for IHD stones.

### PE-289

### Laparoscopic Hepatectomy by Using Hanging Method

Jung Woo LEE, Samuel YOON, Jung Il YOON, Jung Ho PARK, Dong Hyun KIM

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**Aims:** Laparoscopic anatomical liver resection still presents a major technical difficulties. During laparoscopic hepatectomy, deeper parechyma and hepatic vein transection still present a major technical difficulty point. The hanging method has the advantages of less intraoperative bleeding, and better oncolofical outcomes. Here, we review our experience with laparoscopic anatomical liver transection by using haning method.

**Methods:** From September 2015 to January 2018, 71 hepatectomy was perforemed by laparoscopy system in division of Hepatobiliary and Pancreatic Surgery, Hallym Sacred Heart hospital.

**Results:** The mean age was 56.00 years, mean operation times :205.42 min, mean blood loss : 700 ml. The mean hospital stay was 10.67 days. The mean tumor size was 3.4 cm. All resection margin was negative. Conversion rate was 8.33%(only one case). Overall morbidity was 8.33 % and overall mortality rate was 0%.

**Conclusions:** Laparoscopic anatomical liver resection by using haning method appears to be both feasible and safe. The results of current study showthe results in terms of early recovery period. Although, our experience shows that oncologic outcomes are acceptable in terms of margin and early recurrence, further study to evaluate for long-term safety is needed.

## PE-290

### Single Institute Initial Experience of Robotic Major Hepatectomy: 10 Consecutive Cases

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**Aims:** Laparoscopic liver resection is a challenging procedure. However, the robotic surgery system enable to minimal invasive liver resection even for beginners.

**Methods:** Ten consecutive patients underwent robotic liver resection from August 2016 to December 2017. We investigate of short term perioperative outcomes for feasibility and safety of robotic liver resection for beginner.

**Results:** There were eight female patients and two male patients. Among them four patients were diagnosed by hepatocellular carcinoma and three were biliary cystadenoma, three was intrahepatic duct stone. And there was one central

bisectionectomy and six left hepatectomy, three right hepatectomy (including one ALPPS case). The mean operation time were 517minutes and mean estimated blood loss was 336ml and mean length of hospital day was 7.5days. And there was no case of intraoperative transfusion. And there was no major perioperative complication.

**Conclusions:** Robotic liver resection appears to be a feasible and safe procedure even in beginner. The robotic systems can expand the indications of laparoscopic liver resections, especially for more complex major hepatectomies for beginner.

## PE-291

## Pure Laparoscopic Right Posterior Sectionetomy for HCC

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**Aims:** The laparoscopic poster sectionectomy is the major challenge for the laparoscopic liver surgeons. Because the right posterior segment lies deep in the abdominal cavity, it is not easy to access.

Methods: The patient was 61 years old man and diagnosed with 2 cm sized HCC on segment 7. Pringle maneuver was performed during the hepatic parenchymal transection using laparoscopic Bull-dog. During the hepatic transection, the Cavitron Ultrasonic Surgical Aspirator(CUSA) was used. Small hepatic vein branches and small glissonean pedicles were sealed and divided with a THUNDERBEAT™ (Olympus). iDriveTM Ultra Powered Stapling device (Medtronic) was used for division of major glissonean pedicle and large hepatic veins. The specimen was placed in endo-bag and extracted through Pfannestiel incision

**Results:** There was no specific events during operation and no complication after surgery. The operation time was 250 min, and the estimated blood loss was less than 200 ml. On postoperative day 3, computed tomographic scan showed no pathological findings. The patient was discharged on postoperative day 6 without complications.

**Conclusions:** We argue that the laparoscopic posterior sectionectomy is safe and feasible for HCC.

## PE-292

Feasibility of Solo Single-Incision Laparoscopic Surgery in Non-Anatomical Minor Liver Resection for Favorable Located Single Hepatocellular Carcinoma

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**Aims:** We introduced solo surgery using a laparoscopic scope holder to wide an operator's activity range and reduce instrument crowding and clashing in single incisional surgery. This

study aimed to compare the surgical outcomes of solo single incision laparoscopic surgery (SILS) and conventional multiport laparoscopic surgery (MULS) for hepatocellular carcinoma (HCC).

**Methods:** A retrospective analysis for solo SILS (n=20) compared to accumulated data of conventional MULS (n=152) in non-anatomical minor liver resection for patients with a single HCC in the favorable location at a single center was performed between 2003-2017. Baseline characteristics, operative outcomes, and postoperative complications were compared.

**Results:** No significant differences in baseline characteristics and pathologic stage were found between the two groups. Open conversion, postoperative complication (Clavien-Dindo I/ II/IIIa/IIIb) and recurrence rate were not different (0 vs. 12 (7.9%), P=0.364, 1(5%)/0/0/0 vs. 3(2%)/4 (2.6%)/8(5.3%)/1 (0.7%), P=0.650, 6 (30%) vs. 55 (36.2%), P=0.587, respectively in SILS and MULS). However, operative time and hospital stay were significantly shorter in SILS (110.2 ± 57.1 vs 204.5 ± 108.4 mins, 2.5 ±1.9 vs 6.8 ± 3.7 days, both P<0.001,) compared to MULS.

**Conclusions:** Solo SILS had comparable postoperative complications and feasibility in the aspect of operation time and hospital stay compared with conventional MULS for a favorable located single HCC.

## PE-293

Does Low Level of Drain Amylase Warrant the Absence of Postoperative Pancreatic Fistula after Laparoscopic Distal Pancreatectomy?

In Gun HYUN, Yoo-Seok YOON, Ho-Seong HAN, Jai Young CHO, YoungRok CHOI, Sungho KIM, Kil Hwan KIM

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**Aims:** The definition of postoperative pancreatic fistula (POPF) by the international study group in pancreatic surgery (ISGPS) is based on the drainage amylase level. However, this definition is valid as long as abdominal drains are well positioned around the pancreatic anastomosis or stump. The aim of this study is to evaluate postoperative outcomes and the location of drains in postoperative computed tomography (CT) scan in patients with low level of the drainage amylase after laparoscopic distal pancreatectomy

**Methods:** Among 250 patients who underwent LDP from January 2004 to December 2016, 181 patients in whom drain amylase and postoperative CT scan were checked were selected for this study.

**Results:** Eighty-three (43.7%) patients had a low level of drainage amylase (<300 U/L), of whom 38 had malpositioned drains. Among those, 13 (15.7%) patients experienced complicated intra-abdominal fluid collection (defined when associated with fever or leukocytosis, and required antibiotics or percutaneous/ endoscopic intervention). CT revealed that the drain was migrated away from the pancreatic stump in 9 patients and well positioned in 4 patients. Percutaneous drainage was required for complicated fluid collection in 12 patients, of whom 9 patients were newly diagnosed to have grade B POPF due to high amylase level in percutaneous drainage. Finally, the incidence of grade B POPF was 18.8% (n=34).

**Conclusions:** The results suggest that ISGPS definition of POPF based on the criteria of the drainage amylase level has some limitation in application to distal pancreatectomy due to frequent malposition or malfunction of the abdominal drain.

## **Biliary and Pancreatic Disease**

### PE-294

### Internal and External Draining Operations in Chronic Peripanchreatic Peculs of Pancreas

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**Aims:** Peripancreatic pseudocysts (PPC) are the most common complication (20-40%) in patients with chronic pancreatitis (CP). According to the literature, the timing of dynamic observation and the choice of surgical treatment options remain questions for discussion.

**Methods:** Materials and methods. In the period from 2013 -2017. On the basis of the department of surgical hepatology, 29 patients were operated, who had chronic PPC on the background of HP. The lifetime of PPC Me =  $17.4 \pm [6.5-24]$  months. In parallel, the results of treatment of 34 patients who underwent laparotomy and external drainage of PPC were analyzed in connection with the fact that these patients were treated with a clinic for peritonitis or rupture of PPK. The lifetime of the PPC is Me =  $14 \pm [9-21.2]$  months. Before the operation, the examination protocol included transabdominal ultrasound (recently supplemented with endosonography), CKT OBP, MRI cholangiography. In the second group, only ultrasound was performed before the operation.

**Results:** In the first group, consisting of 29 patients, the size of AUC with the presence of a liquid component and sequestrants was up to 60 mm in 4 cases, within 51-100 mm in 20 patients and more than 100 mm in five. In all cases, the fibrous membrane that bounds the AUC was formed. FOC center in 5 patients was located in the zone of the isthmus and the proximal third of the pancreas, the gland bag. In all patients, despite the treatment, the pain syndrome persisted, and there were signs of calcification and fibrosis of the prostate tissue. In this group of patients, cystogastroanastomosis (CGA) was applied with a diameter of at least 5 cm after cystotomy and non-secreces-

trectomy. In 24 patients, PPC was located in the projection of the distal part of the body or tail of the prostate and adjacent to them peripancreatic cellulose tissue. In connection with the zone of localization of PPC, after performing nekrsekvestrektomii superimposed cystoenteroanastomosis (CEA) on the loop on the Root. All patients showed persistent relief of the pain syndrome and an improvement in the quality of life, which was assessed using the Russian version of the SF-36 v.2tm guestionnaire. In 34 patients of the second group admitted to the hospital with a clinic of peritonitis against the background of longlived PPC, laparotomy with non-secrecestrectomy and external drainage of foci of PPC was performed. The sizes of AUC with the presence of a liquid component and sequesters were up to 60 mm in 5 cases, within 51-100 mm in 22 patients and more than 100 mm in the seven. In connection with the progression of the necrotic process or bleeding from the residual cavity, 5 (14.7%) patients underwent a programmed relaparotomy and additional necrosecretrectomy or hemostasis. The lethal outcome occurred in three cases (8.8%). In surviving patients for more than 4-6 months, there were external pancreatic fistulas, which according to the results of the SF-36 v.2.tm questionnaire improved the quality of life to a lesser extent (P=0.009-0.0061) than in the first group and worsened the prognosis of NP flow.

**Conclusions:** Internal drainage operations (CEA, CSA) are preferred, since they provide a greater increase in the indices of physical and psychoemotional components of quality of life in operated patients, which confirms the correctness of active surgical tactics. External drainage after nekrsekvestrektomii are rather a forced option of surgical intervention, which is advisable to use in the presence of complications pseudocyst (rupture, peritonitis).

**Keywords:** Peripancreatic pseudocysts, MRI cholangiography, Sequestrants, Non-secrecestrectomy

### PE-295

### Repair of Bile Duct Injury Experience at TU Teaching Hospital, Nepal

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**Aims:** latrogenic bile duct injuries (BDI) following cholecystectomy is a substantial problem in the era of laparoscopic advancement in surgical gastroenterology. Early and accurate diagnosis and management involving multidisciplinary team are of paramount importance. Though endoscopic procedures are most frequently used in management of BDI, surgical repair is the necessity especially in cases of complete transection. Aim of the review is to analyze our experience of management of BDI **Methods:** This is retrospective analysis of all operated cases of BDI Between May 2014 - December 2017. Patients' clinical details, investigations, operative details, perioperative outcomes and follow-up were recorded. Data were analyzed using Statistical Package of Social Sciences 23

**Results:** Total of 23 cases of BDI were operated at TUTH over 42 months out of which 87% were female with age range 17-59 years. Majority cases occurred following laparoscopic cholecystectomy (34.8% while conversion from laparoscopic to open in 26.1%) and 30.4% following open cholecystectomy. Injury identified mostly in early postoperative period (69.6%). E3 (60.9%) injury was most common followed by E2 (21.7%). Median time of repair were 90 days (7 weeks- 25 years). Roux-en-Y Hepaticojejunostomy (HJ) done in 20 cases, 2 cases had revised HJ while 1 case had Right hepatectomy and HJ. Median duration of follow-up of 20 months (range, 4-44) revealed excellent outcomes.

**Conclusions:** Roux-en-Y HJ is the most frequent surgical treatment along with control of sepsis and delayed repair after delineating the proper anatomy for better outcomes in hands of experienced hepatobiliary surgeons.

**Keywords:** Bile duct injuries (BDI), Roux-en-Y Hepaticojejunostomy (HJ), Cholecystectomy, TUTH

## PE-296

### Prognostic Criteria for the Development of Acute Pancreatitis in the Living Concentration of a Large Papilla of Duodenum

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Aims: Currently, the problem of laboratory diagnosis of acute pancreatitis (AP), which occurs when strangulated concrement of the large papilla of the duodenum (CLPD), is far from being resolved. It becomes obvious that it is almost impossible to predict the development of OP based on traditional diagnostic methods. And we often encounter a situation where the presence of a prolonged ampullar obstruction does not lead to the development of OP, whereas the "transitory" passage of microliths through the BSDK can initiate fatal pancreatic necrosis. Methods: The study group included 102 patients with CLPD on the basis of the Department of Faculty Surgery of the Tashkent Medical Academy. The men were 26 (25.5%), women -76 (74.5%). The elderly and elderly people predominated; 60-74 and 75-89 years respectively, which totaled 73.5%. The average period from the onset of the disease to admission to the clinic was  $2.65 \pm 0.36$  days, with the bulk of patients entering the hospital up to 72 hours (70.6%). The diagnosis of "CLDP" was considered an indication for performing endoscopic papillotomy in the shortest possible time. At the same time, the flow bile was sampled and the biochemical parameters were determined. To predict the development of AP in patients with CLDP, the method of logistic regression was used.

As indicators for inclusion in the mathematical model of the prediction of AP, we selected the parameters of the activity of amylase and lipase in the blood and ductal bile. To assess the quality of the constructed model and determine its information capacity, we calculated the prognostic probability of development of AP, and then compared the results with real data in each specific case.

**Results:** It was found that in a group of patients with AP, the model allowed to correctly predict its development in 74 of 78 patients (prediction accuracy - 94.9%). In the group of patients with absence of AP, the coincidence of the predicted and observed results was noted in 91.7% of cases (22 of 24 patients). We also constructed mathematical models that reflect the degree of influence of each studied trait on the development of AP. It has been established that all the features we have identified have a positive effect on the probability of AP development, while only the parameters of the effect of a-amylase in the blood are statistically insignificant.

**Conclusions:** Thus, the mathematical model we constructed allows us to predict the development of AP in patients with CLDP. In this case, the predictive power of the model significantly increases with an isolated evaluation of the influence of these factors. This circumstance allowed us to distinguish three main prognostic tests for the development of AP in patients with AP: the activity of blood lipase, a-amylase of bile and lipase of bile.

Keywords: Acute pancreatitis, Transitory, Microliths, Ductal bile

### **PE-297**

### Transient Bouveret Syndrome

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**Aims:** Bouveret syndrome which was first described in 1896 Leon Bouveret, is a rare form of gallstone ileus which results in gastric outlet obstruction caused by impaction of a large gallstone through a cholecystoduodenal or choledochoduodenal fistula. Gallstone ileus usually consists of three components called Rigler's triad: pneumobilia, ectopic gallstones and small bowel obstruction. Treatment is surgical or endoscpic stone retrieval. We would like to report a fatal case with transient Bouveret syndrome which was unfortunately not treated.

**Results:** A 89 years old female patient admitted because of whole abdominal pain, nausea and vomiting. She had a history of right pneumonectomy for pulmonary tuberculosis 50 years ago. On admission, BP was 110/60 mmHg, HR 89 beats/min, RR 19 breaths/min, BT 36.5 °C. Initial laboratory findings were; WBC 18,590/mm<sup>3</sup>, Hb 15.4 g/dL, PLT 548,000/mm<sup>3</sup>, PT 13.1 sec, PT (INR) 1.20, AST/ALT 27/35 IU/L, T-bil 3.52 mg/dL, albumin 3.5 g/dL, BUN/Cre 58/1.09 mg/dL, amylase/lipase 55/266 U/L, CRP 2.79 mg/dl. Initial simple abdomen showed stones in duodenum with large amount of retained of gas in stomach

and small bowel ileus. Abdominal CT showed pneumobilia, GB stones, sludge/stones in CBD & small bowel, cholecystocholic/ choledochoduodenal fistula. After 2 days, simple abdomen showed no stones in duodenum and stomach dilatation disappeared, but small bowel ileus was aggravated. Bouveret syndrome was diagnosed, but the family refused any treatment options including endoscopy or surgery due to high risk. On the 4th day of hospitalization, she died of sepsis.



**Conclusions:** Bouveret syndrome is the most commonly reported in elderly women and is associated with high mortality and morbidity due to underlying comorbid conditions and elderly age. This case was diagnosed as transient Bouveret syndrome. However, it is regrettable that the endoscopic treatment did not try due to the refusal of patient 's family.

Keywords: Bouveret syndrome, Gallstone, Ileus, Vomiting

#### PE-298

## Laparoscopic Cholecystectomy Complications - Our Experience

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**Aims:** The aim is to analysis of the complications of laparoscopic cholecystectomy (LCE).

**Methods:** Retrospectively analyzed 1412 LCE, which performed between 2009-2016. The indication to LCE was gallbladder

stone (GS). 914 patients (64,7%) had GS with acute cholecystitis, 498 (45,3%) – chronic cholecystitis. Average age was  $49,5\pm0,37$  year. Woman – 81,4% (n=1150), man – 18,6%(n=262).

Results: Complications occurred in 31 (2,2%) patients. The conversion was in 46 (3,26%) cases. Cause of conversions: infiltrative process of HDL - 34 cases (73,9%), bile duct injure - 5 (10,8%), liver abscess detection - 1 (2,1%), atypical cystic artery - 1 (2,1%), bleeding - 4 (8,6%), duodenum injure -1 (2,1%). Early postoperative complications: bile leakage - 9 patients (in 5 patients stopped own), bleeding - 2, sub-hepatic infiltrate - 4, choleperitonitis - 3. Three patients had relaparoscopy due to bile leakage from cystic duct stump (1 case) and bleeding from cystic artery (2). Reasons of early 4 laparotomy were postoperative bleeding - 1 patient, bile leakage - 3 cases. Abdominal wall wound inflammatory complications were 1,9% (after LCH for acute cholecystites). After LCE 1 patient died due to pulmonary artery tromboemboly. Those, after LCE complications causes were: Inflammatory tissue infiltration in the subhepatic area with acute cholecystitis, adhesions and scarring in chronic process hinders the visualization of anatomical structures. The atypical anatomical structure of the extrahepatic bile ducts and liver vessels. Risk factors of complications include older age, obesity, long duration of GB disease.

Table 1. Ear	y complications	after LCE.
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Nº	Complication	Number	%
1.	Bile leakage	9	0,6
2.	Intraabdominal bleeding	2	0,1
3.	Sub-hepatic infiltrate	4	0,3
4.	Choleperitonitis	3	0,2
5.	Abdominal wall wound inflammation	28	1,9

**Conclusions:** The study of the causes of intraoperative and early postoperative complications of LCE can eliminate risk factors that contribute to it development. Careful comprehensive preoperative examination to the prediction of the complexity of surgical intervention will improve immediate results of all LCE.

Keywords: Laparoscopic, Gall bladder stone, Cholecystectomy

### PE-299

# Choosing Method of Treatment of Complications of Pancreative Pseudoquist

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**Aims:** Evaluate the possibilities of endoscopic treatment of pancreatic pseudocystic complications.

**Methods:** In the clinic of faculty surgery of the Tashkent Medical Academy from 2015 to 2015, 11 patients with pancreatic pseudocystic complications were treated. Of these, there were 9 (81.8%) men and 2 (18.2%) women. In 4 (36.4%) cases, the cyst was complicated by mechanical jaundice, in 7 (63.6%) cases there were signs of suppuration pseudocysts. The main diagnostic methods were: ultrasound, SCT of the abdominal cavity, endosonography, ERCP, and also data from laboratory methods of investigation. When the outflow from the main pancreatic duct (GLP) and the pancreatic cysts were broken, endoscopic drainage was performed. The main drainage interventions were nasopancreatic and cystonasal drainage, as well as endoprosthetics of the pancreatic ducts. Along with this, the stents were placed under the application of cystoduodenoids to maintain the lumen of the newly formed anastomosis, as well as the stents of the common bile duct in order to arrest the phenomena of mechanical jaundice. For the purpose of nasopancreatic and cystonasal drainage, polymeric radiocontrast tubes 120-150 cm in length and 5-7 Fr diameter with a lot of holes at the end left in the lumen of the duct or cyst were used. Positive aspects of nasopancreatic and cystonasal drainage were considered: the ability to control the volume of fluid flowing down the drainage (pancreatic juice, cyst contents); constantly aspirate the contents of the duct and cysts; wash the cavity of the cyst with solutions of antiseptics; to conduct control fistulography. Duration of drainage was determined by clinical, laboratory and instrumental parameters (ultrasound and fistulography data) and was from 7 to 16 days. The nature of the intervention was also determined by the presence or absence of a cyst from the GPP. Thus, patients who had cysts complicated by mechanical jaundice and had a connection with GPP performed: endoprosthetics of the main GPP and stent of the common bile duct - 2 patients. Two patients underwent cystoduodenostomy with the stent in the cyst and the common bile duct, while in one case the intervention was supplemented with cystonasal drainage. In case of suppuration of the cyst (the latter had no connection with the GPP), cystoduodenostomy through the wall of the 12 duodenum and cystonasal drainage was performed in 2 patients; in one patient, the intervention was supplemented by the stent in the cyst cavity. In another case, cystogastrostomy, cyst stenting and cystonasal drainage were performed. Four patients underwent percutaneous puncture, festering cysts, under the control of an ultrasound transducer

**Results:** After endoscopic intervention, there was a complication in one patient who had cystogastrostomy - in the early postoperative period, bleeding from the walls of the anastomosis occurred. When performing percutaneous drainage, the cysts did not have complications, but only in one case out of four, the total cyst cavity was completely eliminated.

**Conclusions:** The use of endoscopic treatments for pancreatic cysts is a good alternative to other treatments and in some cases replaces known treatments.

**Keywords:** Pancreative pseudoquist, Ultrasound, Fistulography, Cystonasal drainage

### PE-300

# Obstructive Jaundice Caused by Portal Biliopathy Associated with Essential Thrombocytosis: A Case Report

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Most of obstructive jaundice is caused by pancreatobiliary malignancy or stone. Extrahepatic bile duct obstruction by peribiliary collateral vessels is very rare and association with essential thrombocytosis has not been reported. Portal biliopathy (PB) refers to biliary obstruction that is associated with portal cavernoma. These changes occur as a result of the peribiliary collateral vessels cause extrinsic compression of the intrahepatic and extrahepatic bile ducts. We report a case of patient with obstructive jaundice caused by PB which is associated with essential thrombocytosis. A 66 years old woman, diagnosed with essential thrombocytosis 6 years ago, presented with jaundice for 2 weeks. Laboratory studies showed AST 37 U/L, ALT 44 U/L, Total bilirubin 20.50 mg/ dL with direct fraction 15.60 mg/dL, Alkaline phosphatase 195 IU/ L, gamma-GTP 124 IU/L, PT 12.9 second, INR was 1.14. Hepatitis B and C were non-reactive. Doppler ultrasound and contrast-enhanced CT abdomen noted portal cavernoma and splenomegaly, however, liver was grossly normal. Magnetic resonance cholangiopancreatography showed cavernous transformation of the portal veins and seen to encircle the extrahepatic bile ducts (Fig. 1). Endoscopic retrograde cholangiography with stent insertion was performed for relieving obstructive jaundice. Cholangiogram showed an irregularly narrowed extrahepatic bile duct caused by extrinsic compression of tortuous collateral vascular structures (Fig. 2). An initial nasobiliary drain followed by self-expandable metal stent deployment was done. There was a significant fall in the serum bilirubin level from 20.50 mg/dL to 5.74 mg/dL after 6 weeks. Obstructive jaundice caused by PB is distinctly uncommon. Proper management is important because prolonged biliary obstruction can lead to chonlangitis or secondary biliary cirrhosis.





**Keywords:** Obstructive jaundice, Portal biliopathy, Portal cavernoma, Essential thrombocytosis

## PE-301

Safety and Feasibility of Solo Single-Incision Laparoscopic Cholecystectomy Compared to Conventional Three-Incision Laparoscopic Cholecystectomy: A Multicenter Cohort Study

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**Aims:** Although increment application of single-incision laparoscopic cholecystectomy (SILC), it had technical difficulties of physical disturbance and unstable surgical view through the small incision, therefore, we introduced solo single-incision LC (S-SILC) using laparoscopic scope holder, a simple, fixed and easily handled by a surgeon.

**Methods:** A comparison of S-SILC (group A, n=566) and conventional three-incision laparoscopic cholecystectomy (C-TILC, group B, n=874) from January, 2013 to December, 2016 at multicenter was performed. Baseline characteristics, perioperative outcomes including complications were compared.

**Results:** Mean operative time was not significantly different between two groups (P = 0.176), however, S-SILC had more intraoperative GB perforation, especially in initial period (17.0% vs. 2.3%, P < 0.001) and increased usage of additional port (3.2% vs. 0.5%, P < 0.001) and shorter hospital stay (3.3 ± 1.7 vs. 1.9 ± 2.7, P < 0.001) than C-TILC. There was no significant difference of major postoperative complications between two groups (P = 0.909) and its identified risk factors were not operation type (P = 0.971), but mean age (P = 0.004) and upper abdominal operation history (P = 0.048).

Conclusions: S-SILC is feasible and safe, but careful selection

of surgical candidates is necessary, in initial period of S-SILC experience.

**Keywords:** Solo surgery, Single incision, Laparoscopic cholecystectomy

## PE-302

### Conventional vs Pylorus-preserving Pancreaticoduodenectomy with Pancreaticogastrostomy

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**Aims:** Between conventional pancreaticoduodenectomy (CPD) and pylorus-preserving pancreaticoduodenectomy (PPPD), there is still controversy about the superiority of adopting one method over the other in combination with pancreaticogastrostomy (PG). There are few reports about cases of PPPD with PG.

**Methods:** We studied cases of pancreaticoduodenectomy (PD) with PG for pancreatic head and periampullary carcinoma in our medical center, retrospectively. The data were gathered from 152 patients who underwent CPD/PPPD with PG from January 2010 to April 2015. Cases under study were divided into two groups: CPD group (group A, 101 cases) and PPPD group (group B, 51cases). The data included preoperative, intraoperative and postoperative conditions of both groups. The outcomes of perioperative data were investigated.

**Results:** No significant statistical difference of the preoperative data was detected between two groups. Despite less blood loss (P=0.011), the overall postoperative complications of group B was significantly higher than that of group A (56.7% vs 34.7%, P=0.009). The single complication, majorly the postoperative pancreatic fistula (POPF) rate, of group B was significantly higher than that of group A (29.4% vs 11.9%, P=0.008).

**Conclusions:** Although PPPD with PG may reduce intraoperative blood loss, it can significantly increase postoperative complications, especially POPF. Therefore, PPPD with PG is not recommended for treatment of pancreatic head and periampullary lesions.

## PE-303

## Optimal Surgical Strategy According to Extent of PNET Wenhui LOU

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Aims: The incidence of pNET is increasing in China as well as

the world in recent years. Surgery is one of the main measures in treating pNET. Generally, there is few disputes on the surgical resection of localized lesion and resectable metastatic disease. There are still some disputes on the treatment combination and sequence of unresectable metastatic disease. In Zhongshan Hospital, the 5-year survival after radical resection of localized disease was 93%, the main cause of treatment failure was liver metastasis, the median metastatic time was 38.7 months. In our retrospective study, we found that liver directed therapy (surgical resection, TACE, Radiofrequency, microwave ablation) were more effective compared with systemic treatment. Whether the primary lesion should be resected when there are unresectable metastatic lesions is another focus of the debate. Until now, there is no evidence-based result support routine resection of primary lesion, unless there are life-threaten complications like jaundice, digestive tract obstruction etc. Liver transplantation is last choice for the treatment of pNET with liver metastasis, but should be restricted to patients with G1 or G2 disease and there is no extrahepatic disease.

## PE-304

# A Comparative Study of Early and Delayed Laparoscopic Cholecystectomy in Acute Cholecystitis

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**Aims:** The treatment of acute cholecystitis, especially regarding the timing of intervention, is still debated in scientific community despite the presence of several studies. So the aim of our prospective randomised study is to evaluate the feasibility of early Laparoscopic cholecystectomy(LC) for acute cholecystitis and to compare the results with delayed LC, in our set up.

**Methods:** Between december 2016 to november 2017, 60 patients with diagnosis of acute cholecystitis were assigned randomly to early group, n = 30 (LC within 72 hours of admission), and delayed group, n = 30 (initial conservative treatment followed by delayed LC, 6–8 weeks later).

**Results:** We found in our study that the conversion rate in early LC and delayed LC was similar (<6%). Operation time for early LC was 30.7 min versus 53.6 min for delayed LC, postoperative analgesia requirements (early, 2.4 days vs delayed, 5.3 days), or postoperative complications (early, <5% vs delayed, 10%). However, both groups had similar blood loss (88 vs 93 ml) but early LC resulted in shorter hospital stay (4.1 vs 10.1 days).

**Conclusions:** Early LC for acute cholecystitis with cholelithiasis is safe and feasible, offering the benefits of shorter hospital stay and less cost to the patients. It should be offered to the patients with acute cholecystitis, provided that the surgery is performed within 72hrs of acute symptoms by an experienced surgeon.

### PE-305

## Double Cystic Duct and Successfully Treated with Laparoscopic Cholecystectomy: A Case Report

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**Aims:** Cystic duct variation is quite common, but a single gallbladder with double cystic duct is an extremely rare variant. These variations increase risks of duck injury or bile leakage unless it was diagnosed preoperatively or intraoperatively.

**Methods:** We report a case of choledocholithiasis in a patient with a cholangitis and cholecystitis who was intraoperatively diagnosed double cystic duct and successfully treated with laparoscopic cholecystectomy.

Results: A 72-year old man was admitted to our hospital due to epigastric pain and fever. He presented with right upper guadrant tenderness and positive Murphy's sign. Total bilirubin, direct bilirubin, liver function test was elevated with leukocytosis. Cholangitis with distal common bile duct stone and gallbladder stone was diagnosed by computed tomography. Endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy was performed with removal of CBD stone and sludges. ERCP revealed normal bile duct anatomy. Under general anesthesia, four ports elective laparoscopic cholecystectomy was done and double cystic duct was found. During operation we ligated cystic duct and cystic artery, more dissection was done for removal pericholecystic connective tissue from hilum. Non pulsatile tubular structure was observed from liver hilum to gallbladder. It was ligated and divided after fully dissected. Postoperatively magnetic resonance cholangiopancreatography revealed that CBD was not injured neither leaked.

**Conclusions:** Double cystic duct with single gallbladder is a very rare anomaly. Although preoperatively image does not reveal this variation, laparoscopic cholecystectomy could be done safely and intraoperative cholangiogram should be considered to prevent ductal injury.

## PE-306

### Comparison of Spectrum of Complications after Pancreaticoduodenectomy in Patients with or without Preoperative Biliary Stents

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**Aims:** Preoperative biliary drainage (PBD) prior to Pancraticoduodenectomy (PD) continues to be routine in many centres despite sufficient evidence showing PBD to increase perioperative complications. This study was planned to see complications of PD and compare between stented and non-stented. **Methods:** Total 59 patients were enrolled in a period of one and half year. During surgery bile aspirate was sent routinely for culture sensitivity. Drain fluid amylase and LFT were obtained on day 3, 7 and 10. Morbidity was graded according to the Clavien–Dindo classification. Pancreatic fistula, haemorrhage and DGE were documented as per international guidelins. USG Abdomen was done on POD7. Patients were assessed daily for complications as per ISGPS definition.

**Results:** Fifty Nine patients were enrolled. 21 were stented and 38 were not stented. Median age was 62 and 55 respectively.. DGE in 13 stented and 24 non-stented patients. Pancreatic fistula occurred in 7 (33%) stented and 8(21%) non -stented group. No significant difference was found in two groups.Fever was documented in 5 stented and 4 non-stented . Post PD haemorrhage occured in three patients and no difference between scented and 28 (73%) non stented patients. This was significant. Enterococci were most common isolate on stented patients accounting for 33% . E coli were most common among non-stetted .

**Conclusions:** We could not find significant difference in morbidity, hospital stay and operative time between the stented and non-stented groups after Pancreaticoduodenectomy. There was significant difference in bile culture positivity.

## PE-307

### Achieving Margin Negative Resection – Doing Less Is Justified: Oncological Outcomes of Wedge Excision of Liver in Gall Bladder Cancer (GBC) Surgery

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**Aims:** The extent of liver resection for gall bladder cancer (GBC) is still debated. We evaluated the post-operative and oncological outcomes of patients who underwent liver wedge excision.

**Methods:** Patients who underwent radical cholecystectomy (with a liver wedge excision of 2.5-3 centimetres) from June 2010 to December 2015 were retrospectively analysed.

**Results:** 97 cases of primary GBC out of 558 patients undergoing surgery for GBC were selected. Majority of our patients had stage III disease (52 %). At a median follow up of 29 months, 65.9 % of patients were disease free where as 13.4% were alive with disease. 2.1 % died in postoperative period, 12.3% patients died of disease and 6.1% died of unrelated causes.9 patients had loco- regional recurrence and 16 failed at distant sites. Only one patient recurred in the gall bladder bed. 3-year overall survival of stage II was 85 % and of stage III was 60 %.

**Conclusions:** Surgical outcomes of radical cholecystectomy with wedge resection of the liver at our centre, parallels published international literature. With low morbidity and mortality, it emphasizes oncological equivalence of liver wedge resection as compared to formal segment IVb/V excision, provided a margin negative resection is achieved.

## PE-308

### Intraoperative Infronous Contact Argonoplasmal Coagulation in the Treatment of Complicated Pancregious Pseudokids

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**Aims:** To evaluate the effectiveness of intraoperative application of non-contact argon-plasma coagulation NCAP) in the treatment of complicated PC of the prostate.

Methods: The analysis of results of treatment of 101 patients, operated on the complicated PC of the prostate. Women were 40 (39.6%), men 61 (60.4%), the average age was  $46.9 \pm 2.8$ . PC complications were presented by suppuration - 56 (55.4%) patients, perforation into the free abdominal cavity - 20 (19.8%) patients. Complication of PC in the form of mechanical jaundice was noted in 19 (18.8%) patients, spleen aneurysm of the spleen artery in 4 (4%) and the formation of internal fistulas in 2 (2%) patients. All patients were divided into 2 groups. 39 patients (Group I) used BAPC during the operation, 62 patients (group II) underwent surgery without BAC. By severity and structure of complications, the groups were comparable. The internal surface of the cavity of the cyst and the parenchyma of the prostate was subjected to the influence of the BAPK when it was dissected. Coagulation was carried out with an Arco-1000 apparatus from Söring, at an argon feed rate of 3.5 | / min.

**Results:** External drainage of cysts was performed in 15 (38.5%) patients of group I and 40 patients (64.5%) in group II, 5 (12.8%) patients in group I and 8 (12.9%) in group II performed distal pancreatosplenectomy group; Internal drainage operations were performed in 19 (48.7%) patients in Group I and 14 (22.6%) in Group II. In the II group, postoperative complications were observed in 49 patients (79  $\pm$  0.5.7%), incl. External pancreatic fistulas were formed in 10 patients (25.6  $\pm$  0.69%), bleeding in 2 cases (5.1  $\pm$  1.25%), suppurative complications in 3 cases (7.7  $\pm$  0.65%). Complications in the early postoperative period in Group I were observed in 15 patients (38.4  $\pm$  1.13%).

**Conclusions:** Intraoperative use of BAPC promotes the expansion of the possibilities of using internal draining operations in complicated PC of the prostate. The frequency of postoperative complications, duration of hospital stay and lethality are significantly reduced.

Keywords: Suppuration, Non-contact argon-plasma coagulation

## PE-309

## Survey on Patients' Awareness of the Single Port Laparoscopy for Cholecystectomy

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ment of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

**Aims:** Single-incision Laparoscopic Cholecystectomy (SILC) is a relatively new procedure in the management of gall bladder disease, compared to Conventional Laparoscopic Cholecystectomy (CLC). We aim to assess the awareness of SILC and its benefits, amongst patients who had undergone cholecystectomy.

**Methods:** We surveyed 54 patients who had undergone cholecystectomy through phone interviews (SILC=44/CLC=10).

**Results:** 70% of the patients surveyed were unaware of SILC prior to their operation. Of the remaining patients who were aware of SILC prior to their operation, 24% attained SILC information by word of mouth, 4% from online sources and 2% from newspapers 83% of the patients believe that SILC is a less painful procedure as compared to CLC. 98% of the patients think that SILC is more beneficial cosmetically 50% of the patients think that SILC would cost at least \$4000 more than CLC 44% of the patients thought that SILC has been present in Singapore for at least 1-3 years. 100% of the patients would recommend SILC to other patients.

**Conclusions:** The majority of surveyed patients were unaware of SILC prior to their operation. However, they believed that SILC is more beneficial cosmetically and with reduced post-operative pain as compared to CLC. All of them would recommend SILC to other patients.

## PE-310

### Lornoxicam Antimediator Therapy Influence on TLR2, TLR4 mRNA Expression at Patients with Systemic Complications of Severe Acute Pancreatitis

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**Aims:** The pathogenic mechanism of severe acute pancreatitis is the appearance of damage associated molecular patterns in the extracellular space which effect through the Toll-like receptors (TLRs) and cause the positioning of the latter as new targets for therapeutic influence. The aim of this study is to examine the TLR2 and TLR4 mRNA expression level (EL) in mononuclear cells in peripheral blood of patients and to analyse the effect of lornoxicam therapy.

**Methods:** 72 patients with systemic complications of severe acute pancreatitis were divided into two groups. 57% (n= 41) received only standard conservative therapy (1st group). 43% (n= 31) had additional lornoxicam antimediator therapy (2nd group). Blood samples were taken on 1,3,7,12 day.

**Results:** Death rate was 19.1% (n=9) (1st group), 6.5% (n=2) (2nd group) (P=0.006). The TLR2 EL in both groups on the 1st day was higher than at healthy donors (P=0.00031). The 1st

group had increased TLR2 EL on the 3rd, 7th and 12 day. The 2nd group had no increase of TLR2 EL on the 3rd day and on the 7th,12 day gradual decrease of TLR2 EL was observed. TLR2 EL was significantly lower in the 2nd group than in the 1st group on the 7th (*P*=0.007), 12 day (*P*=0.013). The TLR4 EL in both groups was significantly increased.

**Conclusions:** Lornoxicam reduces TLR2 and TLR4 EL in peripheral blood of patients which allowed to achieve significant statistically reduction of patients mortality.

## PE-311

### Techniques of Laparoscopic Trans-Choledochal Common Bile Duct Exploration and Its Complications

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**Aims:** Laparoscopic common bile duct exploration (LCBDE) has been proven to be a technically demanding but cost-effective option for the management of common bile duct (CBD) stones. It can be performed trans-cystically for stones that are small (<6mm) or trans-choledochally for bigger stones (>10mm). Laparoscopic trans-choledochal CBD exploration requires more technical skills and it is also associated with specific complications e.g. bile duct stricture, bile leak and rarely injury to the posterior wall of CBD or injury to portal vein

**Methods:** In Changi General Hospital, CBD exploration for CBD stones is usually reserved for stones failed to be removed via endoscopic retrograde cholangiopancreatography (ERCP) or stones identified on intraoperative cholangiogram (IOC). The patients who had laparoscopic trans-choledochal CBD exploration were retrospectively reviewed. The techniques and complications of trans-choledochal LCBDE were described.

**Results:** We identified 2 cases with complications. First one had bile leak from the choledochotomy site, requiring to undergo ERCP and stenting postoperatively. The second one had a very rare posterior CBD wall injury during choledochotomy, which was converted to open biliary bypass.

**Conclusions:** Laparoscopic trans-choledochal CBD exploration is technically demanding. Care should be taken during choledochotmy. This technique should be reserved for cases with dilated CBD.

### PE-312

### Reconstructive Surgeries of Cholangiocarcinoma

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<sup>1</sup>Department of Surgery #1 of Kharkiv national medical university,, Doctor of Medical Sciences, Professor, Head of the Surgery Department No.1, Ukraine; <sup>2</sup>"Zaycev V.T. Institute of General and Urgent Surgery", Doctor of Medical Sciences, Professor, Head of the Department of Intervention Radiology, Ukraine; <sup>3</sup>Department of Surgery #1 of Kharkiv national medical university, Post-Graduate (PhD) student of the Surgery Department No.1, Ukraine **Aims:** A great number of post-operative complications and high mortality accompanies reconstructive surgeries of cholangiocarcinomas. The development of irreversible hepatic decompensation in the post-operative period becomes the main cause of unsatisfactory treatment outcomes.

**Methods:** Treatment outcomes for 22 patients with cholangiocarcinomas were analyzed. All patients underwent reconstructive surgeries. The amount and type of operative treatment depended on the extent, localization of the tumor, and the Bismuth-Corlette classification.

Results: Pre-operative preparation in the form of biliary decompression was performed through percutaneous transhepatic biliary drainage (PTBD) in 11 (50%) patients (target group) and other 11 (50%) (reference group) patients were operated without biliary decompression. Isolated resections of bile ducts were performed in type I and II tumors in 10 (45.5%) patients, rightside and left-side hemihepatectomy with total caudal lobectomy in 3 (13.6%) and 2 (9.1%) cases in patients with type IIIA and IIIB tumors in both groups. Biliodigestive junction performed in 6 (27.3%). Postoperative complications were observed in 2 (18.2%) patients of target group and 3 (27.3%) of reference group: hepatic failure in 1 (9,1%) patients of target group and 2 (18.2%) of reference group, septic cholangitis in 1 (9.1%) patient of reference group, hepaticojejunostomic leakage in 1 (9.1%) patients of target group. Mortality in target group was 9.1% (1 case), in reference group was 18.2% (2 cases).

**Conclusions:** Pre-operative PTBD reduces the number of complications after reconstructive surgeries from 27.3% to 18.2%, and the mortality rate from 18.2% to 9.1% as compared to patients who previously underwent operations without biliary decompression.

## PE-313

## Video: A Case of Aggressive Solid Pseudopapillary Tumor of the Pancreas Treated with Surgery after Neoadjuvant Chemotherapy

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**Aims:** Solid pseudopapillary tumors of the pancreas are considered benign conditions but up to 15% can present with aggressive behavior. Due to the rarity of this disease, there is still much debate regarding the ideal management. We present a video of a surgery performed on a 28/M diagnosed with solid pseudopapillary tumor of the pancreas after neoadjuvant chemotherapy.

**Methods:** A 28/M diagnosed with solid pseudopapillary tumor of the pancreas underwent 10 cycles of neoadjuvant chemotherapy. The patient underwent open pylorus preserving pancreaticoduodenectomy with concurrent portal vein resection and end-to-end anastomosis.

Results: The patient had an uneventful post-operative course

and was discharged without complications.

**Conclusions:** Neoadjuvant chemotherapy combined with enbloc tumor resection is a viable treatment option for patients diagnosed with aggressive solid pseudopapillary tumor of the pancreas.

## PE-314

### Aggressive Management for Metastatic Renal Cell Carcinoma in the Pancreas

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**Aims:** Metastatic cancer to the pancreas is rare and accounts for 2%~5% of all pancreatic malignancies, metastasis from renal cell carcinoma is the most frequent. Pancreatic metastasis from renal cell carcinoma (RCC) can be only site of metastasis and can be surgically resectable. In this study, we report six cases of metastatic rcc of the pancreas which underwent surgical treatment.

**Methods:** Between March 2016 to August 2017, six patients (three men and three women of mean age 61.5±3.7 years) underwent pancreatectomy for RCC metastasis. We retrospectively reviewed clinicopathological data on those patients.

**Results:** Pancreas metaststasis occurred metachronously in all patients, with a mean interval from primary renal cell carcinoma of 5.8±1.0 years. The mean length of hospital stay was 14.8±5.3 day. In-hospital mortality did not occur. Histological examination confirmed the location of a secondary RCC in all patients. Among the six patients, two patients have multiple lesions of the pancreas and 4 patients were a solitary lesion. Median follow-up after pancreatectomy was 8.5 months (5-35months). Four patients were alive with no evidence of disease at 2, 4, 5, and 6 months after resection. Two patients had recurrent disease but were still alive at 17 and 34 months after resection.

**Conclusions:** Single localization of RCC metastasis to the pancreas is rare and it has a slow growing pattern. A hypervascular solid pancreatic tumor, in a patient who has previously undergone nephrectomy for RCC should be considered as suspicious metastasis. In selected patients, standard pancreatic resection might be an option an can be associated good results.

## PE-315

#### **Totally Robotic Central Pancreatectomy**

#### Ji Woong HWANG

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Aims: Central pancreatectomy is a parenchyma-sparing proce-

dure that can be utilized in the resection of tumors of the neck or the proximal body of the pancreas. Despite of the benefit of CP, the complexity of pancreatic surgery has made it difficult to introduce laparoscopic or roboric surgery in this field. In this article, we descirbe a totally robotic central pancreatectomy (RCP) performed to the patient with benign central pancreatic tumor. **Methods:** A 43 years old woman had intraductal papillary mucinous neoplasm in the body of pancreas. She had no medical illness. Tumor size was 2.0 cm. All surgical procedures including central pancreatectomy and reconstruction were performed by using the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, CA). We performed the pancreaticojejunostomy using a dunking technique for panceraticoenteric reconstruction to the distal stump.

**Results:** The operative time was 510 minutes and console time was 480 minutes. It took 90 minutes to perform the pancreaticojejunostomy. The blood loss was 120 mL. A postoperative pancreatic fistula (grade A) was developed at the pancreas head stump, which was managed conservatively. The postoperative hospital stay was 14 days.

**Conclusions:** RCP enables the secure pancreaticojejunostomy compared with laparoscopic surgery. Therfore, RCP is a feasible and useful technique for the removal of benign central pancreatic tumors.

## PE-316

### Validation of Original Fistula Risk Score and Alternative Fistula Risk Score in Postoperative Pancreatic Fistula

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**Aims:** Postoperative pancreatic fistula(POPF) is the most serious surgical complication after pancreaticoduodenectomy(PD). In 2013, Fistula Risk Score(FRS) was developed to assess the risk of clinically relevant postoperative pancreatic fistula(CR-POPF). In 2017, the alternative Fistula Risk Score(a-FRS) was proposed. In this study, we validate the o-FRS and a-FRS to assess statistical significances following PD.

**Methods:** From 2007 to 2016, a total of 1771 patients underwent PD for primary periampullary cancers. POPF was defined and classified according to the International Study Group for Pancreatic Fistula(ISGPF), 2016. All data were reviewed retrospectively.

**Results:** Pathologic diagnosis other than ductal adenocarcinoma(P<0.001), pancreas duct diameter(P<0.001) and BMI(P<0.001) were independent risk factors of CR-POPF by multivariate analysis. However, pancreas texture(P=0.534) and intraoperative blood loss volume(P=0.827) were not associated with CR-POPF. According to o-FRS, the CR-POPF incidence increased as the o-FRS score increased(P<0.001). Within o-FRS groups, incidence of CR-POPF was 2.3%, 8%, 14.2% and 17.5% in the no risk group, low risk group, moderate risk
group and high risk group(*P*<0.001). By comparison, according to a-FRS, CR-POPF occurred in 6.7%, 13.4% and 21.6% of patients in the low risk group, intermediate risk group and high risk group(*P*<0.001). However, discrimination with area under curve (AUC) was only 0.629(95%CI:0.593-0.665) in o-FRS and 0.622(95%CI:0.585-0.660) in a-FRS.

**Conclusions:** o-FRS and a-FRS could reflect the incidence of CR-POPF to some extent, but some risk factors were considered to have no or low statistical significance. These measures are also of low value as predictive models, and further research is needed to modify and revise the FRS.

#### PE-317

#### Initial Experience of Laparoscopic Robot-Assisted Pancreaticoduodenectomy

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**Aims:** Laparoscopic robot-assisted pancreaticoduodenectomy is a novel minimally invasive surgery technique. Robotic surgery has the significant advantage of 3D magnified view, stable handling and precise suturing due to enhanced degree of freedom. We sought to determine the safety and feasibility of the first laparoscopic robot-assisted pancreaticoduodenectomies performed at our institution.

**Methods:** Six patients underwent laparoscopic robot-assisted pancreaticoduodenectomy from January 2017 to December 2017. **Results:** Eight patients were scheduled for laparoscopic robot-assisted pancreaticoduodenectomy; 2 were converted to a mini-laparotomy during the laparoscopic portion of the procedure. The patients were diagnosed as pancreatic adenocarcinoma(n=2), cholangiocarcinoma(n=1), ampullary adenocarcinoma(n=1), and intraductal papillary mucinous neoplasm (n=2). The mean operative time was 545±49 minutes. The mean blood loss was 193±126ml. There was 1 (16.6%) Clavien III–IV complication which required readmission. The mean postoperative hospital stay was 17.9±10.1 days.

**Conclusions:** Laparoscopic robot-assisted pancreaticoduodenectomy could be performed successfully in selected patients.

#### PE-318

#### Prevalence and Clinical Significance of Biliary Intraepithelial Neoplasia in Cholangiocarcinoma

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**Aims:** Biliary intraepithelial neoplasia (BilIN) is a noninvasive precursor lesion which can progress to Cholangiocarcinoma (CC). BilIN is often found synchronously adjacent to the tumor or at the surgical resection margin of resection CC.The aim of

this study was to elucidate its prognostic effect on survival after resection for CC.

**Methods:** We retrospectively analyzed patients with CC who underwent curative surgery from 2010 to 2017. Patients whose resection margins were positive for invasive cancer were excluded. CC associated with IPNB were excluded from analysis.

**Results:** There were 142 patients who underwent curative surgery for CC. BillN was detected in 42 patients (29.5%) and showed a significantly higher prevalence in extrahepatic CC (90.5%) than in intrahepatic CC (9.5%).T3 stage and N1 stage were significantly more common in the BillN-negative group than in the BillN-positive group. On univariate analysis, extrahepatic hepatic CC patients with BillN lesions significantly showed better disease free survival (*P*=0.05). Also, although not significant, extrahepatic CC patients with BillN lesions revealed better overall survival. In addition, presence of any type of BillN lesion at the resection margin was not associated with survival. On multivariate analysis, presence of BillN lesion, irrespective of location, was significantly associated with better disease free (HR=1.959, 95% CI 1.026-3.743, *P*=0.042) and overall survival (HR=2.140, 95% CI 1.006-4.552, *P*=0.048) in extrahepatic CC patients.

**Conclusions:** The presence of BillN lesions was significantly associated with better disease free and overall survival in extrahepatic CC patients. However, larger studies with longer follow up are needed to accurately determine its clinical significance.

#### PE-319

# Prognostic Impact of Metastatic Lymph Node for Distal Cholangiocarcinoma

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**Aims:** The staging system for distal cholangiocarcinoma was changed in AJCC 8th edition. The aim of this study was to investigate the prognostic factors for survival of distal cholangiocarcinoma after curative resection, and to evaluate the impact of metastatic lymph node count for survival, revised in AJCC cancer staging 8th edition.

**Methods:** All patients who underwent pancreaticoduodenectomy or bile duct resection with curative intent for distal cholangiocarcinoma between 2004 and 2017 at Chonnam National University Hwasun Hospital were reviewed retrospectively. Survival outcome was evaluated using Kaplan-Meier method, and the Cox proportional hazards model was used for multivariable analysis.

**Results:** 248 patients were included. Overall survival rates for 1, 3, and 5 years were 81.4%, 49.5%, and 34.9% respectively. Median survival time was 35.0 months. In univariate analysis, the prognostic factors influencing survival were elevated serum total bilirubin(=5mg/dL), infiltrative appearance, histologic differentiation, T-stage, lymph node involvement, new N-stage of

AJCC 8th edition, TNM stage of AJCC 7th edition, perineural invasion, lymphovascular invasion, and margin involvement. Among them, histologic differentiation, N-stage of AJCC 8th edition, and margin status were identified to be independent prognostic factors in multivariate analysis.

**Conclusions:** Histologic differentiation, new N-stage of AJCC 8th edition, and margin status were the independent prognostic factors. The new N-stage of AJCC 8th edition was superior to predict the prognosis after curative resection for distal cholangio-carcinoma, compared to AJCC staging system of 7th edition.

#### PE-320

#### Clinical Differences of Young Population Undersent Laparoscopic Cholecystectomy

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**Aims:** Laparoscopic cholecystectomy (LC) in young population is relatively uncommon, despite being one of the most common surgical procedures in adults. Although clinical characteristic of adult patients with gallbladder (GB) disease is well established, scanty information have been for youth. In the present study, we aimed to comprehensively review the young population underwent LC compared to older population.

**Methods:** A total 2,115 patients who received LC for GB stones were retrospectively analyzed. The patients were categorized into two clinical groups according to the age of patients: (young (<24) group and the elder group). We compared two groups according to its clinical characteristics.

**Results:** In univariate analysis, significant factors between two groups were found in the concomitant of choledocholithiasis and American Society of Anesthesiologists score I/II. By multivariate analysis, the concomitant of choledocholithiasis (OR 1.152, 95% CI, 0.663 – 2.001, P<0.001) were independent factors between young group and the elder group.

**Conclusions:** In our study, young population with gallstone disease had more prevalence of choledocholithiasis. Therefore, young patients with gallstone disease require special attention for choledocholithiasis.

#### PE-321

Photodocumentation of the Critical View of Safety: Retrospective Comparison Study between Needlescopic Grasper Assisted Single Incision Laparoscopic Cholecystectomy and Three Port Laparoscopic Cholecystectomy

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**Aims:** Single incision laparoscopic cholecystectomy (SILC) has some technical problems. Our group has performed needlescopic grasper assisted SILC (nSILC) to overcome these problems. We evaluate the safety and feasibility of this technique comparing with the three port laparoscopic cholecystectomy (TPLC) for obtaining rate of the critical view of safety (CVS) via photodocumentation.

**Methods:** We analyzed the medical records of the patients who underwent nSILC and TPLC with photodocumentation for benign gallbladder disease between January 2011 and December 2015. A needlescopic grasper was used in nSILC, which was inserted through a direct puncture on right upper quadrant of abdomen. The scope and other instrument were inserted through umbilical port.

**Results:** Totally 1221 patients underwent laparoscopic cholecystectomy during the period. Among them, 577 patients underwent nSILC and 644 patients underwent TPLC. CVS obtaining time and main procedure time (skin incision to gallbladder removal time) for nSILC was significantly longer than that of TPLC. But, in terms of CVS obtaining success rate is more higher in nSILC group.

**Conclusions:** We can get high success rate of accurate CVS obtaining rate with photodocumentation in nSILC. So, nSILC is feasible and safe surgical procedure in patient with benign gall-bladder disease.

#### PE-322

# Laparoscopic Choledochoduodenostomy in Complicated Conditions

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**Aims:** Although the feasibility of biliary by-pass procedures for choledocholithiasis was decreased due to endoscopic or interventional treatment, it is still remained as an important treatment option in specific conditions. In era of laparoscopic surgery, laparoscopic choledochoduodenostomy(LCD) also was applied for difficult common bile duct stones (unresolved by ERCP or PTBD). The aim of this study was to analyze the outcomes of patients with complicated choledocholithiasis treated by laparoscopic choledochoduodenostomy.

**Methods:** We reviewed our all LCDs done since 2015 in our hospital, documenting our preoperative, intraoperative, and postoperative experience. A successful LCD was performed as a secondary treatment option on all 8 patients.

**Results:** Four patients had previous episodes of gastrectomy and had been tried PTBD. Others had recurrent episode of choledocholithiasis even after multiple ERCP. We found female predominance (6/8), wide range of age (55-87 years), operative time (180-360min), median lengths of postoperative stay 10 (8-30) days, and a median of 15 (1-35) months of follow-up. Only one patient had a postoperative leakage but spontaneously recovered. The hepatobiliary enzyme levels returned to normal in all of the patients.

Conclusions: LCD with intraoperative cholangioscopic stone

remove seems to be safe and effective treatment for patients with recurrent common bile duct stones failed by ERCP or PTBD. LCD is preferable biliary by-pass for choledocholithiasis and technically easier and faster. We suggest that this procedure can be a good option for patients with complicated conditions.

#### PE-323

#### Pancreatic Acinar Cell Carcinoma with Stomach and Pericolic Adipose Tissue Invasion: A Case Report

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**Aims:** Acinar cell carcinoma of pancreas is an uncommon malignant neoplasm that about 1-2% of pancreatic neoplasm. This case report is about acinar cell carcinoma of the pancreas with stomach and pericolic adipose tissue invasion.

**Methods:** A 73-year old man was visit the local clinic with a 2-month history of epigastric pain and 5kg weight loss for 1-month, Abdomen USG shown about 12cm pancreatic tail mass. The patient was admitted in our hospital. CT scans show that a huge, 12cm, solid and necrotic mass in the anterior aspect of the pancreas body tail, extending to the upper body posterior gastric serosal surface. EUS revealed the mass contained multiple cystic portion and compress the upper body to posterior wall of stomach. Colonoscopy was failed to pass the lesion because of narrowing lumen.

**Results:** Distal pancreatectomy, gastric wedge resection and colonic segmental resection were done. The pathological report showed acinar cell carcinoma, pancreatic tail to body with invasion to the stomach and pericolic adipose tissue, no involvement of spleen.

**Conclusions:** Adjuvant chemotherapy was done. The patient is wellbeing without any recurrence within two years after the operation.

#### **PE-324**

#### Validation of AJCC 8th Edition Stage for Gall Bladder Cancer

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**Aims:** This study evaluated discriminatory value of newly proposed AJCC 8th staging system compared to the AJCC 7th staging system for gallbladder cancer.

**Methods:** We retrospectively reviewed database of 522 patients who underwent curtive intent surgery for gallbladder cancer at a single institute from January 2006 through June 2016. Clinicopathologic characteristics and survival rates were analyzed based on 7th and 8th edition of AJCC staging system, respectively. **Results:** There was significant different in survival rates between T2a and T2b(P<0.001). Among pathologically-stage patients, P values for pairwise comparisons among different 8th AJCC stage were significant(P<0.05) for stage lla vs llb and llla vs lllb. Notably, the new edition improved the power of discrimination slightly in overall survival and disease-free survival (c-indices: 0.812, 0.881) compared with the 7th edition(c-indices:0.810, 0.874). There were no significant difference between N1 vs N2 in both stage group(P=0.578, 0.283).

**Conclusions:** Compared to the 7th system, the 8th system bring significant prognostic improvement for stage IIa vs IIb. However, lymph node staging does not reflect well the prognosis in both classification by number or location based staging system.

#### PE-325

#### Long Term Outcomes and Prognostic Factors of Resected Pancreatic Neuroendocrine Tumors

# Hyung Jun KWON<sup>1</sup>, Sang Geol KIM<sup>1</sup>, Young Seok HAN<sup>2</sup>, Heontak HA<sup>2</sup>, Jae Min CHUN<sup>2</sup>, Yoon Jin HWANG<sup>1</sup>

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**Aims:** Pancreatic neuroendocrine tumors (PNET) are a rare subgroup of tumors. For PNETs, the predictive factors for survival and prognosis are not well known. The aim of the present study was to investigated the clinicopathological and prognosis of the patients with resected pancreatic neuroendocrine tumors (PNET). **Methods:** 42 patients with PNET underwent surgical treatment from April 1992 to June 2017. Data regarding the clinicopathologic factors of these patients were collected retrospectively. Factors influencing the prognosis of advanced gallbladder cancer after resection were analyzed by univariate and multivariate analysis.

**Results:** The patients comprised of 18 men and 24 women. The mean age of the patients was  $53.98\pm12.75$  years. Nine cases (21.4%) were functional tumors and 33 cases (78.6%) were non-functional tumors. The mean tumor size was  $2.99\pm2.08$  cm. The most common location was tail (38.1%) and head (35.7%), followed body (21.4%), and body & tail(4.8%) in pancreas. The differences in the disease specific survival time as grading system based on Ki-67 and mitotic count were only statistically significant (*P*=0.015). The 5-year disease specific survival rates of patients with Grade 3 tumor was 0%. The T category (*P*=0.115), N category (*P*=0.299), TNM staging system (*P*=0.458), lymphovascular invasion (*P*=0.479), and perineural invasion (0.527) were not statistically significant factors.

**Conclusions:** Patient with grade 3 PNET have worse postoperative prognosis. Therefore, we need careful monitoring after surgery.

#### PE-326

#### Laparoscopic Extended Cholecystectomy Including Bile Duct Resection for Gallbladder Cancer

#### Yoo-Seok YOON

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**Aims:** Routine resection of the bile duct for LN dissection during extended cholecystectomy for gallbladder cancer (GBC) is not recommended, because it increases morbidity with no evidence of improving survival. Indications for this procedure include a positive cystic duct margin after cholecystectomy to obtain a negative margin, direct tumor invasion of the bile duct, and inflammation or scarring around the hepatoduodenal ligament compromising complete LN dissection. The feasibility of laparoscopic bile duct excision for GBC has been reported in the literature. Considering the increasing reports on laparoscopic surgery for choledochal cysts and laparoscopic pancreatoduodenectomy, the necessity of bile duct resection is not a contraindication for GBC laparoscopic surgery. The videos describe our technique of laparoscopic extended cholecystectomy including bile duct resection for GBC.

#### **PE-327**

#### Multimodal Approach for Hepatic Recurrence after Surgical Resection of Hilar Cholangiocarcinoma

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**Aims:** The optimal treatment for the recurrence after initial surgical treatment remains not established. We report a case of multimodal treatment using chemotherapy and surgical re-resection for the recurrence after extended right hepatectomy and bile duct resection of hilar cholangiocarcinoma.

**Methods:** A 67-year-old man underwent sugical resection for hilar cholangiocarcinoma (pT2bN0, pStage II) in March 2014. After that, he received adjuvant concurrent chemoradiotherapy (CCRT) with 5-fluorouracil plus leucovorin. After 2 cycles of adjuvant CCRT, he was treated only with adjuvant chemotherapy for 5 cycles. However, S4 segment recurrence involved with inferior vena cava was detected on Computer Tomography (CT) and Positron-Emission Tomography (PET) at 37 months after the initial surgery.

**Results:** The liver biopsy revealed cholangiocarcinoma recurrence in April 2017. After 6 cycles of palliative chemotherapy consisting of gemcitabine plus cisplatin, follow-up CT and PET-CT showed a partial response of S4 recurrent tumor. The reoperation was decided because the recurrence did not show any other metastases and the patient was stable during the 5-month palliative chemotherapy. He underwent S4 segmentectomy and hepaticojejunostomy revision with jejunum segmental resection for recurrent cholangiocarcinoma in September 2017. Subsequently, He received the same chemotherapy

consisting of gemcitabine plus cisplatin after the second surgery. To date, he has been alive for 47 months since the initial resection of primary lesion and for 5 months since the second resection of recurrent tumor.

**Conclusions:** This case shows that multimodal treatment such as surgery with chemotherapy could improve the prognosis for the highly selected recurrent hilar cholangiocarcinoma.

#### Others

#### PE-328

# Efficacy and Safety of Ledipasvir/Sofosbuvir Treatment of HCV Genotype 1b in Mongolia

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**Aims:** The incident of liver cancer in Mongolia generally caused by HBV and HCV, and it is 7 times higher than that of world average. HCV, the most prevalent cause of HCC in Mongolia, is number one public health issue. Mongolia is one of the first countries that registered ledipasvir/sofosbuvir (LDV/SOF) regimen from developing countries. By the support of Access program run by Gilead Sciences, USA, we started HCV treatment program from January 2016.

**Methods:** We followed and evaluated treatment outcome of patients with HCV infection using combination of 90 mg ledispavir/400 mg sofosbuvir (manufactured by Gilead Science) in 937 treatment naïve and 83 treatment experienced patients. All patients were treated with LDV/SOF for 12 weeks and, their treatment was evaluated by quantitative HCV-RNA assays prior and W (week) 4 and W12 of treatment. Sustained virological response (SVR) after 12 weeks treatment was assessed. Virus genotype analysis using cDNA microarray, liver enzymes, CBC and drug related adverse events were assessed in every patient. The laboratory tests were conducted at National Center of Communicable Diseases and Happy Veritas Laboratories.

**Results:** We conducted largest ever (415/1020) HCV genotype (GT) distribution study in Mongolian chronic HCV patients. 96.6% (n = 401) of assessed patients were GT1b; 0.7% (n = 3) were GT2; 0.2% (n = 1) were GT1a and b; 0.9% (n = 4) were GT1b and 2; 0.5% (n = 2) were GT1b and 6; 0.2% (n = 1) were GT5 and 0.2% (n = 1) were GT1b and 80 k mutants respectively. 992/1020 (97.3%) patients achieved SVR12W, 28 (2.7%)

patients who did not achieve SVR12 W were all genotype 1b. Median ALT level significantly dropped during treatment from 95.5  $\pm$  84.1 IU/L to 27.2  $\pm$  18.6 IU/L and slightly increased by the end of treatment 42.9  $\pm$  17.4 IU/L. Total of 39 adverse events were observed in 595/1020 patients (58.3%). Single adverse events were observed in 401/1020 (39.3%) whereas 2 and more events were observed in 194 (19%) patients respectively. Unreported adverse events such as partial facial palsy, AFP (alpha-fetoprotein) increase, melasma were observed.

**Conclusions:** Treatment of HCV in Mongolia using all-oral dual DAA was divided in 3 phases due to shortness of drugs and logistics arrangements. We were able to include only stageone patients in this study. We achieved 97.3% SVR12W for 3 months treatment with LDV/SOF this time. But viral relapse has to be determined repeatedly at weeks 24 and 48 post treatment. All viral relapses (n = 14) and non-responders (n = 14) were GT1 in our study. According to HCV genotype assessment, there was no difference in treatment outcomes between patients who had different genotypes. HCV RNA clearance during treatment was no different than clinical trials, but the slight increase of ALT by the end of treatment was commonly observed. It might have happened due to rebound of immune reaction after clearance of HCV or a drug induced effect. **Keywords:** Sofosbuvir, Ledipasvir, HCV, Genotype

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**PE-329** 

#### Vitamin D Deficiency in Chronic Liver Disease patients

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**Aims:** One of the most nutritional deficiency in the world is the deficiency of 25-hydroxyvitamin D [25(OH)D]. Study assessed that there are more than 1 billion people living in the world that has serum 25(OH)D<20 ng/ml deficiency. Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography. Deficiency of 25(OH)D not only causes children's arthritis but to a range of common chronic diseases in adulthood such as diabetes, cancer, infectious diseases, cardiovascular disease, and autoimmune disease, this continuous to be a major public health problem in the world.

**Methods:** Study participants were 102 chronic liver disease over the age of 18 from the citizens of "Choibalsan" city, "Dornod" province, who were referred to the outpatient of Dornod Medical center, Dornod, Mongolia. Overnight fasting blood samples were collected. All patients had tests for blood 25(OH)D were measured by ELISA and 28 patients who took 6 questionnaire tests.

**Results:** Of all patients, 66 were men (68.1%) and 34 were women (31.9%). The mean age was 46 (between 18 and 89 years). There were 55 patients with cirrhosis (54%), and were

47 patients with chronic hepatitis B and C in the study group. 94 (92%) participants had 25(OH)D<20 ng/ml deficiency. Age and season had no correlation on the 25(OH)D level. From the results of the questionnaire test we can see that 5 have efficient 25(OH)D, 17 had the possibility of deficiency of 25(OH) D, and 6 had to reapply for the tests but these participants had 25(OH)D<10 ng/ml and this has no relevance on the level 25(OH)D (Pearson r=0.07, *P*=0.5).

**Conclusions:** In conclusion, our pilot results show that patients as in 92% have 25(OH)D deficiency.

Keywords: Vitamin D, Chronic liver disease, Mongolia

#### PE-330

#### Effectiveness of Transcutaneous Bilirubin Measurement in Managing Neonatal Jaundice in Postnatal Ward of Dornod Medical Center

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**Aims:** Neonatal jaundice is a common cause of concern in immediate newborn period for parents. Obtaining blood bilirubin samples is a painful procedure; it predisposes the baby to infections and requires skilled health personnel. Moreover, laboratory tests are costly and time consuming, leading to unnecessary delays in commencing phototherapy and discharge from hospital. Transcutaneous bilirubinometer has been in use since 2017 as screening tool in postnatal wards.

**Methods:** Ninety newborns with jaundice were referred to the postnatal ward of Dornod Medical center from 2017 august to 2018 January. For patients, we used breastfeeding, intravenous fluid and phototherapy. Before and after the treatment, transcutaneous bilirubinometer were cheked.

**Results:** From the 90 participants of the age (day) 1-35 (mean 17), male were 53 (58.9%), female were 47 (41.1%), body mass were 1.1-4.9 kg (mean 3.7). Phototheraphy and nursing care had significantly decreased bilirubin level from 129.0-469.0 (mean 295.1) mmol/l to 97-298 (mean 173.4) mmol/l (T test, p=0.05).

**Conclusions:** In conclusion, specially of transcutaneous bilirubin measurement is safe and effective in neonatal jaundice .

Keywords: Neonatal jaundice, Transcutaneous bilirubin measurement

#### PE-331

#### Association of Serum Lipids, Oxidized LDL Antibody and High-Sensitivity C-Reactive Protein with Elevated Liver Enzymes in Subjects with Metabolic Syndrome

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Aims: The presence of multiple metabolic disorders such as diabetes mellitus, obesity, dyslipidemia, and hypertension is associated with non-alcoholic liver disease (NAFLD) that can potentially progress to severe liver disease. Although the pathogenesis of NAFLD is poorly understood, there is a considerable amount of evidence that it is associated with abnormal lipid metabolism and dyslipidemia. Therefore, NAFLD not only increases the risk of advanced liver diseases but also associated with future coronary events. Hence, we aimed to examine the association Serum lipids, anti-oxidized-LDL Antibody (Anti-oxLDL Ab), and high-sensitivity C-reactive protein (hsCRP) in the metabolic syndrome (MetS) patients with and without elevated liver enzymes. Methods: A total of 82 individuals (male/female:35/47) with MetS as defined by NCEP ATP III, and 68 healthy control (male/ female:36/32), were recruited for this study. Fasting blood samples were analyzed for blood glucose, eGFR, lipid profile, liver function test (bilirubin, ALT, AST, ALP, y-GT, LDH, albumin, globulin), anti-oxLDL Ab, and hsCRP. Urine samples were analyzed for albumin-creatinine ratio (UACR).

Results: MetS is significantly associated with elevated serum ALT compared to control. 22.0%, 17.8% and 10.3% of individuals with MetS have elevated ALT, AST, and y-GT, respectively. In contrast, only 6.0%, 4.7%, and 2.6% of healthy control have elevated ALT, AST, and y-GT, respectively. Interestingly, we found significant elevation of anti-oxLDL Ab and hsCRP in MetS with elevated ALT compared to normal ALT level (38.7±24.7 vs 20.35±10.6 U/L, P<0.001 for anti-oxLDL Ab and 5.55±7.6 vs 2.15±1.2 mg/L, P<0.001 for hsCRP). No such association was observed with serum AST and y-GT. In addition, the level of ALT is significantly correlated with anti-oxLDL Ab and hsCRP in the MetS with elevated ALT (P=0.021). Although the mean of serum triglyceride, total and LDL-cholesterol, UACR, and eGFR is significantly increased in MetS compared to controls, no such difference was observed between MetS with normal and elevated liver enzymes.

**Conclusions:** MetS is associated with elevated liver enzymes. The individuals with MetS with elevated liver enzymes are associated with increase in hsCRP and anti-oxLDL Ab. The oxidative and inflammatory process might involved in progressive deterioration of liver functions in the MetS.

**Keywords:** Liver enzymes, Metabolic Syndrome, Oxidized LDL antibody, hsCRP

#### PE-332

#### Protective Effect of Ulvan (Sulfated Polysaccharide) Pretreatment against Hepatic Ischemia-Reperfusion Injury in Mice

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**Aims:** Ulvan is a complex of sulfated polysaccharides derived from marine green seaweeds. One of marine green algae is codium fragile (CF). Ulvan demonstrated antioxidant as well as potential anti-inflammatory properties in previous studies. Ischemia-reperfusion injury (IRI) is a major critical event that commonly occurs after liver transplantation and resection. Reactive oxygen species –mediated release of related inflammatory factors have important roles in hepatic IRI. In this study, we investigated whether CF extract protects against IRI-induced acute liver injury in mice.

**Methods:** Partial (70%) hepatic IRI was induced in male C57BL/6 mice by portal triad pedicle occlusion for 45 min followed by reperfusion for 6 h. CF extract (500 mg/kg body weight [BW], oral) was administered 5 days before the IRI.

**Results:** Treatment with CF extract significantly decreased serum alanine aminotransferase (sALT), serum aspartate aminotransferase (sAST) and serum lactate dehydrogenase (LDH) as well as liver histological changes. CF extract also prevented hepatic glutathione (GSH) depletion, increased malondialdehyde (MDA) and HO-1 levels induced by IRI. Western blotting indicated that the expression of the ERK, C-JUN, and iNOS were significantly decreased in the CF extract treatment group after IRI.

**Conclusions:** CF improved the acute hepatic IRI by reducing oxidative damage, and inflammation. These findings suggest that CF is a promising agent against acute IR-induced hepatic damage.

#### PE-333

# Origin Variability of Hepatic Arteries by the Dissecting Results

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**Aims:** The results of modern anatomical studies of the human blood circulatory system continue to confirm classical works on the standard anatomy and variability of the human body. The study of variant anatomy of the hepatic arteries remains relevant, their new forms are being discovered, the presence of which is of great importance in hepatobiliary surgery. Study the anatomical variants of the hepatic arteries.

**Methods:** The material of his own anatomical study was 48 organ complexes of a man obtained from the university long-term storage of natural preparations. The classical anatomical method of investigation – preparation was applied.

**Results:** While investigating we revealed the following variations in the blood supply of the liver: divergence of the Left hepatic artery from the left gastric; origin of the Right hepatic artery from the abdominal part of the aorta; the Cystic artery was a branch of Proper hepatic artery; combined form: double Proper hepatic artery + double Left hepatic + double Cystic artery and other isolated variations.

**Conclusions:** Russian surgeon N. Pirogov proved the necessity of irreproachable possession of the sum of anatomical knowledge for all doctors without exception. Our research confirms and supplements available information about a rather wide range of variability of the hepatic arteries in humans for anatomical and surgical sciences. In clinical practice deviations from classical anatomy complicate diagnosis, lead to medical errors in operative and endovascular interventions which forces surgeons to always creative and not routine treatment of patients. **Keywords:** Hepatic artery, Variation

#### PE-334

# Subhepatic (Abnormal) Position of the Vermiform Appendix with Adhesion: A Case Report

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**Introduction:** The vermiform appendix is the most variable abdominal organ in terms of position, extent, peritoneal and organ relations. The location of appendix is important when it comes to clinical presentation of a patient with appendicitis.

**Case Report:** During regular dissection classes of first year medical undergraduates, variation in the position of appendix with adhesion were noted in a male cadaver aged approximately 50-55 years. Subhepetic position of appendix might congest the subhepetic region and minimize the intestinal movements. The knowledge of this type of variations may be useful for the radiologist and surgeons.



DAY 1: Thursday, June 14, 2018 (09:00-10:10) WEST TOWER / ROOM C [B1]

# **Publication Forum**

# How to Publish Good Papers (\*K)

Chairs: So Young Kwon (Konkuk Univ.) Jin-Wook Kim (Seoul National Univ.)

### Tips for Writing Papers and Good Cover Letters: How to Do It

#### Hyun Woong Lee

Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, South Korea

## 논문 잘 쓰는 방법을 위한 팁

이현웅

연세대학교 강남세브란스병원 소화기내과

Medical doctors often have to write articles for publication in academic journal. Most doctors appeal to these difficulties and suffer from language barrier. The first tip to overcome these problems is to **just write** articles without hesitation. Second tip is to have good research questions. After developing a **good research question**, authors need to consider whether it can be answered through the existing published literature or whether new data must be collected. Third tip is to make an **original work** that generates new insights and does not duplicate previous research, which can be determined through a literature review.

In part of the structure, precise, accurate and clear writing is essential for communicating in medical science. The title of the article is an important part of manuscript as it is the most often read and will induce the interested readers to read further. The abstract is attractive and contains information needed to decide whether to read the full report. Results show data as tables and figures whenever possible, avoid duplication in the text. The text should summarize the findings. Discussion provides an interpretation of author's results and shows how they logically fit in an overall scheme. Conclusion briefly summarizes the main results of author's study in one or two paragraphs, and how they support author's hypothesis.

#### 1. Just Write

모든 것을 두려워하지 말고 일단 쓰기부터 시작하라는 것이다. 가능한 바로 영문으로 작성하면 좋겠지만, 영 어에 울렁증이 있다면 영어와 한글을 혼용해서라도 작성하는 것이 좋다. 중요한 점은 초안이 있어야 그 다음을 시작할 수 있기 때문이다. 그러나 막상 시작하려고 하면, 머리 속이 하얗게 변하면서 어떻게 시작할 지 두려움이 앞선다. 그러한 이유는 우리가 읽고, 보고 있는 논문은 항상 완벽하게 구성되어 있기 때문이다. 하지만, 논문을 시작할 때 대부분의 저자는 방법과 결과만 있을 뿐 introduction, discussion에 대한 구체적인 계획이 없기 마 련이다. 여기에 논문의 첫 장인 제목과 초록을 생각하면 시작할 엄두조차 나지 않는데 이는 생각과 논리가 정리 가 되지 않은 상태에서 제목과 초록을 먼저 쓰려고 하기 때문이다.

#### 2. Methods and Results

논문을 처음 시작하는 저자들에게 논문 쓸 엄두가 나지 않을 때는 일단, 방법과 결과를 먼저 정리하라고 권하 고 싶다. 논문에 따라 그 형식이 많이 다르지만, 의학에서 주로 사용되는 것은 임상논문과 실험논문이다. 물론, 메타분석이나 빅데이터 처리는 더욱 복잡한 과정을 거치기 때문에 이번에는 배제하였다. 방법을 기술할 때 주 로 대상과 모집기준을 기술한다. 특히 임상연구는 대상 선정에 있어서 어떻게 연구가 계획 되었는 지를 기술해 야 한다. 즉 대상의 참여기준과 배제기준을 정확히 기술하여야 한다. 두 번째로, 참여와 배제 및 대상에게 가해 지는 조치들이 윤리적으로 문제가 없는지 기술하는 것도 잊지 말아야 한다. 최근에는 후향적 연구 및 단순한 임 상연구에도 대부분의 기관에서 IRB승인을 받도록 권고하고 있기 때문에, 연구 시작 전부터 이미 준비되어 있을 가 능성이 높다. 이외에도 실험의 경우, 동물을 대상으로 한 것인지 병원체 또는 미생물을 대상으로 한 것인지 기술하 며, 검체를 어떠한 용량과, 농도로 측정하며, 측정에 필요한 도구들이 무엇인지 표준화된 명명으로 자세히 기술한 다.<sup>1</sup> 마지막으로 통계적인 방법에 대해서 기술해야 한다. 결과의 수치들이 어떻게 분석되었는지, 범주형 변수인지, 연속형 변수인지, 시간의 개념이 포함되어 있는지 등을 고려한다. 특히, 저자의 귀무가설을 반증하기 위해 p-value 는 어떻게 정의하였는지, 이를 적용하기 위한 통계처리 방법은 어떤 것을 이용하였는지 기술하여야 한다.

결과란 저자가 제기한 질문에 대한 해답을 제공하는 부분이다.<sup>2</sup> 즉, 저자가 처음부터 기대했던 것, 우연히 발 견되는 새로운 현상, 이외에도 기대하지 못한 결과 및 예상치 못한 것 들을 기술한다. 그러나 기술할 때는 각각 에 대해 설명이나 반박을 할 수 있어야 한다. 결과를 표현할 때는 가능한 표와 그림으로 설명하고 글로는 중요 한 내용을 간략하게 기술하는 것이 좋다. 그러나, 너무 지나치게 많은 행과 열로 방대한 자료를 다 보여주는 것 은 역효과가 나타나므로 주의를 기울여야 한다. 독자의 입장에서 생각해 보면, 대부분 초록과 결론을 읽어보고 방법과 결과에 대한 기술 보다는 표와 그림을 보고 이 논문이 무엇을 말하고 있는지 예측하게 된다. 논문의 일 차 목적과 결론을 설명할 때, 표현된 표와 그림으로 다 설명할 수 있다면 성공적인 논문이다. 따라서, 항상 논문 을 쓸 때 독자의 입장으로 생각해야 한다. 주의할 점은 표에 요약되어 있는 내용을 그림에 다시 중복 설명하는 오류는 피해야 하며, 특히 결과에 대한 논평은 기술하지 않아야 한다. 또한, 결과를 해석할 때는 과대 해석을 경 계해야 한다. 평균값이 높은 경향을 보인 것을 통계적으로 우월하다고 표현하거나, 하나의 현상을 마치 일반화 시키는 것을 주의해야 한다.

#### 3. Introduction

연구의 결과가 처음 연구를 통하여 얻고자 했던 것과 일치할 수도 있고, 일치하지 않을 수도 있다. 물론, 임 상 또는 실험도중 궁금증이 먼저 생기고 그에 대한 정답을 찾으려는 노력이 연구로 수행되는 것이 가장 바람직 하다.<sup>2</sup> 즉 introduction을 먼저 구성하고 연구를 수행하는 것이 가장 좋다. Introduction의 시작은, 첫째 '현 **재 우리가 알고 있는 것은 무엇인가**?'를 기술하는 것이다. 우리가 논문을 읽을 때 그 분야에 대한 지식이 없을 경우에는 introduction을 보고 최근 연구의 흐름이나 중요한 점을 파악한다. 따라서, 초심자에게 최근 좋은 연 구에 대해 한 줄씩 간단히 요약하며 알려주는 것처럼 소개해 주는 것이 바람직하다. 물론 연구의 목적과 관련이 있는 논문을 인용해야 함은 두 말할 여지가 없다. 왜냐하면, 교과서의 introduction이 아니라, 저자는 논문의 introduction을 쓰고 있으며, introduction의 목적은 독자가 읽고 싶은 마음이 들도록 유혹하기 위함이기 때문 이다. 임상에서는 대부분 질화에 대한 가이드라인이 많이 알려져 있다. 그 가이드라인에는 항상 마지막이나. 첫 부분에 이 가이드라인의 한계점이나 모르는 점에 대해 기술해 놓고 있다. 이를 힌트로 하여 둘째 '우리가 모르는 것이나 논란이 되는 점은 무엇인가?'를 기술한다. 이러한 기술을 할 때는 과거 논문에 대한 단순한 나열을 피하 고 비판적 시각으로 기술한다. 그러나, 타인의 논문을 비판할 때는 가능한 완곡한 표현을 사용하여야 한다. 간 혹 단정적 표현으로 비판할 경우, 저자의 논문을 매력적으로 보이기 위한 표현으로 오인되어 리뷰어에게 신뢰를 잃게 되기 때문이다.<sup>3</sup> 마지막으로 이러한 문제점이나 한계에 근거하여, 저자는 이 논문을 통해 **'새롭게 알고 싶 은 것이 무엇인지'** 기술한다. 즉, 시작은 보편적인 이론과 큰 문제제기부터 시작해서 저자의 연구영역까지 점진 적으로 집중하는 방법이다. 이와 같은 순서로 기술하면 가장 완벽한 introduction이다. 그러나 초심자들은 이 처럼 연구를 진행하기 어렵기 때문에 결과를 분석한 뒤에 위와 같은 삼단계의 논법으로 연결고리를 찾아가는 것 도 또 하나의 방법이다. 숙련된 연구자에 있어서는 현재까지의 연구결과를 논문 검색하여, 마치 메타분석하듯이 저자의 궁금증을 모두 검색한 뒤, 가설을 설정하고, 위와 같은 삼단 논법에 따라 연구를 진행해 나가는데 이는 가장 오류와 편견을 없앨 수 있는 방법이다.

가장 중요한 목표는 '새롭게 알고 싶은 것'인데 이미 알려져 있는 것에 대한 반복 연구는 피하는 것이 좋다. 결

과를 살펴보고 introduction을 쓸 경우 이와 같은 오류를 쉽게 접하게 된다. 따라서, 선행 연구에 대한 분석이 먼저 확실히 되어야 동일한 결과의 반복을 예방할 수 있다. 기술은 주로 간결하고 명확하게 연구목표와 관련된 것만 요약한다. 이전 연구 중 신뢰도가 높은 학술지의 논문을 인용하여 최신 연구의 문제점이나 해결하지 못한 점을 언급한 후 저자가 추가로 얻고자 하는 결과가 무엇인지 그리고 가설이 무엇인지 과장하지말고 단순하고 논리적으로 표현한다. 연구 결과가 의미없이 나왔더라도 가설이 논리적으로 타당하다면, 부정적인 결과도 의미 가 있는 논문이 될 수 있기 때문이다.

#### 4. Discussion and Conclusion

이번 연구에 가장 중요한 결과가 어떻게 나왔는지를 가능한 먼저 기술한다. 저자의 목표와 결과가 discussion 중간에 나오면 독자들이 혼돈을 일으키는 경우가 많다. 따라서, 처음과 마지막 결론 부분에 가장 중요한 결과를 기술한다. 물론 표현을 달리해서 앞부분은 기술적 표현으로, 결론 부분은 결과의 의미를 재해석하여 기술한다. 중간 부분에는 이러한 결과를 예상했거나, 지지하는 논문들을 인용하여 연구의 논리적 타당성을 보여준다. 덧붙 여, 잊지 말아야 할 것은 저자와 다른 의견을 가진 논문이나 자료도 기술하여야 한다. 이를 토대로 다음에 어떠 한 연구가 더욱 필요한지 기술할 수 있다. 추가연구에 대한 기술을 결론 부분에 작성하게 되면 이번 연구의 장점 과 강점을 희석시키는 부작용을 가지고 있어서, 가능한 discussion 중간이나, 연구의 한계점을 기술할 때 작성 한다. 첫 번째 중요한 결과에 대한 토의가 끝나면, 두 번째, 세 번째로 의미가 있는 것들을 기술한다. 동일한 논 리 구성으로 논문을 인용하고 분석하여 작성해 나간다. 이처럼 논리를 전개하다 보면, 이 연구의 한계점이 무엇 인지 알 수 있다. 따라서 마지막에는 이 연구의 한계점을 꼼꼼히 기술한다. 종종 연구의 약점을 기술하지 않고 숨기는 경우가 있지만, 대부분 리뷰어에게 장문의 지적을 받고 수정하게 된다. 따라서 미리 기술하면, 수정해야 하는 수고를 덜 수 있다. 마지막 문단의 결론은 이 연구의 일차 목표에 타당한 결과가 나왔는지, 아니면 의미가 없었는지 짧고, 간결히 기술한다. 다시 한번 첨언하자면, '앞으로 이런 저런 연구가 필요하다'라는 표현은 결론 보다는 한계에 기술하고 결론 부분은 건조하고 객관적인 기술을 하는 것이 도움이 될 것이다.

#### 5. Abstract

가장 어렵고도 중요한 것이 초록이다. 모든 연구자들이 많은 논문을 읽을 수 없기 때문에 항상 초록을 보고 본문을 읽을 것인지 말 것인지를 결정한다. 따라서 초록을 쓰는 것은 가장 힘든 과정이다. 역시 중요한 것은 현재 이 분야에서 해결되지 않는 부분이 무엇이며, 왜 저자가 이 연구를 시작했는지 이유와 목표를 1-2 문장으로 기술한다. 그 외의 연구 배경은 가능한 introduction에 기록한다. 연구방법 또한 이 연구의 일차 목표를 달성하기 위해 꼭 필요한, 대상군 모집방법 및 검사기법, 어떤 변수를 파악했는지를 간략히 기술한다. 결과는 일차 목표를 기술하며, 이에 영향을 준 인자들에 대해 명확한 통계 수치로 기록한다. 결론에는 이 연구를 통해 무엇을 발견하였는지 그리고 의미가 무엇인지 1-2문장으로 기술한다. 불필요한 세부사항을 기록하기 보다는 글자 수가 남더라도 간결하고 명확하게 작성한다.<sup>4</sup> 전부 작성하게 되면 방법과 결과를 제외하고 초록의 목적과 마지막 결론만 다시 한번 읽어 본다. 두 부분이 바로 연결되지 않고 상이한 느낌이 드는 경우에는 초록을 잘못 작성한 경우이다. 마치 시의 댓구처럼 목적과 결론이 하나의 문장으로 자연스럽게 연결되어야 한다. 독자들 중 초록의 목적과 결론을 먼저 읽고 난 후 방법과 결과를 보는 경향이 많기 때문이다.

#### 6. Title

초록이 완성되면 연구의 의미를 간단, 명료, 함축적으로 표현할 수 있는 제목을 선택한다. 모호한 '연관성', '관계', '중요성' 이런 표현 보다는 연구의 일차 목표를 요약하여 명료하게 표현함이 좋다. 과도한 형용사나 명사의 나열은 피해야 한다.

# 7. Cover Letters

대부분의 논문은 학술지의 편집장에게 전달된다. 편집장이 주로 읽고 평가하는 부분은 바로 초록과 cover letter일 가능성이 무척 높다. 대부분의 편집장은 자신들의 학술지에 실린 논문이 타 학술지에 많이 인용될 가능 성이 있는지, 학술지의 목적에 부합하는 지에 따라 논문을 선택한다. Cover letter는 저자의 논문을 편집장에게 간략히 소개하는 편지라는 사실을 잊지 말자. 따라서, 논문의 강점을 편집장의 관점에 맞게 강조해야 한다. 저자 의 논문이 독창적이며, 학술지의 목적에 어떤 점이 부합하는지 또는 왜 이 학술지를 선택했는지 이유를 기술한 다.<sup>5</sup> 또한 이 연구가 중요한 이유를 적극적으로 기술하는 것이 이득이 된다. 추가적으로 저자들 모두가 논문을 읽고 투고에 동의했으며 이해 상충이 없고, 다른 논문에 기고하지 않았음을 기술한다. Cover letter는 저자의 논 문을 읽어주십사 부탁하는 메일이므로 정중한 표현을 사용하며, 학술지의 요구사항에 충실히 따랐음을 기술한 다. 마지막으로 학회지에 꼭 게재되기를 소망한다는 표현과, 감사의 인사로 마무리한다.

요약하면, 먼저 영어 울렁증이 있다고 해서 논문 쓰는데 '겁먹지 마라'고 이야기 하고 싶다. 최근에는 좋은 번 역기들이 있어서, 한글 표현으로만 잘 써도 꽤 훌륭한 영문으로 번역되어 나온다. 다시 말해서, 논문 영어는 우 리가 신문이나, 소설에서 보는 문장과 달리 간결하고 명료하다. 특히 추상적인 표현을 쓰는 논문은 아무리 영어 가 모국어인 저자의 논문이라도 좋은 논문일 가능성이 떨어진다. 따라서, 영어에 자신이 없더라도 간결하고 명 료한 문장으로 짧게 짧게 서술해 나가는 연습을 하면 가능하다. 좋은 논문의 팁은 첫째도, 둘째도 '일단 써야 한 다'이다. 물론 많은 영어 논문을 읽으며 학술 논문에서 주로 쓰이는 문장과 단어에 익숙해진다면, 영문에도 품격 을 지닌 저자가 될 가능성이 높다.

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**Publication Forum** 

# Tips for Responding to Reviewer Comments

#### **Grace Lai-Hung Wong**

Institute of Digestive Disease, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

Writing research papers is an indispensable part of the academic life of a researcher. All peer-reviewed journals send out the papers to several, typically 2 to 6, reviewers for their critical comments. The editors will then make a decision of accepting it, rejecting it, and most often allowing revision (minor or major) based on the reviewers' comments. Getting a chance to revise a research paper is wonderful, just that there is often not guarantee that the journal must accept the paper after revision. Again, this final decision depends heavily on whether the reviewers are satisfied by the authors' responses to their comments. In this talk some practical tips about the review process, how to digest the reviews, revise the paper and finally communicate the revisions to the reviewers and editors will be discussed.

# Things Authors Should Know: Editor's Viewpoint

#### Yoon Jun Kim

Clinical and Molecular Hepatology, Seoul National University, Seoul, Korea

The process of scientific research is only useful if novel and robust results can be communicated to others such that the stock of human knowledge increases. Consequently, publication must be seen as a central part, if not the central part, of the research process. However, authors' interests can be distinct from those of readers, peer reviewers, editors, and publishers. Some authors are well coached by their mentors, while others are not. Then, what are essential lessons authors should know? In this lecture, some advices on the issue of writing scientific papers in the biomedical arena for authors from editor will be discussed.

The Liver Week 2018

DAY 1: Thursday, June 14, 2018 (10:30-12:10) WEST TOWER / ROOM C [B1]

# Academic Forum

# How to Win Research Grants (\*K)

**Chairs :** Kyun-Hwan Kim (Konkuk Univ.), Yong Han Paik (Sungkyunkwan Univ.)

### Lecture 1: How to Win Research Grants

#### Goo Taeg Oh

Department of Life Sciences, Ewha Womans University, Seoul, South Korea

2018년도 정부 R&D 예산은 전년 대비 1.1% (2,066억원)가 증가한 19조 6,681억원으로 확정되었다. 정부예 산의 총지출이 428.8조원으로 전년 대비 7.1% 증가한 것과 비교하여 R&D부문의 증가율은 상대적으로 낮은 수준이다. 총지출의 12대 분야 중 9개 분야가 증가하였고, 3개 분야가 전년 대비 예산이 감소하였는데, R&D는 증가된 9개 분야 중에서 농림·수산·식품(0.5%) 다음으로 증가률이 낮다. 이는 우리경제의 전반적인 성장률 둔 화와 높은 청년 실험의 지속, 그리고 복지수요의 증대 등으로 인하여 R&D투자의 양적확대가 한계에 도달한 재 정여건을 고려한 결과이다. 2018년도 정부 R&D 예산의 부처별 현황을 살펴보면, 과학기술정보통신부가 6조 7,357억원으로 가장 많은 예산이 편성되었는데 이는 전체 R&D 예산의 34.2%에 이른다. 다음으로 산업통상자 원부(3조 1,623억원, 16.1%), 방위산업청(2조 9,017억원, 14.8%), 교육부(1조 7,488억원, 8.9%), 중소벤처기업 부(1조 917억원, 5.6%) 순으로 나타났으며, 이들 5개 부처의 예산은 전체 R&D 예산의 79.6%를 차지한다. 대부 분 부처의 예산이 전년 대비 소폭 증가한 반면, 중소벤처기업부(△256억원, △2.3%), 산업통상자원부(△434억 원, △1.4%), 환경부(△15억원, △0.5%), 과학기술정보통신부(△128억원, △0.2%) 등은 소폭 감소하였다.

2019년도 생명보건의료분야 정부의 투자방향은 생명보건의료분야 바이오산업 및 의료서비스의 경쟁력 강화 를 위해 신개념 바이오융합 R&D 및 바이오의료 빅데이터 연계활용 기반을 강화하고 안전·건강 증진 등 공공수 요 R&D를 지원하여 미래 국민생활문제에 선제적 대응하는 것을 주요 골자로 하고 있다. 생명보건의료분야는 신약, 의료기기, 뇌과학, 유전체, 줄기세포, 바이오융복합, 임상보건 등 총 7개의 중분류로 구성되어있으며, 각 중분류별 투자방향은 다음과 같다.

#### ☞ 신약

혁신신약 개발을 위한 초기단계 투자와 유망 신기술 개발, 공익적 R&D투자는 강화하되, 민간 투자가 활성화된 분야는 직접지원 지양할 필요가 있다. 가령, 혁신신약 개발을 위한 신규 타겟(novel target) 발굴·검증 및 초기 파 이프라인을 강화하고, 신약개발 관련 공공수요 R&D 지원 확대하되, 복제약 개발, 임상3상 등의 지원은 지양하 는 것이 바람직하다.

#### ☞ 의료기기

의료·산업현장 수요에 따른 임상·실용화 R&D지원은 지속하고, 신개념 융합·맞춤형 의료기기 원천기술 개발 은 강화할 필요가 있다. 또한, 의료기기 시장의 영세성을 감안, 의료·산업현장 수요기반 중소기업 R&D지원은 지속하고, 취약계층 복지 증진 등을 위한 ICT 융복합 헬스케어기기 개발 등의 지원 강화할 예정이다.

#### ☞ 뇌과학

파급효과가 큰 뇌공학 실용화 및 뇌질환 연구는 지속 지원하고, 4차 산업혁명의 기반이 되는 뇌과학 기초 원 천 연구는 지원을 확대할 계획이다. 예를 들어, 뇌구조·기능 및 작동원리를 밝히는 기초 원천 등의 연구 지원을

Academic Forum

확대하고 인지기능 강화, 신체 복원 및 재활 등에 높은 파급효과가 예상되는 뇌공학 실용화 연계형 기술을 지원 할 예정이다.

#### ☞ 유전체

다중오믹스 통합·분석 기술 등 유전체 핵심 원천기술 및 임상 유전체 기반 실용화 연계 R&D 중심의 투자가 필요하다. 이를 위해 유전체·전사체·단백질체 등 다중오믹스 기초 원천 연구, 단일세포 유전체 해독·분석 등 미 래수요 대비 유망 핵심 원천기술 개발을 지원하고 유전체 기반 바이오마커발굴, 유전자 제어 기술 등 생체정보 기반 실용화 연계 R&D 투자를 강화할 예정이다.

#### ☞ 줄기세포

기초 원천 R&D 및 줄기세포를 활용한 실용화 연계 R&D 중심으로 지원할 계획이다. 줄기세포 기전·조절·분화 등 기초 원천 연구 지원을 지속하여 재생의료 및 차세대 줄기세포 치료제 개발의 토대를 마련하고 줄기세포를 활용 한 체외질환모델 개발, 생체조직공학 연구 등 타 분야와의 접목을 통한 융복합 원천연구 지원을 강화할 예정이 다.

#### ☞ 바이오융복합

바이오메디컬,바이오·나노·ICT 융복합 R&D, 빅데이터 기반 정밀의료 및 신개념 산업 바이오 기초 원천 연구의 지원을 강화 할 예정이다. 초미세·정밀 진단-치료, 생체·임상·생활 빅데이터 활용 기술개발 등 바이오메디컬 관련 융복합 R&D 투자 를 확대하고 질병 진단·치료 관련 마이크로바이옴 연구 에너지·화학·친환경 관련 합성생물학 연구 등 신개념 기초 원천 연구 투자를 강화하려 한다.

#### ☞ 임상보건

공공적 수요에 대응하는 의료기술·임상연구 및 대학-병원 협력을 지원하고, 보건의료 재난 대응 감염병 R&D 투자를 지속할 필요가 있다. 만성·난치질환, 정신질환에 대한 기초 및 임상연구와 저출산·고령화 극복을 위한 연구개 발 등 국민 체감형 공공적 연구 지원도 확대되어야 한다.

# Lecture 2: Collaborative Research for Clinical Unmet Needs

#### **Don Haeng Lee**

Division of Gastroenterology, Department of Internal Medicine, Inha University School of Medicine, Incheon, South Korea

최근 정부과제의 동향은 연구자 수요보다는 의료현장의 수요를 충족하기 위한 제품을 개발하기 위한 과제가 증가되고 있다. 따라서 필요한 컨소시엄 구성이 과제마다 상이하기 때문에 임상의사의 참여가 반드시 요구되는 과제에서 임상의사의 강점을 부각시킬 수 있는 전략이 필요하다. 실제로 과제 지원 시 중요한 평가요소는 연구과제의 창의성, 연구내용 및 추진체계의 우수 성, 연구책임자의 우수성, 기대 및 파급효과 등이다. 이러한 평가요소들 중 임상적 필요성을 개발 초기단계부터 임상의사들의 참여로 제품의 임상적 유용성을 극대화하는 것이 임상의사들의 중요한 역할이라 판단된다.

임상의들의 미충족수요를 해결하기 위해서는 공학자, 약학자 또는 기초의학자 등과의 협력이 필수적이다. 이를 위해서는 임 상의들이 융합연구에 대한 적극적인 자세가 필요한데 연구하고자 하는 분야의 전문가를 찾아보고 초청하여 강의를 듣고 실제 임상현장에서의 개발이 필요한 부분을 설명하고 관련된 국가과제에 같이 지원하는 것 등이 실질적인 방법 중의 하나라고 생각 한다.

임상의는 공학을 모르고 공학자는 임상적 의의를 모르는 경우가 많기 때문에 병원에 초청하여 실제 현장에서의 필요성을 설명 하는 것이 중요하다. 예를 들면 내시경과 관련된 연구개발을 하는데 공학자들이 내시경을 이해하지 못하면 개발이 실패할 가 능성이 높기 때문에 실제 내시경시술 장면을 보게 되면 개발 타겟을 확실히 알게 되므로 성공가능성을 높일 수 있다. 이러한 융합연구에 있어 열린 마음으로 서로 신뢰하는 자세가 연구 못지않게 중요하다.

Keywords: 임상현장의 수요, 융합과제, 상용화

## Lecture 3: How to Win Research Grants

#### Kwang-Lae Hoe

Chungnam National University, South Korea

# 정부 R&D 시스템의 이해 및 바이오

허광래

충남대학교 의과대학

국가의 연구 전략 및 정책을 이해하는 것은 각자의 연구비를 확보하여 원할한 연구를 수행하는데 중요하다. 우리나라의 대부 분의 연구비는 국책연구비 이므로 국가 R&D 시스템을 이해하는 것은 연구자의 연구비 안정화에도 중요한 부분을 차지한다. 하지만 대부분의 연구자가 기초와 국책의 정의에서부터 이해도가 부족하며, 국가 연구비가 어떠한 과정으로 진행되는지 모르 고 있는 실정이다. 그러므로 국가 연구비에서 바이오가 차지하는 비중과 연구내용을 파악하는 것도 본인의 연구방향 설정에 중요한 부분이 될 수 있다.

국가 R&D 시스템의 경우 등장인물이 많으며 각자의 역할도 복잡하며, 각 정부 부처의 역할이 이중 삼중으로 레이어를 이루고 있으므로, 어떠한 과정으로 연구비 배정 전략과 정책이 작용하는지 이해하는 것이 필요하다. 특히 연구자들이 알 수 없는 많은 법과 계획 및 민간위원회가 존재하고 있다는 것을 이해하는 것이 중요하다.

본 세미나를 통하여 연구자가 국가의 연구비 정책을 좀 더 잘 이해하는 것은 본인의 연구비 확보에도 중요하지만 국가가 연구 정책을 세울 때 올바른 현장의 목소리를 내는 것에도 중요하다. **Academic Forum** 

# Lecture 4: How to Win Research Grants

#### Soon Koo Baik

Yonsei Univ. Wonju

The Liver Week 2018

DAY 2: Friday, June 15, 2018 (08:30-09:50) WEST TOWER / ROOM AB [B1]

# Symposium 1

# **Recent Updates in Chronic Hepatitis C**

Chairs: Youn Jae Lee (Inje Univ.) Sook-Hyang Jeong (Seoul National Univ.)

## How to Eliminate Hepatitis C Virus by 2030

#### **Do Young Kim**

Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

Hepatitis C virus (HCV) infection poses a significant global healthcare burden, accounting for the first or second cause of cirrhosis and hepatocellular carcinoma (HCC). The HCV diagnosis rate and treatment uptake rate are still low in worldwide. Access to HCV treatment is improving, but remains limited. According to World Health Organization (WHO) report in 2015, among the 71 million living with HCV infection globally, 20% knew their diagnosis, 7% of those diagnosed were started on treatment, and half of those started on treatment received direct acting antiviral (DAA). It was reported that only 6% of Korean patients infected with HCV were treated in 2016.

HCV elimination is considered to be a reduction in HCV incidence and HCV-related mortality to a level that are no longer a public health concern. WHO targets HCV elimination by 2030; reduction of new HCV infections from 1.5 million in 2016 to 0.1 million by 2030, and HCV-related deaths from 0.4 million in 2016 to 0.1 million by 2030. In line with this WHO's target, in Korean Association for the Study of Liver Diseases (KASL) Project Report for Korean Center for Disease Control & Prevention (KCDC), the target of HCV treatment rate was set as 70% in 2020 and 90% in 2025.

There are several opportunities and challenges to achieve HCV elimination by 2030 in Korea. First of all, the Korean governmental reimbursement system is covering most of patients with HCV infection, which is an opportunity. The second opportunity is that Korean government is supporting the medical cost partially and additionally, according to each patient's income level. The purpose of this system is in order to minimize the number of neglected patients from the medical service, by reducing the economical burden of patients. If yearly direct medical cost paid by patients exceeds the maximum, the Korean government pay the extra-charge back to the patient. The third opportunity is that mandatory surveillance system for HCV infection by KCDC is working since HCV was officially designated as a disease at the middle of 2017. The last opportunity is that regular national health check-up is being supported for citizens for who are 40 or 66 years old bi-annually. On the other hand, the challenge is that HCV serological test is not yet included in the national health medical examination for all the employees in Korea. Most of the Korean hepatologists think the HCV serological test should be included in the national health medical examination system. For nephrologists and general practitioners in Korea, HCV treatment and diagnosis are not well known. Thus, internal transfer system to hepatologists exits, however, not institutionalized as cascade of care in most of hospitals. Therefore, the necessity of HCV treatment is not well-recognized for nephrologist, as well as general practitioners. In this presentation, a strategy for elimination of HCV infection by 2030 will be presented.

# Upcoming Direct-Acting Antivirals for Prior Treatment Failure

#### Alessio Aghemo

Humanitas University; Humanitas Research Hospital, Rozzano, Italy

Treatment of hepatitis C virus infection (HCV) with directly acting antivirals (DAAs) can achieve sustained virological response (SVR) rates of nearly 97-98% in real life cohorts. Treatment failure although rare can be challenging from a therapeutical point of view as most patients who will fail DAA treatment are characterized by advanced liver disease and thus are the most in need patients. Treatment failure can rarely be the direct consequence of suboptimal DAA treatment (incorrect genotyping, suboptimal schedules or poor adherence), however in most cases treatment failure to DAAs is the consequence of pre-existing Resistance Associated Substitutions (RASs) in the patient's HCV guasispecies. High level RASs defined by an increase in the DAA EC 50 of more than 100 fold, impact on the activity of DAAs in the clinical setting and can significantly reduce SVR rates in the presence of other factors of non-response such as HCV genotype 1a or 3, presence of advanced fibrosis or high baseline viral load. Treatment failure is associated with selection of RASs to the DAA class that was given as first line treatment. While RASs selected after failure of a Protease inhibitor have been shown to revert to wild type within 1-2 years, and RASs to NS5B polymerase inhibitors very rarely occur, RASs to NS5A containing regimens have been shown to persist for at least 2 years following treatment failure. For this reason, most scientific guidelines suggest to perform RAS testing before starting re-treatment to guide treatment selection. This approach clashes with the fact that only 1 regimen is approved for the re-treatment of DAA failures, the combination of Sofobuvir/Velpatasvir/Voxilaprevir. This single tablet regimen has been evaluated in a large Phase III program, which studied 12 weeks of treatment in patients who failed a previous DAA regimen. Included were both patients who failed an NS5a containing regimen (Polaris 1) and those who failed a regimen which did not include an NS5A (Polaris 4). Overall the SVR rates were 96% and 97% respectively, with no significant safety signals. The main limit of this regimen is that Sofosbuvir is metabolized by the kidney, making it not recommended in patients with CKD stage 4-5, and Voxilaprevir is metabolized by the liver making it contraindicated and unsafe in patients with decompensated disease. In patients with decompensated liver diseases the current recommendation for the re-treatment of DAA failures is the combination of Sofosbuvir/Velapatasvir plus Ribavirin for 24 weeks.

## Management in Special Populations: Decompensated Cirrhosis, Chronic Kidney Disease, and Post-Transplantation

#### Woo Jin Chung

Department of Internal Medicine, School of Medicine, Keimyung University, Daegu, South Korea

Liver cirrhotic patients by chronic hepatitis C (CHC) infection have an increased risk of developing severe liver-related complications. CHC patient who is diagnosed with compensated cirrhosis should be considered at a high priority for hepatitis C treatment. For CHC patients with decompensated cirrhosis or HCC, treatment of CHC may provide benefit, but the treatment plans and goals may need modifying if the patient has a plan to undergo liver transplantation.

#### I. Decompensated Cirrhosis

#### <Treatment of CHC Patients with Decompensated Cirrhosis>

The treatment goal for patients with decompensated cirrhosis differs based on whether the patient is a candidate for liver transplantation. The short-term goal of therapy is to achieve an SVR for patients who are not candidates for transplantation, with the hope that liver fibrosis will reverse as a result of therapy and the patient could be stabilized or improved their clinical condition. Pre-transplantation treatment of hepatitis C virus (HCV) should be a part of plan to prevent reinfection of the new liver with HCV and thus improve post-transplantation outcomes.

Ledipasvir/Sofosbuvir: The use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, for 12 weeks in 235 genotype 1-infected patients. The SVR rates were similar in participants receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% and 81%, respectively). MELD scores improved in 42% of treated patients and worsened in 11%.

**Sofosbuvir/Velpatasvir:** Among 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%), 10% of patients were CTP class A or class C at treatment baseline. The SVR rates were 83% among those in the 12-week sofosbuvir/velpatasvir group, 94% in the 12-week sofosbuvir/velpatasvir plus ribavirin group, and 86% in the 24-week sofosbuvir/velpatasvir group. Among genotype 1 patients, SVR rates were 88%, 96%, and 92%, respectively. At week 12 after treatment, 47% of patients had improved in CTP score, and 11% had an increased CTP score.

**Daclatasvir** + **Sofosbuvir**: After 12 weeks of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin use among patients with cirrhosis (CTP class A, B, or C; n=60) or HCV recurrence after liver transplantation (n=53), SVR12 rates were 83% (50/60) among those in the cirrhosis group and 94% (50/53) among those with recurrent HCV infection post liver transplant. In the population with cirrhosis, SVR12 rates were 82% (37/45) genotype 1, 80% (4/5) genotype 2. Response rates differed based on severity of cirrhosis.

#### **Protease-Inhibitor Containing Regimens**

After 12 weeks of elbasvir/grazoprevir use in 30 genotype 1-infected patients with CTP class B cirrhosis. The SVR12 rate was 90% (27/30). 1 patient died of liver failure at post-treatment week 4 and 2 patients relapsed. MELD scores improved in 15 treated patients and increased in 6. There are no safety or efficacy data regarding the US FDA-approved elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Paritaprevir/ritonavir/ ombitasvir  $\pm$  dasabuvir is contraindicated in patients with decompensated cirrhosis due to concerns about hepatotoxicity. All patients with compensated cirrhosis receiving this regimen should be monitored for signs and symptoms of hepatic decompensation. The glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has not been studied in patients with decompensated cirrhosis. The sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) also has not been studied in patients with decompensated cirrhosis.

#### II. Chronic Kidney Disease

#### <Treatment of CHC Patients with Chronic Renal Disease>

Limited data exist regarding the use of newer direct-acting antiviral agents in patients with severe renal impairment, including those on hemodialysis.

**Elbasvir/Grazoprevir:** After use of 12 weeks of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo among genotype 1-infected patients with CKD stage 4 or 5 (eGFR <30 mL/min). SVR12 rates were 94% and 99%, respectively.

**Glecaprevir/Pibrentasvir:** 12 weeks of daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) was administered as three 100 mg/40 mg fixed-dose combination pills to 104 patients who were 19% compensated cirrhosis and 82% hemodialysis dependent. The study reported SVR12 rates of 98% and 100%, respectively.

**Sofosbuvir-Based Regimens:** Safety of sofosbuvir in persons with an eGFR <30 mL/min have not been established. The HCV-TARGET study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction. The SVR12 rates were similar across the eGFR groups. However, there was progressive deterioration of renal function and related symptoms in patients with an eGFR <30 mL/min. So, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events.

**Daclatasvir, Elbasvir, Grazoprevir, Ledipasvir, and Simeprevir:** Daclatasvir, elbasvir, grazoprevir, ledipasvir, and simeprevir are primarily metabolized by liver and undergo minimal renal elimination. They do not require dose adjustments in the setting of renal impairment.

#### III. Post-Transplantation

The immediate goal for patients awaiting liver transplantation is to suppress HCV ideally for at least 30 days prior to transplant. Suppression of HCV RNA levels for at least 30 days prior to transplant markedly reduces the risk of the HCV infected transplanted liver. The long-term goal is to induce a successful liver transplantation.

#### <Treatment of CHC Patients after Liver Transplantation>

For HCV reinfected patients after liver transplantation, the ideal time for initiating HCV treatment has not been well characterized. At first 3 months after transplantation, there are drug-drug interactions to consider, such as ombitasvir-paritaprevir-ritonavir plus dasabuvir and ribavirin co-administered with a calcineurin inhibitor, or sime-

previr coadministered with cyclosporine. So, it is reasonable to wait at least 3 months after transplantation before considering initiation of hepatitis C treatment, allowing for stabilization and reduction of immunosuppression and renal function.

**Glecaprevir/Pibrentasvir:** 12-week course of the glecaprevir (300 mg)/pibrentasvir (120 mg) administered in 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse.

Ledipasvir/Sofosbuvir: 223 liver transplant recipients with genotype 1 or 4 infection were randomly assigned to 12 weeks or 24 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin. SVR was achieved in 96% (53/55) and 98% (55/56) of liver transplant patients without cirrhosis in the 12- and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR was 96% in both the 12- and 24-week treatment arms. Among patients with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12- and 24-week treatment.

**Daclatasvir** + **Sofosbuvir**: 12-week course of daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin was administered to 60 patients with cirrhosis (CTP class A, B, or C) and 53 patients with HCV recurrence after liver transplantation. The SVR12 rate was 94% (50/53) among those with recurrent HCV infection post transplantation.

Simeprevir + Sofosbuvir: Simeprevir (150 mg) plus sofosbuvir (400 mg), with or without weight-based ribavirin, for 12 weeks or 24 weeks was administered to 46 liver transplant recipients (44 non-cirrhotic) with recurrent genotype 1 infection. The SVR12 rates were 100% with simeprevir plus sofosbuvir for 12 weeks, 82% with simeprevir plus sofosbuvir and ribavirin for 12 weeks, and 94% with simeprevir plus sofosbuvir for 24 weeks.

**Sofosbuvir/Velpatasvir:** To date, there have been no studies evaluating the safety and efficacy of sofosbuvir (400 mg)/velpatasvir (100 mg) in liver transplant recipients. For this reason, very limited recommendations on its use post liver transplantation can be made.

#### References

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# Special Issue in Hepatitis C Virus Treatment: Hepatitis B Virus Reactivation and Occurrence and Recurrence of Hepatocellular Carcinoma

#### Chia-Yen Dai

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The overall outcome of patients with chronic hepatitis C virus (HCV) infection may have the chance of improvement from the advancement in the treatment efficacy of antiviral therapies. With higher efficacy of the standard of care (pegylated interferon- alpha (PegIFN) plus ribavirin therapy and/or new all oral direct-acting antiviral agents (DAAs), the sustained virological response (SVR) has greatly improved the treatment efficacy. However, some special issues for some patient groups need to be noticed.

For patients with hepatitis B virus (HBV)/HCV coinfection, hepatitis B reactivation associated with DAA therapy is emerging to be an important cause of morbidity and mortality. The positivity of HBsAg and HBV DNA are the major determinants of hepatitis B reactivation. With the previous reports by the IFN-based therapy, hepatitis B reactivation was observed about 40% during 5-year post-treatment follow-up with rare clinical hepatitis event. After treatment of DAAs for CHC, the hepatitis B reactivation seems different from the IFN-based therapy. Recent data suggest that in patients with positive HBsAg and HCV infection, reactivation of HBV can occur in up to 70% of the subjects during the DAA therapy and within one year after cessation of DAA therapy. Less than 20% of the subjects developed hepatitis flare accompanying HBV reactivation. The major guidelines have highlighted the needs of monitoring for HV reactivation or even initiating the prophylactic therapy with nucleos(t)ide analogues which may need further studies to clarify the predictive factors and the patient groups who will get the benefits.

Another special consideration that should be discussed is related to hepatocellular carcinoma (HCC). The effect of the viral eradication on the development of HCC is an important issue which reflects the outcome of secondary and tertiary prevention in CHC patients with antiviral therapies. With the SVR achieved after the IFN-based therapy, it has been shown that successful antiviral therapy can reduce the risk of HCC development in HCV patients who were without HCC. For patients with HCC receiving HCC therapy, there were some reports revealing no benefit of eradication of HCV on the prevention of the recurrence of HCC. However, large cohort studies have shown that for patients after **HCV-related HCC After curative therapy, IFN therapy has been shown to improve outcomes these patients.** In the DAA era, with the very high cure rate of HCV, most of the reports show that DAAs therapy seems not to be associated with the occurrence of the HCC. There were some reports indicated the effect of secondary prevention of HCC in CHC patients. Nevertheless, the risk of HCC in patients after therapy for HCC, such as the curative therapy has been debated with DAA therapy. Some studies have shown the lack of preventing recurrence of the HCC in these DAAs-treated patients after the curative therapies for HCC. There are more evidences recently reported that no observation about such an increasing of the recurrence of HCC. The efficacy of tertiary prevention needs further long-term studies and assessment.

The Live<u>r Week</u> 2018

DAY 2: Friday, June 15, 2018 (11:10-12:10) WEST TOWER / ROOM AB [B1]

# **Special Lecture**

Chair : Dong Jin Suh (KMP Healthcare Seoul Clinic)

### Towards Hepatitis B Virus Cure and Immunology

#### **Qin Ning**

Huazhong University of Science and Technology, Wuhan, China

Currently, there are two main types of antiviral drugs approved in the treatment of chronic hepatitis B (CHB): nucleos(t)ide analogue with high barrier to resistance (i.e., entecavir and tenofovir), or pegylated interferon alpha.<sup>1</sup> Currently majority of CHB patients require long-term or lifelong treatment dur to limited treatment options, thus there is a need for strategies toward an hepatitis B virus (HBV) cure.

The definition of chronic hepatitis B cure includes 1) absolute or complete cure, which is defined by elimination of cccDNA, undetectable HBV DNA in serum and liver and off-therapy HBsAg loss 2) functional (immunological) cure, which is defined by HBsAg loss or seroconversion 3) disease cure, which is defined by no risk of disease progression to cirrhosis, liver failure or hepatocellular carcinoma (HCC).<sup>2</sup>

However, there are some obstacles for HBV cure. On the one hand, NAs do no directly affect the viral cccDNA or have significant effect on HBsAg level. On the other hand, HBV-specific T cells are exhausted in chronic infection and HBV has evolved mechanisms to evade both innate and adaptive immune responses.<sup>3</sup> Combinations of potent NA with immunotherapeutic approaches are highly promising and should help to circumvent these obstacles in the future.

In patients on long-term NA therapy, PegIFN $\alpha$  can be used as a 'switch to' or 'add-on' strategy. Several cohort studies, including OSST study, Endeavor study, Anchor study, New Switch Study, SWAP study in Asia and PEGAN Study, PEGON study, HERMES study in the West, have been carried on in either treatment naïve or NA suppressed CHB patients. In most of these studes with OSST as the first report, HBeAg seroconversion and/or HBsAg reductions or loss rates increase significantly in the combination/switch group.<sup>4</sup> Based on these studies, a roadmap to clinical cure of CHB has been proposed<sup>5</sup> and recently we launched the COST study to validate the roadmap and OCEAN study to follow up a long term outcome of these approaches.

The novel antiviral therapies aim to cure HBV can be categorized into direct-acting antivirals and immunotherapeutic agents. The direct-acting antivirals include HBV entry inhibitors, drugs targeting cccDNA, siRNA or anti-sense oligonucleotides targeting viral transcripts, nucleocapsid assembly modulators, and approaches to inhibit HBsAg release in serum.<sup>6</sup>

Several potential mechanisms for restoration of immune responses have been suggested. Among them, Toll-like receptor agonists or specific antiviral cytokine delivery are supposed to work for restoration of innate immunity; inhibitors of negative checkpoint regulators, therapeutic vaccines, or autologous transfer of engineered HBV-specific T cells are supposed to work for restoration of adaptive immunity.<sup>5,7</sup>

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solved questions-report of the ANRS workshop on HBV cure. Gut 2015;64:1314-1326.

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# Novel Drivers for Alcoholic Hepatitis and Alcohol-Promoter Liver Cancer

#### Hidekazu Tsukamoto

Southern California Research Center for ALPD and Cirrhosis and Department of Pathology, University of Southern California, Los Angeles, USA

Most devastating seguela of alcoholic liver disease (ALD) are alcoholic cirrhosis, alcoholic hepatitis (AH), and liver cancer which collectively cause more than half million deaths annually in the world. As current therapeutic options are severely limited, identification of new therapeutic targets is urgently needed. Our integrated "omic" analyses of liver tissues from clinically relevant animal models and patients identify CASPASE11/4 (CASP11/4) and GASDERMIN-D (GSDMD) as novel drivers for a transition from chronic alcoholic steatohepatitis (cASH) to AH. This CASP11/4-GSD-MD pathway is activated by translocated bacteria and responsible for programmed lytic cell death called pyroptosis of hepatocytes and hepatic macrophages, local dissemination of bacteria, PAMPs and DAMPs, and intense neutrophilic infiltration, a hallmark of AH. Genetic suppression of this pathway, abrogates liver bacterial load, hepatocyte death, and neutrophilic infiltration and improves the liver. Conversely, genetic upregulation of the pathway, worsens AH. If this pyroptotic pathway activation is excessive, endotoxemia and septicemia may ensue leading to systemic inflammatory response syndrome (SIRS), the major complication of AH. Alcohol and Western diet synergistically promote liver tumorigenesis but the mechanisms underlying this effect is elusive. Our study discloses a novel Wnt positive loop facilitated by stearoyl co-A desaturase (SCD) in activated hepatic stellate cells (aHSCs), which links liver fibrosis to liver tumorigenesis and drives tumor promotion by alcohol and Western diet via lipid metabolic reprogramming. Selective genetic ablation of Scd in aHSCs reduces tumor-promoting lipid metabolites in tumor microenvironment and abrogates tumor progression. Translational relevance of this finding will be discussed.



DAY 2: Friday, June 15, 2018 (13:10-13:40) WEST TOWER / ROOM AB [B1]

# **Presidential Choice**

Chair : Jin Mo Yang (The Catholic Univ. of Korea)

## Spread and Elimination of Hepatitis C Virus in Japan

#### Masao Omata

Yamanashi Central and Kita Hospitals, The University of Tokyo, Japan

## **Curriculum Vitae**

Masao Omata, MD, has made an effort to revitalize the APASL (Asian Pacific association for the study of the Liver) with Dr. S. Sarin and others for the last 10 years. He is a Co-Editor in Chief of the Hepatology International, an official journal of APASL. He graduated from Chiba University School of Medicine (Dr. Okuda), and continued his training at Yale University (Dr. G Klaskin) and in the Liver Unit at University of Southern California (Dr. RL Peters). After 6 years in US, he returned to the Department of Medicine at Chiba University in 1989, and started molecular biological study on Hepatitis B virus.

In 1992, he became Chairman of Second Department of International Medicine at University of Tokyo, Japan and then subsequently became chairman of Department of Gastroenterology. Under his leadership, the Department of Gastroenterology had become one of the foremost centers in its field.

Now, he is the president of the two hospitals at Yamanashi, west of Tokyo, where, although scenic place with Mt. Fuji, hepatitis virus infection is epidemic and his homeland. He and his colleague have published 1,164 articles in English Literature including, NEJM 5, Lancet 6, Ann Int Med 6, Hepatology 59, Gastroenterology 43. The total impact factor is 6,723 and 42,844 citations with H-index of 104 as of July 1<sup>st</sup>, 2017.

**Research Interests** 

Hepatology, Gastroenterology, Oncology

#### Representative Publications

- 1. Interferon therapy reduces the risk for hepatocellular carcinoma:National surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan (Ann Intern Med 1999;131:174-181).
- A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma (Gastroenterology 2005;129:122-130)
- 3. Percutaneous radiofrequency ablation for hepatocellular carcinoma an analysis of 1000 cases (Cancer 2005;103:1201-1209)
- Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy (Ann Intern Med 2000;132:517-524)
- 5. Mutations in the precore region of hepatitis B virus DNA in patients with fulminant and severe hepatitis (N Engl J Med 1991;324:1699-1704)



DAY 2: Friday, June 15, 2018 (13:50-15:30) WEST TOWER / ROOM AB [B1]

# Clinical Hepatology Update (\*к)

Chairs : Yung Sang Lee (Univ. of Ulsan) Joung-Il Lee (Kyung Hee Univ.)

### Hepatitis B Virus

#### Hyung Joon Yim

Division of Gastroenterology, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, South Korea

Hepatitis B virus (HBV) is a small (3.2 kb) enveloped DNA virus which primarily replicate in the hepatocytes.<sup>1</sup> The virions enter into the cells via specific receptors (NTCP) and are released from the hepatocyte through the cellular secretory pathway. The virus has 4 open reading frames encoding 7 proteins: HBeAg, HBcAg, HBV polymerase, HBsAg, PreS1, PreS2, and HBx. After uptake of HBV into hepatocyte, the virus DNA is transported to the nucleus and converted into a covalently closed circular DNA (cccDNA), which is a transcriptional template for different viral transcripts and translated into the different viral proteins as above. Although HBV itself is not a cytopathic virus, viral clearance from the host cells involves the induction of a robust T cell reaction resulting in cytolytic antiviral effect together with the expression of antiviral cytokines and the B cell induction for neutralizing antibody. Chronic carriers often have impairment of HBV specific T cell function mediated by multiple regulatory mechanisms.

The current target for antiviral therapy in chronic hepatitis B (CHB) is polymerase of HBV. During the last two decades, antiviral agents primarily acting on HBV polymerase such as nucleoside or nucleotides analogues (NA) has been widely used. NAs effectively suppress replication of HBV, thereby reducing the liver damage, inflammation and even the regression of liver fibrosis. However, because of frequent relapse of HBV replication after cessation of the therapy, long term antiviral treatment has been necessary, confronting several drawbacks of NAs such as development of antiviral resistance, side effects, and economic burden.<sup>2</sup> Currently, entecavir and tenofovir disoproxil fumarate (TDF) were considered as initial choices of antiviral therapy primarily due to potent antiviral effects and their high genetic barrier to resistance. However, TDF was associated with renal toxicity and reduction of bone mineral density. Tenofovir alafenamide (TAF) is an oral prodrug of tenofovir, which was developed to optimize the antiviral potency and safety of the active moiety of tenofovir diphosphate. In two phase 3 multinational randomized controlled trials in treatment- naïve and experienced CHB patients with positive or negative HBeAg, TAF 25 mg showed effective and sustained viral suppression over 120-week, and the safety profile was better than TDF; TAF was non-inferior to TDF 300 mg in the suppression of HBV DNA (<29 IU/mL) and was associated with higher rate of ALT normalization rates than TDF.<sup>3</sup> In terms of bone and renal safety, more favorable pharmacological profile of TAF reduces systemic exposure to tenofovir, improving bone and renal safety compared to TDF.<sup>3</sup>

Besifovir disoproxil maleate (BSV) is an acyclic nucleotide phosphonate with a potent antiviral activity against HBV.<sup>4</sup> Antiviral effect of BSV for 48-week was shown to be comparable to TDF in the phase 3 trial in treatment naïve CHB patients. The long term efficacy and safety of BSV in CHB patients who were HBeAg positive or negative in extended follow studies are ongoing.

HBsAg loss or seroconversion, which is considered as a functional cure, is rarely achieved with the current therapies.<sup>5</sup> The reasons for the failure to achieve the functional cure of chronic HBV infection is limited efficacy on reducing the amount of cccDNA. In addition, despite the potent suppression of HBV replication in the livers of

Clinical Hepatology Update (\*K)

treated patients, the dysfunction of HBV-specific antiviral immunity persists. These are the fundamental reasons for the chronicity of HBV infection and became a significant challenge for developing therapeutic agents to cure CHB. Therefore, the future targets of drug discovery and development achieving functional cure are cccDNA and associated viral proteins as well as the host innate and adaptive immune systems against HBV.

To reduce cccDNA, HBV replication should be controlled first. HBV entry into hepatocytes, nucleocapside assembly and multifunctional viral DNA polymerase are the major targets. CRISPR/Cas9 mediated gene editing technology can efficiently inactivate cccDNA function in HBV infected hepatocytes. RNA interference-mediated viral mRNA degradation efficiently inhibits HBV replication and reduces viral antigen loads. Reducing antigen load and obtaining HBsAg seroclearance might be important for inducing the antiviral immunity against HBV. The goal of immunotherapy is to accelerate the recovery of exhausted immune response against HBV.<sup>6</sup> Several therapeutic immunization and/or immunotherapy are under development. TLR7 agonist and checkpoint blockade therapy with antibodies against PD1 is in clinical trial.

### Conclusion

Newly approved antiviral agents suppress viral replication effectively, reducing the side effects of the previous NAs. Future therapeutics to reduce viral antigen load and restore HBV specific antiviral immune response are currently under development. It is expected that combination of the different categorical drugs will eventually provide a functional cure for chronic HBV infection.

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## Clinical Update of Chronic C Viral Hepatitis

#### Eun Young Cho, Won Gak Heo

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## 만성 C형간염 치료의 Clinical Update

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There have been many changes in the treatment of chronic hepatitis C since the introduction of new DAA agents in recent years. The standard treatment of chronic hepatitis C was converted to DAA agents from the combination of Pegylated interferon-alpha and ribavirin (PR), and the SVR rate was significantly increased from 50 to 80% for PR combination therapy to 90 to 100% for DAA regimens. However, as drugs have different effective genotypes, the choice of drugs depends on the genotype and subtypes, therefore it is necessary to have an in-depth understanding of each of DAA agents. In addition to the HCV genotype and subtype, several factors should be considered to determine the sort of DAA regimen and duration of treatment, such as the assessment of liver function, history of previous therapy, evaluation of renal function, and drug-drug interaction with concomitant medications. Therefore, despite the use of the DAA regimen with low side effects and excellent therapeutic effect, still, the treatment of chronic hepatitis C is mainly performed by a specialist in the field of hepatology. Pan-genotypic DAA regimens, which are expected to simplify these complex measurements of pre-treatment variables and drug selection criteria, have been approved in the US and Europe since 2016, and use is expected to be available soon. The use of these pan-genotypic DAA regimens simplifies pre-treatment measurement to determine DAA regimen and duration of treatment, and it is likely to make it easier to access the chronic hepatitis C treatment. Thus, as this allows more doctors to contribute to the treatment of hepatitis C, it is expected that it will be closer to the goal of hepatitis C eradication by increasing the interest in chronic hepatitis C and increasing the treatment rate.

## 서 론

만성 C형간염의 치료는 최근 수년간 새로운 DAA제제들이 출시되어 많은 변화가 있어왔다. 만성 C형간염의 표준 치료가 Pegylated interferon-alpha와 ribavirin 병합치료(PR치료) 에서 DAA제제로 전환되었고, SVR 율도 PR치료 50-80%에서 DAA치료 90-100%로 현저히 높아졌다. 그러나 약제들은 효과 있는 유전자형이 각 각 달라서, 유전자형과 아형에 따라 약제선택이 달라지므로 DAA 각 약제에 대한 심도 있는 이해가 필요한 실 정이다.

PR치료가 표준치료 였던 시기에는 치료에 영향을 주는 다양한 요인, 즉, 치료 전 HCV RNA 수치, HCV 유전 자형, 조직학적 섬유화 정도, 그리고 숙주의 IL28B 유전적 다형성, 고령의 나이, 인종, 체중 >70 kg 및 인슐린 저 항성 등이 있었다.<sup>1</sup> 그러나 DAA가 주 치료제로 쓰이면서 간경변의 유무, 유전자형, 이전 치료 유무가 치료효과 에 영향을 주는 주요 요인으로 치료반응의 예측 측면에서는 단순화된 면이 있다. 그러나 우수한 항바이러스 효 과를 보이는 다양한 새로운 약제들이 출시되고, 각 약제마다 각각 다른 특성을 가지고 있어, 각 약제와 환자의

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특성을 고려해 약제를 선택하고 치료기간을 다르게 해야 하는 복잡성이 있다. 약제종류와 치료기간을 정하기 위해서는 HCV 유전자형, 간 질환의 중등도 평가, 이전 치료 병력, 신기능 평가, 병용하는 약물과의 drug-drug interaction 확인 등 여러 요인을 고려해야하는 면이 있어,<sup>2</sup> 부작용이 적고 치료 효과가 우수한 DAA regimen 을 사용함에도, 여전히 만성 C형간염의 치료는 hepatology 분야의 specialist에 의해서 주로 이루어지고 있고, 영국을 포함한 유럽의 몇몇 국가에서는 hepatology 분야의 specialist만 만성 C형간염의 진단-치료-모니터링 의 전 과정을 수행할 수 있도록 제한하고 있기도 하다.

이러한 복잡한 치료 전 평가와 약제 선택의 기준을 단순화해 줄 것으로 기대되는 pan-genotypic DAA 제 제들이 2016년부터는 승인되어 미국과 유럽에서 사용되고 있고, 국내도 곧 사용할 수 있을 것으로 기대 된 다. Pangenotypic DAA는 2016년 Sofosbuvir/Velpatasvir가 승인된 이후 Sofosbuvir/Velpatasvir/ Voxilaprevir, Glecaprevir/Pibrentasvir가 승인되었다. 여기서는 주로 앞으로 사용하게 될 pan-genotypic DAA들에 대해 알아보도록 하겠다.

#### 1. Sofosbuvir (NS5B nucleoside inhibitor) / Velpatasvir (NS5A inhibitor)

Sofosbuvir/Velpatasvir는 모든 유전자형에서 높은 항바이러스 효과를 보인 첫번째 약제이면서 비 대상성 간경변 및 이전 치료 실패 환자와 같은 특수상황의 환자군에서도 치료 효과를 보였는데 이는 Astral-1-4까지의 연구로 확인할 수 있다.<sup>3</sup>

먼저 Astral-1 연구는<sup>4</sup> 유전자형 1, 2, 4, 5, 6을 Sofosbuvir/Velpatasvir로 12주간 치료했는데 19%의 대 상성 간경변 환자와 32%의 치료경험 환자가 포함되었다. Overall SVR12 rate는 99%로 genotype 1a 99% (206/210), genotype 1b 99% (117/118), genotype 2 100%, genotype 4 100%, genotype 5 97% (34/35), genotype 6 100% (41/41)이었다. RAS여부에 관계없이 치료 경험이 있는 간경변 환자들의 SVR도 >99%으로, 이전 치료와 간경변 유무에 관계없이 유전자형 1, 2, 4, 5, 6형에서 Sofosbuvir/Velpatasvir 12주 치료는 가장 강력한 치료 option이 될 수 있을 것으로 보인다.

다음으로 Astral-2 연구는<sup>5</sup> 유전자형 2형을 대상으로, 그리고 Astral-3 연구는 유전자형 3형 환자군을 대상 으로 Sofosbuvir/Velpatasvir12주치료와 Sofosbuvir with ribavirin 24주 치료를 비교하였다. Astral-2 연구 는 14%의 대상성 간경변 환자와 15%의 치료경험 환자를 포함하였고, Astral-3 연구에는 30%의 대상성 간경변 환자와 26%의 치료경험 환자가 포함되었다. Astral-2 연구의 Overall SVR12 rate는 Sofosbuvir/Velpatasvir 치료군 >99% (133/134), Sofosbuvir with ribavirin 치료군 94% (124/132)이었다. Astral-3 연구의 Overall SVR12 rate는 Sofosbuvir/Velpatasvir 치료군 95% (264/277), Sofosbuvir with ribavirin 치료군 80% (221/275)이었고, 간경변이 있는 환자들의 SVR율은 Sofosbuvir/Velpatasvir 치료군 93%, Sofosbuvir with ribavirin 치료군 73%이었다. 또, 치료경험이 있는 간경변 환자들의 SVR율은 Sofosbuvir/Velpatasvir 치료군 89%, Sofosbuvir with ribavirin 치료군 58%였다. 두 연구 결과로 볼 때, Sofosbuvir/Velpatasvir 12주치료 는 유전자형 2형과 3형 환자에 매우 우수한 치료 효과를 제공해 줄 것으로 보인다.

마지막으로 Astral-4 연구는<sup>6</sup> 비대상성 간경변 환자(Child-Turcotte-Pugh class B)를 대상으로 Sofosbuvir/Velpatasvir 12주, Sofosbuvir/Velpatasvir with ribavirin 12주, Sofosbuvir/Velpatasvir 24 주를 1:1:1로 무작위 배정하여 연구를 진행하였다. 총 267명으로 78% GT1, 4% GT2, 15% GT3, 3% GT4와 <1% GT6가 포함되었다. Overall SVR12 rate는 Sofosbuvir/Velpatasvir 12주 치료군 83%, Sofosbuvir/ Velpatasvir with ribavirin 12주 치료군 94%, Sofosbuvir/Velpatasvir 24주 치료군 86%로 각 군간에 유의 한 차이는 확인되지 않았다. 다만 유전자형 3형은 ribavirin이 포함된 치료군의 SVR율이 85%로, ribavirin이 포함되지 않은 치료군의 SVR율 50% 유의하게 높은 치료 효과를 보였다.

치료 중 흔한 부작용은 피로감, 미식거림, 두통, 빈혈(ribavirin과 병용하는 경우)이었고, 안전성이 특히 중시 되는 비 대상성 간경변을 대상으로 한 Astral-4 연구에서는 9명(9/267, 3.3%)이 부작용으로 조기 중단 후 사망 하였는데 이 중 2명이 간 부전으로 사망하였다.<sup>6</sup>

## 2. Sofosbuvir (NS5B nucleoside inhibitor) / Velpatasvir (NS5A inhibitor) / Voxilaprevir (NS3/4A protease inhibitor)

Polaris-1-4 연구는 만성 C형간염과 대상성 간경변증을 대상으로 Sofosbuvir/Velpatasvir/Voxilaprevir 의 효과를 입증한 연구로 Polaris-1은 이전 치료로 NS5A inhibitors를 사용한 환자를 대상으로 하였고, Polaris-2는 초 치료 환자를 대상으로 하였다. Polaris-3는 genotype 3의 초 치료 환자를 대상으로, Polaris-4 는 이전 치료제로 NS5A inhibitors 이외의 DAA를 사용한 환자를 대상으로 SVR율, adverse event, RAS발생 등을 연구하였다.<sup>7</sup>

먼저, naive환자 (HCVRNA ≥10<sup>4</sup> IU/mL, 30% compensated cirrhosis)를 대상으로 한 Polaris-2 연구 는<sup>8</sup> Sofosbuvir/Velpatasvir/Voxilaprevir 8주 치료(501명)와 Sofosbuvir/Velpatasvir 12주 치료(440명)를 비교하였고 cirrhosis가 있는 genotype 3는 제외하였다. Sofosbuvir/Velpatasvir/Voxilaprevir 8주 치료군 의 SVR율은 genotype 1a 92% (155/169), genotype 1b 97% (61/63), genotype 2 97% (91/92), genotype 3 99% (91/92), genotype 4 94% (59/63), genotype 5 94% (17/18), genotype 6 100% (30/30)이었다. 간 경변이 있는 환자의 SVR율은 91% (82/90)였다. Sofosbuvir/Velpatasvir 12주 치료군의 SVR율은 genotype 1a 99% (170/172), genotype 1b 97% (86/89), genotype 2 100% (53/53), genotype 3 97% (86/89), genotype 4 98% (56/57), genotype 6 100% (9/9)였고, 간경변이 있는 환자의 SVR율은 99% (83/84)로 Sofosbuvir/Velpatasvir/Voxilaprevir 8주 치료군보다 우수한 효과를 보였다.

다음으로 간경변이 있는 유전자형 3형을 대상으로 한 Polaris-3 연구 역시 Sofosbuvir/Velpatasvir/ Voxilaprevir 8주치료(110명)와 Sofosbuvir/Velpatasvir 12주 치료(109명)를 비교하였는데 두 군 모두에서 SVR율은 96%로 차이가 없었다.<sup>8</sup>

FDA에 최초로 승인된 pangenotypic DAA regimen인 Sofosbuvir/Velpatasvir 치료는 거의 모든 유전자 형에서 우수한 항바이러스 효과를 보여주었으나, 이전에 DAA regimen으로 치료에 실패한 간경변 환자의 경 우는 90%이상의 SVR율에 도달하지 못하였다. 따라서 이전에 DAA 치료실패 군에서 Sofosbuvir/Velpatasvir/ Voxilaprevir로 치료 효과를 확인하는 Polaris-1, 4 연구가 진행 되었다.<sup>9</sup>

먼저, Polaris-1 연구는<sup>9</sup> 이전 치료로 NS5A inhibitors를 4주 이상 사용하고 치료에 실패한 환자를 대상으 로 12주간 Sofosbuvir/Velpatasvir/Voxilaprevir 투여하였다. Polaris-1 연구의 SVR율은 genotype 1a 96% (97/101), genotype 1b 100% (45/45), genotype 2 100% (5/5), genotype 3 95% (74/78), genotype 4 91% (20/22), genotype 5 100% (1/1), genotype 6 100% (6/6) 였고, 30% 포함된 Cirrhosis 환자들의 SVR 율은 93%로 모든 군에서 90% 이상의 SVR율을 보였다.

Polaris-4 연구는<sup>9</sup> NS5A 억제제를 제외한 DAA제제로 치료 실패한 환자들(4주 이상 투여)을 대상으로 하였고, 12주간 Sofosbuvir/Velpatasvir/Voxilaprevir 또는 Sofosbuvir/Velpatasvir를 투여하였다. Sofosbuvir/ Velpatasvir/Voxilaprevir 투여군의 SVR율은 genotype 1a 98% (53/54), genotype 1b 96% (23/24), genotype 2 100% (31/31), genotype 3 96% (52/54), genotype 4 100% (19/19)였고, 간경변 환자의 SVR 율은 98% (83/84)로 역시 모든 군에서 90% 이상의 SVR율을 보였다. 반면 Sofosbuvir/Velpatasvir 투여군 의 SVR율은 genotype 1a 89% (39/44), genotype 1b 95% (21/22), genotype 2 97% (32/33), genotype 3 85% (44/52)였고, Cirrhosis 환자들의 SVR율은 86% (59/69)였다. 즉 이전 DAA치료에 실패 환자의 경우 는 Sofosbuvir/Velpatasvir/Voxilaprevir 12주 치료가 높은 항바이러스 효과를 보여 현재 KASL, AASLD guidelines 모두에서 1차 선택약제로 제시하고 있다.

치료 중 흔하게 발생한 약물 부작용은 headache (25-27%), fatigue (21-24%), diarrhea (18-20%), nausea (12-14%)였고, Polaris-1과 4에서 angioedema (Ramipril 병용투여 후)로 1명이 치료를 중단하였고, Polaris-2와 3에서는 치료를 중단한 환자는 없었다. 치료와 연관된 내성은 Polaris-1 2명, Polaris-2 1명이 발생하였고, Polaris-3와 Polaris-4는 치료관련 내성이 발생하지 않았다.

#### 3. Glecaprevir (NS4/4A protease inhibitor) plus Pibrentasvir (NS5A inhibitor)

Glecaprevir/Pibrentasvir도 pangenotypic DAA regimen으로 최근 간경변이 없는 유전자형 1형-6형 환 자를 대상으로 시행한 허가 임상 전반의 pooled analysis가 보고 되었다.<sup>10</sup> 총 2041명이 분석에 포함되었고<sup>11-18</sup> 965명은 8주 치료를 1076명은 12주 치료를 받았다. 11%의 F3 fibrosis, 15-18%의 NS5A polymorphisms 과 1%의 NS3 변이가 있었고, NS5A와 NS3동시 변이도 <1%이었다. Overall SVR12율은 8주 치료군 98% (943/965), 12주 치료군 99% (1060/1076)이었고, non-virologic failure환자를 제외하고 분석한 modified intention to treat (mITT)의 SVR12율도 8주 치료군 99.1% (943/952), 12주 치료군 99.6% (1060/1064) 로 치료기간에 따른 SVR12율의 차이는 없었다. mITT분석군을 19개 변수로 subgroup analysis했을 때 sofosbuvir치료 경험이 있는 군의 SVR12율은 8주 치료시 90% (9/10) 12주 치료시 100% (10/10)로 12주 치 료가 높은 SVR12율을 보였고, NS3/4A 또는 NS5A부위의 polymorphism이 단독으로 존재할 때는 치료기간 에 관계없이 98%이상의 SVR12율을 보였으나 동시에 두 군데 모두에 polymorphism이 존재하는 경우는 8주 치료군 67% (2/3) 12주 치료군 83% (5/6)로 낮은 치료반응을 보였다. 이 분석에서 치료 후 재발은 8주 치료군 0.7% (7/965), 12주 치료군 0.3% (3/1057)였고, 치료 중 virologic failure는 8주 치료군 0.2% (2/965), 12주 치료군 <0.1%% (1/1076)이었다. 이상의 결과를 종합하면 간경변이 없는 유전자형 1-6형환자를 Glecaprevir/ Pibrentasvir로 치료하는 경우 8주 치료로 충분하다고 할 수 있다. 그러나 이전에 sofosbuvir based regimen 으로 치료했던 경우는 12주 치료가 필요하고 NS3/4A와 NS5A 동시에 polymorphism이 있는 경우는 다른 약 제를 고려할 필요가 있겠다.

NS3/4A protease inhibitor (PI) 또는 NS5A inhibitor가 포함된 regimen에 치료 실패한 만성 C형간염 환 자들을 대상으로 하는 추가적 연구가 진행되었다. MAGELLAN-1 Part 2 연구는<sup>19</sup> Glecaprevir/Pibrentasvir 의 치료기간을 늘였을 때의 치료반응을 보기 위해 Glecaprevir/Pibrentasvir 12주 치료(44명)와 16주 치료(47 명)의 SVR12율을 비교하였다. 이전 DAA regimen은 NS3/4A PI only, NS5A inhibitor only, NS3/4A PI + NS5A inhibitor로 12주 치료군은 각각 32%, 36%, 32%, 16주 치료군은 각각 28%, 38%, 34%였다. 이전 치료 의 치료반응은 on-treatment failure가 12주 치료군 32%, 16주 치료군 28%였고 치료 후 재발이 12주 치료군 68%, 16주 치료군 72%였다. Overall SVR12율은 12주 치료군 89% (39/44), 16주 치료군 91% (43/37)이었 고 과거 DAA regimen에 따른 SVR12율은 NS3/4A PI only- 12주 치료군 100%, 16주 치료군 100%, NS5A inhibitor only- 12주 치료군 88%, 16주 치료군 94%, NS3/4A PI + NS5A inhibitor- 12주 치료군 79%, 16 주 치료군 81%였다.

즉, NS3/4A PI로 치료한 경험이 있는 환자군은 12주 치료로 충분하며, NS5A inhibitor에만 경험이 있는 환자의 경우는 16주 치료가 필요하겠다. NS3/4A PI와 NS5A inhibitor 둘 모두에 경험이 있는 환자는 낮은 SVR12율을 보여 이 경우 앞서 언급했던 Sofosbuvir/Velpatasvir/Voxilaprevir 투여를 고려해야 하겠다.

#### 4. Sofosbuvir-Containing Pan-Genotypic DAA Regimen vs. Sofosbuvir-Free Pan-Genotypic DAA Regimen

앞서 현재까지 출시된 pan-genotypic DAA regimen의 antiviral efficacy에 대해 살펴보았다. 이를 약제 의 특성에 따라 두 group으로 나눌 수 있는데, 주요 대사 물질이 신장으로 배설되어 간 장애 환자에서 용량 조 절 필요 없이 투여가 가능한 sofosbuvir를 포함하는 regimen과 주요 대사 물질들이 biliary system으로 배 설되는 약제들로 조합되어 중증의 신기능 환자에서 용량조절 없이 투여할 수 있는 sofosbuvir-free regimen (Glecaprevir/Pibrentasvir)으로 분류해 볼 수 있겠다. sofosbuvir를 포함하는 regimen은 신기능이 저하된 환자 (GFR <30) 및 투석을 요하는 환자에게 사용을 피해야 하고, sofosbuvir-free regimen인 Glecaprevir/ Pibrentasvir는 중증의 간장애 환자에서 투여를 권고하지 않는다.

비대상성 간경변 환자(Child-Turcotte-Pugh class B, 유전자형 1-6형)를 대상으로 진행된 Astral-4 연구 에서 Sofosbuvir/Velpatasvir with ribavirin 12주 치료 시 94%의 SVR12율을 보였고, 간기능의 조기 개 선 및 CTP 점수와 MELD점수의 호전을 보였다. 그러나 Sofosbuvir 포함 pan-genotypic DAA regimen 중 Sofosbuvir/Velpatasvir/Voxilaprevir는 중증 간 장애 환자에 사용시 Voxilaprevir의 혈 중 농도가 유의하게 증가될 수 있다. 비대상성 간 경변 환자를 대상으로 진행된 연구결과가 없어서 비대상성 간 경변 환자에는 투여 금기이다. Sofosbuvir/Velpatasvir/Voxilaprevir regimen의 강점은 NS3/4A와 NS5A 동시 변이를 가진 환자 에서 강력한 항바이러스 효과를 보이는 것으로 12주간 Sofosbuvir/Velpatasvir/Voxilaprevir 투여 시 유전자 형에 관계없이 95%이상의 SVR율을 보였고 간경변 환자의 경우에도 98%의 SVR율을 보였다.

한편, 중증 신기능 저하 환자를 대상으로 Glecaprevir/Pibrentasvir의 치료 효과를 확인하는 연구가 진행 되었다.<sup>20</sup> CKD (stage 4와 5 및 혈액 투석 환자)가 있는 만성 C형간염 환자 (유전자형1-6)에게 Glecaprevir/ Pibrentasvir를 12주간 투여 시 98%의 SVR12율을 보였고, 기저에 NS5A polymorphism을 보인 29% (28/96)의 환자도 모두 SVR12를 얻었다. 흔한 부작용은 pruritus 20% (21/104), fatigue 14% (15/104), nausea 12% (12/104)이었고, liver decompensation의 adverse event는 관찰되지 않았으며, 5명의 환자가 치료를 조기 중단했는데 이중 3명은 SVR에 도달했다. 따라서 Glecaprevir/Pibrentasvir는 신기능이 중등도 이 상 저하된 환자들에서 1차 선택약제가 될 수 있을 것으로 보인다.

## 결 론

최근 pan-genotypic DAA regimen이 출시되면서 약제 종류와 치료 기간을 결정하기 위한 치료 전 평가 항 목이 단순해 질 수 있을 가능성이 있다. 치료 전 평가 및 치료 선택 과정의 복잡성이 단순화 되면, 만성 C형간염 치료에 기여할 수 있는 의사들이 많아지고, 따라서 C형간염에 대한 관심도의 증가 및 치료율의 증가를 가져와 C형간염 박멸의 목표에 더 가까워질 수 있을 것으로 기대된다

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## Update of Pharmacological Therapy in Non-Alcoholic Fatty Liver Disease

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## 비알코올 지방간질환의 약물치료 업데이트

#### 김강모

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Clinical significance of nonalcoholic fatty liver disease (NAFLD) in Korea will be increasing in the near future according to the improvement of nutrition and changing dietary habits. According to 2018 practice guideline for NAFLD recently introduced by AASLD, lifestyle intervention including diet control and exercise is a mainstay of treatment for NAFLD. Although drug development for NAFLD has been delayed compared with other liver disease area, a few positive advances are being achieved in NASH patients. Pioglitazone or high dose vitamin E supplement could be used in NASH patients, but long-term safety of these medications has to be confirmed in further studies. Metformin, UDCA and omega-3 fatty acid are not recommended as a treatment of NASH, but metformin and omega-3 fatty acid could be considered as a treatment of combined diabetes or dyslipidemia in NASH patients. Recently liraglutide (GLP-1R agonist), obeticholic acid (FXR agonist), elafibranor (PPAR $\alpha/\delta$  agonist), cenicriviroc (Dual CCR2/CCR5 antagonist) and selonsertib (ASK1 inhibitor) are showing relatively promising data in clinical trials and could be good candidate for NASH treatment in the future. Bariatric surgery could be considered in NASH patients with morbid obesity or medical treatment failure, but the long-term safety and efficacy is not fully confirmed especially in cirrhotic patients.

Keywords: Nonalcoholic fatty liver disease, Lifestyle intervention, Pioglitazone, Vitamin E, Liraglutide

## 1. 서 론

비알코올 지방간질환(Non-Alcoholic Fatty Liver Disease, NAFLD)은 유의한 알코올 섭취, 지방간을 초래 하는 약물의 복용, 동반된 다른 간질환 등이 없으면서 영상의학 검사나 조직 검사에서 간내 지방침착을 보이는 질환을 말하며 비알코올 지방간(Non-Alcoholic Fatty Liver, NAFL)에서 비알코올 지방간염(Non-Alcoholic Steatohepatitis, NASH), 비알코올 지방간연관 간경변증을 포괄하는 진단이다. 최근 우리나라에서 생활 수준 의 향상과 식습관의 변화에 따라 NAFLD의 위험 인자가 되는 비만, 고지혈증, 당뇨병의 유병률이 높아지고 있어 서 이에 따라 NAFLD의 유병률 또한 앞으로 더욱 높아질 것으로 예상된다. 국내에서 일반 인구집단을 대상으로 한 연구는 제한적이지만, 건강검진 수진자를 대상으로 초음파검사를 이용하여 진단한 NAFLD의 유병률은 16-33%이었으며 간이식 공여자를 대상으로 시행한 간조직 검사에서 NAFLD와 NASH의 유병률은 각각 51.4%와 2.2%이었다.<sup>1,2</sup> 이러한 임상적 중요성에 따라 대한간학회에서는 2013년 우리나라 실정에 맞는 비알코올 지방간 질환 진료 가이드라인을 발표하였는데<sup>3</sup> 이후 미국간학회는 2018년 비알코올 지방간질환 진료 가이드라인을 다 시 한번 업데이트 하였다.<sup>4</sup> 본 연제에서는 새로 가이드라인에서 업데이트 된 내용을 정리하고 최근 비알코올 지

방간질환의 약물 치료에 있어서 추가된 연구들을 소개하고자 한다.

## 2. 2018년 미국간학회 가이드라인에 근거한 비알코올 지방간질환의 치료와 추가된 내용들

개정된 미국간학회 가이드라인에서 NAFLD의 정의에 있어서 변화된 바는 없다. NAFLD의 역학에 대해서는 이 전과 다르게 비교적 자세히 다루고 있는데 그동안 추가된 연구 결과를 참고하여 NAFLD의 발생률을 동양에서 는 1,000 인년당 52.34, 서양에서는 1,000 인년당 28명으로 제시하였고 일반 인구 중 NAFLD의 유병률을 1.5-6.45%, NAFLD 환자 중 NASH의 유병률을 6.67-29.85%로 제시하였다. NAFLD의 자연 경과에서 이번에 새로 추가된 내용은 없고, NAFLD 환자의 장기간 사망률에 있어서 가장 중요한 조직학적 특성이 섬유화라고 명시하 고 있다.<sup>4</sup> NAFLD의 치료에 대하여서는 대한간학회 가이드라인과 마찬가지로 생활습관 교정에 의한 체중 조절 을 가장 중요시하고 있으며 약물치료 및 비만수술(Bariatric Surgery) 부분에서 조금의 변화를 보이고 있다.

## 1) 생활습관 교정

식이 조절과 운동 등 생활습관 교정에 의한 체중 감량이 가장 중요한 NAFLD의 치료임에는 변화가 없다. 간 내 지방의 감소를 위해서는 3-5%의 체중 조절이 필요하며 간 섬유화를 포함한 NASH의 조직학적 개선이 있기 위해서는 7-10%의 체중 조절이 필요함을 제시하였다. 식이 조절 방법이나 운동 방법에 있어서 구체적으로 변 경된 것은 없으며 평소보다 30% 정도 줄여 섭취하고 중등도(최대 심박수의 50-70%)의 운동을 추천하고 있다.

## 2) 약물 치료

약물 치료의 대상은 식이요법과 운동요법을 포함하는 생활습관의 교정에도 호전되지 않는 NASH 환자이다. 여기서 NASH 환자는 일반적으로 간조직 검사에 의해 확인된 NASH 환자를 말한다.

(1) 인슐린 저항성 개선 약물(Insulin Sensitizers)

## (7) Pioglitazone

Pioglitazone은 PPAR-7 agonist로 지방조직과 근육, 간에서 인슐린 저항성을 개선시키고, 염증을 억제하는 adiponectin의 분비를 촉진하여, 간내 지방을 감소시키고 간세포의 손상을 호전시키는 것으로 알려져 있다. 당 뇨병이 없는 247명의 NASH 환자를 대상으로 시행한 PIVENS 연구에서 대상 환자들을 pioglitazone (30 mg/일) 군, 비타민 E (800 IU/일) 군, 대조군으로 나누어 24개월 투약 관찰하였는데 pioglitazone군은 대조군에 비해 연구의 1차 평가 지표인 NAS의 개선을 보였으나 통계적으로 유의하지는 않았다(34 vs 19%, *P* = 0.04). 하지 만 2차 평가지표인 NASH 소실에서는 대조군 21%에 비해 pioglitazone군이 47%로 대조군에 비해 유의하게 많 았다(*P* = 0.001).<sup>5</sup> 이를 근거로 미국간학회에서는 pioglitazone을 조직검사로 확인된 NASH 환자에서 치료제로 사용될 수 있다고 권고하였다. 하지만 pioglitazone의 부작용으로 체중 증가(평균 4.4 kg),<sup>6</sup> 장기간 사용시 골 절, 방광암 위험의 증가와 함께 울혈성 심부전 등이 보고되어 있으므로 위험성과 이득에 대해 충분히 논의 후 사용하여야 하며 간조직 검사에 의해 NASH가 확인되지 않은 NAFLD 환자에서는 사용하지 말 것을 권고하였다.

## (나) Metformin

당뇨병 치료에 사용되는 metformin은 간과 근육에서 인슐린 저항성을 개선하고, 간 내 adenosine monophosphate-activated protein kinase (AMPK)를 활성화시켜 간에서 새로운 지방의 생산을 억제하기 때문에 비알코올 지방간염의 치료에 도움이 될 것으로 생각되었다. 하지만 아직 NASH의 치료에 효과적이라는 보고가 없어서 미국간학회에서는 NASH의 치료제로 권고하지 않고 있다.

#### (2) 비타민 E

항산화제인 비타민 E는 지방간염을 악화시키는 산화 스트레스를 감소시켜 간내 염증을 줄여 주는 것으로 생 각되어 사용되었다. 앞에서 언급한 PIVENS 연구에서 24개월 간의 고용량의 비타민 E (800 IU/일) 투여는 대조 군에 비해 유의하게 높은 간 조직소견 개선 효과를 보였다(43 vs. 19%, *P* = 0.001).<sup>5</sup> 하지만 고용량 (400 IU/일) 이상)의 비타민 E를 장기간 투여할 경우 사망률이 증가된다는 연구 결과가 있으며<sup>7</sup> 35,533명의 건강한 남성을 대상으로 비타민 E (400 IU/일)와 셀레니엄의 투여 효과를 장기간 비교한 SELECT 연구에서는 비타민 E를 투 여한 환자에서 대조약을 투여한 환자에 비해 전립선암의 발생률이 높았다 (HR, 1.17, *P* = 0.008).<sup>8</sup> 미국간학회 에서는 조직검사로 확인된 당뇨병이 없는 NASH 환자에서 고용량의 비타민 E (800 IU/일)를 사용할 수는 있으 나 위험성과 이득에 대해 충분히 논의 후 사용하여야 한다고 하였다. 이외에 당뇨를 동반하는 NASH 환자, 간조 직 검사를 하지 않은 NAFLD 환자, NASH cirrhosis 환자에서는 아직 권고하지 않는다고 제한을 두었다.

#### (3) Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonist - Liraglutide

Incretin은 장에서 분비되는 peptide hormone인 glucagon-like peptide-1 (GLP-1)과 gastric inhibitory peptide (GIP)을 말하며 GLP-1R agonist는 인슐린 분비를 촉진하고 글루카곤 분비를 줄이는 기능 이외에 간 에서의 지방산 분해를 촉진하고 간내 인슐린 저항성을 줄이며 식욕을 줄이는 기능도 있다. 현재 당뇨 환자에서 사용하도록 FDA 승인을 받은 liraglutide는 52명의 NASH 환자에서 1년간 투여한 2상 연구에서 위약과 비교 하여 유의하게 높은 NASH 호전률을 보였다.<sup>9</sup> 하지만 이번 가이드라인에서는 NASH 환자에서 일반적으로 사용하기에는 아직 자료가 부족하다고 명시하고 있다.

#### (4) 기타 약제

이번 가이드라인에서는 위에 언급한 약제 이외에 기타 약제로 ursodeoxy cholic acid (UDCA)와 omega-3 fatty acid만 언급하고 있는데 두 약제 모두 NASH의 치료제로 권하지는 않고 있다.<sup>4</sup>

#### 3) 비만수술(Bariatric Surgery)

이번 미국 가이드라인에서는 비만 수술에 대한 그간의 연구 결과를 비교적 자세히 설명하고 있다. 기존에는 내과적인 치료에 반응하지 않고 건강을 위협할 만큼의 심한 비만 환자 즉, BMI가 35 kg/m<sup>2</sup> 이상이면서 고혈압 이나 당뇨병을 동반한 경우, 또는 BMI가 40 kg/m<sup>2</sup> 이상인 경우를 비만 수술의 대상으로 알고 있었는데 이번 가이드라인에서는 이에 대한 명확한 언급이 없어서 비만 수술의 대상을 조금 더 넓게 보고 있다는 느낌이다. 하 지만 역시 간경변을 동반하는 NASH 환자에서는 주의를 기울여 시행하여야 한다는 제한을 두고 있다.<sup>4</sup>

## 3. 새로이 개발되고 있는 약물

#### 1) Farnesoid X Receptor (FXR) Agonist - Obeticolic Acid

전통적으로 담즙산은 간에서 cholesterol로부터 합성되어 cholesterol의 항상성 조절 및 제거, 담즙 형 성, 식이 지질의 흡수 등의 역할을 하는 것으로 생각되어 왔으나 최근 담즙산과 결합하는 특이적인 핵 수용 체(nuclear receptor, farnesoid X receptor, FXR)와 세포막 수용체(membrane receptor, TGR5)가 발견 됨으로서 이들 담즙산이 대사 조절과 인슐린 저항성에 중요한 역할을 한다는 것이 밝혀지고 있다. 친지질성 (lipophilic) 담즙산은 FXR과 결합하여 여러 기전에 의해 인슐린 저항성과 간내 gluconeogenesis를 감소시키 고 혈중 triglyceride를 줄이는 것으로 알려져 있는데 이 FXR의 agonist인 obeticholic acid (OCA)를 이용한 다기관 무작위 대조군 연구가 최근 발표되었다. 간경변이 아닌 NASH 환자 283명을 대상으로 시행된 FLINT 연 구에서 72주간의 25 mg OCA 투여는 대조군에 비해 유의하게 높은 간 조직소견 개선 효과를 보였으며 (45 vs 21%, *P* = 0.0002) 치료군의 35%에서 섬유화의 호전을 보여서(대조군 19%, *P* = 0.004) 중간 분석 후 연구가 조 기 종료되었다.<sup>10</sup> 하지만 본 연구에서 OCA에 의해 전신가려움증이 23%에서 나타났고 또 다른 부작용으로 총 콜레스테롤과 LDL 콜레스테롤의 상승 및 HDL 콜레스테롤의 감소가 나타나서 장기간 사용시 심혈관계의 안전 성에 대해 의문을 던지고 있다. 현재 많은 수의 환자를 대상으로 3상 연구가 진행 중이므로 향후 그 결과가 기대 되는 바이다.

## 2) PPAR- $\alpha/\delta$ Agonist – Elafibranor

PPAR-α/δ 이중 작용제인 elafibranor는 간내 lipogenesis와 gluconeogenesis를 억제하고 간내 염증 및 인

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슐린 저항성을 개선시킬 수 있다고 알려져 있으며 동물 실험에서 간내 섬유화를 호전시킨다고 알려졌었다.<sup>11</sup> 최 근 275명의 NASH 환자를 대상으로 1년간 투여한 2상 연구에서 elafibranor 120 mg을 1년간 투여하였을 때 위약에 비해 유의하게 NASH 호전을 보인다고 알려졌고 (19 vs 12%, *P* = 0.045) 총 콜레스테롤과 LDL 콜레스 테롤의 감소 및 HDL 콜레스테롤의 증가까지 나타내고 있어서<sup>12</sup> 현재 3상 연구가 진행 중이다.

## 3) CCR2-CCR5 Antagonist - Cenicriviroc

Cenicriviroc은 면역 세포 표면에 존재하는 receptor인 CCR2와 CCR5를 억제하여 간세포의 손상에 작용하는 염증 반응을 줄이는 약물로서 이러한 항염증 반응을 이용하여 NASH 환자에서 간섬유화를 줄이는 임상 연구가 진행되었다. 289명의 간섬유화를 동반하는 NASH 환자에서 cenicriviroc을 1년간 투여하였을 때 위약군에 비하여 NAS의 호전에는 차이가 없었으나(*P* = 0.5194) 1 단계 이상의 간섬유화 호전 빈도는 유의하게 높아서 (20 vs 10%, *P* = 0.0234)<sup>13</sup> 현재 간섬유화를 동반하는 NASH 환자에서 3상 연구가 진행 중이다.

## 4) Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitor - Selonsertib

Apoptosis signal-regulating kinase 1 (ASK1)은 산화스트레스에 의한 세포 사멸과 염증 반응에 역할하는 효소로서 이의 억제제인 selonsertib가 항염증 반응을 이용하는 NASH 치료제로 연구되고 있다. NASH 환자를 대상으로 하는 2상 연구에서 대조군인 simtuzumab (mAb to LOXL2)에 비해 유의하게 섬유화를 호전시켜서<sup>14</sup> 현재 3상 연구가 진행 중이다.

## 5) 2상 연구 중인 다른 약물들

NASH의 치료 타깃으로는 metabolic, anti-fibrotic and anti-inflammatory pathway가 있는데 각 pathway를 억제하는 수많은 약물들이 현재 개발되고 있으며 이를 열거하기에도 버거울 정도이다. 간단히 약 물의 이름과 그 기전을 언급하자면 현재 임상 IIb 연구 중인 약물로 aramchol (synthetic fatty acid/bile acid conjugate), emricasan (pan-caspase inhibitor), GR-MD-02 (galectin-3 protein inhibitor)가 있으며 임상 IIa 연구 중인 약물로는 non-bile acid FXR agonist, other PPARa/& agonists, FGF-19 agonist, recombinant FGF-21, semaglutide (GLP-1 analogue), acetyl-CoA carboxylase (ACC) inhibitors, hyperimmune bovine colostrum 등이 있다.<sup>15</sup>

## 4. 결론

생활 수준의 향상과 식습관의 변화에 따라 NAFLD의 임상적 중요성은 증가할 것이며 이에 대한 치료제의 개 발 또한 더욱 활발해 질 것이다. 식이요법과 운동요법을 포함하는 생활 습관의 교정이 비알코올 지방간질환의 치료에 있어 가장 중요하며 모든 비알코올 지방간질환 환자에서 우선 시행되어야 한다. 간조직 검사로 확인된 NASH 환자에서 약물치료로 pioglitazone이나 비타민 E를 사용할 수 있으나 장기간 치료 시 부작용에 대한 연 구가 더 필요하고 그 부작용과 이득에 대한 고려가 필요하다. 당뇨병이나 고지혈증이 동반된 NAFLD 환자에서 는 동반 질환에 대해서도 적절한 치료가 되어야 할 것이다. 최근 liraglutide (GLP-1R agonist), obeticholic acid (FXR agonist), elafibranor (PPARa/ð agonist), cenicriviroc (Dual CCR2/CCR5 antagonist), selonsertib (ASK1 inhibitor) 등이 3상 임상 연구되고 있으며 향후 좋은 결과가 기대된다. 비만수술은 내과적 인 치료에 반응하지 않고 건강을 위협할 만큼 심한 비만 환자의 치료를 위해 고려할 수 있지만 간경변증 환자에 서는 안전성이 확립되지 않았고 수술에 따르는 합병증과 장기간에 걸친 영양 부족 문제 등을 종합적으로 고려 하여 치료를 결정하여야 한다.

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## Liver Cirrhosis

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## 간경변

#### 서 연 석

고려대학교 의과대학 내과학교실

만성간질환에서 간내 염증이 지속되면 섬유화가 진행하여 결국 간경변증으로 진행한다. 간경변증이 있는 경 우 간세포암종의 발생이 증가할 뿐 아니라 문맥압항진증이 발생하여 위·식도 정맥류, 복수 및 간성뇌증 등 치명 적일 수 있는 합병증이 발생하게 된다. 따라서 간경변증의 발생 및 간경변증 합병증의 발생에 대한 정확한 진단 과 이에 대한 적절한 치료가 만성간질환 환자의 예후 향상에 매우 중요하다고 하겠다. 최근 간경변증의 진단과 치료에 있어 많은 변화가 있었으며, 그 중 중요한 사안들에 대해 논의해 보고자 한다.

## 진 단

가경변증은 원칙적으로 간생검 등을 통해 조직학적으로 진단된다. 그러나 간생검은 침습적인 검사로 심각한 합병증을 유발할 수 있고.<sup>1</sup> 전체 간 중 아주 적은 부위만을 관찰하기 때문에 sampling error가 발생할 가능성이 있으며,<sup>2,3</sup> 검사자내 및 검사자간 결과 분석의 차이를 보이는 경우가 많아<sup>3,4</sup> 그 정확성에 의심이 제기되고 있다. 또한, 이러한 이유로 인해 경과에 따른 간생검 재검을 통한 추적관찰이 힘들다는 것도 큰 문제점으로 생각된다. 이러한 문제점들 때문에 실제 임상에서는 임상적 징후나 혈액검사 결과(혈소판 수치 감소, 간기능 이상 등), 영 상의학적 검사 결과(간 표면 결절, 비장종대 등) 및 내시경 소견(정맥류) 등을 이용하여 간경변증을 진단하는 경 우가 많은데, 이러한 여러가지 임상적 진단 기준의 민감도 및 특이도가 제각각 다르며, 어떠한 임상적 진단 기준 이 가장 적절한가는 아직 확실하지 않다. 따라서 간 섬유화 정도나 임상적으로 현저한 문맥압항진증(clinically significant portal hypertension, CSPH)의 예측에 유용한 비침습적 검사가 필요한 실정이다. 최근 여러 연구 에서 transient elastography (TE)를 이용하여 측정한 liver stiffness measurement (LSM)가 간 섬유화 정도 의 예측 및 정맥류 유무 또는 출혈의 예측에 유용하다고 보고되었다. 그러나 LSM에서 간경변증이라고 분류된 환자의 10–15%는 간생검에서는 간경변증이 관찰되지 않는데,<sup>5</sup> 이는 비침습적 검사를 통한 간 섬유화 정도의 판 정에서 severe fibrosis (F3)와 초기의 대상성 간경변증 사이의 구별이 쉽지 않음을 반영한다. 반면, 간경변증 이 전의 severe fibrosis 단계에서도 문맥압항진증이 동반될 수 있으며,<sup>67</sup> 많은 진료지침에서 간경변증 이전 단계 (F3)에서도 간세포암종 발생에 대한 선별검사를 권장하고 있다.<sup>8,9</sup> 따라서 최근 F3 단계와 대상성 간경변증을 구 분하지 않고 compensated advanced liver disease (cACLD)로 분류하자는 의견이 제기되었다.<sup>10</sup> 이는 비교적 자유롭게 시행할 수 있는 검사인 비침습적 검사를 더 많은 수의 환자를 대상으로 시행하여 CSPH를 가지고 있 거나 발생할 가능성이 높은 환자군 선별하여 만성 간질환에 대한 전문적인 검사 및 치료를 받을 수 있는 기회를 증대시키기 위한 시도로 생각된다. TE를 이용하여 측정한 LS가 10 kPa 미만인 경우에는 cACLD가 있을 가능 성이 거의 없고, LS가 10–15 kPa이면 cACLD가 있을 가능성이 있으나 확진을 위한 추가 검사가 필요하며, 15 kPa를 초과하는 경우에는 cACLD가 동반되어 있을 가능성이 매우 높을 것으로 생각된다.<sup>10</sup>

하편, 가경변증 화자에서는 위식도 정맥류가 동반되어 있는 경우가 많은데, 정맥류가 진행하면 결국 정맥류 파열을 통한 출혈을 유발하게 된다. 내시경적 치료방법의 발달 등 치료법의 향상을 통해 정맥류 출혈 환자의 예 후가 많이 좋아지기는 하였으나 아직도 15-20%의 사망률을 보인다.<sup>11,12</sup> 따라서 정맥류 출혈의 위험이 높은 환 자에서는 베타차단제나 내시경적 밴드결찰술 등을 통한 예방적 치료가 필요하다.<sup>10,13</sup> 출혈 위험이 높은 환자들, 즉 치료가 요구되는 정맥류(varices needing treatment, VNT)를 동반하는 환자들을 선별하기 위해서는 상부 위장관 내시경 검사를 시행해야 하는데. 비침습적 검사를 이용하여 VNT가 있을 가능성이 높은 환자들을 선별 하여 그 휘자들에 대해서만 내시경 검사를 시행함으로써 불필요한 검사를 줄이고자 하는 시도가 진행되고 있다. 이에 Baveno VI criteria에서는 cACLD 환자들(복수나 간성뇌증 등 비대상성 간경변증의 소견이 없으며 LS ≥ 10 kPa인 경우) 중 LS < 20 kPa 이면서 혈소판 수 > 150 × 10<sup>9</sup>/L인 경우에는 VNT가 동반되어 있을 가능성이 매우 낮으므로 내시경적 선별검사가 필요하지 않으며, 그렇지 않은 경우에만 내시경적 선별검사를 시행할 것을 권장하였다.<sup>10</sup> 이후 여러 연구에서 Baveno VI criteria의 유용성을 확인하였으며 VNT를 놓칠 수 있는 위험도 (VNT loss rate)가 0-3.8% 정도로 낮아 이 criteria를 통한 선별이 매우 안전함을 확인하였다.<sup>14-17</sup> 그러나 전체 cACLD 환자 중 내시경 검사를 하지 않아도 되는 환자의 비율이 21.4-32.9% 정도를 보여, 이 기준을 이용하였 을 때 내시경 선별검사를 피할 수 있는 환자의 수가 그리 많지 않다는 단점을 보였다.<sup>14-17</sup> 이에 대해 Augustin 등은 VNT loss rate가 5%를 넘지 않으면서 더 많은 환자에서 내시경 선별검사를 피할 수 있는 새로운 기준을 위해 연구하였으며, LS < 10 kPa 이면서 혈소판 수 > 110 × 10<sup>9</sup>/L인 경우에는 내시경적 선별검사가 필요하 지 않다는 새로운 기준을 제시하였다(expanded Baveno VI criteria, eBaveno VI criteria).<sup>14</sup> 이들 연구에서 Baveno VI criteria를 따랐을 때 21.4%에서 내시경 선별검사를 피할 수 있었으며 VNT loss rate는 1.5%였던 반면, eBaveno VI criteria를 따랐을 때 40%에서 내시경 선별검사를 피할 수 있으면서 VNT loss rate는 1.6% 에 불과하였다.<sup>14</sup> 그러나 국내에서 282명의 cACLD 환자를 대상으로 진행된 연구에서는 eBaveno VI criteria 를 따를 때 51.8%에서 내시경 선별검사를 피할 수 있기는 하였으나 VNT loss rate가 6.8%를 보여 적합하지 않 은 것으로 보였다.<sup>15</sup> cACLD 환자 1245명을 대상으로 한 대규모 후향적 다기관 연구결과가 The Liver Week 2018에서 발표될 예정이다.

## 치 료

Carvedilol은 베타차단제이면서 anti-α1-adrenergic activity도 가지고 있어 베타차단제에 의한 내장혈관 수축을 통한 문맥혈류 감소와 함께 anti-α1-adrenergic activity에 의한 간내 혈관확장을 유발하여 문맥압항 진증 치료에 더 효과적일 것으로 기대된다. 이에 대해 최근 메타분석에서도 다른 베타차단제보다 문맥압 감소 효과가 현저히 우월함이 보고되었다.<sup>18</sup> 이러한 효과가 문맥압항진증의 대표적인 합병증인 식도정맥류 출혈 예방 에도 효과를 보이는지를 확인하기 위한 연구들이 있었으나, propranolol이나 nadolol 등 기존의 베타차단제보 다 월등함을 보여주지는 못 하였다.<sup>19-21</sup> 한편, 베타차단제는 중등도 이상의 정맥류 환자에서 정맥류 출혈을 예 방하는 데에는 효과적이었으나, 정맥류의 발생 또는 작은 정맥류에서 중등도 이상의 정맥류로의 진행을 억제하 지 못하였다.<sup>22-24</sup> 최근 연구에서 carvedilol이 작은 정맥류를 가진 환자에서 중등도 이상의 정맥류로의 진행을 억제하는데 효과적임을 보고하였다(2년 진행률: carvedilol군 20.6% vs. 위약군 38.6%; *P* = 0.04).<sup>25</sup> 일반적인 베타차단제는 내장혈관 확장 및 과역동적 순환(hyperdynamic circulation)이 현저한 상태에서 내장혈관을 수 축시켜 문맥압을 낮추는데 정맥류가 없거나 작은 환자에서는 이러한 내장혈관 확장 및 과역동적 순환이 없거나 그 정도가 약해 베타차단제가 효과를 보이기 어려운 반면, carvedilol은 anti-α1-adrenergic activity를 통해 문맥압항진증 초기에 문맥압을 상승시키는 주 기전인 간내 혈관수축을 완화함으로써 이와 같은 효과를 보이는 것이 아닐까 생각된다.

최근 여러 연구에서 statin이 간내 혈관에서 endothelial nitric oxide synthase 활성도 증가를 통해 nitric oxide 생성을 증가시켜 간경변증에서 간내 혈관 저항을 줄이고 간내 혈관 확장을 유발함이 보고되었다.<sup>26-28</sup> 또한, 문맥압항진증(HVPG ≥ 12 mm Hg)을 동반한 간경변증 환자 59명을 대상으로 한 무작위 대조연구에

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서 simvastatin이 문맥압 감소에 더 효과적임이 보고된 바 있다.<sup>29</sup> 이에 대해 Abraldes 등은 베타차단제 및 내 시경적 정맥류 결찰술을 통한 재출혈 예방법에 simvastatin 투여를 더하는 것이 정맥류 재출혈 예방에 효과 적인지를 확인하기 위한 이중 맹검 무작위 대조 연구를 시행하였다.<sup>30</sup> 연구 결과, 2년 재출혈율은 simvastatin 군에서 25%, 위약군에서 28%로 유의한 차이를 보이지 않아 simvastatin은 재출혈 예방에 효과적이지 않았으 나(*P* = 0.583), 위약군에서 22%가 사망한 반면 simvastatin군은 9%만 사망하여 현저히 낮은 사망률을 보여 simvastatin이 간경변증 환자의 예후 개선에 효과적임을 시사하였다(*P* = 0.03).<sup>30</sup> 또한 최근 대만의 국가 건강 보험 자료를 이용한 연구에서 간경변증 환자에서 statin 사용이 비대상성 간경변증으로의 진행, 간세포암종의 발생 및 사망을 감소시켰다.<sup>31</sup>

## 결 론

최근 간경변증의 진단 분야는 침습적 검사 대신 비침습적 검사를 사용하여 고위험군 환자들을 조기에 간편하 게 진단하고 추적 관찰하려는 시도가 진행되고 있다. 간경변증이라는 조직학적 진단명 대신 심한 간섬유화 상 태와 대상성 간경변증을 포함하는 cACLD라는 질환 카테고리의 도입 및 TE를 이용한 심각한 식도정맥류의 예 측 등이 그 예라고 하겠다. 간경변증의 치료 분야에서는 기존의 베타차단제로 내장혈관 수축을 통해 문맥압 저 하를 유발하는 치료에서 carvedilol이나 statin과 같은 약제가 간내 혈관 확장을 통해 문맥압을 떨어뜨려 베타 차단제에 추가적인 효과를 더하거나 베타차단제가 작용할 수 있는 시기 이전의 비교적 초기 간경변증에서도 문 맥압을 떨어뜨리는 효과를 보여주었다. 향후 이 결과들의 유용성을 확인하기 위한 많은 연구가 진행될 것으로 생각된다.

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DAY 2: Friday, June 15, 2018 (16:30-17:50) WEST TOWER / ROOM AB [B1]

# Symposium 2

## **Recent Updates in Steatohepatitis**

Chairs: Dong Joon Kim (Hallym Univ.) Young Nyun Park (Yonsei Univ.)

## Similarities and Differences in Alcoholic Steatohepatitis and Nonalcoholic Steatohepatitis: A Histologic Point of View

#### So-Young Jin

Department of Pathology, Soonchunhyang University Seoul Hospital, Seoul, South Korea

Steatohepatitis is defined by hepatocyte injury resulting from steatosis. It should be differentiated from simple steatosis. Alcoholic steatohepatitis (ASH) is defined as hepatocyte injury resulting from significant amount of alcohol consumption >20-30 g/day. Otherwise, nonalcoholic steatohepatitis (NASH) is a hepatic manifestation of metabolic syndrome and characterized by fat accumulation without any other causes of chronic liver diseases such as viral, autoimmune, genetic, etc. with minimum alcohol intake  $\leq$ 20-30 g/day.

The morphologic findings of NASH are mostly indistinguishable from ASH. Their overlapping features between two are steatosis, lobular inflammation, hepatocyte injury including ballooning degeneration, acidophilic bodies, and lytic necrosis, Mallory hyaline, megamitochondria, and the centrilobular centered pericellular fibrosis. Ballooning degeneration is essential finding in the both steatohepatitis. Ballooned hepatocytes are enlarged, rounded or irregular in shape and their cytoplasm is pale and rarefied wispy or clumpy with or without Mallory bodies. They are noted predominantly in the acinar zone 3 and immunohistochemistry exhibits loss of cytoplasmic staining for CK8/18. Several distinguishable histologic findings might be helpful for the diagnosis of ASH if present; sclerosing hyaline necrosis, veno-occlusive lesion, alcoholic foamy degeneration, cholestasis, and marked ductular reaction in the portal regions. Relative preferential findings are as follows; more numerous distinct Mallory-Denk bodies and dense fibrosis in ASH and more glycogenated nuclei and consistent steatosis in NASH except for the cirrhotic stage. Therefore, the liver biopsy diagnosis should be made after the clinicopathologic correlation. Representative pathology will be presented.

## Non-Obese vs. Obese Non-Alcoholic Fatty Liver Disease, What Is the Difference?

#### **Donghee Kim**

Stanford University School of Medicine, California, USA

Nonalcoholic fatty liver disease (NAFLD) refers to hepatic steatosis that is not caused by significant alcohol consumption. NAFLD is commonly associated with metabolic comorbidities, including obesity, type II diabetes, dyslipidemia, and metabolic syndrome. However, there is also clear epidemiologic evidence demonstrating that not all obese subjects will invariably develop NAFLD and that NAFLD can be found even in non-obese individuals. Recent epidemiologic studies have reported that non-obese fatty liver disease (NOFLD) occurs in children and adults of all ethnicities (particularly Asians), even when using strict ethnicity-specific criteria for defining obesity. The prevalence of NOFLD reaches 16.7% in Western populations and 27.4% in Eastern populations. According to liver biopsy studies, the prevalence of nonalcoholic steatohepatitis and fibrosis does not differ significantly between NOFLD and NAFLD in overweight or obese patients. Visceral obesity as opposed to general obesity, body weight gain within a normal weight range, high fructose and cholesterol intake, hypothyroidism, and genetic risk factors (e.g., APOC3 and PNP-LA3) may be risk factors associated with NOFLD. Currently, lifestyle modification, including dietary changes and physical activity targeting visceral adiposity, is the standard of care in patients with NOFLD.

## Pharmacotherapy against Nonalcoholic Steatohepatitis under Development

#### Sang Hoon Park

Division of Gastroenterology and Hepatology, Hallym University Medical Center, South Korea

## 새로 개발 중인 비알코올성 지방간염 치료 약제

박상훈

한림의대 소화기내과

1980년 Mayo Clinic의 Ludwig와 동료들이 NASH란 질환을 명명한 이후에 40년 가까이 흘렀으나, 현재까지 NAFLD/ NASH 의 치료제로 인정된 약제는 없는 실정이다. 그 사이 NAFLD/NASH 환자는 비만, 당뇨 환자의 증가와 함께 기하급수 적으로 증가되어, 전세계적으로 가장 흔한 간질환이 되었으며, 가까운 시일 내에 간이식의 가장 흔한 원인이 될 전망이다. 최 근 C형간염 치료제 개발이 끝나고 거대 제약회사들의 관심은 NASH 치료제 개발에 몰리고 있으며, 많은 투자도 이루어 지고 있다. 약제 개발에 어려운 점이 많지만, 현재 3상에 돌입한 2-3가지의 NASH 치료제가 향후 4-5년 사이에 효과가 인정되어 시장에 나올 것으로 추정된다. 치료기전이 서로 다른 몇 가지 약제가 개발된 후에는-만성 C형간염의 치료처럼-몇 가지 약제 의 병합치료에 대한 연구가 가까운 미래에 진행될 것으로 생각된다.

색인단어: NASH, 치료제, 신약

#### Introduction

In 1980, Jurgen Ludwig and colleagues at Mayo Clinic describe fatty liver disease in patients who are not heavy drinkers and they name the condition non-alcoholic steatohepatitis (NASH).<sup>1</sup> Since that time, non-alcoholic fatty liver disease (NAFLD) has become one of the most prominent forms of chronic liver disease worldwide, as a direct result of the obesity and diabetes epidemic.<sup>2</sup> Within the general population, the overall global prevalence of NAFLD is estimated to be 25% though substantial variability was found across the geographical regions.<sup>3</sup> The prevalence of NASH among patients with NAFLD is challenging to assess because of the biopsy-based definition.<sup>4</sup> Generally speaking, 10-20% of NAFLD patients progress to NASH. When focusing on liver-related morbidity and mortality, NASH represents the third most common cause of cirrhosis in the US, but it is predicted to become the leading cause over the next few years and to be the leading indication for liver transplant in 2020.<sup>5</sup>

The striking prevalence of NAFLD and its profound complications underscores the critical need for safe, effective, and broadly applicable therapy. However, there are no medications approved by the Federal Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of NAFLD or NASH at present. In current clinical practice, vitamin E is the most commonly used medication, though evidence of efficacy is limited in those with diabetes and cirrhosis and current guidelines (including KASL) recommend its use be restricted to patients with biopsy-proven NASH in the absence of diabetes and cirrhosis.<sup>6,7</sup> It improves steatosis, lobular inflammation, ballooning, and resolution of NASH, but not in fibrosis. There have also been subsequent safety concerns regarding the use of vitamin E, such as a possible increased risk of overall mortality and high rates of prostatic cancer.

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The other drug, insulin sensitizer pioglitazone (thiazolidinedione), has been extensively evaluated in clinical trials result with fairly consistent improvements in various features of NASH and less consistently fibrosis.<sup>8</sup> The main side effect of using pioglitazone is the tendency to induce weight gain (average 4.4 kg). And it should not be used in patients with heart failure and may promote post-menopausal bone loss. So the increasing disease burden and limited efficacy and safety of current treatment options, the development of additional pharmacologic therapies to treat NASH is critical.

There are currently more than 200 active trials of NAFLD treatments. In recent review articles would have considered only a handful of potential therapies; now they include more than 30. There are numerous agents are currently being investigated in phase II and III clinical trials. Some of these studies have shown promising results in steatosis, inflammation and even fibrosis. However, 'commercialization' of NASH drugs as highly challenging, because of 1) the diagnosis is currently tied with liver biopsy 2) Primary and secondary endpoints still require an invasive biopsy 3) NASH progresses very slowly and the natural history is often heterogeneous, and it is difficult to predict which patients will progress 4) Reaching a conclusive answer about outcomes takes several years.<sup>9</sup>

This concise review will be introducing for the future promising, under development NASH drugs.

#### **Drugs Currently under Development**

#### 1. Drugs currently in Phase III of development

#### 1) Farnesoid X receptor (FXR) agonist (obeticholic acid, OCA)

In the phase IIb trial, 283 biopsy-proven NASH patients without cirrhosis were treated with OCA *vs.* placebo for 72 weeks. The proportion of patients with histological improvement by >2 points of the NAS was 45% in the OCA treatment group, but only 21% in the placebo group. However, the rates of complete resolution of NASH and fibrosis improvement were not different between the two groups.<sup>10</sup> For obtaining Food Drug Administration approval, the phase III clinical trial is currently underway, and the study endpoints include histological improvement at 18 months, 6-year mortality, and liver-related events in 2,000 patients with NASH and fibrosis. The study will not only evaluate the improvement of NASH but also the adverse events of OCA, such as pruritis and change of lipid profiles, observed in the phase II trials.

#### 2) Peroxisome proliferator-activated receptor alpha/delta (PPAR-a/b) agonist (elafibranor)

A total of 276 non-cirrhotic patients with NASH were included in the phase IIb trial. The proportion of patients with resolution of NASH was 23% in the treatment group and 17% in placebo group, which was not significantly different. However, when the definition of NASH resolution was based on more stringent criteria (disappearance of ballooning and none or mild persistence of lobular inflammation) recommended by regulatory authorities, a significant histological improvement was found in the elafibranor 120 mg group with good stability results.<sup>11</sup> Currently, the phase III trial of 2,000 patients with NASH is underway for further evaluation. In addition to histological assessment, the effects of elafibranor on drug-related mortality, liver-related complications, and cardiovascular disease would be evaluated at 72 weeks.

#### 3) Chemokine receptor 2 and 5 (CCR2/5) antagonist (cenicriviroc, CVC)

In the phase IIb clinical trial, patients with NASH and fibrosis were treated with CVC for 2 years and histological changes were evaluated. In the first year of the interim analysis, the primary outcome was not satisfactory, but the anti-fibrotic effect of CVC in patients with severe NASH was prominent<sup>12</sup> and now the phase III clinical trial is ongoing.

#### 4) Apoptosis-signal regulating kinase 1 (ASK1) inhibitor (selonsertib)

In the recent randomized, open-label, phase II trial, NASH patients with moderate to progressive hepatic fibrosis

were treated with either selonsertib alone or the combination of selonsertib and simtuzumab for 24 weeks. The selonsertib alone group showed a significant improvement in liver fibrosis compared to the simtuzumab alone group.<sup>13</sup> Large-scale phase III trials have been started in NASH patients with advanced liver fibrosis or cirrhosis.

#### 2. Phase IIb

#### 1) Stearoyl CoA desaturase 1 (SCD1) inhibitor (Aramchol)

In the phase IIa trial, 60 patients with biopsy-proven NAFL and 6 patients with biopsy-proven NASH were treated with 300 mg of Aramchol for 12 weeks. The treatment group showed significant decreases in liver fat content than the placebo group (12.6% *vs.* 6%).<sup>14</sup> Based on this, a phase IIb clinical trial targeting diabetes, overweight, and biopsy-proven NASH patients is underway.

#### 2) Pan-caspase inhibitor (emricasan)

In the phase IIa trial, HVPG decreased in 17.2% of patients with 12 mmHg of mean HVPG at baseline and ALT was significantly decreased in the emricasan group.<sup>15</sup> Based on this, several phase IIb trials are currently underway in NASH patients with either cirrhosis and severe portal hypertension or decompensation.

#### 3) Galectin-3 inhibitor (GR-MD-02)

In the phase IIa trial, 30 patients with biopsy-proven NASH and advanced fibrosis were treated for 16 weeks, but did not meet the primary endpoint, namely, fibrosis improvement as assessed by MRE.<sup>16</sup> The phase IIb clinical trial for patients with compensated NASH cirrhosis and portal hypertension is currently ongoing, with extended treatment duration of 52 weeks. For cirrhosis, liver fibrosis assessed by MRI would be evaluated, and for portal hypertension, HVPG would be measured after 1 year of treatment.

3. Phase Ila<sup>17</sup>

- 1) NGM282
- 2) BMS-986026
- 3) GLP-1 analogues
- 4) Acetyl-CoA carboxylase (ACC) inhibitors
- 5) Hyperimmune bovine colostrum (IMM-124E)

#### Conclusions

There are no approved drugs for the treatment of NAFLD and NASH at present, but numerous agents are currently being investigated in phase II and III clinical trials. Some of these studies have shown promising results in steatosis, inflammation and even fibrosis. It is widely anticipated that drugs for NASH-most probably obeticholic acid and elafibranor-will enter the market in 2020 or 2021, and that others will soon follow. After that, NASH treatments will be rapidly evolving towards combination therapies as experienced in hepatitis C treatments.

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## Nonalcoholic Steatohepatitis R&D from an Industrial Perspective

#### Toru Seo

Pfizer Japan Inc., Tokyo, Japan

Non-alcoholic fatty liver disease (NAFLD) results from hepatic neutral lipid accumulation and contributes to a majority of liver diseases. A significant number of NAFLD patients advance to clinically relevant non-alcoholic steatohepatitis (NASH) via "parallel hits" where metabolic and pro-inflammatory triggers play a concerted role to accelerate inflammation and hepatic fibrosis. In recent years, NASH has rapidly become pandemic and its alarming prevalence has become a major concern in healthcare in a modern society. Metabolic imbalance has been shown to directly correlate with prognosis of NAFLD/NASH in that glucose intolerance is not only a risk factor for NAFLD and changes in HbA1c levels have been suggested to be predictive for fibrosis in Japanese NASH patients. In contrast, how inflammation exacerbates NASH remains promiscuous. As many clinical candidates advance to the later stages, we now have better idea on clinical development strategy for NASH. Nevertheless, drug discovery for effective NASH drugs remains challenging due to lack of understanding on molecular mechanism, natural history and lack of animal models. In my presentation, I will briefly discuss the overview of R&D in industry and its challenges and share with you our current strategy and a future path to tackle this devastating disease.



DAY 2: Friday, June 15, 2018 (11:10-12:10) WEST TOWER / ROOM C [B1]

# Hepatology Associates Course (\*к)

Chairs: Myung Seok Lee (Hallym Univ.) Won Young Tak (Kyungpook National Univ.)

## Management of Cirrhotic Ascites

#### Nae-Yun Heo

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## 간경변성 복수의 관리

허 내 윤 인제대학교 해운대백병원 내과

The occurrence of ascites is one of major signals which indicate that the patients with liver cirrhosis arrive at the stage of decompensation. Although portal hypertension is the most frequent cause of ascites in case of cirrhosis, other causes should be evaluated meticulously such as malignancy, tuberculosis, and congestive heart failure through the ascetic fluid analysis. If the cirrhotic patient presents abdominal distention and complaint of abdominal pain or fever, diagnostic paracentesis is urgent to find out the spontaneous bacterial peritonitis. The general measures to control the large volume of ascites include the low salt diet, diuretics, and therapeutic paracentesis in addition of treatment of underlying liver disease. Refractory ascites is difficult to control by diuretics, and liver transplantation should be considered. In this case, transjugular intrahepatic portosystemic shunt may be a helpful bridge therapy. Clinicians are required to know that the control of ascites is one of most valuable treatments to improve the quality of life in cirrhotic patient, and apply the adequate method effectively.

Keywords: Ascites, Liver cirrhosis, Diet, Sodium-Restrictied, Paracentesis, Diuretics, Portosystemic shunt, Transjugular Intrahepatic

## 서 론

복수는 간성뇌증, 정맥류 출혈과 더불어 간경변증 환자에서 발생하는 대표적인 합병증 중 하나이며 복부 팽 만감을 동반하여 삶의 질을 떨어뜨린다. 난치성 복수로 진행할 경우 예후가 좋지 않아 환자의 26%가 6개월 이 내 사망하며 중앙 생존기간이 1년 이내로 급격히 감소한다.<sup>1.2</sup> 자발성 세균성 복막염이 발생할 경우 패혈증을 동 반한 간부전 사망률이 높다. 간경변성 복수가 있는 환자는 여러 가지 요인에 의해 신장기능의 저하를 동반할 수 있으며, 말기 간질환 합병증인 간신증후군으로 진행할 수 있다. 복수 조절이 어려울 경우 간부전에 관한 근본적 인 치료인 간이식이 요망되나, 현실적으로 간이식을 받을 수 있는 환자 수가 제한적이기 때문에 일상적인 진료 현장에서는 이뇨제, 복수 천자 등을 적절히 적용하여 증상을 완화시키고 기저 간질환의 호전을 도모하여 환자의 장기 생존을 향상시키기 위해 노력해야 할 필요가 있다.

#### 본 론

#### 1. 간경변성 복수의 발생기전

간경변증 환자에서 복수 발생의 주요 원인은 문맥압항진증이다. 문맥압이 증가하는 경우 내장동맥

Hepatology Associates Course (\*K)

(splanchnic artery)의 확장이 발생하게 되며, 이로 인한 유효혈관용적의 저하는 보상작용으로 reninangiotensin-aldosterone계와 교감신경계, 항이뇨호르몬 등이 활성화되고 신장에서 나트륨 및 수분저류가 발 생하게 된다. 몸에 저류된 수분와 염분은 혈관 내에서 복강 내로 계속 새어나가복수를 형성한다. 또한, 문맥압항 진증에 의한 장모세혈관의 압력과 투과성이 증가하여 복강 내 림프액의 형성이 촉진된다.<sup>3</sup>

#### 2. 복수의 진단

소량의 복수는 증상이 없고, 신체검사에서 발견되기 어렵다. 배가 부르다고 호소하는 환자에서는 우선 배의 모양이 대칭성인지 관찰하고, 복부 타진 시 이동둔탁음(shifting dullness)나 액체파동(fluid wave)이 있는지 확 인해야 한다. 간경변증 환자는 복수가 고이기 전 헛배가 부르며 가스가 많이 나온다. 심한 긴장성 복수가 있는 경우 배꼽 탈장이 보이고, 음낭 수종을 동반하기도 한다. 이동둔탁음은 복수가 1.5 L 이상 존재할 때 확인할 수 있으며, 비만 환자의 경우 평가가 어려울 수 있으므로 이 경우 초음파가 유용하다. 복막에 염증이 없는 간경변증 환자는 누운 자세에서 복벽이 좌우로 쳐지는 양상을 보이나, 세균성 혹은 결핵성 복막염이 있거나 암성 복수의 경우에는 복막자극으로 인해 복벽이 처지지 않고 꼿꼿하게 보이며 근육이 경직되어 있다.<sup>3</sup>

#### 3. 복수 천자

처음으로 복수가 확인된 경우나 복수가 있던 환자가 발열과 복통을 호소하는 경우 진단 목적으로 복수 전차 가 필요하다. 주로 좌하복부 배꼽과 전상장골극(anterior superior iliac spine)을 연결한 가상선의 외측 1/3 지점(counter-Mcburney point)을 천자하나, 복수 양이 많을 경우 우하복부도 천자할 수 있다. 천자 부위를 무 균 소독하고 국소 마취를 한 후 시행하는데, 21G 이하의 바늘을 이용한다. 21G 이하의 바늘은 장을 천공했을 때 대부분 자연치유를 기대할 수 있다. 18G 이상의 바늘을 사용할 경우 천자 부위 자국이 커 천자 후 누출 가 능성이 있고, 장벽을 파열 시킬 위험이 있기 때문에 대량 복수를 신속하게 배액할 경우에 사용하는 것이 적절하 다.<sup>4,5</sup> 복수 천자 후 심한 출혈은 0.2-2.2% 정도에서 발생하며, 수액공급, 수혈, 응고인자 교정으로 대부분 호전 되나 심한 경우 혈관 색전술을 고려해야 한다. 최근에는 초음파 유도하에 복수 천자를 시행하는 경우가 많으며 시술의 성공률을 높이고, 시술 후 합병증을 줄이는데 도움이 된다. 복수천자 전 출혈 위험을 줄이기 위해 신선동 결혈장이나 혈소판 등의 혈액제제를 투여하는 것은 일반적으로 추천되지 않으나, 심한 혈액응고 이상을 보이는 간경변증 환자에서는 복수 천자 시 출혈에 관한 주의가 필요하며 한 부위를 여러 번 천자하지 않도록 한다.<sup>6</sup>

## 4. 복수의 감별진단

복수의 원인은 대부분 간경변증으로 국내 단일 기관의 보고에서 60%라 언급한 바 있다.<sup>7</sup> 그 외에도 암성 복 수, 결핵, 심부전, 췌장염 그리고 신증후군 등이 복수의 원인이다. 복수의 기본적인 선별검사로는 세포 수와 분 획, 알부민, 총 단백 등이다. 또한, 복수 천자와 동시에 혈청 알부민을 측정하여 혈청-복수 알부민 차(serum ascites albumin gradient, SAAG)를 구해야 한다. SAAG는 복수의 원인이 문맥압항진증인지 확인하는데 유용 하다. SAAG ≥1.1 g/dL인 경우 문맥압 항진증에 의한 복수를 시사하고, 간경변증, 심장질환, 버드키아리 증후 군, 굴폐쇄증후군, 광범위 간전이 등이 원인이다. 반면, SAAG <1.1 g/dL인 경우는 결핵복막염, 복막 암종증, 췌 장성 복수 등이 있다. SAAG ≥1 g/dL이면서 복수 총 단백 농도 ≥2.5 g/dL인 경우 심장질환, 초기 버드키아리 증후군, 굴폐쇄증후군 등이며, SAAG <1.1 g/dL이면서, 복수 총 단백 농도가 <2.5 g/dL인 경우는 간경변증, 진 행된 버어드 증후군, 광범위 간전이가 포함된다(그림 1).<sup>6</sup>

복수에 세균이 침투할 경우 복막염이 발생하는데, 간경변증 환자의 경우 장천공 없이 장내세균의 복강 내 이 동으로 염증이 발생할 수 있으며, 이 경우 자발성 세균성 복막염이라고 한다. 간경변성 복수 환자가 발열 및 복 통이 있거나 백혈구증가증이 있을 경우 우선적으로 자발성 세균성 복막염을 의심해야 하나, 임상적으로 증상이 뚜렷하지 않는 경우도 흔하다. 따라서, 복수 환자에서 다른 원인 없이 간성 뇌증이 발생하거나, 신장 기능이 떨 어지는 경우 진단적 복수 천자를 시행하여야 한다. 복수 세포 수 검사 결과 중성구가 250/mm<sup>3</sup>인 경우 자발성 세균성 복막염으로 진단하며 즉시 항생제 투여가 필요하다. 염증이 강하게 의심되는 경우에는 세포 수 검사 시 복수 배양검사를 바로 시행할 수 있으며, 중성구수 확인 후 배양검사를 시행하기도 한다. 이 경우 복수는 바로 혈액배양용기에 담아야 원인균 확인이 용이하다.<sup>6</sup>

결핵복막염의 경우 백혈구 수가 1,000/mm<sup>3</sup> 이상이며 통상 림프구 분율이 50% 이상이나, 초기에는 중성구 우세로 나타날 수 있다.<sup>8</sup> 결핵이 의심될 경우 결핵균을 위한 도말 및 배양검사를 시행하나, 검출되지 않는 경우 가 흔하다. Adenosine deaminase (ADA)가 결핵복막염 진단에 유용하며, 32 U/L의 진단 기준으로 민감도 98%, 특이도 92%의 국내 보고가 있다. 췌장성 복수나 장천공의 경우 복수 내 아밀라아제 농도가 높은데, 대개 췌장성 복수일 때 아밀라아제는 2,000 IU/L 이상으로 장천공에 비해 훨씬 높다. 유미성 복수(chylous ascites) 는 림프액이 복강 내로 누출되어 생기는데, 성상이 우윳빛이다. 외상이나 복강 내 수술 후 림프관 손상에 의해 발생할 수 있으며, 그 외 악성종양 특이 림프종이 원인인 경우가 많다. 중성지방이 200 mg/dL보다 높고, 때로 는 1,000 mg/dL 이상으로 상승하기도 한다. 악성 복수의 가장 흔한 원인은 복막 암종증이며, 여러 가지 악성 종양이 복막으로 전이하여 생긴다. 10%에서 혈성 복수이며, 세포 분율이 림프구 우세로 나타난다. 장천공과 관 련된 이차성 세균성 복막염은 포도당이 50 mg/dL 미만이며, 복수 LDH가 혈청 LDH보다 높다.<sup>3,6</sup>



그림 1. 복수의 감별진단을 위한 알고리듬<sup>6</sup>

#### 5. 간경변성 복수의 치료

#### 1) 원인 간질환의 치료

복수의 가장 근본적인 치료는 원인 간질환의 치료이다. 최근 여러 연구에 따르면, 만성 바이러스 간염(HBV, HCV)의 의한 간섬유화가 항바이러스 치료 후 장기간 추적하였을 때 호전되는 양상을 보였으며, 간경변증 소견 도 역전되는 경향을 보였다. 복수가 발생한 비대상성 간경변증 환자의 일부에서도 이러한 항바이러스 치료 후 영양상태가 개선되고, 간의 합성능력이 향상되며 복수가 줄어드는 양상을 보였다. 또한, 알코올 간질환 환자에서 지속적인 단주가 가능할 경우 복수가 소실되고 이뇨제 요구량이 줄어들며 생존율을 향상 시킬 수 있다.<sup>6</sup>

#### 2) 영양 요법 및 염분 섭취 제한

비대상성 간경변증 환자는 대부분 영양 상태가 불량하다. 하루 35-40 kcal의 열량과 1.5 g/kg의 단백 공급을 권장하나 복수에 의한 복부 팽만감 및 식욕 감퇴가 심한 경우 충분한 영양 섭취가 쉽지 않다. 이 경우 하루 4-6 회로 식사를 소량씩 나누어 먹는 것이 도움이 된다. 간경변증 환자는 공복 시간이 길어질 경우 이화 작용이 두드 러지게 되므로, 밤 9시 이후 200 kcal 정도의 간식을 제공하는 것을 권고한다. 비대상성 간경변증 환자에게 24 주 동안 분지쇄아미노산 제제를 투여하여 혈중 알부민 농도의 호전과 복수 및 부종 발생 감소시켰다는 보고가 있다.<sup>6</sup>

열량요구량 계산 시 사용하는 체중은 일상체중 혹은 건체중이나 복수나 부종이 심한 환자에서는 추정이 어렵 다. 치료적 복수 천자 후나 이뇨제 사용으로 하지 부종이 호전되었을 때의 체중을 건체중으로 추정할 수 있다.

나트륨 1 g은 200 mL의 수분을 체내에 저류시킨다. 따라서, 복수 조절을 위해서는 염분섭취 제한이 매우 중 요하다. 복수를 동반한 간경변증 환자는 염분 섭취를 하루 5 g 이하로 제한할 것을 권장한다. 하지만, 저염식에 순응하지 못하는 환자의 경우 적당량의 염분을 허용하면서 이뇨제를 증량하여 복수를 조절하는 것이 효과적일 수 있다.<sup>3.6</sup>

#### 3) 이뇨제

중등도 이상의 복수가 있는 경우 빠른 증상 회복과 체내 나트륨 균형을 맞추기 위해 이뇨제를 사용한다. 간경 변성 복수 환자에서 발생하는 이차 고알도스테론혈증은 말단 세뇨관과 집합관에서 나트륨과 수분을 재흡수한 다. 알도스테론 수용체 길항제는 이와 같은 병리 기전을 차단하여 복수 조절에 효과적이다. Spironolactone은 반감기가 길고 작용시간이 늦어 안정 농도에 도달하는데 3-4일이 소요된다. 하루 50-100 mg로 시작하여 3-5일 간격으로 용량을 조절하며 하루 최대 400 mg까지 투여할 수 있다. 고칼륨혈증과 여성형 유방이 대표적인 부작 용이다. Amiloride는 spironolactone에 비해 이뇨 효과는 떨어지나 항안드로겐 작용이 적어 spironolactone에 의한 유방통 발생 시 유용하게 사용할 수 있으며, spironolactone 용량의 1/10을 사용한다.<sup>6</sup>

루프이뇨제는 헨레고리의 비후 상행각에서 Na-K-2Cl 수용체를 차단하여 이뇨작용을 나타내며, 대표적인 약 제로 furosemide나 toracemide가 있다. Furosemide는 하루 20-40 mg으로 시작하여 160 mg까지 증량한 다. Torasemide는 furosemide에 비해 반감기와 작용시간이 길며 furosemide 용량의 1/4을 사용한다. 이들 약제는 저칼륨혈증을 일으킬 수 있다.<sup>6</sup>

간경변성 복수 치료의 기본 약제는 알도스테론 수용체 길항제이므로, spironolactone 단독 요법으로 시작하 여 효과가 떨어질 경우 furosemide를 추가할 수 있다. 또한, 복수 조절 속도를 높이고, 고칼륨혈증 부작용 빈도 를 줄이기 위해 알도스테론 수용체 길항제과 루프이뇨제를 동시에 투여하는 병합요법을 사용할 수 있다. 이때 두 약의 비율은 100:40의 비율로 시작하고, 혈청 칼륨의 증감에 따라 관련 이뇨제를 적절히 감량하거나 중단한 다.<sup>6</sup>

체중 감소의 목표는 전신 부종이 있는 경우 하루 1kg 감량, 전신 부종이 없는 경우에는 하루 0.5 kg 감량이다. 이뇨제는 합병증 예방을 위해 복수가 조절되면 가능한 최소 용량으로 사용한다. 이뇨제 사용의 부작용은 간성 뇌증, 저나트륨혈증, 급성 신손상 등이 있으며, 혈청 나트륨이 125 mmol/L 이하로 감소하면 이뇨제를 감량하 거나 중단해야 하며 수분 섭취를 제한할 수 있다. 근육경련은 대개 유효혈류량이 감소하여 발생하는 것으로 알 려져 있는데, 증상이 심한 경우 이뇨제를 줄이거나 중단해야 한다.<sup>3</sup>

#### 4) 치료적 복수 천자

복벽이 과도하게 팽창된 긴장성 복수의 경우 복부 팽만감이 심하고, 호흡곤란을 일으켜 삶의 질이 현저히 떨 어질 수 있다. 이 경우 치료 목적으로 대량의 복수 천자를 한꺼번에 시행할 수 있다. 대량 복수 천자는 복수 1L 당 8 g의 알부민을 투여하였을 때 안전하였다. 치료적 복수 천자는 이뇨제로 조절이 어려운 난치성 복수 환자에 서 효과적인 치료 방법이다.<sup>9</sup>

5) 경경정맥 간내문맥전신 단락술(Transjugular Intrahepatic Portosystemic Shunt, TIPS)

난치성 복수 환자에게 TIPS를 시행할 경우 반복적인 복수 천자에 비해 복수의 재발이 적고 생존율 향상 효과 가 보고되었다. 하지만, 시술 후 30-50%에서 간성뇌증이 동반될 수 있어 이에 대한 대처가 필요하다.<sup>9</sup>

#### 결 론

간경변성 복수는 만성 간질환 환자들이 겪게 되는 가장 흔한 증상 중 하나로 외래에서 적절한 평가를 시행하

여 입원 여부를 결정하고 복수 천자 여부 및 이뇨제 사용 등 환자 상태에 적합한 처치가 요망된다. 간경변증 환 자라 해도 문맥압항진증 외 다른 원인에 의한 복수가 발생할 수 있으므로 복수 검사 결과를 잘 해석할 수 있어 야 하겠다. 기저 간질환에 관한, 특히 바이러스 간염에 의한 간경변증은 기저 간질환의 치료가 가능해졌기 때문 에 복수 조절은 단순히 간이식 대기 중 시행되는 교량 치료가 아니라 기저 간질환의 적극적인 치료 중 한 가지 요소로 생각하여 세심한 관심을 가지고 접근할 필요가 있다.

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## Management of Hepatic Encephalopathy

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## 서 론

간성 뇌증(hepatic encephalopathy)은 간기능 저하 상태에서 발생하는 기면, 혼란, 추체외로 과긴장성, 경 련과 혼수 등의 증상을 특징으로 하는 가역적인 신경정신학적 증후군이다.<sup>1</sup> 급성 혹은 만성으로 분류되며, 다음 3가지 주요 임상상에서 비롯된다. 선행하는 만성 간질환 없이 발생하는 중증 급성 간부전(A), 선행하는 만성 간 질환 없이 문맥대정맥 문합술로 발생하는 경우(B)와 간경증(C)에 의해서 생기는 경우이다. C형 간성 뇌증은 신 경학적 증상의 지속 기간 및 양상에 따라 간헐적(episodic), 지속적(persistent), 미세(minimal) 간성 뇌증으로 나눈다(Table 1).

간경변증에서의 첫 번째 간성 뇌증의 발작은 불량한 예후 인자이며 간질환의 진행에 주요한 전환점을 의미한 다. 간성 뇌증이 발생하면, 1년 생존율이 42%이며, 3년 생존율은 23%에 불과하다.<sup>2</sup> 이처럼 간경변증 환자에서 기대여명을 좌우하는 중요한 문제이며, 뚜렷한 증상 없이 환자 삶의 질을 현저히 낮추는 경한 형태의 간성 뇌증 의 발생 또한 중요한 임상 문제로 대두되고 있다.

Table	1. 간성	뇌증의	분류
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Туре	Nomenclature	Subcategory	Subdivisions
A	HE associated with acute liver failure		
В	HE associated with portal-systemic bypass and no intrinsic hepatocellular disease		
С	HE associated with cirrhosis and portal hypertension/or systemic shunts	Episodic HE	Precipitated Spontaneous Recurrent
		Persistent HE	Mild Severe Treatment-dependent
		Minimal HE	

## 병 인

간성 뇌증의 병태생리는 매우 복잡하며 여러 가지 다양한 원인인자들이 관여하는 것으로 알려져 있으나 아직 도 밝혀지지 않은 부분이 많다(Figure1).<sup>3</sup> 장내 세균에 의해서 생성되는 암모니아는 간성 뇌증의 발생에 있어서 가장 중요한 독성 물질이다.

간세포와는 달리 요소회로(urea cycle)가 없는 뇌에서는 암모니아를 제거할 수 있는 유일한 세포가 성상세포 (astrocytes)이다. 급성 간부전에서는 성상 세포의 부종(edema, swelling)이 특징인 뇌부종이 초래되는데 비해 만성 간부전에서는 Alzheimer type II astrocytosis로 불리는 변화가 나타난다.



Figure 1. Pathogenesis of hepatic encephalopathy

## 1. 암모니아(Ammonia)

암모니아는 급만성 간부전 환자에서 뇌에 축적되어 간성 뇌증을 유발시키는 잘 알려진 신경독소이다. 문맥대 정맥단락술을 받은 개에서 고기를 먹이면 뇌증이 유발되고 혈액보다 뇌에서 암모니아 농도가 현저히 증가되었 다는 사실과 간경변증 환자에서 복수 치료를 위해 암모니움 이온교환 수지를 사용하면 간성 뇌증 또한 호전이 있었다는 보고는 암모니아가 간성 뇌증의 원인임을 추측하게 하는 근거가 되었다.<sup>4</sup>

문맥을 통해 간으로 유입된 암모니아는 정상적으로는 요소회로를 통해 요소와 글루타민(Glutamine)으로 전 환되는데 간질환이 진행되면 간에서 요소합성이 감소하여 암모니아 대사가 충분하게 되지 못하고 문맥전신단락 을 통해 암모니아가 간에서 제대로 대사되지 못하므로 고암모니아 혈증이 나타난다. 이와 같이 문맥 전신 단락 이나 간부전으로 혈중 암모니아가 상승되면 뇌의 성상세포 안에 존재하는 미토콘드리아의 장애, 글루타메이트 (glutamate)와 글루타민 사이의 변화 등이 발생하여 뇌기능장애가 생긴다.

## 2. 망간

망간은 뇌의 기저핵에 잘 침착하는 신경독소로서 간경변증 환자의 80% 이상에서 T1강조 자기공명영상소견 상 침착이 관찰되었다. 망간은 성상세포의 수송체 단백을 자극하여 신경스테로이드 합성 증가와 GABAergic tone을 증강시키고, 기저핵의 성상세포가 Alzheimer type II 유형으로 변하도록 한다.<sup>5</sup>

## 3. 신경전달 물질

장에서 생성되는  $\gamma$ -aminobutyric acid type A (GABAA) 수용체 복합체는 동물 뇌에서 중요한 억제성 신경 전달계이다. 이는 암모니아에 의해 영향을 받는 또 다른 신경전달체계로 간에서 제거되지 못한 GABA가 혈액뇌 장벽의 결함으로 뇌 유입이 증가되고 postsynaptic membrane에 전달하는 GABA 수용체의 항진을 초래하여 신경전도를 억제하게 된다는 GABA시냅스 내 이용도 증가의 가설이 있다.<sup>6</sup> 그러나 간성 뇌증 환자에서 GABA나 GABA 수용체의 농도가 증가하지 않는다는 점을 고려하면 GABA나 GABA 수용체보다는 GABA 수용체에 친 화성이 있는 내인성 benzodiazepine 등에 의한 신경전도 억제가 간성 뇌증의 원인일 가능성도 제시되고 있다.<sup>7</sup> 신경스테로이드는 중추신경계에서 자체 생성되는 스테로이드를 말하며 프로게스테론의 대사물질과 내인성 신경활성 물질이다. 간성 뇌증 환자에서 말초성 벤조디아제핀 수용체는 염증에 의해 미세아교세포(microglial cell)에서 수용체 수가 증가하는데 이 수용체가 발현 증가되면 미토콘드리아 내 신경스테로이드 합성이 증가된 다.<sup>8</sup>간부전 환자에서 증가하는 암모니아와 망간은 수송단백을 활성화시킴으로써 신경스테로이드 합성을 증가 시킨다.

글루탐산은 대표적인 흥분성 신경전달물질이다.<sup>9</sup> 간부전에서는 뇌내 암모니아의 상승이 성상세포 특이적인 효소인 글루타민 합성효소에 의해 이화되면서 글루탐산을 글루타민으로 전환 합성한다. 간부전에서 글루탐산 수용체의 감소는 글루탐산 매개성 흥분성 신경전도 감소로 이어지고 이는 억제성 신경전달 상승과 같은 효과이 므로, 간성뇌증의 증상은 억제성 신경전달의 증가 효과처럼 나타나는 것이다. 전격성 간부전 동물모델에서 글루 탐산 수용체인 N-methyl-A-aspartate (NMDA)의 경쟁적 길항제인 memantine을 투여하면 간성뇌증의 증상 및 전기생리학적 이상이 경감되고 뇌척수액에서 글루탐산의 감소가 관찰된다는 실험이 이를 뒷받침한다.<sup>10</sup>

고암모니아혈증으로 인해 뇌에 글루타민이 축적되면 혈액뇌장벽을 통해 방향족 아미노산(aromatic amino acid) 유입이 늘어나고 세로토닌(serotonin, 5HT)의 전구물질인 tryptophan이 증가하면서 serotonin 대사효 소인 monoamine oxidase(MAO-A)의 활성도 같이 증가되어 serotonin 대사 산물인 5-hydroxyindolacetic acid(5-HIAA)로의 대사가 촉진됨으로써 신경세포 내 세로토닌이 고갈되어 수면장애를 초래하게 된다.<sup>11</sup>

#### 4. 염증반응

감염은 잘 알려진 간성 뇌증의 유발인자이나 그 기전은 완전히 밝혀지지는 않았다. 간경변증 환자는 면역억제 상태로 감염에 취약하나 감염 자체가 간성 뇌증을 악화시키는지 이로 인한 염증반응이 간성 뇌증을 악화시키는 지는 불확실하다.

또 다른 강력한 인자는 장내 세균의 이동인데 이것이 만성적인 내독소혈증을 유발시켜 proinflammatory cytokine, chemokine, Toll-like and chemokine receptor를 통한 호중구를 활성화시킨다.<sup>12</sup> 간성뇌증 환자 에서 글루타민 길항제인 memantine 또는 비스테로이드성 항염증제인 ibuprofen을 투여하면 학습 및 기억력 장애가 호전됨을 관찰한 바 있다.<sup>13</sup>

## 진단

간성 뇌증은 간질환 환자에서 신경정신학적 이상을 보일 때 다른 뇌 질환을 배제함으로써 진단할 수 있으나 실제 임상에서의 진단이 간단하지 않을 수 있다. 현재까지 간성 뇌증의 진단과 정도의 평가를 위한 다양한 신 경정신학적, 신경생리학적 방법들이 발전되어 왔으나 표준화된 진단 방법이 없고 임상적 척도가 최선의 방법으 로 간주되는 경우가 많다. 임상적 척도에는 West-Haven (WH) criteria, Hepatic Encephalopathy Scoring Algorism (HESA), Glasgow Coma Scale (GCS) 및 Clinical Hepatic Encephalopathy Staging Scale (CHESS) 등이 있다. WH criteria는 30년 이상 사용되어 온 척도로, 환자의 의식상태, 지적능력, 습관 및 신경 운동학적 기능의 변화에 따라 정상 상태부터 혼수 상태까지 분류한다(Table 2). 이 기준은 현증 간성 뇌증에 대 한 많은 연구에서 사용되어 왔으나. 경한 정도의 간성 뇌증 진단시는 관찰자 간 평가의 차이가 있을 수 있어 유 용하지 않다.<sup>14</sup> 실제로 간성 뇌증 환자의 80% 이상에서 유발인자가 확인되므로 병력 청취 때 위장관 출혈, 요독 증, 향정신성약제 사용, 이뇨제 사용, 단백질 과다 섭취, 감염, 변비, 탈수, 전해질 불균형 등의 유발인자 유무를 확인해야 한다. 그리고 국소 신경학적 결손이 간성 뇌증에서 매우 드물게 보이는 것으로 알려져 있지만, 의식변 화를 보이는 모든 간경변 환자는 국소 신경학적 결손여부를 검사해야 한다. 만약 기질적인 질환이 완전히 배제 되지 않으면 CT나 MRI와 같은 영상의학 검사를 시행할 수 있고, 필요에 따라서 뇌척수액 천자를 시행하게 된 다. 저혈당증, 저인산혈증, 저산소증, 고탄소혈증과 허혈성 발작과 같은 대사 이상도 간성 뇌증의 증세와 유사 하다는 것을 유념할 필요가 있다. 전산단층화촬영(CT), 자기공명영상(MRI)에 의한 영상은 대개 뇌위축을 보 이거나 뇌증의 급성시기에는 뇌부종을 보인다.<sup>15-17</sup> 간경화 환자에서의 MRI에서 담창구(globus pallidus)에 고 신호의 강도를 보이는 것은 매우 유력한 징후이다. 이는 망간의 침착에 의한 것으로 알려져 있다. 또한 Fluidattenuated inversion recovery sequences (FLAIR) T2 강조영상은 대뇌 백질의 전반적인 고강도 신호를 확 인하는데 민감한 검사인데 이 병변은 가역적인 뇌부종과 비가역적인 뉴런 손상으로 인해 나타난다.<sup>18</sup> 만성간질 환 환자에서 FLAIR T2 강조영상에서corticospinal tract을 따라 고강도 신호와 간이식 후 정상화 됨을 확인한 바 있다.<sup>19</sup>

전기생리학적인 검사로서의 뇌전도(EEG)는 때때로 분명한 상파를 지닌 저속의 파형을 보인다.<sup>20</sup> 한편, 정맥혈 암모니아 수치는 간성뇌증의 정도와 비례하지 않고 모든 환자에서 상승하지도 않으므로 진단에 도움이 되지 않 는다. 동맥혈 암모니아 가스 분압이 혈관-뇌 장벽에서의 암모니아 농도를 평가하는 좀 더 정확한 방법이나, 역시 임상적 유용성을 가지지 못한다.

Grade	Consciousness	Intellect and Behavior	Neurologic Findings
0	Normal	Normal	Normal examination; if impaired psychomotor testing then MHE
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behavior	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behavior	Muscular rigidity and clonus; hyperreflexia
4	Coma	Coma	Decerebrate posturing

Table 2. 간성 뇌증의 West-Haven (WH) criteria

MHE, minimal hepatic encephalopathy.

## 치료

간성 뇌증의 적절한 치료를 위해서는 유발인자를 찾아내어 교정하는 것이 제일 중요하다. 또한 전통적으 로 대장에서 암모니아 생성을 줄이는 방법에 치료의 초점이 맞추어져 있었으므로 항생제 투여(neomycin, metronidazole, rifaximin), 비흡수성 이당류 투여(lactulose,lactitol)와 단백질 섭취제한이 가장 중요한 치료 의 근간이 되고 있으나 이에 대한 추가적인 연구가 이루어지고 있다.<sup>34</sup> 또한 신경전달 관련약제의 투여와 간이식 도 치료에 이용된다.

#### 1. 유발 인자의 교정

간성 뇌증 환자의 80% 이상에서 유발인자가 확인되며 유발인자의 제거만으로 간성 뇌증이 호전될 수 있으므 로 이를 확인하고 신속하게 제거하여 주어야 한다(Table 3).

#### 1) 위장관 출혈

위장관 출혈은 간성 뇌증의 주요 유발인자이며 대부분의 경우 쉽게 진단을 할 수 있다. 출혈이 불분명한 경우 수지직장검사와 상부위장관 내시경 검사가 필요할 수 있다.

#### 2) 세균 감염

유발인자인 세균감염의 확인을 위해서 면밀한 신체 검진이 필요하고 적절한 체액 배양이 요구된다. 세균감염 은 감염 장소에 상관없이 간성 뇌증의 빈번한 유발인자이며 간성 뇌증을 가진 모든 간경변증 환자에서 감염의 확인 및 치료는 필수적이다. 특히, 자발성 세균성 복막염에 대한 감별이 이루어져야 한다.

#### 3) 변비

변비도 간성 뇌증의 유발인자이며 수지 검사를 통해서 잔변이 많이 있는지 확인해야 한다. 그러나 변비만으로

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는 간성 뇌증을 잘 일으키지 않으므로 다른 유발인자가 있는지 같이 규명해야 한다.

#### 4) 단백질 과다 섭취

환자나 가족에게 과다한 고단백 식이를 문진해야한다.

5) 대사 이상

대사성 알카리증, 신기능 부전, 저칼륨혈증, 탈수와 이뇨제에 의해서 간성 뇌증이 유발될 수 있다. 신기능 부전과 저나트륨혈증은 간경변증 환자에서 간기능 이상과 간성 뇌증이 악화되는 주요 원인이며, 저나트륨혈증은 성상세포 의 풍선양 변성을 일으키고, 신기능부전은 신장에서 암모니아 생성을 증가시킴으로써 간성 뇌증의 원인이 된다.

6) 향정신의약품의 사용

모든 향정신물질은, 특히 benzodiazepine, morphine, H1 antihistamine, hypnotic, sedative 등은 간성 뇌증의 발현과 악화에 주요 역할을 한다. 이들 약물의 복용 여부를 환자와 가족들에게 자세히 문진해야 하며 복 용이 불분명한 경우는 flumazenil을 투여하여 회복 여부를 확인해 볼 필요가 있다.

유발인자	유용한 검사법	치료
위장관 출혈	내시경, CBC, 직장수지검사,	수혈, 내시경 및 중재방사선 지혈
	변장혈검사	치료, vasoactive drugs
감염	CBC, 흉부 X-ray, 요 검사 및	광범위 항생제
	균배양검사, 혈액배양검사,	
	진단적 복수천자	
변비	병력청취, 복부 X-ray	관장 또는 약물요법
단백질 과다섭취	병력청취	단백질 섭취 제한
탈수	피부 탄력도, 혈압, 맥박수,	이뇨제 중단 또는 감량, 수액요법
	BUN/Cr	
신기능 장애	BUN/Cr	이뇨제 중단 또는 감량,
		알부민투여 등 수액 요법
저나트륨혈증	혈청 나트륨 농도	수분섭취 제한,
		이뇨제 용량조절 또는 중단
저칼륨혈증	혈칭 칼륨 농도	이뇨제 용량조절 또는 중단
벤조디아제핀	병력청취	약물투여 중단,
		Flumazenil 투여 고려
급성 간기능 악화	간기능 검사, 프로트롬빈 시간	보존적 치료

Table 3. 간성 뇌증의 유발인자와 감별 진단

#### 2. 암모니아 생성 감소

#### 1) 단백질 섭취 제한

지속적인 식이 단백의 제한은 특히 영양결핍의 문제 때문에 피해야 한다. 그러나 과도한 단백질이 장내로 유 입되면 장내세균에 의해 대사되어 암모니아 형성이 증가할 것이라는 근거를 바탕으로 임상에서 일반적으로 권 고되는 지지요법이다. 질소 균형을 양성으로 유지하여야 간 재생에 의해 간기능이 호전되고 근육량의 증가로 인 한 암모니아 대사율이 향상되므로 초기 급성단계에서는 하루 0.5 g/kg 미만으로 단백질을 제한하더라도 장기 간의 단백질 섭취제한은 영양불량을 초래하고 예후를 악화시키므로<sup>21</sup> 임상반응이 호전되면 가능한 빨리 단백질 섭취를 1-1.5 g/kg까지 늘리도록 한다. 만성 간성 뇌증에서는 식물성 고단백섭취가 선호된다. 만성 간질환은 종 종 아미노산 대사의 불균형이 나타나는데 이를 교정시키고자 분지사슬 아미노산을 투여하는 연구들이 있었으 나 이에 대한 메타 분석에 의하면 급성 및 만성 간성 뇌증 환자에서 분지 아미노산의 투여가 별다른 효과를 보이 지 못했다.

#### 2) 비흡수성 이당류(Non-Absorbable Disaccharides)

삼투성 하제인 락툴로스(lactulose, β-galactosidofructose)는 소장에서 장내 이당류 분해효소에 의해 분해

되지 않고 대장에 도달한 후 장내세균에 의해 초산(acetic acid)과 젖산(lactic acid)으로 분해되어 대장을 산성 화시키므로 요소분해효소인 유레아제(urease)를 생산하는 세균의 서식이 어려워져 암모니아 형성이 감소되고 암모니아 체내흡수도 적게 된다.<sup>22</sup> 급성 뇌증에서는 락툴로스 30-50 mL를 설사가 나타날 때까지 1-2시간마다 복용시키고 의식저하가 심하면 동량을 비위관을 통해 투여하거나 물 700 mL에 락툴로스 300 mL를 희석하여 관장요법을 한다. 이후 하루 2-3회의 묽은 변을 볼 수 있도록 용량을 조절하는데 대개 하루 2-4번 15-45 mL씩 투여한다. 장폐쇄나 장마비가 있으면 락툴로스를 경구 투여하면 안되고 관장을 하면 경구복용보다 복부팽만이 덜 하므로 심한 복수, 자발성 세균성 복막염 등에서는 관장이 선호된다. 단맛이 덜 하고 가스팽만이 덜 한 락티 톨(lactitol, β-galactosidosorbitol)은 하루에 30-45 g 정도 투여하면 락툴로스와 거의 유사한 효과를 나타낸 다. 많은 환자에서 투여되고 대부분의 임상의가 이의 효과에 동의함에도 불구하고 메타분석을 통해 확인한 결과 비흡수성 이당류의 투여는 위약에 비해 별다른 효과가 없으며 항생제투여보다 열등하다고 분석되었다.<sup>23</sup> 그러나 간성 뇌증 치료효과를 판정하기에는 변수로 작용할 다양한 인자가 산재해 있으며 이를 대체할 만한 약제가 없 어 여전히 치료제로 추천된다.

#### 3) 경구용 항생제

간경변증의 급, 만성 간성 혼수에서 비흡수성 이당류 대신 사용할 수 있으며 많은 연구에서 효과가 입증 되었 다. 메타분석에서 비흡수성 이당류보다 우수함을 보여주었으며,<sup>24,25</sup> 장관내 요소분해효소를 가진 세균에 대한 항균효과를 통해서 암모니아 생성을 감소시킨다. 네오마이신은 처음 사용되었던 약제로서, 체내 흡수율이 낮 고, 급, 만성 간성 뇌증에서 락튤로스와 동등한 효과를 보이지만, 신독성 및 청각기능 이상의 부작용의 위험성 으로 인해 사용되어 지지 않고 있다.<sup>26</sup> Metronidazole은 만성 간성 뇌증에서 네오마이신과 동등한 효과를 보이 며, 장관 내에서 흡수되어 강력한 간 초기 투과효과로 인해 신경 독성을 일으킬 수 있어서 권장되지 않고 있다. Rifaximin은 rifamycin의 유도체이며, 생체 이용율이 0.5%로 낮은 약제로서 대부분 분변으로 대사되지 않고 배출된다. 그래서 간이나 신장기능 이상소견을 보이는 환자에서도 용량 조절이 필요치 않으며, 약물간 상호작용 도 없는 장점이 있다. 비흡수성 이당류 혹은 항생제와 Rifaximin의 효과를 비교한 9개의 open label 연구들과 4개의 이중 맹검 연구에서 80-90%에서 좋은 치료 반응을 보였으며 락튤로스와 비교하여 보다 우수한 효과를 보였다.<sup>27-29</sup> 하지만, 대부분의 연구가 open-label 연구이며 대상 환자가 이질적이고 치료 효능 평가기준이 모호 한 문제점이 있다는 것을 고려해야 한다. 그럼에도, Rifaximin은 간성 뇌증의 효과적이고 안전하게 사용할 수 있는 약제로 인정받고 있다.

#### 4) Probiotics

고용량의 probiotics는 특히 요소분해효소가 없는 Lactobacillus acidophilus나 Enterococcus faecium SF68등의 장관 내 세균총으로 변화시킨다. 미세 간성 뇌증 환자에게 투여하면 요소분해효소가 없는 세균들이 의미 있게 증가하며, 50%의 환자에서 암모니아 혈중 농도의 감소와 더불어 의식상태의 호전을 보인다. 새로운 치료법인 probiotics에 대한 연구는 대규모 대조 연구가 필요한 상태이다.

#### 5) L-Ornithine-L-Aspartate (LOLA)

L-Ornithine-L-Aspartate (LOLA)는 암모니아를 요소와 글루타민으로 대사시키는 기질로 작용하여 암모니 아 농도를 감소시키는 물질이며 일부 연구에서 효과적이고 안전하다고 제시되었다.<sup>30</sup> 고암모니아 혈증과 만성 간성 뇌증을 가진 126명의 무작위, 이중 맹검 연구에서 LOLA 20 mg을 5일간 투여한 결과 위약군에 비교해서 정신의학적 검사의 호전과 고암모니아 혈증의 감소를 확인하였다.

#### 6) Zinc 결핍

Zinc는 요소 회로의 조인자로 요소생성을 증가시켜서 암모니아 이온을 감소시킨다. Zinc 결핍은 영양상태가 불량한 간경변증 환자에서 흔하게 관찰되므로 모든 환자에서 결핍여부를 확인하여, 결핍이 확인되면 하루 2번 zinc 200 mg 투여를 권고하고 있다.<sup>14</sup> 아직 zinc 투여가 간성 뇌증을 호전시키는 지는 논란이 있다.

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#### 7) L-Carnitine

L-carnitine는 에너지 대사를 증가시켜서 암모니아를 감소시킬 수 있는 물질로 아직 연구는 많이 부족하다. 150명의 간경변증 환자를 대상으로 한 연구에서 위약군에 비교하여 투여군이 공복 암모니아 농도를 감소시키 고 정신과적 검사의 호전을 보여주었다.<sup>31</sup>

#### 3. 신경전달 관련약제

Flumazenil과 Bromocriptine의 투여는 일부 환자에서 좋은 효과를 보인다는 보고가 있으나,<sup>14</sup> Bromocriptine과 L-DOPA는 추체외로 증세를 가진 간성 뇌증 환자들에게서 최근의 메타분석에 의하면 별 다른 효과가 없다고 나타났다. Flumazenil은 benzodiazepine 과량 투여시 사용되며 간성 뇌증에서 많은 연 구가 이루어졌으며 신경학적 상태의 호전을 보여주었다.<sup>32</sup> 뇌파 검사에서도 투여군이 3, 4 단계 뇌증에서 각각 27.8%, 21.5%의 호전을 보여주었다. Flumazenil 투여 후 임상적인 호전은 항상 만족스러운 것은 아니지만, benzodiazepine을 복용한 간성 뇌증환자에서는 1 mg 정주를 권장한다.

#### 4. 간이식

치료에 반응하지 않는 심한 간성 뇌증 환자는 간이식의 대상이 되며, 초기증상으로 간성 뇌증을 보인 급성 간 부전 환자의 경우 예후가 불량하기 때문에 간이식을 고려한다.<sup>33</sup> 또한, 간성 뇌증의 정도가 예후와 연관이 있으 며, 현성 간성 뇌증이 발생한 후 1년 및 3년 생존율이 각각 42% 및 23%로 불량하므로, 간성 뇌증이 발생한 환 자에서는 간이식을 고려한다. 하지만 일반적으로 간이식대상자 선정에 이용되는 model for end-stage liver disease (MELD) system은 다양한 이점에도 불구하고 간성혼수가 발생했던 환자의 예후를 제대로 반영하지 않 는 단점이 있다.<sup>34</sup>

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## Antiviral Therapy for Chronic Hepatitis B and C

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## Introduction

Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) are global health burden and important risk factors of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC).<sup>1,2</sup> Development of potent nucleos(t)ide analogues (NAs) with high resistance barrier represents the treatment of choice for chronic hepatitis B virus (HBV). With the emergence of direct acting antivirals (DAAs), the success rate of elimination of hepatitis C virus (HCV) has improved dramatically. The goal of this review is to suggest up to date recommendations for using antiviral therapy in chronic HBV and HCV infection in Korea.

## Antiviral Therapy for Chronic hepatitis B (in Korea)

#### 1. Goals of Treatment

The reason to treat patients with chronic HBV infection is to prevent disease progression, and occurrence of HCC. The goal of nucleos(t)ide analogue (NA) therapy is to suppress HBV replication. Proper timing of therapy, disease state of liver and the patients' age when treatment are important to achieve this goal successfully.

## 2. When and in Whom? (in Korea)

Table 1. Guidance statements on CHB treatment in Korea

Patients with HBeAg-positive and HBV DNA ≥20,000 IU/ml & ALT≥80 U/L should start treatment regardless o	of the
degree of fibrosis.	

Patients with HBeAg-negative and HBV DNA ≥2,000 IU/mI & ALT≥80 U/L should start treatment regardless of the degree of fibrosis.

Patients with compensated cirrhosis, and HBV DNA ≥2,000 IU/ml should start treatment. Patients with decompensated cirrhosis (or hepatocellular carcinoma), and HBV DNA-positive should start treatment.

#### 3. What Regimens We Can Choose

There are several treatment options for CHB patients: treatment with a NA or with Peginterferon (Peg-IFN). The NAs that have been approved in Korea the treatment of patients with chronic hepatitis B include lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine, clevudine, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), and recently besifovir. The preferred regimens were ETV, TDF, TAF, Peg-IFN and besifovir can be considered.

### 4. Endpoints of Therapy

The induction of complete HBV suppression is the main endpoint of all antiviral therapy and the level of HBV replication is the most important predictive marker of antiviral therapy. HBsAg loss, with or without anti-HBs seroconversion is an optimal endpoint, but it is very hard to achieve.

Indefinite antiviral therapy for CHB should be done in patients with HBeAg-negative, immune active CHB or cirrhosis unless there is a stone rationale for discontinuation. HBeAg-positive patients without cirrhosis but with CHB who seroconvert to anti-HBe during therapy can discontinue NAs after treatment consolidation.<sup>3</sup>

#### 5. Summary

ETV, TDF, TAF, Peg-IFN, besifovir can be first line therapy. Discontinuation of therapy should be carefully decided and can be done in limited condition.

## Antiviral Therapy for Chronic hepatitis C

#### 1. Goals of Treatment

Recently, many DAAs have been developed and the pace of change has accelerated dramatically.<sup>4</sup> Unlike chronic hepatitis B, the primary goal of HCV therapy is to eradicate HCV infection. HCV cure is needed in order to prevent HCV-related complications, onward transmission, and improve quality of life. The HCV infection is cured in more than 99% of patients with SVR.<sup>5</sup> A sustained virological response (SVR) is defined as undetectable level of HCV RNA 12 weeks (SVR 12) or 24 (SVR 24) weeks after treatment completion.

#### 2. When and in Whom?

Evidence supports treatment for all patients with HCV infection, without contraindications for treatment. Treatment must be considered especially in patients with significant fibrosis or cirrhosis, although treatment is best administered before progression of liver fibrosis. Patients with short waiting time for liver transplantation will benefit from transplantation first before antiviral treatment.<sup>5</sup> DAAs can be used except few contraindications, but certain cytochrome P450 inducing drugs can't be used simultaneously with all DAAs due to decreased concentrations of DAA. Treatment is generally not recommended in patients with limited life expectancy because of non–liver-related comorbidities.

## What Regimens We Can Choose (HCV DAA)?

#### 1. Genotype 1a

Grazoprevir/elbasvir+/-Ribavirin(RBV)- [NS5A RASs for elbasvir] Sofosbuvir+ledipasvir+/-RBV Paritaprevir/ombitasvir/ritonavir+Dasabuvir+RBV Sofosbuvir+daclatasvir+/-RBV

## 2. Genotype 1b

Grazoprevir/elbasvir+/-RBV Sofosbuvir+ledipasvir+/-RBV Paritaprevir/ombitasvir/ritonavir+Dasabuvir Sofosbuvir+daclatasvir+/-RBV Daclatasvir+asunaprevir

3. Genotype 2

Sofosbuvir+RBV

#### 4. Pangenotype

Glecaprevir/pibrentasvir Sofosbuvir/velpatasvir Sofosbuvir/velpatasvir/voxilaprevir

#### Table 2. HCV DAAs approved or not in Korea in 2018.

Product	Approved in Korea
Pangenotypic drugs or drug combinations	
Sofosbuvir	0
Sofosbuvir/velpatasvir	x
Sofosbuvir/velpatasvir/voxilaprevir	x
◊ Glecaprevir/pibrentasvir	x/o
Genotype specific drugs or drug combinations	
Sofosbuvir/ledipasvir	0
Sofosbuvir/daclatasvir	0
Paritaprevir/ombitasvir/ritonavir	0
Dasabuvir	0
Grazoprevir/elbasvir	0
Asunaprevir/Daclatasvir	0

## 5. Endpoints of Therapy

The endpoint of therapy is a SVR, defined by undetectable HCV RNA in blood 12 weeks (SVR12) or 24 weeks (SVR24) after the end of DAA therapy, confirmed by a sensitive molecular method. Both SVR12 and SVR24 have been accepted as endpoints of therapy because their concordance is more than 99%.<sup>6</sup>

## 6. Follow Up after Therapy

Untreated patients or those who failed SVR should be regularly followed. A fibrosis evaluation using non-invasive methods is recommended. HCC surveillance must be done in patients with advanced fibrosis or cirrhosis.

## Summary

CHC can be cured using DAAs, but in patients with advanced liver diseases and non-sustained virological responders should be followed up after therapy.

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## Treatment for Hepatocellular Carcinoma

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## 간세포암종 치료

조 성 범

전남의대 내과

간세포암종 치료는 암종의 다양성과 동반된 간경변 상태에 따라 적절한 치료에도 일관된 경과를보이지 않는 경우가 많아 다 양한 임상 요소를 고려한 다학제 접근을 통한 치료방법이 추천되고 있다. 최근 간세포암종 치료는 기존 치료법의 진보와 더불 어 새로운 표적치료제와 면역치료제가 도입되면서 패러다임의 변화가 시작되고 있으며 이를 반영하여 2018년도 유럽간학회 에서는modified BCLC 병기와 함께 간세포암종 치료 가이드라인이 새롭게 업데이트 되었다. 이번 발표를 통하여 다양한 치 료법과 특성을 소개하여 간세포암 치료를 시작하려는 임상의 및 연구자에게 도움이 되고자 하였다.

Keywords: 간세포암종, 치료, 병기

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancer-related death globally although trying to treat by various therapeutic modalities. The choice of treatment methods for HCC patients is hard to make for many clinicians because of lack of consistent outcome after HCC treatment under the heterogeneity condition of tumor and background liver disease. Recently, the treatment paradigm has been changed to advances of conventional treatment modalities and target agents and to introduce immunotherapy for HCC. Barcelona Clinic Liver Cancer (BCLC) staging system has been widely used and recently modified according to change prognosis and reflect new clinical trials (Figure 1). Modified BCLC staging system is changed to focusing several reasons. First, radiofrequency ablation (RFA) is recommended as first line option than surgical resection for BCLC 0 stage. Second, preoperative multi-parametric assessments of liver function and tumor status are emphasized and clarified on the key conditions affecting surgical decision. Third, newly approved systemic agents beside sorafenib are recommended as first (lenvatinib) and second line treatment (regorafenib, cabozantinib, and nivoulmab). Fourth, prognosis according to stage is changed to reflect new clinical trials. Therapeutic decision for HCC should understand the characteristics of various therapy as well as guidelines considering widely different patient's condition. In clinical practice, multidisciplinary approach to share experience and judgment is most important to overcome clinical heterogeneity of HCC according to various patient's condition and tumor status. I hope this presentation can help young clinician for treating HCC that summarized HCC guidelines.



Figure 1. Modified BCLC staging system and treatment strategy

## 1. Very Early Stage (BCLC Stage 0)

Very early HCC is defined as the presence of a single tumor <2 cm in diameter without vascular invasion/satellites in patients with good health status (ECOG-0) and well-preserved liver function (Child-Pugh A class). The patients are recently increased at this stage because of surveillance programs for high risk patients. MRI should be needed to diagnose and find another satellite nodule in early HCC. Recent data have shown a five-year survival in 80–90% of patients with solitary HCC smaller than 2 cm treated with resection or radiofrequency ablation (RFA). RFA might become the first line option at this stage, leaving surgery for those patients with nodules not suitable RFA. Because RFA is able to offer a complete tumor necrosis with a safe margin in the majority of cases and provided similar life expectancy and quality-adjusted life expectancy at a lower cost. The only advantage of surgical resection would be the opportunity to assess the risk of early recurrence by pathology (microvascular invasion, poor differentiation or presence of satellites).

## 2. Early Stage (BCLC Stage A)

Early HCC is defined in patients presenting with single tumors >2 cm or three nodules <3 cm in diameter, ECOG-0 and preserved liver function. Median survival of patients with early HCC reaches 50% to 70% at five years after resection, liver transplantation or local ablation in selected candidates. The complete local tumor control by initial therapy in patients with early HCC is very important for preventing progression to advance stage with concerning the balance of effects and complications. Tumor status is defined by the size of the main nodule and multi-centricity (single lesion, three nodules  $\leq$ 3 cm), each of these categories showing significantly different outcomes. For single tumor beyond 5 cm without clinically relevant portal hypertension, surgical resection is considered as a first option. Liver transplantation may potentially cure both the tumor and the underlying liver disease, as prognostic factors (single tumors  $\leq$ 5 cm or three nodules  $\leq$ 3 cm), defining the so-called Milan criteria.

## 3. Intermediate Stage (BCLC Stage B)

Median survival for untreated patients at an intermediate-stage (multinodular asymptomatic tumors without

vascular invasion or extrahepatic spread) is 16 months or 49% at two years. TACE is considered the first-line treatment with a super-selective approach according to the positive results for survival benefit in randomized studies and cohort studies. The current intermediate HCC definition includes a wide range of patients according to liver function and tumor burden. This has triggered a major controversy and willingness to further stratify the BCLC-B category according to tumor burden and liver function. Some of these proposals classify large solitary HCC beyond 5 cm with an expansive growth as intermediate- stage, although vascular invasion or tumor dissemination has been excluded after proper imaging evaluation. However, if technically feasible they may benefit from surgical resection, and these patients should be classified as BCLC A.

## 4. Advanced Stage (BCLC Stage C)

Patients with cancer-related symptoms (symptomatic tumors, ECOG 1-2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a poor prognosis, with expected median survival times of 6–8 months or 25% at one year. Until 2007, there was no FDA-approved first-line treatment for patients with advanced HCC. Sorafenib, a multi-tyrosine kinase inhibitor, was only approved target agents that showed survival benefits for advanced HCC. The positive results of sorafenib opened the door for evaluation of other targeted agents. Lenvatinib, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor  $\alpha$ , RET, and KIT, demonstrated non-inferior survival to sorafenib in an open-label, multicenter, non-inferiority, randomized trial. Regorafenib, an oral multi-kinase inhibitor with a similar mechanism of action to sorafenib, demonstrated an impact on survival in a phase III trial in patients with HCC who progressed but were tolerant to sorafenib and had Child-Pugh A liver function and performance status 0 or 1. Cabozantinib, a MET, VEGFR2 and RET inhibitor approved for thyroid and renal cancer, has shown survival benefit compared to placebo in second-line.

## 5. Terminal Stage (BCLC Stage D)

End-stage HCC: Patients with end-stage disease are characterized by very poor performance status (Eastern Cooperative Oncology Group 3–4) that reflects a severe tumor-related disability. Their median survival is 3–4 months or 11% at one year.

## 6. Summary of HCC Treatment

- 1) Surgical Treatment
  - a. Surgical resection
  - b. Liver transplantation
- 2) Loco-Regional Treatment
- A. Local Ablation Therapy
  - a. Radiofrequency ablation
- b. Microwave ablation
- c. Percutaneous ethanol injection therapy (PEIT)

#### B. Regional Therapy

- a. Transarterial chemoembolization
  - Conventional lipiodol TACE
  - Drug eluting bead TACE (DEB-TACE)
  - Transarterial radioembolization (TARE)

- b. Hepatic arterial infusion chemotherapy (HAIC)
- c. Radiation therapy
- 3) Systemic Therapy
  - a. Tyrosine kinase inhibitor
    - First line: sorafenib, lenvatinib
    - Second line: regorafenib, cabozantinib
  - b. Cytotoxic systemic chemotherapy
  - c. Immune check point inhibitor (anti-PD1, anti-CTLA4)
  - d. Cell based immunotherapy
- 4) Combined Modalities (various)
  - a. TACE+RFA
  - b. TACE+SBRT
  - c. Sequential treatment

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (13:10-15:10) WEST TOWER / ROOM E [2F]

# KLTS Coordinator Session (\*к)

Chairs: Hea Seon Ha (Asan Medical Center) Seung Heui Hong (Samsung Medical Center)

## Liver Transplantation in Alcoholic Liver Disease

## Jun Yong Park

Yonsei University, South Korea

## Counselling, Education, and Monitoring for Patients with Alcoholic Liver Disease before Liver Transplantation

#### Hyung Sook Kim

Seoul ST. Mary's Hospital, Organ Transplantation Center, Seoul, South Korea

## 알콜성 간질환의 간이식 전 상담, 교육, 모니터링

### 김형숙

서울성모병원 장기이식센터

2010년 9월 미국 장기이식관리센터(United Network for Organ Sharing: UNOS)의 통계에 따르면 알코올성 간질환은 미 국의 전체 간이식 원인의 2위를 차지했다.

2016년 우리나라 장기이식관리센터(Korea Network for Organ Sharing: KONOS)에 따르면 간이식을 받은 19.56% 가 알코올성 간질환이 원인이었으며 이중 생체로 간이식을 받은 경우는 12.65%이고 뇌사자로부터 간이식을 받은 경우는 32.68% 였다. 이는 2012년 간이식을 받은 원인이 알코올성 간질환에서 9.89%였던 때보다 1.98배 증가하였다.

알코올로 인한 간질환은 지방간, 급성 알코올 간염이나 알코올 간경변으로 변화되며 이는 이따금씩 폭음을 하는 습관보다는 지속 적인 음주습관자에서 흔하게 발생한다고 한다. 알코올성 간염의 경우 금주를 시행하고 steroid를 포함한 약물요법을 시행할 경우 간기능의 회복을 기대할 수 있으나 3-6개월 이상의 치료에도 불구하고 호전증세가 보이지 않을 경우 간이식을 고려할 수 있다.

그러나, 간이식 후 음주를 계속하는 경우가 생겨서 Dew들은 메타분석을 통해 간이식 전 사회적인 지지의 부족, 알코올 중독 이 있는 가족력이 있는 경우와 금주기간이 6개월 미만인 경우를 간이식 후 음주에 노출될 수 있는 3가지 요인이라고 하였다. 6개월 미만의 금주에 대해서는 논쟁의 여지는 있지만 6개월 금주기간의 예측 유용성에 대해서는 널리 사용하는 편이다.

예전의 연구들은 알코올 중독으로 간이식을 받고 나면 이식 후 관리에만 집중하여 알코올 중독에 관한 치료를 꺼려한다고 하 였다. 이를 바탕으로 알코올성 간질환으로 간이식을 대기하는 동안, 이식 전의 일반적인 건강상태를 증진하고 간 이식 후 음주 를 줄이기 위해 심리 치료법을 테스트하게 되었다.

국내에서도 병원에 따라서는 알코올성 간질환의 대한 이식 전부터 금주를 위한 프로그램을 진행하면서 이식을 하는 경우도 있으나 병원별 차이가 있고 이에 대한 규정이 없는 상황이다.

알코올 중독에 의한 간이식을 진행되는 경우 가족 관계에도 변화가 생겨서 알코올 중독으로 인해 고통을 받았던 가족 구성원 은 환자의 상태가 급박하여도 생체로 간을 기증할 의사는 없지만, 뇌사자에 의한 이식을 원하는 가족들을 만나게 될 경우가 많 다. 뇌사자에 의한 간이식은 응급도에 의해서만 진행 될 뿐 알코올에 대한 금주여부가 규정으로 없기에 실제 간이식 후 음주를 하는 환자들도 있어서 소중한 뇌사자 간이식을 통한 생명 나눔의 본 취지가 퇴색되지 않도록 하는 규정이 필요하다고 본다. 또한 알코올성 간질환으로 인한 간이식의 경우 간이식 전부터 프로토콜을 가지고 준비를 하는 것에 대한 필요성들을 있으며 더 나아가 알코올 중독인 환자로 인해 상처받고 피폐된 다른 가족구성원들에 대한 심리적 지지 역시 필요성을 제기하고 싶다.

Keywords: 알코올성 간질환, 간이식, 이식 전 금주

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## Counselling, Education, and Monitoring for Patients with Alcoholic Liver disease after Liver Transplantation

#### Jeon Kyung Ock

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## 알코올성 간질환 환자의 간이식 후 상담 및 교육

### 전경옥

세브란스 병원 장기이식센터

성인에서 간이식의 주된 적응증은 B형 간염 바이러스에 의한 간경변증이며 그 외 C형간염 바이러스로 인한 간경변, 간세포암, 알코올 의존성 간경변 등이 있다. 그 중 B형 바이러스성 간경변이 가장 많은 원인 질환으로 알려져 있지만 최근 들어 알코올 의존성 간경변으로 인한 간이식이 증가하고 있음을 여러 보고들에 의해 알 수 있다. 하지만 알코올 의존성 간경변의 간이식에 있어 뇌사장기의 경우 공공성의 문제, 수혜자의 수술 전 단주 기간 등 여러가지 면에서 논란의 여지를 갖고 있는 측면이 있다. 알코올 의존이나 남용으로 인한 정신질환은 우리나라 정신장애 중 불안장애 다음으로 높은 유병율을 갖고 있다.<sup>1</sup> 2001년부 터 정신질환 유병율에 대한 통계청의 자료에 따르면 점차 감소하고 있는 추세이기는 하지만 간이식 환자들의 원인질환 분류 에 있어 알코올 의존성 간질환으로 간이식을 시행하는 환자는 증가 추세에 있다. KONOS 연보에 따르면 알코올성 간질환으 로 간이식을 시행한 환자는 2012년, 2013년, 2014년, 2015년, 2016년 각각 9.88%, 12.6%, 14.8%, 16.8%, 19.5% 로 점점 증가하는 추세를 보이고 있다.2 알코올성 간질환으로 간이식을 시행하는 환자가 증가할수록 간이식 후 재 음주의 방지에 대한 관심이 높아지고 있으며 재 음주로 인한 이식장기 소실 등의 문제들이 대두되고 있다. 실제로 보고된 연구에 의하면 알코 올 사용 5.6건/100명/년, 과음이나 폭음 2.6건/100명/년에 이르는 것으로 보고되고 있고<sup>3</sup> 5년동안 약 3-40%의 간이식 환 자가 음주를 한다는 보고도 있으며 정신질환성 알코올 의존자의 비율도 약 10-15%에 이른다는 연구 결과도 있다. 이러한 결 과들을 볼 때 간이식 후 재음주 방지를 위한 교육과 모니터링은 이식장기 소실 예방을 위해 간이식 후 환자 관리의 중요한 부 분이라 할 것이다. 간이식 후 재음주에 대한 모니터링과 교육, 상담 등은 수술 후 환자와 간이식 팀뿐만 아니라 가족까지 포함 한 구체적이고 적극적인 교육이나 상담이 이루어져야 한다. 여러 연구에서 알코올 의존환자 가족의 공동의존에 대해 보고하 고 있는데 즉, 알코올 의존 환자의 경우 그 가족들 또한 알코올 의존 환자와의 지속적인 관계 속에서 건강하지 못한 삶의 방식 을 유지시켜나가는데 이를 공동의존이라 한다. 공동의존이 생긴 환자 가족들은 인지와 정서 기능이 알코올 의존 환자를 중심 으로 구조화되어 있기 때문에 환자가 이식을 받은 후 익숙해져 있던 역할이 더 이상 필요하지 않게 되면서 목표를 상실했다는 생각이 들고 공허감을 느끼게 된다고 한다. 이 때문에 환자의 재음주에 대해 방관할 수 있는 성향이 있다고 하는 연구들이 보 고된 바 있다.<sup>4</sup> 또한, 2013년 보고에 의하면 알코올 의존환자의 수술 전 단주 프로그램보다 간이식 후 단주 프로그램 교육을 실시하는 것이 음주 재발율을 낮추었다는 보고도 있는데 교육의 강도는 영향을 크게 미치지 않는 것을 알 수 있었다.<sup>5</sup> 여러 연 구를 통해 알코올 의존성 간질환으로 간이식을 시행한 환자들을 위해 수술 후 재음주 예방을 위해 간이식팀, 가족, 환자의 유 기적인 협력을 통한 적극적인 재활치료가 필요하며 이에 대한 체계적인 프로그램의 도입이 필요한 시점임을 알 수 있다. 지속 적인 음주 모니터링과 함께 알코올 의존 환자의 재활치료인 동기 강화치료, 인지행동치료, 자조집단을 통한12단계 치료, 개인 상담 치료, 가족 상담 치료가 시행될 수 있어야 하며 이에 대한 재정적인(보험수가) 문제와 환자들을 참여시키는 방법에 대한 논의가 우선 해결되어야 된다고 사료된다. 이를 통해 알코올 의존성 간질환으로 간이식을 시행한 환자들의 graft survival과 삶의 질을 향상시킬 수 있어야 할 것이다.

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (08:30-09:50) EAST TOWER / ROOM A [2F]

# **KLTS Symposium 1**

## Transplantation Related Registries: Present and Future

Chairs: Curie Ahn (Seoul National Univ.) Myoung Soo Kim (Yonsei Univ.)

## A2ALL, SRTR

## John Lake

Univ. of Minnesota


## Israel Penn International Transplant Tumor Registry

#### E. Steve Woodle

Division of Transplantation, Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Registries are essential for epidemiologic studies of cancer risk in transplant recipients. A number of registries exist that collect data on cancers in recipients, both prior to and following transplantation, and also in donors. These registries can be classified as either registries with mandatory data reporting registries or as registries with voluntary data reporting. In general, mandatory data reporting registries are limited in the data required, whereas voluntary registries generally collect more robust data. Mandatory registries have the advantage of a known at-risk population whereas voluntary registries do not. Data reporting rates can be disappointingly low in mandatory registries, but this can be addressed at least in part by combining with other non-transplant cancer registries. In addition, the ability to merge databases from insurance providers has also enabled improved assessment of reporting rates. Finally, we will describe new approaches for epidemiologic studies of the effect of transplantation on recurrent cancer risk.

## European Liver Transplant Registry<sup>\*</sup>: Achievements and Evolution within a 30-Year History

#### René Adam, Vincent Karam, Valérie Cailliez, Christophe Duvoux and all the centers contributing to ELTR

Paul Brousse Hospital, Villejuif, Paris, France

\*The ELTR accounts now for 154,861 liver transplantations (LT) performed in 174 centers from 33 countries across Europe (January 1968-June 2017).

**Methods:** Data from participating centers are collected on a voluntary basis at regular intervals using a two-part, standardized questionnaire designed by the ELTR Coordinating Committee to capture information on donors and recipients. Part 1 focuses on donor and recipient data, on technical aspects of liver transplantation and induction immunosuppression. Part 2 comprises questions on post-transplant mortality, graft failure and maintenance immunosuppression during patient follow-up. Audits of contributing centers are randomly performed each year to assess the quality of the data. The methods used to populate the registry and obtain the data have been described previously.<sup>1</sup> The ELTR represents around 95% of all the LT procedures performed in Europe. It is in close connection with all the national and multi-national organ sharing organizations for the exchange and quality control of the data.

Results: We analyzed the ELTR data within the period from January 1988 to December 2016 with 147,161 LT. Patient survival was 83% at 1 year (yr), 71% at 5 yrs, 61% at 10 yrs, and 41% at 20 yrs. Forty-six percent of deaths and 67% of re-LTs occur within the first year after LT. Cirrhosis was the most frequent indication (50%) followed by cancer (17%), cholestatic diseases (10%), acute hepatic failure (9%) and metabolic disease (6%). 10-yr patient survival was 59% for cirrhosis and for acute hepatic failure, and 50% for cancer (P < 0.001). In cirrhotic patients, 10-yr survival was better for primary biliary cirrhosis (71%) than for alcoholic or virus-related cirrhosis (58%)(P < 0.001). In viral cirrhosis patients, 10-yr survival of HBV patients was better than HCV (68%) vs 52%, P < 0.01). 10-yr patient survival in pediatric recipients was 78%. Age influenced 10-yr survival in adults (66%: 18-45 yrs, 59%: 45-60 yrs, 49%: 60-70 yrs, 40% in septuagenarians) (P < 0.001). In recent years, alternatives to the full-size graft LT after brain death (FSDBD) represent more than 20% overall, and more than 70% in pediatric patients. The best 10-yr graft survival was obtained with living donors and split-liver grafts (61% and 58%, respectively), intermediate with reduced and Full-Size Donor Brain Death (DBD) grafts (54% and 53%, respectively), and the worst with Donor Cardiac Death (DCD) and domino grafts (47% and 44%, respectively). Recently, different new cold static preservation solutions have been increasingly used as alternative to the UW. 10-yr graft survival for the main solutions was 62% for UW, 61% for Celsior and IGL-1, and 55% for HTK. Accordingly, this latter solution has been independently associated to a risk of graft loss in a recent publication.<sup>2</sup>

**Comments:** The ELTR has become the reference to assess the outcome and evolution of LT in Europe. Along its 30-year history, it has contributed to better define the indications of LT, to report the results of living related LT, to assess the risk for the living donor, as well as to choose the best preservation solutions for the liver graft (2) and the type of immunosuppression.<sup>3</sup> It represents a model of European scientific collaboration that gathers prospectively and analyses continuously more than 150,000 liver transplantations. With the analysis of this Big Data, ELTR provides valuable information not only to the professionals, but also to the patients.

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (11:10-12:10) EAST TOWER / ROOM A [2F]

# **KLTS Symposium 2**

## Various Approaches to Overcome Portal Vein Thrombosis (with videos) (\*K)

Chairs: Kyung-Suk Suh (Seoul National Univ.) Donglak Choi (Catholic Univ. of Daegu)

## Bidirectional Thrombectomy for Extensive Portal Venous Thrombosis in Living Donor Liver Transplantation

#### **Kwang-Woong Lee**

Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea

**Background and Aims:** In living donor liver transplantation (LDLT), portal vein reconstruction is a major challenging in case with portal venous thrombosis (PVT), because of the limited length of the graft portal vein from live donor and lack of readily available tissue for reconstruction. To overcome this critical surgical challenge, various techniques have been introduced to remove the thrombus, depending on the extent of PVT. We report a surgical technique of bidirectional thrombectomy for the patient of extensive PVT after skeletonization of spleno-mesentric vessels in LDLT.

Video Contents: A 52-year-old woman with hepatitis b related liver cirrhosis, recipient for LDLT had partial bland thrombosis in the main portal vein, extended to superior mesenteric vein (SMV). Intraoperative ultrasonography (US) showed weak portal blood flow only originated from splenic vein that it was insufficient for portal vein reconstruction and other procedures might be needed. At first, spleno-mesentric venous junction was identified with assistant from US, delicate dissection was performed to clarify the anatomic structure of PV, SMV and splenic vein. There was an unexpected coronary vein originated from near the upper portion of confluence of portal vein and it was also separated. After an extraction of the liver, SMV below the thrombus, splenic vein and coronary vein was temporarily clamped and then, SMV was partialy opened and eversion thrombectomy was performed on the both sides of the veins. Thrombus was completely removed and SMV was reconstructed. Portal blood flow was improved due to recanalization of SMV and there was no residual thrombosis. At postoperative day 7, computed tomography findings showed intact portal and mesenteric blood flow without any other complications.

## Portal Inflow Reconstruction from Varix

#### Dong-Sik Kim

Korea University School of Medicine, Seoul, South Korea

Complete obstruction of portal vein used to be considered as a contraindication of liver transplantation. With advancement in surgical techniques, various methods to overcome this condition have been suggested. In cases that patient has a significant collateral veins especially as one from choledochal vein or coronary vein, those veins can be used as an alternative source of portal inflow for reconstruction.

Specific cases will be presented with video clips. If adequate amount of blood flow can be obtained from varices, no additional procedure for portal vein thrombectomy will be required. In patient with diffuse mesenteric thrombosis, disappearance of intractable ascites and improvement of mesenteric thrombosis was observed with long-term follow-up after portal reconstruction with inflow from varix. Since the vein wall of varix is very thin and friable, special caution in dissection and anastomosis is required.

## **Reno-Portal Anastomosis**

### Bong-Wan Kim

Ajou University School of Medicine, Suwon, South Korea

간이식 대상자들에게 종종 발생하는 문맥혈전증은 간이식의 계획과 성공에 있어서 기술적인 문제점으로 여겨지고 있으며, 정 도에 따라 간이식을 불가능하게 하는 원인이 되기도 한다. Reno-Portal bypass anastomosis는 이러한 문맥 혈전증의 문제 를 극복할 수 있는 대안이 될 수 있다. Reno-Portal bypass anastomosis의 술전 계획에 있어서 Spleno-renal shunt 존재 를 확인하는 것은 Reno-Portal bypass anastomosis 후 이식 간으로의 적절한 혈류량을 유지하게 하고, 이식 후 문맥압 항 진증의 해소를 위해서 중요한 요소가 될 것이다. Reno-Portal bypass anastomosis 후 과도한 문맥 혈류의 경우에 비장 동 맥의 결찰(Splenic artery embolization)을 통하여 문맥 혈류를 조절할 수 있을 것으로 생각 되며, 너무 부족한 문맥혈류의 경우 부가적으로 reno-portal bypass conduit에 portal branch의 연결도 가능하리라 생각된다. 본 비디오 연제에서는 생체 간이식 중 시행된 reno-portal bypass 후 부족한 문맥혈류를 보충하기 위해 부가적으로 bypass conduit에 수혜자의 portal vein을 end-to-side anastomosis 경험을 소개하고자 한다.

## Jump Graft from Superior Mesenteric Vein

## Deok-Bog Moon

University of Ulsan, South Korea

The Liver Week 2018

DAY 2: Friday, June 15, 2018 (14:40-15:30) EAST TOWER / ROOM A [2F]

## KAHBPS-KLTS Joint Symposium (Debate with Panel Discussion)

Primary vs. Salvage Liver Transplantation in Patients with Borderline Liver Function (\*K)

Chairs : Jae-Won Joh (Sungkyunkwan Univ.) Shin Hwang (Univ. of Ulsan)

## Primary vs. Salvage Liver Transplantation in Patients with Borderline Liver Function

#### Jae Geun Lee

Department of Surgery, Yonsei University College of Medicine, Seoul, South Korea

Liver transplantation (LT) represents the ideal treatment for early hepatocellular carcinoma (HCC) as it removes the tumor and also resolves the underlying liver disease. In fact, LT offers the patient survival that reaches 70% at 5 years, and disease-free survival (DFS) of 90% at 5 years: a valid oncological treatment. Before the introduction of Milan criteria, the results of liver transplant for HCC were rather disappointing. As trans-plant has become the victim of its own success, because of organ shortage the risk of drop-out for tumor progression and the deterioration of the patients' clinical conditions constitute an important problem.

An improved staging of the patient with early HCC based on an accurate evaluation of hepatic function and portal pressure associated with refining of the surgical and anesthetic techniques has given results of survival up to 70% at 5 years in selected patients after LR for HCC. These data have reopened the debate on the surgical treatment of HCC in patients with a small HCC and preserved liver function.

In recent years, some authors have proposed LR as the front-line treatment for HCC for patients with compensated hepatic cirrhosis, offering a subsequent transplant for patients who developed limited hepatic recurrence or in the event of deterioration of hepatic function.

Initial LR of HCC as a primary therapy, in patients who otherwise could have been transplanted, offers a good quality of life and is less demanding than LT. The strategy of LR followed by salvage transplant potentially offers an advantage with respect to liver transplant: a therapy with good long-term survival, immunosuppression-free and the theoretical possibility of saving the organ to transplant in a patient who needs one.

However, SLT is based on the pre-supposition that the recurrence of HCC after hepatic resection is still found in those shared limits of transplantability. This is unfortunately not always true and various authors have emphasized that the histological characteristics analyzed on the specimen removed after the hepatic resection can help to stratify the population in high- and low- risk groups. It must also be emphasized that half of the patients had a devastating recurrence which precluded the subsequent transplant. There are few clinical studies documenting salvage LT as a viable treatment in patients who underwent LR prior to LT for HCC.

However, some patients dropped from the waiting list because their tumors progressed during this time. For example, recipients with HCC that met the Milan criteria had a decreased 3-year survival rate (from 80% to 60%) as a result of this dropout. It has been reported that almost one-third of patients with advanced HCC beyond the Milan criteria who are waiting for PLT will drop out. The second concern regarding SLT is the rate of postoperative complications. Adhesions between the cut surface from a previous LR and the omentum or intestine are the main technical difficulties encountered. However, a recent study suggested that sharp dissection and meticulous hemostatic control would reduce the difficulty of repeated surgery and decrease the incidence of postoperative complications. Meta-analysis shows that the risks of sepsis and biliary complications are similar for SLT and PLT patients, but there is an increased risk of bleeding with SLT. One explanation for this finding is that transplantation procedures after previous upper abdominal surgery generally involve more bleeding because of vascular adhesions and a degree of portal hypertension.

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## Favoring Salvage Liver Transplantation with Borderline Liver Function

#### Je Ho Ryu

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### Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related death worldwide, and its incidence is increasing.<sup>1</sup> Among the treatments of HCC, resection and transplantation remain the major curative therapies available to patients with HCC.<sup>2,3</sup>

Unlike liver resection (LR), LT eliminates the tumor itself as well as the underlying oncogenic liver disease and provides the widest surgical margin possible.<sup>4</sup> Despite these advantages, however, shortage of donor organs greatly limits the application of primary liver transplantation (PLT). In addition, a fraction of patients (range from 25% to nearly 40% at 1 year)<sup>5</sup> with HCC, who are listed for transplantation, have tumor progression and lead to dropout or death prior to receiving an organ.

Salvage liver transplantation (SLT) is a protocol that offers LR first and subsequent liver transplantation for tumor recurrence or deteriorating liver function.<sup>6</sup> SLT, which reduces the risk of HCC progressing during the time awaiting transplantation, might offer a good strategy for relieving patients with a good prognosis and also alleviate the burden on the donor organ pool.<sup>7</sup> Although there has been controversy about the suitability of PLT or SLT after LR for HCC patients for more than 15 years, it is uncertain whether the short- and long-term outcomes of SLT are as good as PLT.

A total of 4 meta-analysis and reviews 8-11 on the PLT versus SLT strategy have been published in the last 5 years (2012 - 2014). There was no randomized controlled trial (RCT) on this subject.

Now, we examine closely 4 meta-analysis and reviews on the PLT versus SLT strategy.

Recipient Outcomes of Salvage Liver Transplantation versus Primary Liver Transplantation: A Systematic Review and Meta-Analysis (Liver Transpl. 2012)<sup>8</sup>

Methods: Among 2799 screened references, 7 eligible studies were identified.

**Results:** There were no statistically significant differences in the overall survival rates of SLT and PLT: the pooled relative risk (RR) was 0.99 [95% confidence interval (CI) ¼ 0.90-1.09, P ¼ 0.87] at 1 year, 0.97 (95% CI ¼ 0.83-1.13, P ¼ 0.68) at 3 years, and 0.96 (95% CI ¼ 0.81-1.13, P ¼ 0.61) at 5 years. As for postoperative complications, there were no statistically significant differences in the incidence of sepsis and biliary complications between SLT and PLT, but there was a significantly higher incidence of bleeding with SLT (RR ¼ 2.84, 95% CI ¼ 1.57-5.13, P ¼ 0.001).

**Conclusion:** The overall survival (OS) associated with SLT is similar to that associated with PLT. Because of the limited organ donor pool, SLT might be an acceptable therapy for patients undergoing primary LR for hepatocellular carcinoma.

## Salvage Liver Transplantation in the Treatment of Hepatocellular Carcinoma: A Meta-Analysis (World J Gastroenterol. 2012)<sup>9</sup>

**Methods:** Literature on SLT versus PLT for the treatment of HCC published between 1966 and July 2011 was retrieved. There were 410 papers. Via steps of screening the title, abstract reviewing and article reviewing, 11 studies which included 141 SLT cases and 872 PLT cases were identified.

**Results:** The differences in overall survival and disease-free survival rates at 1-year, 3-year and 5-year survival rates were not statistically significant between SLT group and PLT group (P > 0.05).

After stratifying the various studies by donor source and Milan criteria, we found that: (1) Living donor liver transplantation recipients had significantly higher 1-year survival rate, lower 3-year and 5-year survival rates compared with deceased-donor liver transplantation (DDLT) recipients. And in DDLT recipients they had better 1-year and 5-year disease-free survival rate in SLT group; and (2) No difference was seen in 1-year, 3-year and 5-year survival rates between two groups who beyond Milan criteria at the time of liver transplantation.

**Conclusion:** SLT can be effectively performed for patients with recurrence or deterioration of liver function after hepatectomy for HCC. It does not increase the perioperative mortality and has a similar long-term survival rates compared to PLT.

Short- and Long-Term Outcomes after Salvage Liver Transplantation versus Primary Liver Transplantation For Hepatocellular Carcinoma: A Meta-Analysis (Transplant Proc. 2013)<sup>10</sup>

**Methods:** A systematic literature research was performed to identify comparative studies on SLT and PLT. Perioperative and long-term outcomes constituted the end points. Pooled odds ratios (OR) and weighted mean differences (WMD) with 95% confidence intervals (95% CI) were calculated using either fixed-effects or random-effects model.

**Results:** A total of 1508 patients from 14 studies were included. Although SLT spent more operative time than SLT (WMD: 28.69 min; 95% CI: 11.30-46.08; P ¼ .001), the two groups had no significant differences in the postoperative morbidity, perioperative mortality and length of postoperative hospital stay. No significant difference was observed between two groups for long-term outcomes of overall survival. Although 5-year disease free survival was inferior in SLT, 1- and 3-year disease-free survivals were similar. After stratifying the various studies by Milan criteria, no difference was seen in 1-, 3-, and 5-year survival rates between two groups who meet Milan criteria at the time of liver transplantation.

**Conclusion:** The current study demonstrates SLT for recurrent HCC is feasible and it can achieve the same short- and long-term outcomes as PLT. Therefore, SLT may be accepted as the treatment of choice for patients with recurrent HCC.

## Systematic Review of Efficacy and Outcomes of Salvage Liver Transplantation after Primary Hepatic Resection for Hepatocellular Carcinoma (J Gastroenterol Hepatol. 2014)<sup>11</sup>

**Methods:** Electronic searches of Pubmed, Embase, and Medline databases identified 130 abstracts, from which 16 eligible studies comprising 319 patients were selected for review. Studies adopting SLT following primary hepatic resection for recurrent HCC with more than five patients were included. Demographic details, morbidity and mortality indices, and survival outcomes were collected from each study and were tabulated.

**Results:** All patients included in the studies had liver cirrhosis, with the majority being Child-Pugh A (50%) and B (33%). The etiology of liver disease was hepatitis B in the majority of patients (84%). Disease recurrence occurred in 27–80% of patients at a median of 21.4 months (range 14.5–34) following initial resection. SLTs were performed on 41% of recurrences, and were associated with biliary complications (8%), infection (11%), bleeding (8%), and vascular complications (7%). There were 18 perioperative deaths (5.6%). The median 1-, 3-, and 5-year

overall and disease-free survival was 89%, 80%, and 62%, and 86%, 68%, and 67%, respectively.

**Conclusion:** Synthesis of available observational studies suggests that SLT following primary hepatic resection is a highly applicable strategy with long-term survival outcomes that are comparable to upfront liver transplantation.

## Conclusion

Few centers have successfully detected recurrences early and performed SLT in up to 61% of patients with recurrence after resection, but a majority of the studies have shown that only 22% to 28% of patients actually remain transplantable and can undergo SLT<sup>12-13</sup> after tumor recurrence. SLT good perioperative outcomes, and almost comparable OS and DFS as compared with PLT patients, and is a feasible alternative for HCC recurrence within Milan criteria. We suggests that a better selection of HCC patients with borderline liver function for the "resection first" approach and close follow-up for recurrence may help in achieving better outcomes with the SLT strategy.

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (08:30-09:50) EAST TOWER / ROOM BC [2F]

# **KLCA Symposium 1**

## Very Early Stage Hepatocellular Carcinoma: How to Detect and Diagnose?

Chairs : Seung Kew Yoon (The Catholic Univ. of Korea) Jaeseok Hwang (Keimyung Univ.)

## Detect or Not to Detect Very Early Stage HCC?: The Western Perspective

#### Ju Dong Yang

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Very early stage hepatocellular carcinoma (HCC) is defined as a single tumor with a largest diameter of 2 cm or less according to BCLC (Barcelona Liver Cancer) staging system. Detection of very early stage HCC is important for several reasons. First, patient presenting with very early stage HCC has excellent prognosis. 5 year overall survival after surgical resection or local ablation for very early stage HCC was reported to be around 70%. Second, attempt to diagnose very early stage HCC may enable clinicians to identify a small subgroup of patients with intrahepatic cholangiocarcinoma, who could potentially benefit from liver transplantation (LT). Of note, patients with very early stage intrahepatic cholangiocarcinoma (single tumor, less than 2 cm) have an excellent post LT outcome and several centers in the US transplant this highly selective group of patients. Most transplant center in the US would not consider LT in patients with multifocal intrahepatic cholangiocarcinoma even if patients present within Milan criteria, highlighting a critical need for diagnosing the tumor at a very early stage.

While diagnosing very early stage HCC is important, diagnosis of very early stage HCC is challenging in the western population. Quality of liver ultrasound as a surveillance test is often limited due to high prevalence of obesity and metabolic liver disease (NASH/Alcohol) which are associated with a lower sensitivity of detecting HCC. Routine use of MRI or CT scan as a surveillance test can pose physical or psychosocial harm and may not be cost effective. Detection of very early stage HCC is further complicated by the fact that patients with very early stage HCC are not prioritized for LT in the US organ allocation system. Thus, patients with very early stage HCC often have to wait until tumor grows beyond the very early stage so that they can receive MELD exception score. A recent study from UCSF investigated the outcome of the "wait and not ablate" approach in 114 patients with T1 HCC (1 lesion < 2cm). Patients were monitored with cross-sectional images every 3 months. Vast majority of HCC patients (88%) had stage progression from T1 to T2 (1 lesion 2-5 cm or 2-3 lesions  $\leq$  3 cm) at a median of 6.9 months. Only six (5.3%) patients progressed from T1 directly to beyond T2 criteria at a median of 5.1 months. Tumor biology may change with the progression of disease. Previous studies have shown that tumors start developing microvascular invasion as it grows above 2 cm. It is therefore controversial as to how aggressively clinicians should diagnose HCC at a very early stage especially in liver transplant candidate as they have to wait until tumors reaches T2 to receive MELD exception score. It is less debatable in patients who would not be a candidate for LT as detection of very early stage HCC seems to improve clinical outcome.

In conclusion, detection of very early stage HCC should be sought in patients who would not be a candidate for LT as it will improve the clinical outcome. On the other hand, confirming the diagnosis of HCC at very early stage remains controversial in patient who would be a candidate for LT in the current organ allocation system.

## HCC Surveillance in Non-Transplant Setting: An Eastern Perspective

#### So Yeon Kim

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## 아시아 지역의 관점에서 본 간세포암종의 감시 검사

## 김 소 연

울산의대 서울아산병원 영상의학과

아시아 지역에서는 간세포암종의 치료술로 간절제술이나 국소 소작술이 뇌사자 간이식보다 선호된다. 따라서 간절제술과 국 소 소작술로 좋은 결과를 얻을 수 있는 2-3 cm 이하의 작은 간세포암종을 조기에 발견하는 것이 중요하다. 현재 많은 가이 드라인에서 초음파를 감시 검사의 주된 방법으로 삼고 있으나. 2 cm 이하의 작은 간세포암종을 발견하는 민감도가 매우 낮 다. 최근 간세포암종의 진단 검사에 높은 민감도를 보이는 간세포특이조영제 조영증강 MRI를 사용하면 감시 검사의 민감도 를 향상시킬 수 있을 것으로 기대된다. 다만, 이러한 검사들을 사용하였을 때 비용 대비 효과, 발생할 수 있는 위해, 의료 자원 의 이용에 대한 문제들에 대한 고려가 필요할 것으로 생각된다.

Keywords: 간세포암종, 감시 검사, 진단 검사

Curative therapies for hepatocellular carcinoma (HCC) include liver transplantation, surgical resection, and image-guided tumor ablation. Treatment patterns of HCC vary substantially across regions or countries according to the demographic characteristics, prevalence, socioeconomic status and availability of medical resources.<sup>1</sup> In Asian countries, there is a shortage of deceased donor liver grafts. Cultural and religious barriers account for the low rate of deceased donation. Particularly Confucian values which associate an intact body with respect for ancestors or nature even after death seem to make people hesitate to donate the liver.<sup>2</sup> In addition, the most common risk factor for HCC is hepatitis B virus (HBV) infection in this area except for Japan.<sup>1</sup> Infection with HBV may be correlated with the emergence of HCC even in the absence of liver cirrhosis,<sup>3</sup> which can increase a change to detect HCC in the non-cirrhotic liver. Thus, in Asian countries, the remaining options, i.e. surgical resection and image-guided ablation are preferred over deceased donor liver transplantation (DDLT).

In this setting, the main target for HCC surveillance should be different from that in a setting where liver transplantation especially DDLT is the primary option. While DDLT requires a high specificity comparable to histopathologic diagnosis to maximize organ utilization, resection and thermal ablation emphasize the importance to detect HCC at a very early stage. The outcomes of surgical resection<sup>4,5</sup> and image-guided ablation<sup>6-8</sup> are closely related to the size of HCCs. 2 cm is suggested as one of the cut-off sizes for the aggressiveness and invasiveness of HCC.<sup>4,9,10</sup> Especially for radiofrequency ablation (RFA), the preferable size is smaller than 2 cm,<sup>8</sup> considering the fact that a 360-degree, 0.5 - 1.0 cm ablative margin should be produced all around the target tumor.<sup>11</sup>

Current clinical guidelines suggested surveillance using ultrasound (US) with or without serum tumor markers

such as alpha-fetoprotein (AFP) every six months in at-risk population for HCC.<sup>12-15</sup> A meta-analysis found US sensitivity for the detection of early-stage HCC in patients with cirrhosis (one nodule <5 cm or 3 nodules each <3 cm in diameter) as 63% and US with AFP sensitivity as 69%.<sup>16</sup> When it comes to HCC smaller than 2 cm, the sensitivity of US is further decreased. A recent prospective study revealed the HCC detection rate for very early stage cancer was only 27.3%.<sup>17</sup> Given this disappointing result, a more sensitive surveillance tool is required in order to aim HCC at a very early stage.

Among diagnostic tool for HCC, the most sensitive one is known as gadoxetic acid-enhanced magnetic resonance imaging (MRI).<sup>18</sup> Gadoxetic acid-enhanced MRI has an advantage to detect small HCCs by detecting signal intensity changes in hepatobiliary phase (HBP) images caused by the reduced expression of organic anion-transporting polypeptide (OATP) 1B3 before changes in the vascular profile of HCC occur.<sup>19-23</sup> In this regard, recent guidelines including the latest Korean Liver Cancer Study Group-National Cancer Center (KLCA-NCC) Practice Guidelines, started to propose the use of gadoxetic acid-enhanced MRI as a surveillance tool.<sup>12,14</sup> According to the study comparing US and gadoxetic acid-enhanced MRI, the detection rate of MRI (84.8%) was significantly better than that of US (27.3%) (P < .001) for HCC at a very early stage.<sup>17</sup> Abbreviated MRI (AMRI) as a shortened and simpler version of a complete contrast-enhanced MRI can be also considered as an option.<sup>24-26</sup> AMRI are usually composed of HBP T1-weighed sequence and diffusion-weighted imaging (DWI) for sensitive detection of HCC, and T2-weighted image to improve specificity by excluding cysts or hemangiomas. AMRI achieve sensitivities of 80-90% and specificities of 91-98%.<sup>24-26</sup> Non-enhanced MRI with T2-weighed images and DWI has a potential to be a promising surveillance tool. In patients in whom US evaluation look limited or insufficient in the evaluation of HCC, alternative surveillance methods using MRI can be considered. However, further study to clarify the most appropriate niche for cost effective use of these new approaches are warranted. Potential harms related to the alternative approaches and availability of medical resources need to be considered as well.<sup>27</sup>

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## Non-Invasive Diagnosis of Very Early Stage Hepatocellular Carcinoma: Focused on Subcentimeter Nodules

#### **Mi-Suk Park**

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## 조기 간세포암의 비침습적 진단: 1 cm 미만 결절

박 미 숙

연세대학교 세브란스병원

Hepatocellular carcinoma (HCC) is the second largest cause of cancer mortality in the world. The prognosis of patients with HCC largely depends on tumor stage, and curative treatments are available only for patients diagnosed when the cancer is at an early stage. Even for patients with early stage HCC, the chance of liver transplantation is often limited owing to donor shortage, and surgical resection is seldom possible because of considerable portal hypertension.<sup>1</sup> Given that the mainstay treatment for HCC in Korea is locoregional treatment rather than liver transplantation, detection of smaller lesions susceptible to locoregional treatment appears meaningful.<sup>2</sup> Additionally, new diagnostic techniques, such as fusion of real-time ultrasonography (US) images with CT/MR or contrast-enhanced US images, have made it possible to accurately localize small lesions for local treatment, thus bridging the distance between gadoxetic acidenhanced liver MRI and optimal treatment.<sup>3</sup>

A recent meta-analysis demonstrated moderate sensitivity of 78% and high specificity of 92% of dynamic contrast-enhanced MR imaging for the diagnosis of small (< 2 cm) HCC.<sup>4</sup> Heterogeneity was higher for sensitivity (range, 30%–99%) than specificity (range, 61%–100%).<sup>4</sup> The subgroup analysis showed that potential sources of bias for sensitivity were the difference in reference standard, contrast agent, and origin of the study. In addition to that, one practical issue in the diagnosis of small (< 2 cm) HCC is the different criteria used by the different guidelines. EASL and LI-RADS have provided different diagnostic criteria for nodules of sizes ranging from 1 to 2 cm and for those with sizes > 2 cm, but AASLD, KLCSG-NCC, JSH, and APASL have not. For sub-centimeter nodules, the AASLD and EASL-EORTC guidelines do not allow imaging diagnosis of HCC. KLCSG-NCC, JSH, APASL, and LI-RADS allow imaging diagnosis of subcentimeter-sized HCC. However, the criteria are completely different among them. In this talk, I will briefly touch on the pro and cons of each guidelines for the diagnosis of small HCC, especially focusing on subcentimeter nodules.

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### New Biomarkers to Detect Very Early Stage Hepatocellular Carcinoma

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## 조기 간암을 진단하기 위한 단백체 다중마커패널의 개발

김영수

서울대학교 의과대학 의공학교실

High-throughput '-omics' technologies are now available, allowing one to measure the abundance of thousands of molecular targets in their assessment as biomarkers. Triple quadruple mass spectrometer-based proteomic assay (multiple reaction monitoring-mass spectrometry, MRM-MS) is recently developed and provides reproducible and accurate quantitative result for targeted human proteins.<sup>1</sup> One of the benefits for the targeted proteomic technology is to provide the capability of multiplexing assay for a large set of selected peptides and thus, it is suitable for carrying out validation stages in biomarker development.<sup>2</sup> Further, multiple reaction monitoring-mass spectrometry (MRM-MS), which is a highly selective and sensitive approach to quantitating targeted proteins. MRM-MS is a targeted proteomic technology that does not require antibody and simultaneously measures more than 300 protein targets per one assay run.

Serum alpha-fetoprotein (AFP) has long been used as a diagnostic marker for hepatocellular carcinoma (HCC), albeit controversially. Although it remains widely used in clinics, the value of AFP and AFP-L3 in early HCC diagnosis has recently been challenged due to its significant rates of false positive and false negative findings. To establish a new type of HCC diagnostic biomarkers superior to AFP, we developed a method of measuring proteomic multi-marker panel by MRM-MS.<sup>3,4</sup> We have been developing multi-marker panels for the diagnosis of early HCC using MRM-MS by validating biomarker candidates in a large clinical cohort (n = 450) from single center, thereafter it will be validated further with multi-center samples with more than 1000 blood samples. The panel comprised newly discovered 5-20 protein markers including AFP, assembled from a training set (n = 300) and tested in an independent sample set (n = 150). As a result, the proteomic multi-marker panels exceeded the diagnostic performance by more than 15 - 30%, compared to AFP.

This assay is the first proteomic multi-marker panel for early HCC diagnosis that is based on MRM-MS technology. Particularly, the proteomic multi-marker panels were examined for surveillance diagnosis, which consists of both hepatitis B virus (HBV) and liver cirrhosis (LC) patients, resulting in excellent efficacy. Moreover, our multi-marker panels would help to facilitate the patient stratification for optimal HCC therapy in the future.<sup>5</sup>

Keywords: Hepatocellular carcinoma (HCC), Multiple reaction monitoring-mass spectrometry (MRM-MS), Proteomic multi-marker panel

질량분석기 Triple Quadruple LC-MS/MS의 다중반응검지법이 바이오마커의 개발에 이용되고 있다. 이 방법은 한번의 질 량분석기 정량분석으로 300개 이상 후보 마커를 정량 분석할 수 있다.<sup>1</sup> 특별히, 다중반응검지법은 항체 등이 필요하지 않고 60분에 300개 이상 마커를 단순히 질량 지문(transition) 만을 측정하기 때문에 신속하고 저가로 분석이 가능하다.<sup>2,3</sup> 이러한 MRM-MS분석의 효율성과 신속성 때문에 단백체 다중마커패널의 분석 플랫폼으로 개발이 진행되고 있다. 본 연구에서는 다 중반응검지법을 이용하여 간암 다중 마커를 개발하여 검증하고 이들 다중마커들을 조합하여 다중마커패널을 만들었다. 이들 다중마커패널은 Triple Quadruple LC-MS/MS의 다중반응검지법을 이용하여 정량분석 에세이가 수행되었다.

Serum alpha-fetoprotein (AFP) 은 간암 진단을 위한 마커로 사용되고 있으니 효용성이 만족할 만하지 않다고 알려져 있 다. 따라서 본 연구진은 AFP 효용성을 15-30% 향상시킨 단백체 다중마커패널을 제작하였다. 다중마커패널을 제작하기 위 해서 기존 AFP 를 포함하여 5-20개 단백질 마커가 새롭게 발굴되었고, 이들을 이용하여 다양한 단백체 다중마커패널이 제작 되었다.<sup>4</sup> 시료 코호트 기반으로 모델링 된 단백체 다중마커패널은 간암 감시진단 코호트(B형간염환자, 간경화환자, HCC환자; N=450 혈액시료)을 이용하여 패널이 확립되었고 독립 된 시료 세트 코호트(N=150 혈액 시료)에서 검증되었다. 이렇게 확립 되어진 단백체 다중마커패널은 특히 감시진단을 위한 마커로 효능이 높아서 감시진단 목적으로 이용될 수 있으리라 전망된다. 또한 장래 간암 약물투여 및 수술 등의 치료 전략을 위한 간암 환자의 감별 진단에 중요하게 사용될 것이라 예측된다.<sup>5</sup>

색인 단어: 간암, 다중반응, 단백체 다중마커패널

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (16:30-17:50) EAST TOWER / ROOM BC [2F]

# **KLCA Symposium 2**

## Systemic Treatment for Advanced Hepatocellular Carcinoma

Chairs: Joong-Won Park (National Cancer Center) Ho Yeong Lim (Sungkyunkwan Univ.)

## Predictive Genomics and Proteomics in Hepatocellular Carcinoma: In the Era of Targeted Therapy

#### Ju-Seog Lee

Department of Systems Biology, UT MD Anderson Cancer Center, Texas, USA

Recent massive sequencing studies of HCC genomes revealed many new genetic alterations that might be accountable for HCC development and provided comprehensive view of malignant disease. However, genomic profiling of tumors is limited by a loose correlation between genetic alterations and their functional products such as proteins and metabolites. To overcome such limitation, several approaches such as proteomics and metabolomics have been developed to add more functional information to genomic characteristics of tumors. Reverse-phase protein array (RPPA) is one of such approaches and allows us to simultaneously measure multiple protein features, such as expression, modification of proteins, and interaction with ligands from the samples. By integrating multiple data sets from same tissues, several clinically distinct subtypes were identified and further analysis of integrated data revealed characteristics of underlying biology that may dictate clinical outcomes of each subtype. Further analysis showed that proteomic subtype is more correlated with copy number alterations than somatic mutations. Integration of multiple data sets also identified many genetic and proteomic alterations significantly correlated with clinical outcomes. Functional validation with cell lines demonstrated that some of correlated genes are essential for growth and survival of HCC cells. In conclusion, HCC can be classified into distinct subtypes by proteomic features independent of mutation profile. Proteomic analysis has identified potential key biomarkers with prognostic importance that can be easily translated to clinics. Current study demonstrated merit of integrated analysis of proteomic data with genomic data to uncover potential driver genes of HCC development.

## First Line Treatment for Liver Cancer

#### Stephen Lam Chan

The Chinese University of Hong Kong, Hong Kong SAR, China

Sorafenib is the first drug treatment demonstrating survival benefits in advanced hepatocellular carcinoma (HCC). From 2008 to 2016, a number of randomized clinical trials have been conducted to test novel agents in comparison to sorafenib but none was successful. In 2017, REFLECT study demonstrated that lenvatinib, another multi-targeted tyrosine kinase inhibitor (TKI), to be non-inferior to sorafenib in the first-line setting. At the time of writing, although Lenvatinib is still under awaiting US FDA approval, many clinicians consider Lenvatinib to be reasonable alternative to Sorafenib as the first-line agent in treating advanced HCC, especially for patients at risk of hand-foot skin complications. Apart from TKIs, a number of phase III clinical trials have been initiated to evaluate the first-line role of check-point inhibitors. In the lecture, the current status of 1<sup>st</sup>-line treatment as well as ongoing/future direction of drug development will be presented.

## Second Line Treatment

#### **Thomas Yau**

The University of Hong Kong, Hong Kong SAR, China



## When to Switch Locoregional Therapy to Systemic Therapy

#### Hwi Young Kim

Department of Internal Medicine, Ewha Womens University College of Medicine, Seoul, South Korea

Transarterial chemoembolization (TACE) is a standard treatment for patients with intermediate-stage hepatocellular carcinoma (HCC),<sup>1,2</sup> based on its survival benefit in patients with unresectable HCC from previous studies.<sup>3,4</sup> Although TACE is usually given repeatedly in individual HCC patient due to its palliative nature,<sup>5</sup> development of untreatable progression of HCC is regarded as TACE refractoriness or failure, in which TACE cannot be considered any further.<sup>4,6</sup> Recently, several studies attempted to define TACE refractoriness. In a single-institutional study from Korea, researchers defined stage progression under repeated TACEs as a surrogate endpoint of TACE refractoriness. They suggested predictors of TACE refractoriness as either development of disease progression or need for three sessions of TACE during first 6 months from the initial TACE, which enable prompt switch to other treatments.<sup>7</sup> However, these criteria did not include deterioration of hepatic function, and have not been fully validated. The Assessment for Retreatment with TACE (ART) score was developed by researchers from Austria, which integrated radiologic tumor response, impairment of hepatic function and liver damage (increase in aspartate aminotransferase).<sup>8</sup> The ART score identified poor prognostic patients (ART score  $\geq 2.5$  after the first TACE) who would not benefit from repeated TACE sessions. Similarly, a French group developed ABCR score which combined alpha-fetoprotein, tumor stage, change in liver function, and radiologic tumor response, suggesting score  $\geq$ 4 may not benefit from further TACEs.9 Recent practice guidelines on HCC have defined TACE refractoriness in different ways. Previous Korean guidelines regarded upward stage migration following repeated TACE as refractoriness, suggesting switch to sorafenib therapy.<sup>10</sup> Japanese guidelines provided criteria for TACE refractoriness as follows: i) consecutive insufficient tumor response (>2); ii) two or more consecutive progression in tumor number; iii) continuous elevation of tumor markers; iv) development of vascular invasion; v) development of extrahepatic spread.<sup>11</sup> The guidelines from the European Association for the Study of the Liver recommended switch to sorafenib in case of untreatable progression on TACE in patients with intermediate-stage HCC.<sup>12</sup>

To date, various definitions of TACE refractoriness exist, and thus treatment strategy to overcome such condition has not been well established. Sorafenib has been recommended for a treatment option for TACE refractoriness, based on its survival benefit in advanced HCC. A subanalysis of the Sorafenib Hepatocellular Carcinoma (HCC) Assessment Randomized Protocol (SHARP) trial showed survival benefit of sorafenib in patients with prior TACE compared with placebo.<sup>13</sup> A retrospective study from Japan demonstrated prolonged time to disease progression and overall survival with switch to sorafenib compared with continued TACE in patients with TACE refractoriness.<sup>14</sup> In a retrospective study including patients with TACE refractoriness from Japan, hepatic arterial infusion chemotherapy (HAIC) showed promising results in terms of tumor response and survival.<sup>15</sup> In a multi-institution-al study also including patients with TACE refractoriness from Korea, patients treated with HAIC demonstrated better time to progression and overall survival than those treated with sorafenib.<sup>16</sup> However, TACE refractoriness was not defined in detail in this study. Collectively, direct evidences on the efficacy of various treatment modalities in TACE refractoriness are insufficient. Japanese guidelines recommended HAIC or sorafenib for the subsequent

treatment following the development of TACE refractoriness.<sup>17</sup> Therapeutic role of recently developed systemic agents needs to be investigated in the setting of TACE refractoriness in the near future.

Given the potential ischemic injury due to tissue ischemic following TACE, combination treatment strategies are under investigation, such as TACE plus systemic agents with antiangiogenic property (e.g., sorafenib).<sup>18</sup> Enrolled patients in those clinical trials appear heterogeneous in terms of tumor stages.<sup>19</sup> In other words, clinical trial designed solely for TACE refractoriness is absent to date. Several recent studies on combination treatments have reported mixed results. A systematic review with meta-analysis reported that prolonged time to progression without significant improvement in overall survival was achieved with combined TACE and sorafenib compared with TACE alone.<sup>20</sup> A global clinical trial of combined sorafenib plus TACE with doxorubicin-eluting beads did not reach clinical significance in terms of time to tumor progression.<sup>21</sup> Another large-scale European study comparing TACE using drug-eluting beads plus sorafenib versus TACE with placebo did not improved progression-free survival in unresectable, liver-confined HCC.<sup>22</sup> Likewise, an Asian multi-institutional study comparing orantinib versus placebo combined with TACE did not improve overall survival in patients with unresectable HCC.<sup>23</sup> In conclusion, evidences supporting combination treatment of TACE and systemic agents are insufficient at present. Further studies are urgently required regarding the diagnosis and treatment of TACE refractoriness.

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The Liver Week 2018

DAY 2: Friday, June 15, 2018 (13:10-14:30) EAST TOWER / ROOM ABC [2F]

## KAHBPS-KLTS-KLCA Joint Symposium

## New Treatment Modalities for Early Stage Hepatocellular Carcinoma

Chairs: Yun Hwan Kim (Korea Univ.) Hee Jung Wang (Ajou Univ.)

## Local Ablations: Microwave Ablation and Cryoablation

#### Min Woo Lee

Department of Radiology and Center for Imaging Science, Samsung Medical Center, Seoul, South Korea

## 국소 소작술: 초단파열치료술과 냉동소작술

이민우

성균관의대 삼성서울병원 영상의학과

Radiofrequency ablation (RFA) has been widely used as a standard local ablation therapy for hepatocellular carcinoma (HCC). Recently, microwave ablation (MWA) is emerging as an alternative to RFA as it provides faster and larger ablation zone. For this reason, MWA seems to be more effective than RFA for HCCs larger than 3 cm. However, most comparative studies reported that therapeutic outcomes including complication, local tumor progression, and overall survival are similar to each other.

Cryoablation can destroy tumors by freezing and thawing. It has several advantages over RFA such as well visualization of iceball during image guidance, absence of severe pain, and less damage to great vessels and bile duct. Despite insufficient data, percutaneous cryoablation for HCCs seems to be comparable to percutaneous RFA in terms of long term therapeutic outcomes and complications.

Keywords: Radiofrequency ablation, Microwave ablation, Cryoablation, Hepatocellular carcinoma

고주파열치료술은 간암의 국소 소작에 있어 표준치료로 이용되어 왔다. 최근 초단파열치료술이 고주파열치료술의 대체 치료 로서 주목 받고 있으며, 보다 크고 빠는 소작 성능으로 인해 3 cm 이상의 큰 종양에서 고주파 열치료술보다 우수한 국소 소작 성능을 보일 것으로 기대된다. 그러나, 치료 후 합병증 및 국소 재발률, 생존율 등은 두 치료간에 유사한 것으로 보고되고 있다. 냉동 소작술은 냉동과 해동을 통하여 종양을 파괴하는 치료이다. 고주파열치료술과 비교하여, 치료 중 모니터링이 용이하고, 통증이 경미하며 혈관과 담도 주변에 위치한 종양도 보다 안전한 치료가 가능한 것이 장점이다. 아직 데이터가 충분하지 않으 나, 최신 기종을 이용한 냉동 소작술은 고주파열치료술과 유사한 장기 치료 성적과 합병증을 보이는 것으로 여겨진다.

색인단어: 고주파열치료술, 초단파열치료술, 냉동소작술, 간세포암

According to recently updated European Association for the Study of the Liver (EASL) practice guideline, ablation is recommended as the first line treatment modality for very early stage hepatocellular carcinoma (HCC); and it is also recommended for early stage HCC patients who are not candidate for resection or transplantation.<sup>1</sup> Radiofrequency ablation (RFA) has been widely used as a standard local ablation therapy for HCCs as it showed promising therapeutic outcomes including local tumor control, overall survival, and complications.<sup>2-4</sup>

## **Microwave Ablation**

Microwave ablation (MWA) is getting popular in the field of liver tumor ablation. It can reach high temperature  $(100-150^{\circ}C)$  around the probe more rapidly than RFA and consequently, larger ablation zone can be created with MWA during the same time. MWA has advantages over RFA in terms of less susceptibility of so called heat-sink effect, which is the cooling effect from blood flow that leads to incomplete ablation of liver tumors near large blood vessels. Unlike radiofrequency, microwave is capable of propagating through and effectively heating many types of tissues, even those with low electrical conductivity, high impedance, or low thermal conductivity such as lung or charred, desiccated tissue.<sup>5</sup>

In terms of therapeutic outcomes between MWA and RFA for HCCs, a few randomized controlled trials (RCTs) are available in the literatures.<sup>6,7</sup> In a recent study for HCCs 5 cm or smaller,<sup>7</sup> although MWA showed better outcomes than RFA including lower local tumor progression (LTP) rate for 3-5 cm tumors (6.7% vs. 13.0%) and tumors adjacent to vessels (4.3% vs. 7.7%) or gallbladder (0% vs. 7.1%), it did not reach statistical significance. Moreover, it was not statistically different between two ablation groups in terms of technique efficacy, LTP rate, intrahepatic distant recurrence, extrahepatic recurrence, overall survival, disease-free survival and major complication rate.<sup>7</sup> Similar results were found in another RCT for single HCC 4 cm or smaller.<sup>6</sup> Although the authors did not find that MWA was more effective than RFA for treatment of HCCs, the LTP rate at two years after MWA had a tendency to be lower than that of RFA (6% vs 12%). Similarly, recent meta-analyses indicate a similar therapeutic efficacy between the two ablation methods, with possible superiority of MWA in larger HCCs.<sup>8,9</sup> Given that there are varieties of MWA devices and different devices produce substantially different ablation volumes and shapes, more evidence is warranted in well-designed prospective studies.<sup>10</sup>

#### Cryoablation

Unlike thermal ablation techniques such as RFA and MWA, cryoablation destroys tumour cells by the applying alternating freezing and thawing. This technique which produces ice-ball for ablation has several advantages over thermal ablation such as lower pain and more clearly visible ablation zone under either ultrasound or CT guidance.<sup>11</sup>

Regarding therapeutic efficacy after cryoablation, clinical data with new cryoablation devices comparing with RFA are limited. According to a recent RCT comparing cryoablation and RFA in patients with one or two HCCs 4 cm or smaller,<sup>12</sup> cryoablation resulted in a significantly lower LTP than RFA, although both cryoablation and RFA were equally safe and effective with similar 5-year survival rates. This higher efficacy of local tumor control may be attributed to the larger ablation zone created by multiple probes used in the cryoablation group. More data is needed to verify these results in well-designed prospective study with different population and devices.

In terms of complications after cryoablation; excessive bleeding, and cryo-shock, which means multi-organ failure, severe coagulopathy, and disseminated intravascular coagulation, were reported in earlier studies when large ablation zone was created with old generation cryoablation system.<sup>13</sup> However, new generation of cryoablation system with thin cryoprobes that use argon-helium as cryogen has been introduced. According to the recent RCT, this kind of fatal complication was not observed in cryoablation group and the rate of major complication was not different between the two groups.<sup>12</sup> Unlike RFA, cryoablation seems to be relatively safe for ablating tumors close to great vessels, gallbladder, kidney, stomach, colon and central bile duct.<sup>14-16</sup>

#### Conclusion

MWA is a new thermal ablation technique with better physical properties compared to RFA. It may be more ef-

fective than RFA for HCCs larger than 3 cm as it can provide faster and larger ablation zone than RFA. However, other treatment outcomes including LTP rate, complication and overall survival are similar with RFA.

Cryoablation with new generation system seems to be equally effective and safe for treating HCCs compared to RFA. It has advantages over RFA in terms of lower complication rate especially for perivascular and periductal tumors.

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## New Treatment Modalities for Early Stage HCC: SBRT, Proton Beam

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#### SBRT

This study was conducted to compare clinical outcomes and treatment-related toxicities after stereotactic body radiation therapy (SBRT) with two different dose regimens for small hepatocellular carcinomas (HCC)  $\leq$ 3 cm in size. We retrospectively reviewed 44 patients with liver-confined HCC treated between 2009 and 2014 with SBRT. Total doses of 45 Gy (n = 10) or 60 Gy (n = 34) in 3 fractions were prescribed to the 95% isodose line covering 95% of the planning target volume. Rates of local control (LC), intrahepatic failure-free survival (IHFFS), distant metastasis-free survival (DMFS), and overall survival (OS) were calculated using the Kaplan-Meier method. Median follow-up was 29 months (range, 8 to 64 months). Rates at 1 and 3 years were 97.7% and 95.0% for LC, 97.7% and 80.7% for OS, 76% and 40.5% for IHFFS, and 87.3% and 79.5% for DMFS. Five patients (11.4%) experienced degradation of albumin-bilirubin grade, two (4.5%) degradation of Child-Pugh score, and four (9.1%) grade 3 or greater laboratory abnormalities within 3 months after SBRT. No significant difference was seen in any oncological outcomes or treatment related toxicities between the two dose regimens. SBRT was highly effective for local control without severe toxicities in patients with HCC smaller than 3 cm. The regimen of a total dose of 45 Gy in three fractions was comparable to 60 Gy in efficacy and safety of SBRT for small HCC.

#### **Proton Therapy**

This study aimed to evaluate the initial outcomes of proton beam therapy (PBT) for hepatocellular carcinoma (HCC) in terms of tumor response and safety. HCC patients who were not indicated for standard curative local modalities and who were treated with PBT at Samsung Medical Center from January 2016 to February 2017 were enrolled. Toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Tumor response was evaluated using modified Response Evaluation Criteria in Solid Tumors (mRECIST). A total of 101 patients treated with PBT were included. Patients were treated with an equivalent dose of 62-92 GyE10. Liver function status was not significantly affected after PBT. Greater than 80& of patients had Child-Pugh class A and albumin-bilirubin (ALBI) grade 1 up to 3 months after PBT. Of 78 patients followed for three months after PBT, infield complete and partial responses were achieved in 54 (69.2%) and 14 (17.9%) patients, respectively. PBT of HCC patients showed a favorable infield complete response rate of 69.2% with acceptable acute toxicity. An additional follow-up study of these patients will be conducted.

Keywords: Hepatocellular carcinoma, Stereotactic body radiation therapy, Proton therapy

## Laparoscopic Liver Resection for Hepatocellular Carcinoma

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Laparoscopic liver resection is gaining wide acceptance for treatment of Hepatocellular carcinoma (HCC).<sup>1,2</sup> Laparoscopic left lateral sectionectomy and minor laparoscopic liver resection (LLR), especially for tumors located in the anterolateral segments of the liver, are considered as standard approach.<sup>3</sup> Even for living donors, laparoscopic left lateral sectionectomy in adult donor for child liver transplantation is performing in many centers.<sup>4</sup> Recently, laparoscopic major liver resection including left hepatectomy and right hepatectomy has been tried.<sup>5</sup> Laparoscopic donor hepatectomy is increasing due to demand from young living donors by its minimal invasiveness and excellent cosmetic result. Several centers have already performed total laparoscopic donor right hepatectomy for adultto-adult living donor liver transplantation. Besides of cosmetic outcome, many meta-analyses showed that LLR is better than open liver resection (OLR) in terms of short-term outcome (Table 1).<sup>6</sup> Although there is no randomized control trial to compare LLR and OLR, recent case-matched studies showed comparable results in terms of longterm oncologic outcomes (Table 2).<sup>7</sup>

Author	Туре	Blood loss	Transfusion	Operative time	Hospital stay	Complications	Resection margin
Zhou et al. [40] (2011)	Meta-analysis 21 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Rao et al. [41] (2011)	Systematic review 10 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Fance <b>ll</b> u et al. [42] (2011)	Meta-analysis 9 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Li et al. [43] (2012)	Meta-analysis 10 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Xiong et a <b>l</b> . [44] (2012)	Meta-analysis 16 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Yin et a <b>l</b> . [45] (2013)	Meta-analysis 15 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD

Table 1. Previous studies comparing the outcomes of laparoscopic liver resection versus open resection.

LLR, laparoscopic liver resection; OLR, open liver resection; NSD, no significant difference.

Study	Туре	1 year survival	3 year survival	5 year survival	1 year DFS	3 year DFS	5 year DFS	Overall and DFS
Lee et a <b>l</b> . [50] (2011)	Case matched	L <del>-</del> 86.9% O - 98%	L – 81.8% O – 80.6%	L – 76% O – 76.1%	L – 78.8% O – 69.2%	L – 51% O – 55.9%	L – 45.3% O – 55.9%	NSD
Parks et al. [51] (2014)	Meta-analysis	L <del>–</del> 92% O – 91.3%	L <del>–</del> 77.7% O – 76.5%	L <del>–</del> 61.9% O – 56.5%	NA	NA	NA	NA
Cheung et a <b>l</b> . [52] (2013)	Retrospective	L <del>–</del> 96.6% O <del>–</del> 95.2%	L <del>–</del> 87.5% O <del>–</del> 72.9%	L <del>–</del> 76.6% O <del>–</del> 57%	L <del>–</del> 87.3% O <del>–</del> 63.5%	L <del>–</del> 72.6% O <del>–</del> 50%	L <del>–</del> 54.5% O <del>–</del> 44.3%	NA
Kim et a <b>l</b> . [53] (2014)	Case matched with PSM	L – 100% O <b>–</b> 96.5%	L – 100% O <b>–</b> 92.2%	L – 92.2% O <b>–</b> 87.7%	L – 81.7% O <b>–</b> 78.6%	L – 61.7% O <del>–</del> 60.9%	L – 54% O <b>–</b> 40.1%	NSD
Han et a <b>l</b> . [54] (2015)	Case matched with PSM	L – 91.6% O – 93.1%	L – 87.5% O – 87.8%	L – 76.4% O – 73.2%	L – 69.7% O – 74.7%	L – 52% O – 49.5%	L – 44.2% O – 41.2%	NSD
Takahara et a <b>l</b> . [46] (2015)	Case matched with PSM	L <del>–</del> 95.8% O – 95.8%	L <b>–</b> 86.2% O – 84%	L <del>–</del> 76.8% O – 70.9%	L <del>–</del> 83.7% O – 79.6%	L – 58.3% O – 50.4%	L <b>-</b> 40.7% O - 39.3%	NSD

Table 2. Recent studies on long-term outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma

DFS, disease free survival; PSM, propensity score matching; L, laparoscopic liver resection; O, open liver resection; NSD, no significant difference; NA, not analyzed.

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## Liver Transplantation for HCC: What Is New

#### John Lake

Univ. of Minnesota



The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (08:30-09:50) WEST TOWER / ROOM AB [B1]

# Symposium 3

## **Recent Updates in Cirrhosis and Sarcopenia**

Chairs: Kwang-Hyub Han (Yonsei Univ.) Soon Ho Um (Korea Univ.)

### Sarcopenia: Definition and Measurement

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근감소증은 주로 나이가 증가함에 따라 발생하는 것으로 알려져 있고, 만성 간질환을 포함한 만성 질환 환자에서도 발생할 수 있다. 근감소증은 근육량의 감소뿐 만 아니라 근력 또는 신체 활동 능력의 감소를 포함한다. 근육량은 전산화 단층촬영, 이중 에너지 X선 흡광분석법, 바이오임피던스 등을 이용하여 측정할 수 있지만, 만성 간질환 환자에서는 수분저류가 근육량 측정에 영향을 미칠 수 있기 때문에 해석에 주의가 필요하다. 근력은 악력 검사를 이용할 수 있고, 신체 활동 능력은 보행 속도를 통해 측정할 수 있다. 근감소증은 인종 및 성별에 따라 다르게 나타나기 때문에 여러 가이드라인에서 서로 다른 기준치를 제시하고 있다. 또한 만성 간질환 환자에서 예후를 예측할 수 있는 적절한 근감소증 기준에 대한 연구도 부족하다. 따라서 근감소증을 진단하기 위한 적절한 검사 방법과 적절한 기준치에 대한 연구가 필요하다.

Keywords: Sarcopenia, Muscle mass, Muscle strength, Measurement, Diagnosis

#### Introduction

Aging gradually causes the decline in physical function and activity. The term 'sarcopenia', which Irwin Rosenberg proposed in 1989, has been used to describe the loss of muscle mass and strength that occurs with aging.<sup>1,2</sup> Age-related sarcopenia is associated with reduced physical capability, poorer quality of life, fall, fracture, disability, and mortality of the elderly.<sup>3-7</sup> Although sarcopenia is a ubiquitous change, it can occur in chronic disease conditions, including chronic liver disease.<sup>8,9</sup> Sarcopenia is also a significant factor associated with morbidity and complications in patients with chronic liver disease.<sup>10,11</sup> Therefore, the importance of sarcopenia in chronic liver disease is emerging. In this article, we will review the definitions, diagnostic criteria of sarcopenia and various methods assessing sarcopenia.

#### Definition of Sarcopenia

There is no broadly accepted definition of sarcopenia yet. However, several consensus definitions were proposed; European Working Group on Sarcopenia in Older People (EWGSOP),<sup>12</sup> International Working Group on Sarcopenia (IWGS),<sup>13</sup> and Asian Working Group for Sarcopenia (AWGS).<sup>9</sup>

EWGSOP recommends screening for sarcopenia among community-dwelling people aged 65 years and older. On the other hand, IWGS and AWGS recommend screening not only the patients with certain conditions but also the old people. Table 1 shows the conditions that require screening for sarcopenia by IWGS and AWGS.

All three definitions defined sarcopenia as low muscle mass and low muscle function. In EWGSOP definition, diagnosis of sarcopenia requires low muscle mass plus documentation of either low muscle strength or low physical performance. In AWGS definition, muscle strength and physical performance are measured as a screening test, and those with low muscle mass are diagnosed as sarcopenia.

#### IWGS

Noted decline in function, strength, "health" status

Self-reported mobility-related difficulty

History of recurrent falls

Post-hospitalization

Other chronic conditions (eg, type 2 diabetes, chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, and cancer)

#### AWGS

Community settings

People aged 60 or 65 years and older (according to the definitions of elderly in each individual country) living in communities

Specific Clinical Conditions in All Healthcare Settings

Presence of recent functional decline or functional impairment

Repeated falls

Undernutrition

Chronic conditions (eg, chronic heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions)

## Assessment Methods

#### Computed Tomography (CT) Scan

CT scan is a very precise method for the assessment of body composition, and it is gold standard for estimating muscle mass. Since the cross-sectional areas of tissues in a single image in the lumbar area are strong correlates of whole body adipose tissue, muscle, and lean tissue mass,<sup>14</sup> an axial image of the 3rd or 4th lumbar vertebra (L3 or L4) is used. Two approaches are generally used for quantifying muscle cross-section area and density (Hounsfield units) on abdominal CT scans. One method measures the total skeletal muscle mass on an axial image at the L3 level, with image analysis software set to include tissue between -29 and 150 HU (Figure 1).<sup>15,16</sup> Another method measures the cross-section area or thickness of psoas muscle at the L3 or L4 level (Figure 2).<sup>17,18</sup> CT scan also can assess fat infiltration in the muscle, which impacts on muscle quality.

However, high cost, limited access to equipment at some sites and concerns about radiation exposure are the limitation of CT scan.



Figure 1. The patient on the left is sarcopenic and patient on the right is not sarcopenic. Red color indicates skeletal muscle, green color indicates intermuscular adipose tissue, yellow color indicates visceral adipose tissue.<sup>16</sup>



Figure 2. Measurement of psoas muscle thickness<sup>18</sup>.

## Dual energy X-ray Absorptiometry (DEXA)

DEXA measures the relative attenuation of two different energy X-rays by the body. It allows measurement of three body composition compartments and can provide regional estimates of each of them. The property of regional analysis allows the measurement of both total muscle mass and appendicular muscle mass. The radiation dose of DEXA is very small, which makes DEXA a safe option for repeated body composition measurements.<sup>19</sup> The main disadvantage of DEXA is that the equipment is not portable, which may preclude its use in large-scale epidemiological studies. In addition, diseases with water retention can affect results because it cannot differentiate between water and bone-free lean tissue.<sup>20,21</sup> Therefore, DEXA can be inaccurate in the patients with liver cirrhosis and ascites.

#### **Bioelectric Impedance Analysis (BIA)**

BIA is a method consisting of the passage of a painless electric current of low amplitude and low and high frequencies through the body. As current is conducted by body water, impedance is inversely related to total body water, thus allowing calculation of total muscle, which is the largest water-rich tissue in the body.<sup>22</sup> Muscle mass is calculated using the equation developed by Janssen et al.: Skeletal muscle mass (Kg) = [(height2/BIA resistance X 0.401) + (gender X 3.825) + (age X -0.071)] + 5.102, for gender, men = 1 and women =  $0.^{22}$  BIA method is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients. In addition, prediction equations have been validated for multiethnic adults.<sup>12</sup> However, muscle mass measurement by BIA can also be distorted by hydration status and edema.<sup>23</sup>

#### Anthropometric Measures

Anthropometric measurements are objective, noninvasive, rapid and low-cost tools evaluating nutritional status. Calculations based on mid-upper arm circumference and skinfold thickness have been used to estimate muscle mass. Midarm muscle circumference (MAMC) is calculated from triceps skinfold (TSF) and midarm circumference. It is considered to be the most sensitive marker of body cell mass in patients with end-stage liver disease.<sup>24</sup> However, anthropometric measures are vulnerable to error and not recommended for routinely use in the diagnosis of sarcopenia.

#### Handgrip Strength (HGS)

HGS is used to diagnose both sarcopenia and frailty. It can be quantified by measuring the amount of static force that the hand can squeeze around a dynamometer,<sup>25</sup> and it is an indicator of overall muscle strength.<sup>26</sup> It has good intra- and inter-tester reliability and can be recommended the use in clinical practice.<sup>27</sup> While HGS is considered a reliable measure to assess muscle strength, it can be influenced by several factors; posture, positions of the elbow and wrist, the hand used to test, and the setting of the dynamometer. However, there is still a lack of consistency in the studies' protocols to evaluate HGS.<sup>27</sup>

#### **Usual Gait Speed**

Gait speed (GS) is a quick, low-cost and reproducible method to screen for frailty.<sup>28</sup> This method measures the patients' gait speed at the usual pace, over a short distance. A slow GS over a distance of 4 m was predictive of mortality in ambulatory elderly patients.<sup>29</sup> In addition, GS in patients with cirrhosis was an independent risk factor for complications that require hospitalization.<sup>30</sup> In AWGS definition, 6-meter usual GS for measurement of physical performance is recommended<sup>9</sup>.

## **Defining Cut-Off Points**

The same cut-off value cannot be uniformly applied because the muscle mass and strength varies according to race. EWGSOP recommends using the cut-off points at two standard deviations below the mean reference value, using the value of healthy young adult as reference.<sup>12</sup> AWGS recommends using 2 standard deviations below the mean value or the lower quintile as the cut-off value determination.<sup>9</sup> EWGSOP and AWGS use gait speed as assessing the physical performance, and two definitions suggest 0.8 m/s as the cut-off point, while IWGS use gait speed less than 1 m/s as the cut-off point. Only AWGS recommend the handgrip strength cut-off point of <26 kg for men and <18 kg for women or using the lower 20<sup>th</sup> percentile of handgrip strength of the study population before outcome-based data is available.<sup>9</sup>

Muscle masses assessed by CT, DEXA, or BIA can be adjusted by height or weight. As the cut-off value of L3-skeletal muscle index (SMI) which was adjusted by the square of height,  $38.5 \text{ cm/m}^2$  for women and  $52.4 \text{ cm/m}^2$  for men were usually used. However, this cut-off value was from obese cancer patients.<sup>31</sup> Recently, Carey et al. recommended new cut-off value for end-stage liver disease patients; 39 cm/m<sup>2</sup> for women and 50 cm/m<sup>2</sup> for men.<sup>32</sup> Appendicular skeletal muscle mass which can be assessed by DEXA and BIA is also usually adjusted by the square of height. IWGS suggested using  $\leq 7.23 \text{ kg/m}^2$  for men and  $\leq 5.67 \text{ kg/m}^2$  for women as the cut-off for sarcopenia.<sup>13</sup> In AWGS definition, suggested cut-off values were 7.0 kg/m<sup>2</sup> in men and 5.4 kg/m<sup>2</sup> in women by using DEXA, and 7.0 kg/m<sup>2</sup> in men and 5.74 kg/m<sup>2</sup> in women by using BIA, defined by appendicular skeletal muscle mass/height.<sup>2</sup>

#### Conclusions

Sarcopenia means the low muscle mass and low muscle function. Although sarcopenia is the age-related condition, chronic diseases including chronic liver disease can cause sarcopenia. Muscle mass can be measured by CT, DEXA, and BIA, and it can be adjusted by height or weight. Muscle strength can be assessed by handgrip strength, and physical performance can be assessed by gait speed. Because muscle mass and function can vary according to races and gender, the uniformed cut-off value cannot be applied. In addition, water retention or ascites can affect the measurement of muscle mass in the patients with the chronic liver disease. Therefore, further study is needed to determine the methods to assess sarcopenia and the proper cut-off values in patients with the chronic liver disease.

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## Sarcopenia: Ammonia Metabolism and Hepatic Encephalopathy

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Muscle wasting is a cardinal manifestation of advanced cirrhosis. Its key consequence is frailty; a state of vulnerability to stress that is now recognized in transplant hepatology as an important risk factor for functional decline, waitlist removals, hospital and transplant deaths, and major transplant complications. Frailty assessments in cirrhosis are gaining attention, both as measurements of anatomic muscle loss (sarcopenia), and measurements of functional decline in physical performance. Excess ammonia as a pivotal cause of muscle loss and functional impairment in cirrhosis has long been understood in terms of a shift in its predominant metabolism from liver to muscle. Three new mechanisms now help to account for ammonia's adverse impacts on muscle in cirrhosis.

Normal regulation of total body and circulating ammonia requires a delicate interplay in ammonia formation and breakdown between several organ systems. In the setting of cirrhosis and portal hypertension, the decreased hepatic clearance of ammonia leads to significant dependence on skeletal muscle for ammonia detoxification; however, cirrhosis is also associated with muscle depletion and decreased functional muscle mass. Thus, patients with diminished muscle mass and sarcopenia may have a decreased ability to compensate for hepatic insufficiency and a higher likelihood of developing physiologically significant hyperammonemia and hepatic encephalopathy.

#### Cirrhosis Drives Inter-Organ Shifting of Ammonia Metabolism

In health, ammonia is predominantly metabolized in the liver to urea. Skeletal muscle and brain also process ammonia to a much lesser extent for utilization and detoxification via glutamine synthesis from glutamate. Cirrhotic patients with progressive hepatocyte damage have deficient urea synthesis, and shunting of ammonia past hepatocytes also contributes to its escape from the liver with increased muscle uptake. The shift to skeletal muscle as the prime site for ammonia metabolism requires diversion of branched-chain amino acids to generate the glutamate needed for ammonia detoxification, leading to the well-described depletion of these substrates needed for protein synthesis and maintenance of muscle mass. Mathematical modeling suggests that shunting in cirrhosis is sufficient to explain excess delivery of ammonia to muscle with its consequent adverse impact on protein synthesis.

#### Ammonia Mediates Myostatin Transcription and Expression

Myostatin is a potent autocrine growth inhibitor produced by myocytes that inhibits skeletal muscle growth and reduces muscle mass in cirrhosis. Qiu et al. recently showed that exposure of mouse skeletal muscle myotubes in culture to ammonium acetate caused a time- and concentration-dependent increase in myostatin mRNA and protein expression. They found that hyperammonemia-activated transcription factor p65 NF- $\kappa$ B bound to the myostatin promoter with transcriptional upregulation. Pharmacologic and genetic silencing of NF- $\kappa$ B during hyperammonemia decreased myostatin expression. They also found that myotube diameter was significantly greater in the NF- $\kappa$ B knockdown cells compared with the control cells, further supporting their proposal that NF- $\kappa$ B regulates

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myostatin expression during hyperammonemia. Their observations show that hyperammonemia induces myostatin expression in myotubes via an NF- $\kappa$ B-dependent pathway.

### Ammonia Mediates Muscle Autophagy

Autophagy is a normal process through which damaged proteins are degraded or recycled to maintain essential cellular function. Qiu et al. studied autophagy in skeletal muscle from 13 cirrhotic patients undergoing liver transplantation and 13 control patients having elective abdominal surgery. They found that expression of three autophagy pathway components, beclin-1, LC3-I cytosolic protein, and p62/SQSTM1, was enhanced in cirrhotic human muscle, in the same pattern that they observed with hyperammonemia-induced change of the same autophagy marker components in portacaval-shunted rats. They also found that hyperammonemia induced the formation of autophagosome vesicles observed by electron microscopy of ammonia-treated murine myotubes in culture.

### Ammonia Impairs Skeletal Muscle Contractility

McDaniel et al recently explored the effect of hyperammonemia on skeletal muscle contractile function, independent of muscle mass. They found that hyperammonemic portacaval-shunted rats showed impaired initial maximum grip strength compared with controls. They also found that rat soleus muscles treated with ammonium acetate generated significantly less contractile force than did control muscles, and that the rates of force development and relaxation were depressed in the ammonia-treated muscles, replicating observations in cirrhotic patients. Although the mechanism by which hyperammonemia impairs muscle contractile function remains unclear, this report shows that that hyperammonemia contributes to muscle dysfunction.

## Ammonia as a Myotoxin—an Old Culprit With New Injury Mechanisms

To conclude, ammonia is now implicated in three recently reported muscle injury pathways involving myostatin, autophagy, and functional muscle impairment. These new injury mechanisms appear to amplify the well-known muscle wasting impact of inter-organ shifting of ammonia metabolism to deplete essential amino acid protein sub-strates.

## Sarcopenia: Prognostic Impact on Cirrhosis

#### Sang Gyune Kim

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Sarcopenia is a new clinical entity related to muscle decline, which has attracted a great deal of attention among clinicians because of its detrimental effect on clinical outcomes. Relevant pathways may vary depending on the underlying disease, but muscle depletion occurs due to imbalances in muscle formation and breakdown.

According to recent meta-analysis, sarcopenia in patients with liver cirrhosis is an important prognostic factor, independent of MELD and CTP scores (Figure 1).<sup>1</sup> In this study, the prevalence rate of sarcopenia among all cirrhotic patients was about 48%, and 2-fold more among men with a rate of 62% compared to that of 36% for women. Interestingly, Asians had a HR 2.45 (95% confidence interval (CI) =  $1.44 \pm 4.16$ , P = 0.001) of mortality whereas Westerners had a HR 1.45 (95% CI =  $1.002 \pm 2.09$ , P < 0.05). This might be due to discrepancy of muscle measurement and sarcopenia definition.

Cirrhotic patients with sarcopenia suffered from poor quality of life and functional disability and increased infection and mortality.<sup>2</sup> Recently, not only sarcopenia, but also combined obesity, which is called "sarcopenic obesity", is known to be associated with higher rates of mortality and have a greater impact on physical function than either alone. The proposed mechanisms include increased pro-inflammatory cytokines, decreased physical activity, reduced protein synthesis, aging.

Durand et al. suggested that MELD-sarcopenia scores combined with MELD and psoas muscle area scores were superior to MELD score alone in predicting prognosis of cirrhotic patients<sup>3</sup>. These results indicated that sarcopenia is an excellent predictor of organ allocation in liver transplant recipients. However, Tandon et al reported that the effect of Sarcopenia was significant in patients with low MELD scores (<15; P = 0.02), but not in patients with high MELD scores<sup>4</sup>. Therefore, sarcopenia seems to be an important prognostic factor and needs to be treated in early and intermediated stage rather than advanced liver cirrhosis. On the other hand, Van Vugt et al. reported that among patients with cirrhosis listed for liver transplantation in the Eurotransplant registry, MELD-sarcopenia combined scoring system had limited value in predicting waiting list mortality, although low skeletal muscle mass was significant related with mortality on the waiting list, particularly in patients who were listed with low priority based on a low MELD score<sup>5</sup>. In this competing risk analysis, mortality was significantly higher in patients with sarcopenia<sub>M</sub><sup>6</sup> than in patients with and without sarcopenia<sub>C</sub> (for liver transplant candidate)<sup>7</sup>. Since there are no universally accepted cut-off values to classify patients with sarcopenia, care should be taken when analyzing the effect of sarcopenia on prognosis in patients with cirrhosis.



Figure 1. Sarcopenia as a prognostic factor in liver cirrhosis



Figure 2. Difference of cumulative incidence for patients between sarcopeniaC and sarcopeniaM

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## Management of Malnutrition in Cirrhosis

#### Tae Hee Lee

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In the case of liver cirrhosis, malnutrition is prevalent and can occur due to a variety of causes, including poor oral intake, maldigestion, malabsorption, associated renal disease, and metabolic abnormalities. For a nutritional assessment, it is important to check the dietary intake, change in body composition, including anthropometry, and a functional assessment.

Stepwise approach is recommended: counseling, oral or enteral nutrition and parenteral nutrition. If esophageal varices are present, caution should be taken when installing a feeding tube, but if there are ascites, percutaneous endoscopic gastrostomy is contraindicated because of the risk of complications. Calories of 25-40 kcal/kg/day and protein from 1.2 to 1.5 g/kg/day are appropriate. Protein restriction is unnecessary unless hepatic encephalopathy is severe,. A late evening snack (pm9-am7) and branched chain amino acids can be helpful. In the case of cholestasis, the supply of manganese and copper should be restricted. Sarcopenia in patients with liver cirrhosis is also prevalent and associated with the prognosis.

General recommendations
Stepwise approach: counseling, supplements, tube feeding, parenteral nutrition
Adequate energy intake (total energy 25-40 kcal/kg/day, non-protein energy 25 kcal/kg/day)
Use indirect calorimetry if available
Enough protein (1.0-1.5 g/kg/day) without restriction
Avoid re-feeding syndrome
Oral diet
Small/frequent meals ("nibbling" pattern > "gorging" pattern)
Bedtime snack or late evening meal (PM9-AM7)
≤2,000 mg sodium daily if ascites/edema present
Enteral nutrition
Initiate if unable to meet protein-energy needs via oral diet
Standard, energy-dense formula
Nasoenteral tube precautions
Percutaneous gastrostomy tube relatively contraindicated
Aspiration precautions
Parenteral nutrition
Indicated only if nutrition needs cannot be met via oral and enteral routes
Monitor glucose levels closely
If hyperglycemia present, limit glucose to 2-3 g/kg/day
Lipids ≤1 g/kg/day
Limit manganese and copper in setting of cholestasis
Cyclic regimen recommended
Concentrated solution to prevent fluid overload

The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (11:10-12:10) WEST TOWER / ROOM AB [B1]

# KLTS-KASL Joint Symposium (Voting)

## Liver Transplantation for Alcoholic Liver Disease (\*K)

Chairs: Myoung Soo Kim (Yonsei Univ.) Jong Young Choi (The Catholic Univ. of Korea)

## Severe Alcoholic Hepatitis, How to Manage?

#### **Dong Hyun Sinn**

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## 중증 알코올 간염, 어떻게 할 것인가

신동현

성균관대학교 삼성서울병원 내과

Alcoholic hepatitis includes a broad spectrum of pathological process. In case of severe alcoholic hepatitis, the prognosis is worse with a 1-month mortality of 40%. Drink excessively, may induce recurrent episodes of alcoholic hepatitis in patients with alcoholic liver disease, and if this is severe or associated with liver cirrhosis, complications occur due to liver failure and portal hypertension, leading to a high short-term mortality. Recently, liver transplantation (LT) has shown improved outcome for patients with severe alcoholic hepatitis who were not abstinence for 6 months. In Korea, there is no limitation to enlist patients into waiting-list for patients with severe alcoholic hepatitis who presented to hospital while drinking. This brings a several questions that needs critical evaluations. Is it justifiable to transplant severe alcoholic hepatitis patient who were not abstinence? If so, when is optimal time to list patients into waiting-list?

중증 알코올 간염은 예후가 매우 불량하여 단기 사망률이 40%에 이르는 심각한 상태이다.<sup>1</sup> 중증 알코올 간염 은 임상적으로 진단할 수 있는 병으로 보통 남성 60 gram, 여성 40 gram이상의 알코올을 6개월 이상 섭취하 던 사람이며, 황달이 나타나기전 2달이내 음주를 하고 있던 사람에서, 8주이내에 황달이 발생하며, aspartate aminotransferase (AST)가 50U/L이상, AST/alanine aminotransferase (ALT) >1.5 이상이고, AST/ALT가 400 U/L 이하이면서, bilirubin이 3.0 mg/dl 이상인 사람을 뜻한다.<sup>2</sup> 따라서 모든 중증 알코올 간염 환자는 정 의상 최근 또는 2달이내에 음주력이 있는 사람들이다. 일반적으로 알코올 사용장애가 있는 사람들은 이식 후에 도 다시 위험음주를 시작할 가능성이 높고, 음주를 다시 시작하는 경우 장기 예후가 나빠진다.<sup>3</sup> 따라서 많은 이 식 센터에서 6개월 이상의 금주기간을 가진 알코올 간질환 환자들에게 간이식을 권유하거나 시행하여 왔다. 그 러나 최근에는 금주기간을 지키지 않았던 중증 알코올 간염 환자에게 조기 간이식을 시행한 결과 생존율 향상이 있으며, 이식 후 알코올 사용장애의 재발도 드물어 선택적인 사람들에게는 조기 간이식이 도움이 될 수 있음을 보여주었다.<sup>4</sup> 우리나라는 현재 뇌사자 간이식 대기자 등록시 금주기간에 대한 제한이 없다. 따라서 중증 알코올 간염 환자들도 뇌사자 이식을 통해 생존율 향상을 기대할 수 있다. 다만 뇌사자 간이 사회 공공적 성격이 있다 는 점과 뇌사자 간이식을 원하는 분들에 비해 뇌사자 간이 매우 부족하다는 점을 고려한다면 모든 알코올 간염 환자가 아니라 잘 선택된 환자에게 시행하는 것이 필요하겠다.<sup>5</sup> 어떤 환자를 어느 시점에 뇌사자 간이식에 등록 하고 시행하는 것이 좋을지는 매우 중요한 임상 질문이다.

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## How Should We Do It? Optimal Management of Severe Alcoholic Hepatitis: A Hepatologist's View

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## 김 원

서울대학교 의과대학 보라매병원 내과

Alcoholic hepatitis (AH) is an acute hepatic manifestation occurring from heavy alcohol ingestion. Alcoholic steatohepatitis (ASH) is histologically characterized by steatosis, inflammation, and fibrosis in the liver. Despite the wide range of severity at presentation, those with severe ASH (Maddrey's discriminant function  $\geq$  32) typically present with fever, jaundice, and abdominal tenderness. Alcohol abstinence is the cornerstone of therapy for AH and, in the milder forms, is sufficient for clinical recovery. Severe ASH may progress to multi-organ failure including acute kidney injury and infection. Thus, infection and renal failure have a major impact on survival and should be closely monitored in patients with severe ASH. Patients with severe ASH have a reported short-term mortality of up to 40%-50%. Severe ASH at risk of early death should be identified by one of the available prognostic scoring systems before considering specific therapies. Corticosteroids are the mainstay of treatment for severe ASH. Responsiveness to steroids should be assessed at day 7 and stopping rules based on Lille score should come into action. Strategically, future studies for patients with severe ASH should focus on suppressing inflammation based on cytokine profiles, balancing hepatocellular death and regeneration, limiting activation of the innate immune response, and maintaining gut mucosal integrity.

Keywords: Alcoholic steatohepatitis/cirrhosis, Fibrosis, Inflammation, Regeneration, Stem cell, Hematopoietic growth factor

## Optimal Treatment for Severe Alcoholic Hepatitis: Transplant Surgeon's Perspective

#### Young Kyoung You

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아직까지 알코올 중독 자체가 죄악시 여겨지고 있는 전 세계적인 분위기에서 금주 또는 절주여부가 불확실한 알코올 중독자 에 대한 간이식의 필요성에 관한 논의는 조심스럽기만 하다. 그러나 실제 말기 간경화에 이르는 환자의 많은 인자 중에는 알코 올 섭취의 영향에 의한 간 기능의 악화가 상당한 관계가 있다고 추정되고 있다.

알코올성 간염은 최근 과량의 음주력이 있는 환자에서의 갑작스러운 간기능 저하를 초래하는 임상증상들을 말하며 급격 한 황달 발생을 동반한다. 알코올성 간염의 심각정도는 prothrombin time과 bilirubin 값을 이용하여 계산한 Maddrey's discriminant function (DF)으로 평가하며 이 점수가 32점 이상일 때 심한 알코올성 간염이라고 정의한다. 알코올성 간염 은 내과적 치료로 호전되지 않으면 매우 치명적 결과를 보이는데, corticosteroid로 일주일 치료한 후 bilirubin, prothrombin time, creatinine, age, albumin, change in bilirubin의 수치를 이용하여 계산한 Lille score가 0.45를 초과한 경우이거나 Model for End-Stage Liver Disease (MELD) score가 지속적으로 상승하는 경우는 6 개월 이내의 사망률이 70% 에 이 르는 것으로 알려져 있다.

알코올과 관련되어 있는 간질환의 내과적인 치료는 아직까지 적절한 치료법이 없고 사망률도 높아서 간이식 수술이 효과적 인 치료법인 것은 분명해 보이지만 여러 가지 이유로 간이식의 적극적인 도입은 망설여지고 있다. 미국을 비롯한 서구의 대부 분의 이식센터에서는 알코올과 관계된 간이식수술의 전제조건으로 적어도 6 개월 이상의 완전한 금주를 요구하고 있다. 이식 수술 전 금주 기간이 이식수술 후의 금주를 예측할 수 있는 중요한 인자중의 하나라는 데에는 대체로 동의하고 있으며 6 개월 이상의 금주 기간 동안 간기능이 회복되면 간이식에 까지 이르지 않아도 된다는 이론적인 장점이 있다. 그러나 6개월 이상 금 주한 환자들도 장기적으로 관찰하였을 때 이식 수술 후 약 30 %에 해당하는 환자들이 다시 알코올 섭취를 시작하였고 10% 이상의 환자들은 이식 수술 전의 알코올 의존 상태로 회귀하는 것으로 조사되면서 과연 이식 수술 전 6개월 간 금주 조건에 대 한 회의적인 시각이 대두되고 있다, 더욱이 심한 알코올성 간염의 경우는 2 개월 이내의 사망률이 70 - 90%에 이르며 마땅 한 내과적인 치료법도 없으므 금주 6개월 이내라도 환자의 상황에 따라 간이식을 급히 서둘러야 하는 것이 아니냐는 의견 또 한 심심치 않게 발표되고 있다.

알코올 섭취와 이에 의한 간손상의 결과로 간이식이 필요하게 되는 과정에서 환자 자신에 대한 책임을 따지는 문제는 의학적 인 결론을 내기가 불가능한 윤리적인 첨예한 논쟁의 대상이며 이식 수술 후 금주가 보장되지 않은 알코올성 간염환자에 대한 우호적인 입장을 찾아내는 것 또한 매우 어려울 듯 하다. 현재 우리나라의 경우 뇌사자 간이식의 경우 급성 간염의 경우 알코 올성 간염여부에 대한 제한없이 이루어지고 있으며 공여자 수의 절대적인 부족으로 인하여 실제 뇌사자 간이식을 받는 대부분 의 환자가 MELD 점수의 상위권을 차지하는 심한 알코올성 간염환자들이다. 이에 대한 진지한 논의가 이루어져야 할 시점이 라고 생각한다.

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DAY 3: Saturday, June 16, 2018 (13:10-13:40) WEST TOWER / ROOM AB [B1]

# **Special Lecture**

Chair : Kwan Soo Byun (Korea Univ.)

# Mechanisms of Hepatic Triglyceride Accumulation in Non-Alcoholic Fatty Liver Disease

#### David E. Cohen

Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, USA

Non-Alcoholic fatty liver disease (NAFLD) is characterized by hepatic lipid accumulation in the absence of excess alcohol intake and represents the most common chronic liver disease in the United States. NAFLD is present in approximately 20% of the general population, but in 80% of individuals with the metabolic syndrome. NAFLD is present in 50% of patients with type 2 diabetes and nearly 100% with type 2 diabetes plus obesity. Although the proportion of non-alcoholic steatohepatitis (NASH) is generally low in the overall population of NAFLD patients, it is enriched in diabetics up to nearly 90% of NAFLD cases, with as many as 20% of patients being cirrhotic. Under normal conditions, steady-state triglyceride concentrations are low in the liver, and this is attributable to a precise balance between uptake of non-esterified fatty acids from the plasma plus de novo lipogenesis, versus triglyceride elimination by fatty acid oxidation and by the secretion of triglyceride-rich very low-density lipoproteins (VLDL). Insulin resistance in NAFLD patients leads to hepatic steatosis by multiple mechanisms. These include increased uptake rates of plasma non-esterified fatty acids into the liver, which are attributable to greater release from an expanded mass of adipose tissue in the setting of diminished insulin responsiveness. Hyperinsulinemia and hyperglycemia promote the transcriptional upregulation of genes that promote de novo lipogenesis in the liver. Increases in hepatic lipid accumulation are not offset by fatty acid oxidation or by increased secretion rates of VLDL. Because current approaches to the management of NAFLD are very limited, ongoing research efforts are focused on understanding the underlying the pathobiology of hepatic steatosis with the anticipation of identifying novel therapeutic targets.



DAY 3: Saturday, June 16, 2018 (13:40-15:00) WEST TOWER / ROOM AB [B1]

# Symposium 4

# **Recent Updates in Chronic Hepatitis B**

**Chairs :** Chang Min Kim (National Cancer Center) Jong Eun Yeon (Korea Univ.)

### Unmet Needs in Chronic Hepatitis B Management

#### **Grace Lai-Hung Wong**

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Unmet needed in chronic hepatitis B (CHB) management are present in various aspects related to education, vaccination and prevention, diagnosis and treatment. Screening and diagnosis of CHB, appropriate evaluation of patients with CHB, initiation of antiviral therapy, and retention of patients on treatment, all which need to be addressed at the levels of healthcare systems. Oral nucleos(t)ide analogues (NAs) have revolutionalised the chronic hepatitis B treatment by good on-treatment viral suppression, a daily oral dosing, few side effects and improved patient outcome.<sup>1,2</sup> Long-term, if not life-long, NA treatment is still a necessity. Furthermore, functional cure as evidenced by hepatitis B surface antigen (HBsAg) seroclearance is uncommon in NA-treated patients, especially in Asian patients who acquire HBV infection through perinatal transmission.<sup>3</sup> New treatment of finite duration and high rate of HBsAg seroclearance is very much wanted and currently under clinical evaluation at different phases of clinical trials.<sup>4</sup> Biomarkers to predict treatment responses and clinical outcomes are also needed. Apart from the conventional serum HBV DNA and HBsAg levels, serum HBV RNA, HB core-related antigen (HBcrAg) have evolving roles in these aspects.<sup>5</sup>

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## Navigating New Indications of Antiviral Treatment

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High levels of serum hepatitis B virus (HBV) DNA (> $10^4$  copies/mL or >2,000 IU/mL) are associated with a high risk of hepatocellular carcinoma (HCC) and disease progression irrespective of serum alanine aminotransferase (ALT) levels, HBeAg, and cirrhosis in patients with chronic hepatitis B (CHB).<sup>1,2</sup> Long-term suppression of HBV DNA with nucleos(t)ide analogs (NUC) reduces the risk of HCC and mortality in immune-active (IA) phase CHB patients.<sup>3-7</sup>

Chronic infection with HBV progresses through different phases. The first, which is the immune-tolerant (IT) phase, is characterized by high circulating HBV DNA and normal ALT levels. Antiviral treatment is generally not recommended for these patients by most practice guidelines because of the notion that the histologic activity is dormant and the risk of disease progression is low in the IT phase.<sup>8-12</sup>

However, recent studies have claimed that the histologic activity and HBV-specific immune responses do occur in the IT phase and are comparable to those occurring in the IA phase.<sup>13-15</sup> Moreover, a high level of chromosomal HBV DNA integration and clonal hepatocyte expansion was found in patients considered to be in the IT phase, indicating that hepatocarcinogenesis could be underway in these patients.<sup>16</sup> These findings suggest that therapeutic interventions to minimize further damage to the hepatocytes should be considered for IT phase patients. However, virtually no clinical evidence exists regarding whether long-term antiviral treatment of IT phase patients reduces the risk of HCC and mortality.<sup>17</sup>

Therefore, we investigated the long-term risks of HCC and death/transplantation in IT phase patients. Due to the lack of treatment recommendations provided by the current practice guidelines as well as reimbursement policies for IT phase patients in real-world practice settings, we compared the long-term outcomes of untreated IT phase patients with those of treated IA phase patients.

Our study results showed that the untreated IT phase patients were associated with significantly higher risks of HCC and death/transplantation than the immune-active (IA) phase patients treated with nucleos(t)ide analogs.<sup>18</sup>

Interestingly, lower HBV DNA levels (but above 20,000 IU/mL) were independently associated with a significantly higher risk of clinical events. The REVEAL-HBV studies on the natural history of HBV infection showed a direct correlation between serum HBV titers and the risk of HCC. The risk of HCC was highest with HBV titers above  $10^5$  copies/mL (approximately 20,000 IU/mL). However, virus titers above  $10^6$  copies/mL were not quantified, and most of the patients were HBeAg-negative (85%), with a median age of 45 years. The progression of these HBeAg-negative patients would not be identical to that of young HBeAg-positive IT phase patients with very high HBV DNA levels.<sup>17,19</sup> Therefore, results from the REVEAL study could not be extrapolated to patients in the IT phase. In fact, the very high virus titers (>8 log<sub>10</sub> IU/mL) often seen in immunotolerant young patients are not generally considered an HCC risk factor.<sup>10,12,20</sup> Instead, lower viral titers above 20,000 IU/mL may reflect a higher HCC risk because they also reflect cumulative immune damage to the infected liver.<sup>16,20,21</sup> In fact, subsequent studies from the REVEAL cohort also showed that compared with those with persistent HBV DNA levels >10<sup>7</sup> copies/mL, patients with HBV DNA levels at  $10^5-10^7$  copies/mL (approximately 4–6 log<sub>10</sub> IU/mL) had a higher risk of HCC, <sup>22,23</sup> which was consistent with our results.

In conclusion, the present cohort study showed that the untreated patients in the IT phase had significantly higher risks of HCC and death/transplantation than the IA phase patients treated with NUCs. Our results suggest that many unnecessary deaths could be prevented by earlier antiviral intervention in the IT phases before the appearance of clinically active liver disease.

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## New Biomarkers of Chronic Hepatitis B

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Since HBsAg, HBeAg and HBV DNA have been standardized and used as viral markers for chronic hepatitis B infection for many decades, their profiles are well characterized in the natural history and treatment of the disease. These existing markers have been proven to be useful in the disease outcome prognostication and treatment efficacy. With the profound viral suppressive effects from nucleos(t)ide analogues (NA), their roles are rather limited in reflecting the cccDNA content. In addition, there are also lacks of reliable markers to predicting viral rebound after cessation of long-term NA therapy. In the 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 cccDNA level in the liver even in patients with undetectable serum HBV DNA. In addition, it has significance in different scenarios of HBV disease including its reduction in levels during treatment, rates of HBeAg seroconversion, 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 investigated. Pregenomic HBV RNA acts as the template for reverse transcription to relaxed circular DNA after encapsidation. HBV RNA is therefore present in all HBV patients. Under normal circumstance, serum HBV RNA levels are lower than that of serum HBV DNA. It has been shown to have good correlations with HBV DNA and cccDNA. The reduction of HBV RNA was shown to predict HBeAg sero-conversion in patients receiving Peg-IFN and/ or NA. Novel treatments targeting HBV RNA knockdown had shown decrease in HBV RNA levels. In addition, detectable HBV RNA was associated with a higher chance of HBV relapse after cessation of the NA treatment.

The development of measurements of these two new markers would provide more informative resources for clinicians to have better disease prognostication and management for HBV patients.

### Therapeutic Challenge Towards Hepatitis B Virus Cure

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#### Introduction

"Chronic hepatitis B" and "Cure" have been regarded as incompatible both semantically and mechanistically. Recent advances in the development of innovative strategies, however, prompts HBV experts to reconsider the feasibility of this ambitious goal.<sup>1</sup>

#### Operational Definition of "Hepatitis B Cure"

When we consider the definition of "operational definition", that is "a process of defining the measurement of a phenomenon that is not directly measurable", it becomes clear that the recently proposed definitions of hepatitis B cure are operational: the definition of cure, that is "elimination of HBV, thereby allowing treatment to be stopped with no risk of virological relapse and no risk of liver disease progression" is operationalized as the following hierarchical sub-definitions: (1) complete sterilizing cure: undetectable HBsAg in serum and eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA; (2) functional cure: sustained, undetectable HBsAg and HBV DNA in serum with or without seroconversion to hepatitis B surface antibody (anti-HBs) after completion of a finite course of treatment, resolution of residual liver injury, and a decrease in risk of hepatocellular carcinoma (HCC) over time (3) partial cure: detectable HBsAg but persistently undetectable HBV DNA in serum after completion of a finite course of treatment.<sup>1</sup>

The complete cure, although ideal, calls for the methodology of screening the entire genome of the whole hepatocytes of chronic hepatitis B (CHB) patients, which might be as challenging as the complete cure itself. Moreover, we may have to demonstrate that the magic bullet that pull out the integrated HBV DNAs over the entire genome does not do any harm on the host chromosome for the rest of the lives of CHB patients. This may be compared to the ideal cure of hypertension with cleaning of all arteries and arterioles in the body.

The partial cure, seemingly the most readily achievable goal, is also fraught with problems: first we may have to demonstrate that the long-term outcome such as HCC risk is better than or at least not inferior to the continued suppression of HBV by potent NAs, since the HBsAg persists in either treatment strategies. Second, this treatment should prove its advantage over control, i.e., stable CHB patients who choose to stop NA therapy, among whom some remain DNA negative, some show low steady levels and others will have virological full-relapse with or without biochemical flare-up. This task would be much demanding compared to the NA trials. Considering the theoretically marginal benefit, i.e., stopping NA, the demonstration of non-inferiority may not be a very enticing task for big pharmas. Consequently, the goal of cure would be targeted to the 2nd category in the meantime.

#### Toward the Goal of Functional Cure

Before we set out further steps, several issues are better to be settled. First, the clinical benefit of functional cure

needs to be demonstrated. Since the aim is in itself operational, each surrogate marker warrants self-validation in terms of long-term benefit, most importantly risk reduction for HCC. HBV-induced hepatocarcinogenesis is a complex phenomenon, involving several mechanisms common to viral carcionogenesis.<sup>2,3</sup> Inflammation and viral DNA induced oxidative stress may be amenable to potent antiviral strategies, whereas genomic integration remains a formidable obstacle in HCC risk reduction.<sup>3,4</sup> Although HBsAg titre is an important predictor of HCC in HBeAg-negative CHB patients with low viral tier,<sup>5</sup> it does not necessarily guarantee that forced reduction of HB-sAg decrease the HCC risk. Rather, reduction in HBx protein may be a more mechanistically appropriate surrogate marker.<sup>3</sup> It is also uncertain whether suppression of HBsAg may reverse fibrosis, as inhibition of HBV DNA does. Otherwise, the benefit of functional cure may be incremental in patients with advanced fibrosis.<sup>6</sup> Second, the treatment is better to be of limited duration, otherwise the overall benefit may not be very attractive compared to lifelong NA therapy. In that case, the sustained suppression of HBV-miR17-92, an oncogenic micoRNA cluster.<sup>7</sup> The novel anti-HBV therapy for functional cure has to compete with current NAs, not also for efficacy and economy, but also for safety.

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The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (08:30-09:50) WEST TOWER / ROOM C [B1]

# **KAHBPS Symposium 1**

Obstructive Jaundice: How Does It Affect Outcomes in Hepatic and Non-Hepatic Surgeries?

Chairs: Hyung Chul Kim (Soonchunhyang Univ.) Sang-Geol Kim (Kyungpook National Univ.)

## The Impact of Hyperbilirubinemia on the Progression of Hepatic Dysfunction: Comprehensive Experimental Review

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Cholestatic liver injury is one of the major causative factors for the development of liver fibrosis and cirrhosis in patients with chronic liver disease. Based on the fact that these diseases produce imponderable health care costs, it is comprehensible that many researchers are trying to understand the pathogenic mechanisms of ongoing hepatic fibrosis. Therefore, experimental models have been generated that mimic various aspects of the complex mechanisms that lead to hepatic inflammation, fibrosis and cirrhosis. We herein have described some of the elements that can be involved in the progression into hepatic failure following cholestasis induced by bile duct ligation in experimental mice, which recruits immunocompetent cells, possibly by the increased levels of inflammatory cytokines, a decrease of regulatory T cells, and failure of bile duct epithelial cell homeostasis. Surgical bile duct ligation (BDL) is one of the most widespread experimental models that is used to induce obstructive cholestatic injury in mice and rats. In most of the protocols, animals are anesthetized and a midsection laparotomy is performed. Subsequently, the bile duct is uncovered from the abdominal cavity and ligated twice using surgical twine. As a consequence, the mice and rats that received this surgery develop a strong fibrotic reaction that at first originate from the periportal fields. During the establishment of this model, we demonstrated that it reproducibly causes cholestasis with only minimal histological tissue injury and does not proceed to chronic cholestasis. We also found the correlation between the serum levels of hyperbilirubinemia and the degree of hepatic failure. In conclusion, it is critically important to attempt to lessen the progression of hyperbilirubinemia before reaching irreversible hepatic dysfunction.

KAHBPS Symposium 1 Obstructive Jaundice: How Does It Affect Outcomes in Hepatic and Non-Hepatic Surgeries?

# Impact of Obstructive Jaundice on Outcomes after Major Hepatic Resection

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Obstructive jaundice is characterized by hyperbilirubinemia due to biliary obstruction, which induces not only liver dysfunction, but also systemic complications. The intestinal mucosal barrier is disrupted due to the lack of bile in the gut, resulting in the increased absorption of endotoxin and the subsequent endotoxemia. The principal clinical manifestations include hemodynamic in stability and acute renal failure, cardiovascular suppression, immune compromise, coagulation disorders, nutritional impairment, and wound healing defect.<sup>1</sup>

In clinical practice, most patients with hilar cholangiocarcinoma (HCCA) present obstructive jaundice at diagnosis and major hepatectomy is usually required in these patients. In this lecture, we will be discussing morbidity and mortality after major hepatectomy for hilar cholangiocarcinoma.

#### Early Outcomes after Major Hepatectomy for HCCA

Major liver resection is usually necessary to cure HCCA. In patient with HCCA, the regenerative capacity of the liver is an important factor for safe recovery following liver surgery. However, hepatic regeneration is impaired and causes a serios problem in the setting of biliary obstruction. The mechanism responsible for impaired hepatic regeneration in patients with biliary obstruction includes decreased portal venous flow, attenuated production of liver proliferation associated factors, an increased rate of apoptosis, and lack of enterohepatic circulation.<sup>2</sup>

Obstructive jaundice from HCCA has been identified as an important risk factor for postoperative mortality. Western center showed that liver resection in patients with complete obstructive jaundice and cholangitis is associated with severe complications, including intraoperative bleeding, postoperative subphrenic abscesses due to biliary fistula and liver failure.<sup>3</sup> Asian center also reported that postoperative mortality is still high, nearly 10%, and the cause of death is mainly hepatic failure.<sup>4</sup>

Recent two western studies showed the same results. Olthof et al reported 24% postoperative liver failure after major hepatectomy in 217 patients and revealed that jaundice at presentation and immediate preoperative bilirubin (> 2.9 mg/dL) were risk factors for liver failure.<sup>5</sup> Ribero et al also demonstrated that preoperative bilirubin level was one of risk factors for postoperative liver failure after major hepatectomy in 133 patients.

#### Preoperative Biliary Drainage for HCCA: Not Routine, but Selective Approach

The relationship between obstructive jaundice and postoperative liver failure has contributed to the hypothesis that preoperative biliary drainage can reduce the risk of postoperative liver failure and mortality after major liver resection. Most Asian centers and Belghiti's group have preferred to undertake routine preoperative biliary drainage, resulting in increased resectability and improved early postoperative outcomes.<sup>7</sup> Seyama and Makuuchi reported an extensive use of preoperative drainage in all jaundiced patients, the authors advocated the use of biliary drainage in all patients who are candidates for biliohepatic resection. The authors applied the preoperative drainage

only in the future liver remnant (FLR), and the liver resection was performed only when the hepatic function was fully restored.<sup>8</sup>

In contrast, other authors have argued against the utility of preoperative biliary drainage because cholangitis caused by biliary instrumentation and contamination might increase infectious complication and mortality.<sup>7</sup> A systematic review of preoperative biliary drainage before resection for HCCA did not find any evidence of a clinical benefit for using percutaneous transhepatic biliary drainage in jaundiced patients with HCCA who were to be submitted to surgery.<sup>9</sup> In addition, preoperative biliary drainage is frequently complicated by cholangitis, which is associated with an increased risk of postoperative hepatic insufficiency and death from liver failure.<sup>6,7</sup>

Because of high incidence of cholangitis, risk and benefits of preoperative biliary drainage should be balanced. A multicenter European study demonstrated that preoperative biliary drainage did not affect overall postoperative mortality, but was associated with a decreased mortality rate after right hepatectomy and an increased mortality rate after left hepatectomy.<sup>10</sup> Memorial Sloan Kettering Cancer Center reported the outcomes of patients stratified by FLR volume and adequacy of biliary decompression. Patients with FLR of less than 30% and without biliary decompression had an increased risk of liver failure and death. Conversely, patients with FLR of more than 30% preoperative biliary drainage did not modify postoperative outcomes.<sup>11</sup> Recently, they reported that mortality risk score can be used for decision making about the benefits and harm of surgery based on preoperative available risk factors. FLR volume, FLR drainage status and preoperative cholangitis were found to modifiable risk factors. They demonstrated that complete preoperative drainage of the FLR segments is associated with lower postoperative mortality in patients with a FLR volume <50%. By contrast, there was no evidence to support preoperative biliary drainage in the presence of a FLR volume >50%.<sup>12</sup>

#### Conclusion

Obstructive jaundice is the most important risk factor for postoperative liver insufficiency and mortality from liver failure after major hepatectomy in patients with HCCA. However, preoperative biliary drainage should be cautiously considered due to the strong correlation with preoperative cholangitis that is the important risk factors for postoperative mortality. The current indications of preoperative biliary drainage may be presence of acute cholangitis and candidate to portal vein embolization for small FLR volume. In patients with enough FLR volume (>50%), preoperative biliary drainage is not recommended because the risk of cholangitis and related mortality developing after drainage seems to outweigh the questionable benefit of biliary drainage. Strategies to reduce the risk of preoperative biliary drainage-induced cholangitis should be further investigated to optimize the outcomes after major liver resection in patients with HCCA.

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### Impact of Obstructive Jaundice on Outcomes after Non-Hepatic Surgery

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#### Introduction

It is well known that obstructive jaundice causes various local and systemic effects. Patients with obstructive jaundice may be at risk of liver dysfunction, renal failure, cardiovascular suppression, malnutrition, bleeding tendency, immune compromise, and wound complications.<sup>1</sup> All these consequences of obstructive jaundice are bound to increase morbidity and mortality of surgical patients. First, the pathophysiology of obstructive jaundice will be briefly discussed to understand the impact of obstructive jaundice on surgical patients. Then, whether the consequences of obstructive jaundice itself or the effort to decompress it is more harmful will be explored through literature review.

#### The Pathophysiology of Obstructive Jaundice

#### 1) Biliary Tree

Cholestasis allows microbes to grow and proliferate within the bile. The increased intraluminal pressure results in increased permeability and bile backflow, which allows infection and causes bacteremia.<sup>2</sup> In addition to cholangitis which is usually manifested in acute obstruction, chronic obstruction may result in biliary cirrhosis and severe hepatocellular damage.<sup>3</sup>

#### 2) Liver

Cholestasis affects the metabolic and synthetic capacity of the liver. Backflow of substances that should have been excreted into systemic circulation causes major toxicity. In addition, increased bile salts inhibit hepatic cytochrome P450 and reduction of oxidative or aerobic metabolism leading to the oxidative stress and hepatic apoptosis.<sup>4</sup> The reduced synthetic capacity results in low levels of albumin, coagulation factors and immunoglobulins.

#### 3) Gut and Intestinal Barrier Effects

The lack of bile salts in the intestine induces the proliferation of the normal microbial flora, dysfunction of the intestinal mucosal barrier, bacterial translocation, and ultimately increases endotoxin absorption.<sup>5</sup> In particular, failure of intestinal barrier plays an important role in the development of septic and renal complication.<sup>6</sup>

#### 4) Endotoxin

The increased absorption of gut origin exdotoxin, together with liver dysfunction leads to systemic inflammatory response syndrome or multiple organ dysfunction syndrome if severe.

#### 5) Hemodynamic Effect

Cardiac depression, so called "jaundice heart", occurs resulting in compromised contractility, elasticity, and

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low cardiac output along with decreased peripheral resistance. This predisposes the patient to postoperative shock event.<sup>7</sup> Other than heart, atrial natriuretic peptide (ANP) released by the heart atrium causes water retention and sodium retention through the action of antidiuretic hormone (ADH) and aldosterone, respectively.

#### 6) Acute Renal Failure

Acute renal failure occurs in 10% of cases with obstructive jaundice, and is related with a high mortality rate reaching up to 70 to 80%. Acute renal failure occurs in close relation to the hemodynamic effect of obstructive jaundice and increased circulating endotoxins.

#### 7) Immune System

Impaired immune function is the result of the disturbances in the gut-liver axis homeostasis and the endotoxemia.8 The impairment of immune function predisposes the patient to septic conditions.

#### 8) Coagulation Disturbances

Coagulation disturbance occurs due to the complement activation by endotoxin and the reduced synthesis of prothrombin in the liver and other vitamin K dependent coagulation factors (VII, IX, X) and protein C, S, Z.

#### 9) Wound Healing

Harmful effect of endotoxin on fibroblast disturbs wound healing. In addition, poor nutritional status and protein deficiency with lo albumin levels caused by reduced hepatic synthetic capacity hinders wound healing.

### Decompression of Obstructive Jaundice in Non-Hepatic Surgery: Friend or Foe?

As described previously, obstructive jaundice is undoubtedly detrimental to the patient. Therefore, it is obviously rational to decompress the biliary system in these patients. This seems particularly important in severe ill or pre-/ postoperative patients. Obstructive jaundice in patients with periampullary cancer awaiting pancreatoduodenectomy is a common subset of patients who may be candidate for biliary decompression.

There have been numerous studies investigating the effect of preoperative biliary drainages. The results varied in greatly. Some studies showed decreased mortality and morbidity rates in the drained patients.<sup>9,10</sup> However, most of the studies supporting beneficiary effects of preoperative biliary drainage in pancreatoduodenectomy are early results and retrospective with limited number of patients. Furthermore, many of these early studies include many bypass or palliative surgeries and relatively few pancreatoduodenectomies.

On the other hand, other randomized controlled studies and more recent observational studies reported that the preoperative biliary drainage failed to show significant benefits of preoperative biliary drainage.<sup>11-13</sup> Furthermore, some studies found that preoperative biliary drainage itself, along with the instrumentation is associated with increased morbidity and mortality rates in patients undergoing pancreatoduodenectomy. They suggest that preoperative biliary drainage should be avoided whenever possible in patients with resectable lesions.<sup>14</sup>

More recent large studies did not show a significant benefit of preoperative biliary drainage but rather demonstrated greater frequency of surgical site infection and mortality rate.<sup>14-16</sup> In addition, many literature reviews and meta-analyses point to the conclusion that routine preoperative biliary drainage shows no beneficial effect on the surgical outcome for patients with periampullary tumor and should be employed on selective basis.<sup>17,18</sup>

A relatively well-designed randomized controlled study was performed by van der Gaag and colleagues.<sup>19</sup> This study was a multicenter randomized controlled trial comparing preoperative drainage followed by surgery with surgery alone for patients with pancreas head cancer. The study enrolled 202 patients with pancreas head cancer

and bilirubinemia between 2.3 and 14.6 mg/dL. After exclusion of patients that did not meet the inclusion criteria, 94 patients underwent surgery within 1 week after diagnosis and 102 patients underwent preoperative biliary drainage for 4 to 6 weeks and then underwent surgery. The surgical complication rate was lower in early surgery group (37% vs. 47%, P = 0.14). The severe complication rate within 120 days in early surgery groups was significantly lower in early surgery group (39% vs. 74%, P < 0.001). The mortality rates and hospital stay lengths were similar.

#### Summary and Conclusion

Considering the detrimental systemic consequences of obstructive jaundice, it seems only rational to perform preoperative biliary drainage. In the early reports and studies, the preoperative biliary drainage was reported to have protective effect. However, in more recent studies with large number of patients, well-designed randomized controlled studies, and meta-analyses dictate that routine preoperative biliary drainage should not be performed in pancreatoduodenectomy because of increased complications and prolonged hospitalization without any significant improvement in major morbidity and mortality.

Preoperative biliary drainage should not be performed on routine basis and should be performed only in selective patients. Perhaps preoperative biliary drainage should be recommended in patients with 1) long-standing jaundice, 2) cholangitis, 3) renal failure, 4) malnourishment, or 5) indications for neoadjuvant chemotherapy.

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## Optimal Method to Minimize Postoperative Complications in Patients with Obstructive Jaundice

#### **Masato Nagino**

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#### Introduction

Hilar malignancy, including perihilar cholangiocarcinoma and gallbladder cancer involving the hepatic hilus, is the most difficult to treat, and surgical resection of hilar malignancy is still demanding and challenging. Recently, with improvement of diagnostic and surgical techniques, many surgeons have adopted an aggressive approach to hilar malignancy, and now liver resection is commonly performed.

#### **Biliary Drainage**

Most of patients with hilar malignancy are jaundiced at initial presentation; therefore, biliary drainage is required to relieve jaundice and, in turn, to make hepatectomy safer. Previously, we believed that percutaneous transhepatic biliary drainage (PTBD) is the best as preoperative biliary drainage and preferred this method. For the past 10 years, however, we have gradually changed our strategy for preoperative drainage, due to PTBD-related complications. The most serious complication is seeding metastasis including PTBD sinus tract recurrence or peritoneal dissemination, which worsens survival. Considering this serious complication, endoscopic naso-biliary drainage (ENBD) is now routinely selected when possible, and PTBD is used only when endoscopic drainage is not feasible.

Complete drainage of all obstructed segmental bile ducts is difficult to achieve endoscopically, especially in Bismuth type IV perihilar cholangiocarcinoma. Our recent strategy for biliary drainage is that only hepatic segment(s) to be preserved is drained by ENBD. Importantly, the occurrence of cholangitis after ENBD, unlike endoscopic biliary stenting (EBS), is less frequent. A recent report have shown that 1) tube occlusion with cholangitis is a frequent complication associated with EBS, 2) PTBD is associated with serious complications such as vascular injury and cancer dissemination. In summary, ENBD is the most suitable method for initial preoperative biliary drainage for hilar malignancy.

#### Bile Replacement

Several authors have reported that internal biliary drainage is superior to external drainage. However, it is unclear whether bile replacement following external drainage on intestinal permeability, integrity, and microflora, we examined 25 patients who underwent external drainage for biliary cancer before and after bile replacement. The L/M ratio decreased from  $0.063 \pm 0.060$  before bile replacement to  $0.038\pm0.032$  after bile replacement (P < 0.05). Serum DAO activity increased from  $3.9 \pm 1.4$  U/L before bile replacement to  $5.1 \pm 1.6$  U/L after bile replacement (P < 0.005), and the magnitude of change in serum DAO activity correlated with the length of bile replacement (r = 0.483, P < 0.05). Neither the L/M ratios nor serum DAO activities before bile replacement correlated with the interval between

PTBD and the beginning of bile replacement. Fecal microflora and organic acids were unchanged. These findings indicate that impaired intestinal barrier function does not recover by external drainage without bile replacement. Bile replacement during external biliary drainage can restore the intestinal barrier function in patients with biliary obstruction, primarily due to repair of physical damage to the intestinal mucosa. Now, we use bile replacement in all patients with external biliary drainage.

#### Inchinkoto (ICKT)

Inchinkoto is a Japanese herbal medicine and has choleretic and hepatoprotective effects. We confirmed an increase in biliary bilirubin and bile acid concentration after administration of ICKT in patients with external drainage and now routinely use ICKT in such patients.

The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (11:10-12:10) WEST TOWER / ROOM C [B1]

# **KAHBPS** Symposium 2

Controversies in Surgical Management of Intrahepatic Cholangiocarcinoma

Chairs : Dong Wook Choi (Sungkyunkwan Univ.) Sang-Jae Park (National Cancer Center)

# Quest for Tumor Origin of Cholangiocarcinoma

#### Baek-hui Kim

Department of Pathology, Korea University Guro Hospital, Seoul, South Korea

Cholagniocarcinoma is a heterogenous malignancy arising from anywhere of biliary tree, from canals of Hering to common bile duct. Most of cholangiocarcinoma is adenocarcinoma, which resembles bile duct or ductules, with a few variants including mucinous carcinoma, adenosquamous, squamous, and lymphoepithelioma-like carcinomas. Normal intrahepatic bile duct can be classified into large intrahepatic bile ducts and small intrahepatic bile duct. Large bile ducts have thick fibrous stroma with peribiliary glands, but small bile ducts have no peribiliary gland. Gross morphology of cholangiocarcinomas is classified as mass forming, periductal infiltrating, papillary, and mixed type. Mass forming type is more common in the periphery of liver and periductal infiltrating type is more common around large bile duct.

Recently, some studies have revealed that microscopic features of cholangiocarcinoma also can be classified as bile ductular type, small duct type and large bile duct type. Bile ductular type and small duct types are more common in the periphery of the liver, and large bile duct types are more common around large bile ducts. Bile ductular type or small duct type tumors shows morphologic characteristics of bile ductules and small bile ducts, and large bile duct type tumors show more mucinous tumor and dense fibrous stroma. These differences in tumor location, gross morphology, microscopic features may be due to differences in origin of tumor cells. Canals of Hering cell are thought to be the origin of bile ductular type and small duct type tumors, and bile duct precursor cells of peribiliary glands to be the origin of large bile duct type tumors. Some immunohistochemical expression study and molecular study results also corresponds to morphologic features of each type of tumors.

Although, these morphologic classifications of cholangiocarcinomas cannot be applied to all tumors, these study results give us important clues to understanding cell origin of cholangiocarcinoma.

# Is There an Optimal Extent of Liver Resection in Patients with Intrahepatic Cholangiocarcinoma?

Masakazu Yamamoto, Shun-ichi Ariizumi

Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

**Aim:** No evidence of anatomical hepatectomy or extended hepatectomy for patients with intrahepatic cholangiocarcinoma (ICC) shows good surgical outcomes. We compared the surgical outcomes of ICC with those of hepatocellular carcinoma (HCC).

**Methods:** From 1990 to 2014, 1784 patients with HCC and 118 patients with mass-forming type ICC underwent hepatectomy at Tokyo Women's Medical University. 60 ICC and 1350 HCC patients were selected according to the criterion of a single nodular type tumor less than 5 cm in diameter. Surgical procedures, recurrent sites, recurrence-free survival (RFS) and overall survival (OS) were compared between HCC and ICC patients.

**Results:** With regard to the background, the ratio of males and the rate of liver cirrhosis were significantly higher in HCC patients. With regard to the tumor and surgical factors, the tumor size was smaller, and the rates of vascular invasion, lymph node metastasis and major hepatectomy were significantly lower in HCC patients. RFS and OS were 35%, 32% and 59%, 69% in ICC and HCC, respectively. There were no significant differences in RFS and OS between ICC and HCC. However, the early recurrence rate and the rate of distant metastasis were higher in ICC patients.

**Conclusion:** The optimal extent of liver resection could not be found in our data. To improve the long-term survival, we need effective systemic adjuvant therapy after hepatectomy for ICC.

## Lymph Node Dissection: To-Do or Not-to-Do?

#### **Chang Moo Kang**

Division of HBP Surgery, Department of Surgery, Yonsei University College of Medicine, Yonsei Pancreatobiliary Cancer Center, Severance Hospital, Seoul, South Korea

Although intrahepatic cholangiocarcinoma (IH-CCC) is a relatively rare malignancy, it is the second most common malignant hepatic tumor after hepatocellular carcinoma (HCC). It accounts for 5-30% of all primary liver cancers. Surgical resection is known to be the only hope of cure. Despite advances in hepatic resection techniques and decreased perioperative mortality, 5-year overall survival (OS) in resected IH-CCC patients is only 15-40%.

Little data exist on the clinic-pathologic factors associated with outcome following surgical resection of IH-CCC, because of the rarity of disease and the relatively low resectability rates. In addition, optimal treatment strategy for IH-CCC has yet to be defined.

Especially, LN metastasis has been identified as worse prognostic factor in treating IHCC. For resected patients, numerous studies have demonstrated that metastatic disease to regional LNs is associated with poor survival in IH-CCC. However, there is no consensus on systematic LN dissection for IHCC based on a definitive comparative study. All reported studies to date have been retrospective case series' or non-controlled prospective. Most studies are single center- based limited data not enough to evaluate the utility of routine lymph node dissection in treating IH-CCC. Therefore, no acceptable rationales for the appropriate approach for IHCC LN metastases has been established, and the value of LN dissection remains unclear.

Recently, Korea-Japan collaborative study investigated this issue; (1) To evaluate oncologic efficacy of LN dissection in treating. (2) To provide general consensus and clinical information of routine LN dissection in treating IHCC. (3) To provide the strong backbone to perform future randomized controlled trial.

In this presentation, recent updated data will be presented and the potential strategy for lymph node management will be discussed in treating IHCC.



DAY 3: Saturday, June 16, 2018 (13:10-13:40) WEST TOWER / ROOM C [B1]

# **KAHBPS Special Lecture**

Chair : Dong-Sup Yoon (Yonsei Univ.)

# Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) Registry: What Have We Learned?

#### Hauke Lang

Department of General, Visceral and Transplantation Surgery, University of Mainz, Mainz, Germany

In 2007, now more than 10 years ago, Hans Jürgen Schlitt from Regensburg performed, moreorless by incident, the first ALPPS procedure, or, as it was initially and still is called in Germany "In-Situ Split". The idea of the "In-Situ Split" soon spread all over Germany, but it was not all known outside of Germany. The concept was first presented at the E-AHPBA meeting in Capetown 2011, where it gained tremendous interest. In 2012, the initial experience of five German centers (Regensburg, Göttingen, Mainz, Tübingen, Giessen) in a total of 25 patients was published in the "Annals of Surgery". In an editorial, the acronym ALPPS ("Associating Liver Partition and Portal vein ligation for Staged hepatectomy") was proposed. Since then, HPB groups from all over the world started to work on this novel technique. As a result, the technique has been improved and refined, but also disadvantages and drawbacks have been identified. Nevertheless, ALPPS is currently the most fascinating and controversial technique in HPB surgery, since it enables extensive liver resections in otherwise unresectable cases. Originally, the ALPPS procedure was designed for right trisectionecomy, but the newly created "ALPPS registry" showed that it was also used for standard right hepatectomy in about 50% of cases. In 2015, an International Expert meeting was held in Hamburg in 2015 resulted in eight recommendations regarding preoperative diagnostics, operative technique and indication for ALPPS. One year later a consensus for the different technical variations was suggested to standardize terminology. During the 12th congress of the E-AHPBA in Mainz, Germany, the 10th anniversary of ALPPS was "celebrated" in expert meeting in order to discuss the status quo of this novel technique. The main findings and conclusions of this meeting, mainly drawn from data of the ALPPS registry which now gathers more than 1000 cases, were the following: Precise anatomical knowledge, in particular of the vasculo-bilary variants is paramount for the success in ALPPS. Preoperative imaging is mandatory to assess all individual anatomical details. More than anatomy, the two main diagnostic issues in ALPPS are the volumetric assessment of the future liver remnant and the timing of stage 2. Of note, volume increase is not necessarily associated with increased liver function. For this reason, imaging techniques such as 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) and single photon emission computed tomography (SPECT) have been used to estimate FLR function and to predict PHLF preoperatively. In addition, improvements have been achieved by patient selection and in particular by refining the surgical technique mainly aiming at reducing post stage 1 morbidity. Thus, the concept of only partial hepatic transection was created, named "partial ALPPS". Other modifications, such as the combination of partial ALPPS and PVE, either simultaneously ("Mini ALPPS") or subsequent, aimed to further limit interstage morbidity by avoiding surgical manipulation of the hepatic hilum. All these improvements led to a reduction of overall complications, and thus, in the second large publication from the ALPPS Registry a mortality rate of now only 5% for ALPPS in CRLM could be reported. Consistently, recent data from the only prospective randomized controlled trial confirmed significant higher resection rates in ALPPS with similar peri-operative morbidity and mortality rates compared to conventional two-stage hepatectomy including PVE.

Currently, CRLM are supposed to be the best indication for ALPPS. Though recurrence rates appear higher than after conventional liver resections, ALPPS is offering a chance for cure for those patients who otherwise would never have any surgical option. However, long-term clinical and oncological outcome studies of ALPPS for CRLM are still lacking.

Currently, CRLM are supposed to be the best indication for ALPPS. Though recurrence rates appear higher than after conventional liver resections, ALPPS is offering a chance for cure for those patients who otherwise would never have any surgical option. However, long-term clinical and oncological outcome studies of ALPPS for CRLM are still lacking. In contrast to CRLM, there is a major controversy regarding ALPPS in biliary tumors. The first report of the ALPPS registry included 11 patients with PHCC with a 90 day-mortality rate of 27%. In a recent matched case-controlled study, Olthof et al. compared ALPPS from the ALPPS registry versus PVE and right trisectionectomy for PHCC in two centers of excellence for HPB surgery. Postoperative mortality was twice as high in the ALPPS group (48% vs 24%). However, newly developed variants such as Mini-ALPPS which avoid surgical manipulation of the hepatic hilum may be attractive in particular for PHCC.

Regarding treatment of HCC it is important to know that ALPPS is also effective in fibrosis and mild cirrhosis but the degree of FLR hypertrophy appears less than in non-cirrhotic livers.

In summary, continuous efforts to improve patient selection and timing of stage 2 as well as refinements of the operative technique have allowed to perform ALPPS with morbidity and mortality rates comparable to standard major liver resections. Meanwhile, the "ALPPS" technique has been established as a new liver resection concept, but its place is still to be defined. ALPPS does definitely not replace other techniques such as portal vein embolization and standard two-stage hepatectomy but adds to the toolkit of liver resection in the hands of experienced hepatobiliary surgeons. Long-term oncological outcome results are needed to establish the place of ALPPS in the treatment of patients with initially non-resectable liver tumors.



DAY 3: Saturday, June 16, 2018 (13:40-15:00) WEST TOWER / ROOM C [B1]

# **KAHBPS Symposium 3**

# Resectability Revisited: Current Changes and Challenges

**Chairs :** Hee Chul Yu (Chonbuk National Univ.) Kyung Sik Kim (Yonsei Univ.)

# Resectability Revisited: Current Changes and Challenges for Hepatocellular Carcinoma

#### **Hee Jung Wang**

Department of Surgery, Ajou University School of Medicine, Suwon, South Korea

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with an annual occurrence of one million new cases. The prognosis depends on tumor stage and liver function which affect the tolerance to invasive treatments. Although hepatic resection (HR) is generally accepted as the treatment of choice for HCC, new treatment strategies, such as local ablative therapies, trans-arterial embolization (TAE) and liver transplantation (LT), have become available nowadays. With increasing detection rate of small HCCs from screening programs for cirrhot-ic patients and established novel staging classification, I herein, reviewed our available data, regarding selection criteria for HR in the setting of HCC and underlying liver disease.

In cases of early stage HCCs, a 5-year survival rate of 60 to 75% can be achieved after HR. The incidence of early stage HCC became more than 40% of total cases in the developed countries through the HCC screening for high risk patients. The expansion of selection criteria of HR was driven by limited liver resection or laparoscopic surgery under the more accurate patient assessment such as preoperative liver function assessment and 3D imaging analysis. Sometimes we can also use preoperative portal vein embolization (PVE) for enlargement of future remnant liver and do LT for patients with poor functional reserve. According to national cancer registry (2017), the distribution on BCLC stage of Korean HCC patients were 49.6% in stage A, 11.3% in stage B, 33.0% in stage C, and 6.2% in stage D, and 29.5% were performed HR. Among stage A HCC patients, 42% were done HR. The 5 year survival rate after HR was more than 70% in stage A.

We have to admit, however, that the long-term survival of advanced HCC patients has hardly improved, owing to their high recurrence rate. This is the reason why we should continuously give an effort in HCC screening program for high risk patients. We should do HR to get the survival results beyond that of other modalities in the selected patients with advanced stage HCC and sometimes perform extended/combined resection, conversion surgery after down-staging, and major HR after PVE for increasing resectability. Therefore, I would like to propose that we revise the role of HR for intermediate and advanced stage HCCs in BCLC staging classification. Currently, TAE and systemic agent (ie. sorafenib) are the established treatments of choice for intermediate and advanced stage HCCs, respective-ly. The prognostic goals after recommended therapies are 20 months for intermediate, and 10 months for advanced stage HCCs. If HR can provide better survival compared to TAE and systemic agents, the selection criteria of the HR can be expanded. The conditions that meet our expanded selection criteria for non-curative HR are as follows; 1) unilaterally located HCC, 2) acceptable liver functional reserve, and 3) informed consent under the clinical trial concept. In my clinic, 35% of patients with intermediate stage HCCs were 0% in operative mortality rate, 60% in 1 year survival arate, 20% in 5 year survival, and 21 months in mean survival period.

I suggest that we could recommend HR as first-line therapy for higher curability in early stage HCC patients with preserved liver function, and as an alternative therapy for better survival beyond that of recommended modalities in selective advanced HCC patients.

# Colorectal Cancer Liver Mets: Multiple Bilateral Lesions

#### Hauke Lang

Department of General, Visceral and Transplantation Surgery, University of Mainz, Mainz, Germany

Hepatic resection is the treatment of choice for CRLM. Depending on patient selection 5 year-survival rates of up to 50-60% can be achieved. However, at the time of diagnosis, only a minority of about 15-30% of patients are candidates for upfront hepatic surgery. Most often, multifocal intrahepatic tumor spread in both liver lobes, extensive tumor burden or diffuse extrahepatic metastases result in either technical or functional irresectability or make a resection questionable from an oncologic point of view. In recent years, therapeutic options for CRLM have steadily improved and several strategies have been developed to increase resectability. The two most important steps were the development of effective downsizing chemotherapy regimens and the introduction of preoperative liver volume modulation techniques, mainly the invention of portal vein embolization (PVE) or ligation (PVL). Furthermore, two-stage hepatectomy (TSH) enables complete resection of bilateral multinodular hepatic metastases not amenable to resection in a single procedure, not even after effective downsizing chemotherapy. However, despite all these progresses, treatment of bilateral metastases in the setting of an estimated small future liver remnant (FLR) remained a big challenge. To cope with this problem, conventional TSH was further modified by combining tumor clearance of the FLR with simultaneous contralateral portal vein ligation or subsequent portal vein embolization (PVE) to stimulate growth of the FLR. The hypertrophy rates observed after this approach usually range between 20% - 40% but can reach almost 60-70% in highly specialized centers. Reported survival data after two stage hepatectomy with and without PVE/PVL vary tremendously depending on patient selection criteria. The best results are comparable to outcome data after surgery for primarily resectable CRLM, with a 5-year-survival of about 30% or, in selected cases, even higher. However, the two main risks inherent to this strategy are an ineffective liver hypertrophy and a probable stimulation of growth of both, the FLR and the tumor. This has been shown in several studies where up to 25-38% of patients did not proceed to step 2, mainly due to a tumor progression and less often due to an insufficient volume gain. ALPPS can overcome this problem by inducing a more effective hypertrophy in a shorter time period, thus allowing an almost 100% resectability rate. However, initial enthusiasm was hampered by high rates of morbidity and mortality and also early and frequent recurrence rates. Technical refinements and an improved patient selection led to a stepwise reduction of the perioperative complication rate of ALPPS. In the second large publication from the ALPPS Registry a mortality rate of now only about 5% for CRLM was found which is similar to the reported mortality after major conventional hepatectomy. One alternative to TSH or ALPPS may be one stage hepatectomy (OSH). In this concept, major anatomical resections are avoided if possible, and metastases are mainly removed by atypical resections. The charm of this approach is – next to avoiding the morbidity of a second or (in case of PVE) a third operation/intervention – minimizing parenchymal loss but at the expense of a high risk of tumor positive resection margins. Although in recent years the potential benefit of an R1-resection has been pointed out – in particular in multifocal CRLM with good response to chemotherapy – R0-resection is still the standard goal of surgery for CRLM. In OSH for multifocal CRLM, however, R1-resection is widely accepted, the more as also the detachment of metastases from major vascular structures (R1 vascular margin) has been shown to be almost equivalent to R0 resection.

In conclusion, treatment of bilateral CRLM is still a challenge. Due to advances in medical and surgical therapy, treatment options have widened. Downsizing chemotherapy and liver volume modulation techniques enable to do liver resections even in initially extensive tumor burden and critical small FLR. Whenever applicable, OSH hepatectomy or conventional TSH should be the preferred method, while ALPPS should be reserved for those cases where there is no other possibility for resection.

### Klatskin Tumor: Combined Vascular Invasion

#### **Masato Nagino**

Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

#### Introduction

Perihilar cholangiocarcinoma is the most common type of cholangiocarcinoma, accounting for approximately 60% of cases, followed by the distal and then the intrahepatic forms. Although its surgical resection is technically demanding, many surgeons have adopted an aggressive approach to perihilar cholangiocarcinoma, as surgical resection is the only way to cure this intractable disease. In the past two decades, with advances in diagnostic and surgical techniques, the surgical outcomes and survival rates have gradually improved. In this lecture, I discuss the benefit of combined vascular resection.

#### Portal Vein Resection

Portal vein invasion was previously the main cause of unresectability of perihilar cholangiocarcinoma. However, combined portal vein resection is now a routine procedure in leading centers in both the East and West, and its clinical benefit has been validated by many studies. Portal vein resection is performed primarily in cases of right-sided hepatectomy, most likely due to technical feasibility. However, we should note that vessel resection is often required in cases of left-sided hepatectomy for advanced tumors with left-sided predominance. In our previous study, we reported a mortality of 9.6% and a 5-year survival rate of 9.9% in combined liver and portal vein resection for perihilar cholangiocarcinoma (n = 52; study period from 1979 to 2000). Since then, the outcome has markedly improved as we have gained more experience: in 185 patients between 2001 and 2012 (portal vein resection alone in 111 patients, simultaneous resection of the portal vein and hepatic artery in 74 patients), the mortality decreased to 3.2% and the 5-year survival rate increased to 24.6% (unpublished data). Portal vein resection should be performed only when the vessel adheres to and cannot be freed from the tumor during the skeletonization resection of the hepatoduodenal ligament. We have never used the "no-touch technique" introduced by Neuhaus et al., as it lacks scientific validation.

#### Hepatic Artery Resection

Recent advances in surgical techniques and knowledge, which have been gained from experiences with liver transplantation, have facilitated the performance of hepatic artery resection with reconstruction. These advances have encouraged some aggressive hepatobiliary surgeons to perform this difficult resection for locally advanced tumors. Most of the previous studies, however, showed negative results and did not recommend the combined resection of the hepatic artery for biliary cancer. For example, In 2010, we reported our experiences with major hepatectomies with simultaneous resections and reconstructions of the portal vein and hepatic artery (n = 50) and showed that this challenging surgery can be performed with an acceptable mortality rate of 2% and offers a better chance of long-term survival, with a 5-year survival rate of 30%. Thereafter, the number of patients who underwent com-

bined hepatic artery resection for perihilar cholangiocarcinoma has increased, now reaching 136 (including the 50 patients mentioned above). Of them, 40 patients underwent hepatic artery resection alone and the remaining 96 patients underwent simultaneous resection of the portal vein and hepatic artery. The types of hepatectomy performed included left trisectionectomy in 83 patients, left hemihepatectomy in 45, right-sided hepatectomy in 7, and central bisegmentectomy in 1. The resected hepatic arteries were reconstructed mainly by end-to-end anastomosis: an interposition graft using the radial artery or greater saphenous vein was required in 22 patients, and an arterioportal shunt was performed in 4 patients, due to the failure of reconstruction. The overall mortality rate was 2.9%, and the 5-year survival rate was 31.1% (unpublished data). The clinical significance of hepatic artery resection is still debatable, and further follow-up studies are needed in some leading centers. However, we believe that our data are promising and encourages hepatobiliary surgeons to perform this technically demanding resection.

## The Impact of Neoadjuvant Chemotherapy for Borderline Resectable Pancreatic Cancer

Manabu Kawai, Seiko Hirono, Ken-ichi Okada, Motoki Miyazawa, Yuji Kitahata, Ryohei Kobayashi, Masaki Ueno, Shinya Hayami, Hiroki Yamaue

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**Backgrounds:** According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, pancreatic ductal adenocarcinoma (PDAC) can be classified as resectable, borderline resectable, or unresectable. Although borderline resectable PDAC (BRPC) may technically be resectable, it has particularly high risks of margin-positive resection and postoperative recurrence. Therefore, preoperative treatment is recommended for BRPC patients in both the NCCN Guidelines and an expert consensus statement. However, the establishment of the most appropriate neoadjuvant therapy is needed by further studies. The aim of these studies is to evaluate the impact of neoadjuvant chemotherapy for BRPC and confirm the safety and efficacy of two regimens of neoadjuvant therapy for BRPC.

Our Clinical Trials: First, we evaluated the impact of neoadjuvant chemotherapy for BRPC. 143 BRPC-A patients undergoing pancreatectomy were reviewed from among 330 pancreatic cancer patients, including 111 potentially resectable pancreatic cancer patients and 76 BRPC with portal vein involvement patients. We compared the clinicopathological factors of 40 BRPC-A patients treated with neoadjuvant treatment followed by surgery and those of 103 BRPC-A patients treated with upfront surgery. The RO rate and progression-free survival of BRPC-A patients who received neoadjuvant therapy and subsequent surgical resection were significantly better compared to those who received upfront surgery (R0: P = 0.041; progression-free survival: P = 0.033), but overall survival was not significantly different. Neoadjuvant treatment followed by surgery might provide clinical benefits for BRPC-A patients; however, the establishment of the most appropriate neoadjuvant treatment is needed by further studies. To evaluate appropriate neoadjuvant treatment, two prospective pilot trials were conducted as follows; modified FOLFIRINOX (without bolus 5-FU and LV, also decreased the dose of irinotecan; FIRINOX) and nab-paclitaxel plus gemcitabine therapy. Modified FOLFIRINOX was given to the first five patients in the 4-cycle group of the regimen and next five patients in the 8-cycle group. The primary end point was the toxicity of the therapy and one of the secondary end points were the optimal duration. The overall rate of grade 3 and 4 events was 80 %: 3 patients (60%) in the four-cycle group and five patients (100%) in the eight-cycle group had grade 3 or 4 adverse events. There was no incidence of serious adverse effect such as febrile neutropenia, sepsis, liver abscess or uncontrollable diarrhea. There was no clinically relevant morbidity presented in patients who underwent surgery. R0 rates by intention to treat were 60.0% in the four-cycle group and 40 % in the eight-cycle group (P = 0.999). The histopathologic treatment effect based on the Evans grade revealed grade I (n = 1), Ila (n = 3) in the four-cycle group and grade I (n = 2), Ila (n = 1) in the eight-cycle group. Nab-paclitaxel plus gemcitabine therapy: the primary endpoint was the toxicity, and secondary endpoints were the resection rate, the R0 resection rate. The overall rate of any grade and grade 3-4 events were 100% and 90%. The majority of these adverse events represented expected neutropenia. The resection and R0 resection rates were 80% and 70%, respectively.

**Conclusion:** FIRINOX therapy was feasible and safe for strictly selected patients with BRPC. On the other hand, nab-paclitaxel plus gemcitabine therapy was safe and feasible without strict selection of patients with BRPC. A multicenter phase II study is in progress to investigate the efficacy of neoadjuvant nab-paclitaxel plus gemcitabine therapy on overall survival (UMIN000024154).

The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (08:30-09:50) WEST TOWER / ROOM D [B1]

# Common Concerns between Hepatologists and Surgeons (\*к)

**Chairs :** Dae-Ghon Kim (Chonbuk National Univ.) Koo Jeong Kang (Keimyung Univ.)

## Evaluation of Remnant Liver Function before Hepatic Resection

#### Bong-Wan Kim

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안전하고 광범위한 간절제술을 위해서는 정확한 술전 간 기능 평가가 필요하다. 현재까지 상당히 많은 간기능 평가 도구들이 개발 되어있으며, 그 중 단순한 간기능 검사들을 이용한 Child-Pugh score와 같은 점수 등급 방법들과 약물의 혈중 청소율 을 이용한 방법들이 있다. 일반적 점수(general score)를 이용한 간기능의 평가는 등급의 증가에 따른 술후 간기능 부전등의 발생율이 비례하여 증가함에 의의가 있으나, 등급이 좋은 간경변 환자와 간경변이 없는 환자의 간 기능 예비력의 차이를 분별 할 수 없고, 좋은 등급의 간경변 환자에서도 상대적으로 높은 술 후 간기능 부전이 발생하는 등의 문제가 있다. 이러한 일반 점 수에 따른 간기능 평가의 단점을 보완할 수 있는 방법으로 혈중 약물 청소율을 이용한 방법이 사용되는데, 그 중 현재까지 가 장 널리 사용되는 방법은 indocyanine green (ICG)을 이용한 방법이다.

ICG 의 최대 제거율(Rmax), 제거율(ICGK), 또는 15 분 정체율(R15)의 방법 등이 사용되며, 각각의 방법은 안전한 환자의 회 복을 위한 간 절제의 정도를 예견할 수 있다. 그러나, 문맥색전술, 편엽 담도 확장증, 주 문맥 침범 종양 등과 같은 전체 간의 기능이 부분적으로 다른 영역이 존재하는 경우의 간기능 평가는 ICG 등의 혈중 청소율을 이용한 검사만으로는 정확한 측정이 한계가 있으며, 방사선 동위원소를 이용한 핵의학 검사로 간의 부분적인 간기능의 평가가 시행된다.

<sup>99</sup>mTc galactosyl human serum albumin (<sup>99</sup>mTc GSA)은 대표적인 동위원소 약물로써 부작용이 없고 asialoglycoprotein (ASGP) receptor을 통하여 간에서만 흡수되는 특성이 있어 간 예비력 평가에 유용하다. 동위원소 <sup>99</sup>mTc GSA를 이용 한 SPECT 나 scintigraphy 는 간의 지역적인 기능을 확인할 수 있어 전반적 간기능이 균일하지 않은 상황에서 절제 부위와 잔존 부위의 간기능의 평가가 가능하여 더욱 안전하거나 수술의 적응증을 확장할 수 있는 방법이 될 수 있을 것이다.
# Laparoscopic Liver Resection for Hepatocellular Carcinoma: Progress and Current Limitations

# Yangseok Koh

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고양석

전남대학교 의과대학 외과학교실

간세포암의 치료에 간절제술은 간이식과 함께 근치적 치료법 중의 하나이다. 통상적으로 40 센티미터 이상의 피부절개가 필 요하며 이는 술후 회복의 지연, 면역력의 저하 및 수술후 유착 등의 이슈를 동반한다. 모든 외과 수술의 술기에 복강경 시술이 적극 도입이 되면서 최근 10년 동안 간절제술에도 복강경 술식이 점차 확대되기 시작해 왔고, 간이식 공여자 수술에까지 적용 되고 있다.

복강경 간절제는 두차례의 international consensus meeting에서 세 분절이하의 minor resecton에서는 표준 술식으로 인 정하지만, major resection에 대해서는 아직도 숙련된 간수술의사에게 시행되어야 한다고 권고한다. 간기능이 대부분 저하 된 간세포암의 경우에는 복강경 간절제가 개복간절제술에 비해 조기 회복이 가능하고, 수술중 출혈 감소 및 수술 후 유착이 적어 재수술이 용이하다는 점 등의 장점이 많다. 수술에 관련한 여러가지 점에서 개복간수술에 비해 대등하거나 장점이 많다 는 보고가 시행 초기부터 많았다. 하지만 미상엽 혹은 복강경 접근이 어려운 간 후엽 및 주요 혈관에 근접한 병변에 대해서는 아직 논란이 있으며, 종양학적인 장기 결과에 대해서는 지켜볼 여지가 있다. 본 강의에서는 현재 간세포암에 대해서 복강경 간 절제술의 발전 과정과 제한점에 대해서 알아보고자 한다.

# Surgical Approach of Liver Tumors in Caudate Lobe: How Much Location Can Change Surgical Plan?

## Young Seok Han

Hepatobiliary Pancreas Surgery and Liver Transplantation, Department of Surgery, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea

# 미상엽에 발생한 간종양에 대한 수술적 접근: 다양한 수술 전략?

## 한 영 석

경북대학교 의학전문대학원, 경북대학교병원, 간담췌외과 및 간이식 외과

Caudate lobectomy remains a surgical challenge because hepatic tumors in the caudate lobe is deeply located in the center of the liver and close to the vena cava and hepatic hilum. Hence, precise anatomic knowledge of the caudate lobe and improvement in the surgical techniques are necessary for more performance of caudate lobectomies.

Caudate lobectomy is technically classified as an isolated or combined resection.

Isolated caudate lobectomy is a procedure that required knowledge of liver anatomy, experience in liver resection and safe management of vascular structures. Although it has been considered a technically difficult and dangerous procedure, an isolated caudate lobectomy is the viable surgical option in patients with a marginal liver functional reserve.

For huge tumors in the caudate lobe, anterior trans-hepatic approach seems to be recommended. However, this approach requires splitting the liver parenchyma and long operation time.

For patients with sufficient liver functional reserve, caudate lobectomy combined with an additional partial hepatectomy is preferred because such an approach is technically less demanding and offers an adequate surgical margin.

Recent reports suggest that minimally invasive liver resection provides better quality of care and improvements of patient outcome by minimizing blood loss and postoperative pain or morbidity, and shortens hospital stay than open surgery. With today's high definition display unit, the intrinsic illumination and magnified view of the video image system, the laparoscopic approach for caudate lobectomy can provide excellent visualization for dissection and vascular control in addition to the known benefits of a minimally invasive procedure. Therefore, pure laparoscopic caudate lobectomy can be suggested as a feasible and safe treatment option for well-selected caudate lesions and bring about the post-operative benefits. However, laparoscopic caudate lobectomy is one of the most difficult procedures in laparoscopic liver resection and have only been reported rarely. It can be still performed to patients in center by surgeons with experience in both hepatobiliary surgery and laparoscopic skills.

In this session, I will present my experiences and reviews for caudate lobectomy.

Keywords: Caudate lobe, Liver tumor, Laparoscopic hepatectomy

# Salvage Liver Transplantation: Pros and Cons in LDLT Settings

## **Dong-Hwan Jung**

Division of HepatoBiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Liver transplantation (LT) is theoretically the best treatment for patients with hepatocellular carcinoma (HCC) and cirrhosis, since it cures both the tumor and the underlying liver disease. Its main limit is the scarcity of donor resources, leading to a high risk of patient drop-out from the waiting list, and thus of death before the LT. Liver resection (LR) is still the first-line treatment in patients with HCC and preserved liver function (Child class A), however, the long-term prognosis is undermined by a high incidence of HCC recurrence, up to 50–70% of cases 5 years after surgery. The combination of both treatments can be a reasonable strategy: HCC patients, within Milan criteria and with preserved liver function, can successfully undergo LR, limiting the transplantation option to cases of tumor recurrence or hepatic decompensation. LR as a primary therapy with LT in mind for tumor recurrence or deterioration in liver function, so-called salvage transplantation.

The two largest initial studies on salvage LT have reported convicting results. Belghiti et al. concluded that liver resection before transplantation does not increase the morbidity or impair long-term survival after LT. Whereas the other report (Adam et al.) associated LT after resection with higher operative mortality, an increased risk of recurrence, and a poorer outcome than primary LT. Our center reported that combinations of recipient prior hepatectomy and living-donor liver graft were feasible for salvage living donor LT (LDLT), suggesting that salvage procedures should be extended to the living-donor setting. To date, small reports have analyzed the results of salvage LDLT after liver resection for HCC and few studies have been performed to compare the short and long-term outcomes of LDLT and DDLT in patients with recurrent HCC after LR.

The intraoperative blood loss and required blood transfusion after salvage LT were more frequent than primary LT group. The larger volume of intraoperative blood loss in the salvage LT group might be caused by intra-abdominal adhesion. However, the overall survival and recurrence rates did not significantly differ between the primary LT and salvage LT groups.

The most common cause of death in patients who underwent either LR or LT was HCC recurrence. The pathologic factors associated with biologic aggressiveness include tumor differentiation grade histologic type, presence of a peritumoral capsule, and microscopic vascular invasion. Salvage LT is restricted to patients who develop recurrence within Milan criteria and could represent a loss of opportunity for the subgroup of patients who develop recurrence beyond Milan criteria. To solve that problem, enlistment or accomplishment of LDLT in patients at high risk of HCC recurrence after LR but before recurrence development seems a valid strategy and is associated with excellent long-term outcome; as early (<6 months) recurrence reflects an aggressive tumor behavior leading to tumor extent exceeding transplant criteria, it is reasonable to wait at least 6 months before enlistment or LDLT.

The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (11:10-12:10) EAST TOWER / ROOM BC [2F]

# KASL-KLCA Joint Symposium

How to Manage Hepatitis C Virus-Related Hepatocellular Carcinoma Patients?

Chairs: Shuichiro Shiina (Juntendo Univ.) Seung Woon Paik (Sungkyunkwan Univ.)

# Direct-Acting Antivirals and Risk of Hepatocellular Carcinoma Recurrence: What Are the Facts?

#### Hyung Joon Kim

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# DAA치료와 간세포암의 재발, 팩트는 무엇인가?

# 김형준

중앙대학교 의과대학 내과학 교실

The impact of DAA-based regimens on the occurrence of HCC in patients with cirrhosis, and especially on the incidence of the recurrence of HCC after successful curative treatment is controversial after the observation by Reig et al of an "unexpected" high rate of HCC recurrence in HCV patients treated with DAAs after their original HCC had been successfully cured. Patients with HCC who are successfully treated or with active disease were not included in pivotal clinical trials assessing the antiviral efficacy of DAA. The aim of this article was to review published data on the occurrence or recurrence of HCC following DAA therapy. Afterwards, several studies have not put an end to the debate since they have produced controversial results for both the incidence of HCC after DAAs therapy and the relationship between the occurrence of HCC and response to DAAs. In conclusion, there have been a number of studies evaluating the occurrence of HCC after DAA therapy. The majority of the studies are retrospective; many were single center with small number of incident HCC and lack control groups. The overall data does not suggest an increase in the occurrence of HCC after DAA therapy. The studies on recurrence of HCC after DAA therapy are better designed and have failed to corroborate the findings of an increased incidence after DAAs. However, DAA therapy may potentially be associated with decrease in time to recurrence.

# 서 론

만성 C형간염 환자에서 지속적으로 높은 바이러스 혈증은 간세포암종 발생의 독립적인 위험요인이다. 따라 서, 항바이러스제 치료로 HCV의 증식을 억제하면 간세포암종의 발생을 감소시킬 수 있을 것으로 기대된다. 최근 도입되고 있는 direct acting antivirals (이하 DAA)로 만성 C형간염의 치료는 획기적인 발전을 거듭하고 있다. 과 거 간세포암종의 근치적 치료 후 인터페론이 간세포암종의 발생을 감소시킬 수 있다고 보고되었지만, 간세포암종 치료 후 완해상태에서 DAA와 간세포암종의 재발 혹은 새로운 발생에 대해서는 논란이 많다. 본고에서는 DAA치 료가 간세포암종의 발생 및 간세포암종 치료 후 재발에 영향을 미치는지에 대해서 기술하고자 한다.

# DAA 치료와 간세포암종 발생

만성 C형간염 치료의 목표는 치료 종료 시점으로부터 12주 이후로 혈중 바이러스 미검출 상태가 유지되는 지 속바이러스반응(sustained virological response, SVR)을 달성하는 것이다. 지속바이러스반응의 달성으로 간 경변증으로의 진행 및 간세포암종의 발생을 예방할 수 있다. 하지만, 치료 전에 이미 진행된 간섬유화증을 가진 환자들에서는 지속바이러스반응 달성 이후에도 간세포암종이 발생할 위험이 지속되기 때문에 정기적인 감시검 사가 필요하다.

최근 HCV에 대한 DAA의 SVR 달성률은 98-100%에 이르고 있다. DAA로 인한 간세포암종의 재발 혹은 발 생과 관련되어 몇 개의 연구에서 DAA가 인터페론과 분명히 다른 숙주의 면역학적 조절을 하는 것으로 제시되 었다. 이들 연구에서는 DAA치료로 급격히 혈청 HCV의 바이러스 농도가 감소하면 HCV 특이 CD8+ T세포의 복원 /고갈, 기억 T세포의 재분화, 림프구의 탈활성화, 자연살해세포기능의 정상화가 일어나며, 이는 항 HCV 면역반응의 급격한 소실을 일으키며, 이는 종양세포에 대한 방관자적 면역반응의 자연 소실을 야기하여서, 간세 포암종 발생을 더욱 조장할 수 있다.

DAA치료와 간세포암종 발생과 관련된 연구는 다음과 같다. Conti 등의 후향적 연구에서 과거 간 세포암종의 과거력이 없는 285명의 간경변증 환자를 대상으로 DAA치료 후 평균 6개월의 짧은 관찰 기간동안 3.1%에서 간세포암종이 발생하였으며, 이는 과거 DAA 도입이전과 비교하여 조기발생율이 다르지 않았지만, 단 기간의 추적기간과 감시기간 중 간세포암종을 놓쳤을 가능성, 대조군이 없었고 인터페론군과 비교하여 보다 고 령이고 보다 섬유화가 진행된 환자들이 많았다는 제한점이 있다. ' 과거 간세포암종이 없었던 66명의 간경변증 환자를 대상으로 한 단일기관 후향 연구에서 치료 6개월 이내에 간세포암이 9.1%에서 발생하였으나 대조군이 없고 대상환자수가 매우 적고, 추적기간이 짧은 문제점이 있다.<sup>2</sup> 24주 DAA치료를 받은 54명의 환자를 대상으 로 1년간의 추적 연구에서 새로운 간세포암종의 발생은 7.4%이었으며, 간세포암종 발생시간은 SVR획득 후 평 균 7.6개월이었다. 하지만 이 연구 역시 대조군이 없는 제한점이 있었다.<sup>3</sup> 인터페론 기반치료로 SVR을 획득 한 578명과 DAA치료를 받은 413명의 환자를 대상으로 연령, 간경변증 유무에 따라서 간세포암종의 발생율을 분석한 일본 연구에서는 간세포암종 발생율은 DAA치료 군에서 높았지만, 연령과 간경변증을 보정 후 분석에 서 DAA 치료군에서 보다 많은 간경변증환자와 고령 환자를 포함하였기 때문인 것으로 나타났다. 미국 보훈병 원의 22.500명의 대규모 후향 코호트 연구에서 DAA 치료로써 SVR을 획득한 경우가 획득하지 못한 경우 보다 간세포암종 발생 위험도가 0.28배로 의미있게 낮았다. 그러나 SVR이 획득되었어도 간경변증이 있는 경우 간세 포암종 발생 위험도가 4.73배 높았다.4 62.354명의 환자를 대상으로 미국 보훈병원자료를 분석한 또 다른 후향 연구에서는, DAA로 SVR에 도달한 경우 간세포암종의 발생을 71%감소시켰다. 이 연구에서 SVR은 치료 방법 의 종류와 상관없이 간세포암종의 발생을 감소시켰다. [DAA단독(adjusted hazard ratio [AHR] 0.29, 95% CI 0.23-0.37), DAA+인터페론 (AHR 0.48, 95% CI 0.32-0.73), 인터페론 단독(AHR 0.32, 95% CI 0.28-0.37)].<sup>5</sup> Kozbial등의 호주 연구에서는 198명의 간경변증 환자 중 195명의 간세포암종 과거력이 없는 환자들을 48주 관찰하였으며 6.6%에서 간세포암종이 발생하였다. 역사적인 대조군이었던 인터페론 치료군은 SVR달성 후 평 균 7.8년동안 1% 년당(per year)으로 간세포암이 발생하였다. 하지만 두 군 사이 추적기간과 기저 인구학적 특 성이 다른 문제점이 있으며, 두 군 모두 주기적인 간세포암종 감시검사를 받았는지가 불명확하였다.<sup>6</sup> Ogata등 의 일본 연구에서 1170명의 환자를 대상으로 DAA치료를 시행하였으며, 역시 대조군이 없었으며 평균 연령이 67세로 고령이었다. DAA치료 후 평균 1.3년을 추적 관찰하였으며 간세포암종 발생율은 치료 1년, 2년째 각 각 1.4, 1.8%였다(평균 0.9% 년당). 이 연구의 제한점은 아시안인종만 포함되었으며, 과거 보고들보다 간세포 암종의 발생빈도가 낮았고 관찰기간이 길었다.<sup>7</sup> Cheung등의 전향적인 연구에서는 비대상성 간경변증 환자에 서 DAA치료 후 간세포암종의 발생율은, SVR을 획득한 경우 5%, 획득하지 못한 경우 10%로 더 높았다. SVR를 획득하지 못한 경우 Child C가 더 많았다.<sup>8</sup> 한편, 인터페론 기반치료를 받은 1,145명의 환자와 인터페론을 기반 으로 하지 않은 치료를 받은 752명의 후향적 분석연구에서 두 군간 간세포암종의 재발(P = 0.49)과 발생율(P = 0.54) 차이를 보이지 않았다.

이탈리아의 대규모의 전향적 인구 기반연구에서 DAA 치료는 첫해 간세포암종의 발생율이 F3인 경우 0.46%, Child A 1.49, Child B 3.61%에 불과하였으며 APRI >2.5 (HR: 2.03, 95% CI: 1.14-3.61; *P* = 0.016) 와 HBV (HR: 3.99, 1.24- 12.91; *P* = 0.021), SVR 획득 실패(HR: 9.09, 5.2-16.1; *P* = 0.0001)가 간세포암종발생과 연 관이 있었다.<sup>9</sup> 또 다른 이탈리아의 대규모 전향적 연구에서 DAA치료를 받은 간경변증 환자 에서 14개월의 추적 기간동안 3.5%에서만 간세포암종이 발생하였으며 Child A 간경변증은 DAA치료 첫 1년 후 SVR 달성군에서는 2.1%, 달성하지 못한 경우에는 6.6%에서 간세포암종이 발생하여서 SVR이 주요 예측인자였다.<sup>10</sup>

또한, DAA 치료와 인터페론간의 간세포암종 발생위험에 대한 비교를 시행한 메타분석에서는 추적기간과 연 령을 보정한 후, 간세포암종의 발생과 재발율은 인터페론과 DAA사이에 차이가 없었다. 요약하면, 비록 대부분 짧은 관찰기간과 후향적 연구들이었다는 제한점이 있지만, DAA 치료로 SVR을 획득하면 간세포암종의 발생이 감소하였다.<sup>11</sup> 대부분 짧은 관찰기간과 대조군이 없는 후향적 연구들이었다는 제한점이 있으며, 대조군이 있어 도 치료 군과 기저 인구학적 특성을 매칭하지 못하였다. 또한 대부분 단일기관이고 추적 기간 동안 소수에서만 간세포암종이 발생하였으며 상대적으로 짧은 기간동안 간세포암종이 발생하여서 이미 간세포암종이 있었을 개 연성을 배제할 수 없다. 한편, 2개의 미국 보훈병원 자료도 기저 대상환자들의 간세포암종 감시 검사에 대한 자 료가 없기 때문에 분석에 제한이 있었지만, DAA 치료로 SVR을 획득하면 간세포암종의 발생이 감소하였다. 향 후 발생과 관련하여서 앞으로 대규모의 다기관, 장기적인 전향적 추적 연구가 필요하다.

# DAA 치료와 간세포암종의 재발

HCV 만성 감염 환자들에서 간세포암종의 근치적 치료 후 DAA 치료제가 단기간의 재발을 증가시킬 수 있다 는 소규모 증례 보고가 있다. 하지만, 이에 대해서 비뚤림없이 잘 수행된 연구가 없는 실정이다. 우선 DAA가 간 세포암종의 재발과 관련이 있다는 연구를 살펴보면 다음과 같다. Reig 등의 스페인 연구에서는 58명의 DAA 치 료 전 완전 치료반응을 보인 간세포암종환자가 DAA치료 후, 16명(28%)에서 재발하였다. 중간 추적기간은 5.7 개월이었으며, DAA치료 시작 후 재발까지의 중간기간은 3.5개월이었다. 55명(95%)이 기저 간경변을 가지고 있 었으며, 과거 치료 경험을 가진 가 29명(50%)였으며, 대조군이 없는 제한점이 있었다.<sup>12</sup>

하지만 대조군이 없는 사례들 연구이며 재발까지의 평균 추적기간이 매우 짧았다는 제한점이 있었다. 또한 DAA치료 시작 시점 AFP이 높았던 환자들이 있어서 이미 간세포암종을 가지고 있었을 가능성을 배제할 수 없 었다. 이집트에서의 연구에서는 116명의 완치판정을 받은 간세포암종 환자 중에서 53명이 DAA치료를 받았고 63명은 대조군이었으며 평균 16개월의 추적기간동안 DAA 군에서 37.7%의 높은 재발을 보였고 대조군은 23 개월동안 25.4%에서 재발하였다.<sup>13</sup> 비록 스페인연구와 달리 대조군이 있었지만 대조군에서 보다 높은 비대상 성 화자과 장기간의 추적이 이루어진 점이 달랐으며. 이 연구에서는 SVR여부에 따른 재발은 분석하지 않았다. Conti 등의 연구에 따르면 이전 완치판정을 받은 간세포암종 59명의 환자에서 평균 6개월 추적 기간 중 28.8% 의 높은 빈도로 간세포암종이 재발하였으나 대조군이 없다는 제한점이 있었다.<sup>1</sup> 이탈리아에서 시행된 연구에서 는 간세포암종 치료 후 6개월간 재발이 없었던 173명의 DAA 치료군과 63명의 텔라프레비어 혹은 시메프레비 어와 페질레이티드 인터페론과 리바비린 병용 요법군간 간세포암종 재발율은DAA 치료 군에서 인터페론 기반 치료군 보다 높았다. 하지만, 인터페론 기반 치료군의 평균 연령이 DAA치료군보다 낮았으며, DAA군에서 간경 변증을 동반한 경우와 과거 간세포암종의 과거력을 가진 경우가 많았다. 결론적으로 DAA치료로 SVR이 달성 되어도 기저 간경변을 가진 경우와 간세포암종의 과거력이 있는 경우 재발이 더 많았다. 반면, DAA 치료와 간 세포암종의 재발 혹은 새로운 발생과는 관련이 없다는 연구들은 다음과 같다. 간세포암종의 근치적 치료 후, 6000명 이상의 DAA치료 화자를 포함한 프랑스의 전향적 코호트 연구에서<sup>14</sup> 189명의 DAA 치료군과 78명의 대조군의 간세포암종 재발율은 차이를 보이지 않았고, 대상성 간경변증 코호트에서는 DAA군보다 대조군에서 재발율이 높았다. 또한, 간이식 수혜자 314명의 DAA 치료 코호트에서는 7명(2%)에서만 간세포암종이 발생하 였으며 평균 재발시간은 70.3개월이었으며, DAA치료군과 대조군간 간세포암종 재발율은 차이가 없었다. 치료 로 완치된 간세포암종 143명 환자를 대상으로 한 전향적인 다기관 코호트 연구에서 전체 환자의 28/143(19%) 에서 재발이 관찰되었으며, 6개월, 12개월, 18개월간의 조기 재발율은 12%, 26.6%, 그리고 29.1%였다. 이 연구 에서 과거 간세포암종이 완치되었던 환자 101명을 과거 간세포암종 완치 후 항바이러스 치료를 받지 않은 대조 군 701명과 비교하였으며, 주 종양의 크기(HR:2.73:95% CI: 1.23-6.06; P = 0.014) 와 과거 재발한 적이 있었 던 경우 (HR: 2.22; 95% CI: 1.02-4.83; P = 0.043)가 재발 위험예측인자였으며, DAA치료는 대조군과 비교하 여 간세포암종 재발은 차이가 없었다. 과거 고주파열소작술로 완치된 후향적 코호트 연구에서, 간세포암종 재

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발은 DAA치료군 8/27(30%), 인터페론 기반 치료군 26/38(68%), 비치료군 553/861(64%)으로, DAA군에서 재발율이 가장 낮았다. 재발 예측 인자는 다발성 종양(HR 1.33; *P* < 0.001), 2 cm 이상 종양크기((HR 1.46; *P* < 0.001), AFP >100 ng/mL(HR 1.41; *P*-0.001), Child-Pugh A(HR 0.79; *P* = 0.01) 로 DAA치료는 재발 과 연관이 없었다.

# 결 론

비록 관찰기간이 짧고, 후향적 연구들이었다는 제한점이 있지만, DAA치료를 통해서 SVR을 획득하면 간세포 암의 발생이 감소하였다. 한편, DAA 치료 중 혹은 치료 후 간세포암의 재발은 일어날 수 있다. 하지만, 인터페 론과 비교하여 간세포암의 재발은 차이를 보이지 않았으며, DAA 치료성공이 간세포암 재발을 줄인다는 보다 확실한 근거가 부족하므로 대규모의 장기간 추가 연구가 필요하다.

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# Hepatocellular Carcinoma Risk after Direct-Acting Antivirals Treatment: Who Is at Risk?

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#### 권정현

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# Introduction

An infection with hepatitis C virus (HCV) is at significant risk of liver disease, such as chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The short-term goal of the treatment of chronic hepatitis C (CHC) is to achieve a sustained virological response (SVR), i.e., the eradication of virus, by administering an antiviral agent. The ultimate goal is to decrease the incidence of the liver-related mortality. Patients with SVR after pegylated interferon (Peg-IFN)-based treatment had a marked reduction in death/liver transplantation and in liver related morbidity/mortality.<sup>1-3</sup>

Since the introduction of oral direct acting antiviral (DAA) therapy, an SVR rate was markedly increased over 95% and the rate of adverse events was low. It is being expected to lead to all-cause mortality benefits, as seen with Peg-IFN based treatment. However, an unexpected high rate of HCC recurrence/occurrence after DAA therapy were reported in the short-term observational studies.<sup>4,5</sup> After these reports, there are so many studies refuting these findings have been published.<sup>6-14</sup> Most of studies suggested that more cirrhotic background and old age in the oral DAAs groups may play a role in increasing HCC risk.<sup>11,15,16</sup>

Here, I focus on the early development of de novo HCC and recurrence of previous treated HCC after DAA treatment. I review the recently reported studies about the risk factor for HCC occurrence and recurrence after DAA treatment.

## The Risk Factors of De Novo HCC Occurrence after DAA Treatment

In the early report of 344 consecutive cirrhotic patients, HCC was detected in 9 of 285 patients without previous HCC after 24-week follow up.<sup>5</sup> This study firstly suggested that the occurrence of liver cancer was not reduced even in DAA treated cirrhotic patients. Child-Pugh Class B, more severe liver fibrosis, lower platelet count, and previous HCC were significantly associated with HCC development.<sup>5</sup> After this, several conflict studies reported DAA treatment reduced HCC risk in CHC patients. However, there is still uncertain about the risk factor for early development of de novo HCC after DAA treatment.

In general, old age, cirrhotic liver, and poor Child-Pugh class were known as the risk of HCC development. In the largest cohort of 22,500 patients treated with DAA, patients with cirrhosis had the highest annual incidence of HCC after SVR (1.82 vs 0.34/100 person-years in patients without cirrhosis; adjusted hazard ratio, 4.73. 95%

CI, 3.34-6.68).<sup>9</sup> Also, SVR was associated with a considerable reduction in the risk of HCC. Similarly, in the large 17,836 Veterances database (ERCHIVES), untreated cirrhotic persons had a higher HCC incidence rate (45.3 per 1,000 person-year) compared to those treated with either IFN or DAA (P = 0.03).<sup>10</sup> In Italy real world data, 78 of 2249 (3.5%) consecutive cirrhotic patients treated with DAA developed HCC during a mean follow up of 14 months.<sup>12</sup> At one year after DAA exposure, the patients with Child-Pugh class A and SVR developed less HCC than those with Child-Pugh class B without SVR. Albumin level below 3.5 g/dL (hazard ratio, 1.77; 95% CI, 1.12–2.82; P = .015), platelets count below 120x109/L (hazard ratio, 3.89; 95% CI, 2.11–7.15; P < .001), and absence of SVR (hazard ratio, 3.40; 95% CI, 1.89–6.12; P < .001) were independently associated increased risk for HCC.

There are two reports about serum a-fetoprotein level at the end of treatment (EOT-AFP) as a risk factor of de novo HCC in Japan and Korea. In large-scale, multicenter Japan cohort study included 1,523 consecutive patients without HCC who achieved SVR by treatment with sofosbuvir-based regimens, 46 (2.7%) patients developed de novo HCC. Cirrhotic patients had a higher one-year cumulative rates of de novo HCC than non-cirrhotic patients (4.9 % vs 0.4%, P < 0.001). In cirrhotic patients, EOT-AFP was the strongest predictor of de novo HCC. The 1-year cumulative de novo HCC rates were 1.4% and 13.1% in the EOT-AFP < 9.0 ng/mL and  $\ge$  9.0 ng/mL groups (cut-off value) respectively (P < 0.001).<sup>16</sup> In the Korean 785 cohort study, de novo HCC developed in 6/574 patients receiving DAA and in 1/211 patients receiving PEG-IFN within 24 weeks post-treatment.<sup>17</sup> All seven patients who developed de novo HCC had cirrhosis. The cumulative incidence of early HCC development did not differ between the treatment groups. Similarly, EOT-AFP > 9.5 ng/ml was the only independent risk factor for early development of de novo HCC in patients treated with DAAs.

In the immune study, 10 patients who developed de novo HCC within 18 months after DAA treatment had significantly higher levels of 12 immune mediator (cytokines, growth factors, and apoptosis markers) before treatment compared with controls.<sup>18</sup> A panel of 9 cytokines, measured in serum before treatment (MIG, IL22, TRAIL, APRIL, VEGF, IL3, TWEAK, SCF, IL21), identified patients who developed de novo HCC with an area under the receiver operating characteristic curve value higher than 0.8. In another micro-environmental study, liver angiopoietin 2 is a key predictor of de novo HCC after DAA treatment.<sup>19</sup> In de novo HCC patients, tumor and non-tumor angiopoietin-2 showed a positive relationship with liver stiffness (r = 0.525, *P* = 0.003). Baseline circulating VEGF and cirrhotic liver angiopoietin-2 were significantly related (r = 0.414, *P* = 0.044). Angiopoietin-2 expression in cirrhotic tissue before DAA was independently related with the risk of HCC occurrence (OR 1.604, 95% CI 1.080–2.382; *P* = 0.019).

However, there are reports about the importance of screening and surveillance of HCC before and after DAA therapy.<sup>20, 21</sup> In Belgian experience, 80% (490/567) of patients were only screened for HCC by radiological follow up at least 6 months after the end of treatment for HCV.<sup>20</sup> In 20%, screening for HCC was inadequate. In non-contrast MRI study before DAA, pretreatment lesions exit in patients with de novo HCC after initiating DAA therapy.<sup>21</sup> This non-contrast MRI protocol was used to measure portal hypertension.<sup>22</sup> The lesions colocalizing with subsequently formally diagnosed HCCs exist before DAA therapy supported that the increased prevalence of HCC after DAA treatment is because DAA-treated patients have more advanced liver disease rather than the risk attributable to DAA therapy.

# The Risk Factors of HCC Recurrence after DAA Treatment

Reig et al. firstly reported unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing DAAs.<sup>4</sup> Among 58 patients with prior treated HCC received DAA after a median follow-up of 5.7 months, 16 developed radiologic tumor recurrence (27.6%). Another study also reported an incidence of 28% HCC recurrence 24 weeks after DAA treatment of CHC.<sup>5</sup>

In Japan report, the recurrence rate increased in accordance with treatment times in the past<sup>6</sup> One-year recurrence rates were 18.1, 28.2, and 60.2%, and 2-year rates were 22.1, 41.6, and 74.5%, respectively (P < 0.0001) in patients with one time, two or three times and four or more times of HCC therapy. In contrast, DAA therapy per se is a favorable factor to reduce recurrence rate when it was performed after initial HCC therapy.<sup>6</sup> After curative treatment (resection or radiofrequency ablation) of HCC adjusting age, gender, BCLC staging, HCC recurrence rates at first and second year were 18.1 and 25.0% in patients with DAA therapy and 21.8 and 46.5% in those without DAA therapy, respectively (P = 0.003).

In the evaluation of biomarkers of HCC development after DAAs, higher levels of EOT-AFP or *Wisteria floribunda* agglutinin positive Mac-2 binding protein (WFA+M2BP) were independently associated with HCC occurrence and recurrence after viral eradication.<sup>23</sup> Only post-treatment WFA+M2BP level was significantly associated with HCC occurrence and recurrence among patients without severe fibrosis.

In addition, a genome-wide association study (GWAS) showed that HLA-DQB1 was independently associated with HCC; HCV genotypes modified the effects of HLA-DQB1 on the risk of HCC.<sup>24</sup> In another GWAS, there was an association between the SNP rs17047200, within the intron of tolloid like 1 gene (TLL1), and development of HCC in patients who achieved an SVR to treatment for chronic HCV infection.<sup>25</sup>

# Conclusions

In 2016, the World Health Organization (WHO) drafted a strategy for combating viral hepatitis and set a goal for the elimination of viral hepatitis by 2030. Investigating the risk factors to identify high-risk patients for the surveillance of HCC is essential. Conventional or novel biomarkers may provide insights into risk stratification for successfully treated patients. In addition to the glycol-marker, host genetic variants would be useful for implementing a personalized surveillance of HCC in patients with HCV infection. Therefore, it is widely accepted that all patients with chronic hepatitis C should be treated regardless of their symptoms or disease stage.<sup>26,27</sup>

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# Direct-Acting Antivirals Response in Hepatocellular Carcinoma: Does the Presence of Hepatocellular Carcinoma Matters?

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Since the first directly acting antivirals (DAA) approved in 2011, the progress of DAA in HCV treatment is moving from IFN (IFN)-containing regimens to IFN-free regimens in 2013, which are currently standard-of-care.

Currently, there are 14 DAAs approved in the treatment of HCV and at 9 major combination regimens are applied in the clinical practice for HCV treatment. The regimens include: 1) sofosbuvir-based therapy: sofosbuvir plus weightbased dose of RBV for HCV-2 with 12-week regimen with SVR12 rate of 90%-95%; 12-week sofosbuvir-based therapies, plus ledipasvir or simeprevir or daclatasvir, with the SVR12 rates of > 90% for HCV-1-4 patients and 12 weeks of sofosbuvir/velpatasvir for all HCV genotype with SVR12 rates of 95%-99%. 2) Protease inhibitor-based therapy, including 24-week daclatasvir plus asunaprevir for HCV-1b with SVR rates of 85%-90%; PrOD regimen (co-formulated paritaprevir/r [NS3/4A Pl boosted by ritonavir]/Ombitasvir and Dasabuvir) +- RBV for 12 weeks with SVR rates of 90%-95% for HCV-1/4 patients; 12-16 week of elbasvir/grazoprevir HCV-1/ 4 with SVR12 rate of > 90%; and 8-12 weeks of glecaprevir/pibrentasvir for all genotype with SVR rate of 96-99%.

However, concerning the efficacy of DAA on HCV patients with pre-existing hepatocellular carcinoma (HCC), there is no data available from clinical trials. Most of the data come from real-world clinical practice and the results are conflict among different studies due to heterogeneity in study population, regimens, baseline patient characteristic and hepatic fibrosis. Nevertheless, there is a trend showing that the SVR12 rate was lower among patients with active HCC when compared to those achieving curative therapy for HCC. Further well controlled, large-scaled studies are needed to clarify the controversial.

# Hepatitis C Virus Treatment Awaiting Liver Transplantation: When Is the Right Time?

#### **Kwang-Woong Lee**

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Liver transplantation (LT) for HCV has been increasing. It accounts for 10% of LT in recent 5 years from 2011 to 2015 at Seoul National University. The long-term outcome has been known poorer than that of other indications. However, the availability of new DAA changed many things in HCV treatment strategy. Now, it poses new questions about the optimum time to give treatment to prevent HCV recurrence, taking into account efficacy, tolerance, and drug–drug interactions. Treatment is acceptable before and after transplantation, but the two strategies have subtle differences.

There are advantages and limitations of treating HCV before liver transplantation.<sup>1</sup>

#### Advantages

- Prevention of HCV recurrence when SVR achieved.
- Liver transplantation can be avoided in about a third of patients, whose MELD scores improve with treatment.
- Allows treatment of hepatocellular carcinoma in patients whose hepatic function improves with treatment.
- Reduced number of drug-drug interactions (immunosuppressive agent related interaction).
- Beneficial effect on hepatocellular recurrence, although degree of benefit unclear.

### Limitations

- Despite negative HCV RNA, if SVR is not achieved, HCV might recur in 20-30% of patients.
- Likelihood of SVR is reduced in patients with decompensated cirrhosis (mainly Child-Pugh class C disease) compared with those who have received a transplant.
- If liver transplantation remains indicated despite improvement, treatment might disadvantage patients if the allocation system for liver grafts is based on MELD scores.
- No adjustment needed due to hepatic impairment when patients are treated early after liver transplantation.
- Treatment is futile in about 30% of patients, and they are likely to drop off the waiting list, meaning that they die before receiving a transplant, or have early hepatocellular carcinoma recurrence after transplantation.
- Controversial risk of HCC progression after treatment.

Therefore, we have to decide optimal timing of HCV treatment considering availability of donor or living donor, degree of cirrhosis, previous treatment history and HCC status. If HCC is not aggressive or well controlled, liver function and cirrhosis is not far advanced, treatment before LT is recommended.

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DAY 3: Saturday, June 16, 2018 (08:00-10:00) EAST TOWER / ROOM A [2F]

# Abdominal Ultrasonography (USG) Training Course for Certified Trainer (Session I) (\*к)

Chairs: Sung Won Cho (Ajou Univ.) Soon Koo Baik (Yonsei Univ. Wonju)

# **Course Introduction**

## Hyung Joon Yim

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As abdominal ultrasonography help physician to visualize the organs and structures in the abdomen, it became one of basic and essential initial evaluation tools of abdomen currently. As of 2018, upper abdominal ultrasonography can be reimbursed to health insurance system. In addition, resident of Internal Medicine should learn ultrasonography and get proper training for applying the Board Certified Internal Medicine Specialist.

With this regard, Korean Association for the Study of the Liver (KASL) launched "the Quality Management Committee of Upper Abdominal Ultrasonography". The committee will be responsible for qualification of internists performing upper abdominal ultrasonography and issuing the certificate of upper abdominal ultrasonography subspecialist. For getting the certificate, experience of 200 cases of upper abdominal sonography and 9 points of educational credits are mandatory. Among the 9 points, 4 points should be obtained from the ultrasonography educational session sponsored by KASL. During the Liver Week meeting, maximum 6 points will be issued from lectures in this session and hands-on courses. Additional educational credits can be obtained from the academic meeting sponsored by the Korean Association of Clinical Ultrasound. KASL will receive the application for the upper abdominal ultrasonography subspecialist in October.

The Korean Association of Internal Medicine indorsed the Korean Association of Clinical Ultrasound and the Korean Society of Gastroenterology for the education of abdominal ultrasonography trainer. KASL will approve the qualification for abdominal ultrasonography trainer together with the Korean Society of Gastroenterology. For obtain the qualification for abdominal ultrasonography trainer, 9 points of educational credits are also needed from next year, but this will be exempted in 2018. Experiences as a speaker or a chair at ultrasonography session of academic meeting are also required in addition to 200 cases of abdominal sonography practice.

Residents of Internal Medicine will learn basic skills of performing abdominal ultrasonography through class room lectures and hands-on practice workshops. Three hour education can replace the experience of abdominal sonography of 17 patients.

In conclusion, this ultrasonography sessions were planned to educate the ultrasonography and to issue the educational credits, eventually for the better qualification of knowledge and technique of ultrasonography for members of KASL and trainees.

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- Korean Association for the Study of the Liver http://www.kasl.org/bbs/index.html?code=notice&number=3454&mode=view.

# Setting-Up of Ultrasonography Examination Facilities

#### Soung Won Jeong

Soonchunhyang University, Asan, South Korea

복부초음파는 내과의사에게 임상적으로 빠른 진단을 내릴 수 있는 유용한 검사로 비침습적이며 간편하고 쉽 게 검사할 수 있는 장점이 있다. 처음 복부초음파실을 세팅하기 위한 세부사항에 대해서 정리하였다.

# 1. 초음파실 세팅을 위한 기본 준비 사항

## 1) 초음파실 공간 확보

초음파실 세팅의 첫번째는 초음파실 공간의 확보이다. 일반적으로 소화기내과 내부 공간에 환자의 이동에 어려움이 없고 공간의 크기가 적당한 곳으로 초음파실을 정하는 것이 중요하다. 많은 경우에 있어서 초음파와 내시경 검사, ERCP, CT 등의 검사가 연속되어 이루어지고, 외래 환자 및 입원 환자 등이 검사 대상이므로 이 런 점을 고려하여 초음파실의 위치를 정한다.

#### 2) 초음파 장비의 선택

초음파 장비는 여러 회사 초음파들의 각각의 특성과 최신 기능을 꼼꼼히 살펴보고 실제 초음파 검사를 시행 하는 검사자들의 의견을 모아서 장비를 선택한다. 대부분의 초음파 장비 회사에서 미리 시연할 수 있는 기회를 주기 때문에 관심있는 장비를 최종적으로 시연해 보고 선택한다.

#### 3) 초음파실에서의 역할 분담

초음파 검사 시에는 검사자 옆에서 환자의 검사 목적과 이전 검사 내용등을 파악해서 알려주는 보조자가 필 요하다. 일반적으로 전공의가 이 역할을 하게 되는데 초음파 옆에 컴퓨터와 좌석을 준비하여 위치하고 검사 전 에 환자 파악을 통해서 검사자에게 검사 정보를 제공한다. 또한 검사 시의 초음파 소견을 기록하여 검사 후에 결과를 기록한다. 또한 초음파실에는 피검자의 초음파 준비 및 이동 등을 담당하는 간호 인력이 필요하다.

#### 4) 초음파 검사를 위한 세부 사항

## ① 탈의와 물품 보관을 위한 공간

외래를 통한 초음파 검사의 경우에는 검사 전에 피검자가 탈의와 물품을 보관하고, 검사가 끝난 후 복부에 남은 젤리를 닦고 정리할 공간이 필요하다.

#### ② 초음파 검사를 위한 젤리의 보관

초음파 검사 시에 필요한 젤리는 검사에 적당한 온도를 유지할 수 있도록 적정한 온도로 세팅된 온장고에 넣어서 보관한다.

## ③ 초음파실의 조명과 온도

조명은 검사 시에 검사에 적합한 조명 상태를 유지해야 하므로 적절한 간접 조명 또는 조명 조절장치를 설치 한다. 피검자가 더위나 추위에 영향을 받지 않도록 실내 온도도 잘 조절해야 한다. ④ 초음파실의 침대 및 시트

높낮이 조절이 가능하고 이동과 고정이 자유로운 침대를 준비한다. 또한 침대와 시트의 청결과 위생 상태를 잘 유지하고 감염의 우려가 있는 환자의 검사 후에는 검사 후 철저한 소독을 통해서 감염의 전파가 이루어지지 않도록 주의한다.

⑤ 장비의 관리

탐촉자는 알코올로 닦지 않고 전용세정제(무알코올) 또는 깨끗한 티슈를 사용한다. 알코올은 고무가 딱딱해 지며 검사 때 사용되는 젤리도 나트륨 성분이 소량 포함되어 있어서 사용 후 깨끗이 닦도록 한다. 모티터는 안 경 닦는 천 등을 사용하여 닦고, 계기판은 마른 걸레를 이용하여 닦는다. 장시간 전원을 켜 두지 않도록 주의 하고 검사가 종료되면 전원 오프를 하여 기계 손상을 방지한다. 탐촉자는 가격이 비싸고 접촉면이 쉽게 손상 될 수 있으므로 떨어지지 않도록 주의하고 탐촉자 표면에 미세한 손상등이 발생하지 않도록 조심한다.

# 2. 초음파실에서 시행될 수 있는 각종 검사와 시술들

1) 복부초음파 진단 검사 - B mode와 도플러 초음파 검사
 2) 간조직 검사
 3) 복수 천자 및 흉수 천자의 위치 표기나 시술
 4) 간농양의 흡인과 카테터 삽입
 5) 조영초음파 검사
 6) 알코올 주입술
 7) 고주파 열치료술

# 3. 초음파 검사의 기본 세팅

#### 1) 적절한 탐촉자의 선택

초음파검사에서 사용되는 탐촉자는 굴곡형(curved), 선형(linear), 구역형(sector) 등이 있다. 복부초음파 검사에서 기본적으로 사용되는 탐촉자는 굴곡형 탐촉자(curved probe)이며, 경우에 따라서는 선형 탐촉자 (linear probe)를 사용할 때도 있지만 병변이 피부에서 가까운 경우일 때에 이용되며, 실제 사용은 드물다. 구 역형 탐촉자(sector probe)는 심장초음파에서 주로 사용되며 복부초음파에서는 늑간검사 시에 사용해 볼 수 도 있다. 그러나, 복부초음파 검사에서는 1-6 MHz에 해당하는 굴곡형 탐촉자를 기본적으로 사용한다.

## 2) 초음파 진단 장치의 세팅

① Gain

생체로부터의 에코신호는 탐촉자에 의해 전기신호로 변환되지만, 이 상태로는 너무 약하기 때문에 화상이 맺혀지지 않으므로, 이때 모니터에 충분한 화상이 맺히도록 전기신호를 강하게 올려주는 것이 gain이다. gain 을 너무 강하게 하면 화상 전체가 하얗게 되므로, 흰색에서 검은색까지 전체의 농도를 조절하여 좋은 화상이 맺혀지도록 한다.

② STC (Sensitivity Time Control)

STC는 생체내의 깊이에 따라 감도를 조절할 수 있도록 한 장치로, 간과 같은 실질성 장기에서 간실질이 전체 적으로 균등한 밝기(brightness)로 나타나도록 near gain과 far gain을 조정하는 것이 표준적인 STC의 조정 법이다. 초음파 화면을 통해서 각각의 깊이에서의 gain 을 조정하여 전체적으로 균등한 영상을 얻도록 한다.

#### ③ Dynamic Range

Dynamic range (동적 구역)는 휘도가 다른 것들을 명확하게 보이게 할지, 부드럽게 보이게 할지를 정해주 는 설정이다. Dynamic range를 너무 높이면 강한 휘도로 표시되어 거칠고 딱딱한 영상으로 표현되고, 낮추 면 부드러운 영상이 된다.

④ Depth

초음파 영상의 투과 깊이를 조절해 주는 기능으로 적절한 깊이를 선택하여 스캔하고자 하는 대상에 맞추어 서 설정한다. 탐촉자로부터 가까운 부위를 관찰할 때는 Depth를 낮추어서 확대하여 관찰하고, 탐촉자로부터 먼 곳의 깊은 영역의 관찰 시에는 Depth를 높여서 화면에 깊은 부위가 포함되도록 한다.

Abdominal Ultrasonography (USG) Training Course for Certified Trainer (Session I) (\*)

(5) Focus

초점영역(focal zone)에서 해상력이 가장 좋으므로 검사 하고자 하는 부위에 초점영역을 위치시키면 영상을 좋게 할 수 있다.

# 3) 초음파 도플러의 활용

상복부 초음파에서는 B (Brightness) mode와 D (Doppler) mode가 주로 이용되며, 펄스파 도플러 (Pulsed wave Doppler), 색 도플러(Color Doppler), 파워 도플러(Power Doppler) 등의 방법을 활용할 수 있다. 상복부 초음파 도플러를 활용하여 무에코 병변으로부터 혈관의 구별, 종괴의 혈관성, 상복부 혈관의 혈 류 방향과 속도 등을 파악할 수 있다.

결론적으로 복부초음파실의 효과적인 세팅을 통해서 실제 임상에서 복부초음파를 이용한 빠르고 효과적인 진단과 치료를 시행할 수 있다.

# Standard Report System for Ultrasonography Results

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# 1. 초음파 검사 판독소견서작성 가이드라인의 필요성

초음파 검사 판독소견서는 검사를 의뢰하는 의료진과 검사를 실제로 수행하는 의료진과의 의사소통의 도구 로서 정확한 검사 결과 전달을 위해 필수적이다. 또한 환자가 추적 검사를 받는 경우 검사를 수행하는 검사의의 입장에서 환자의 이전 상태를 파악하기 위해서도 필요하다. 이에 국내외 다양한 초음파 관련 학회에서는 초음 파 검사 판독소견서에 대한 중요성의 강조와 함께 판독법 가이드라인을 재정하여 공유하고 있다<sup>1-3</sup>. 국내에서는 2008년 발표한 간암 검진 질 지침서<sup>4</sup>에 일부 초음파 검사 및 판독법에 대한 권고 내용이 포함되어 있으며, 최근 일부 초음파 급여화와 관련하여 국내 초음파 관련 여러 학회가 주축이 되어 초음파 검사의에 대한 인증 제도를 마련함과 동시에 초음파 검사의 표준 검사 및 판독법에 대한 가이드라인을 제시하고 있다. 이를 참고로 하여 기 관별로 표준화된 초음파 판독소견서 형식을 갖추는 것이 필요하며 이와 같은 과정은 양질의 검사가 이루어 질 수 있도록 할 뿐 만 아니라 나아가 향후 의료적 분쟁 발생과 같은 여러 임상적 상황에 대비한 근거자료가 될 것이다.

# 2. 초음파 검사 및 판독소견서 작성 단계와 기본 항목

초음파 검사 및 판독소견서 작성의 단계는 다음의 순서로 이루어 진다; (1) 환자의 임상정보 확인; (2) 초음파 술기를 동원한 검사의 시행; (3) 결과 분석; (4) 의학적 해석 및 제안; (5) 의뢰의와의 적절한 소통. 이러한 일련의 순서를 바탕으로 검사를 진행하고 판독소견서를 작성한다면 검사 과정에서 정보의 누락을 막을 수 있을 것이다. 초음파 판독소견서에는 필수적으로 포함되어야 할 기본 항목이 있다. 우선 기본 의료정보로는 병원이름, 환자 이름, 환자등록번호, 환자의 성별/나이, 검사명, 검사 일시, 판독소견서 작성 일시, 검사의 이름과 면허번호가 포 함되어야 한다. 검사 정보로는 각 검사 장기의 기술항목과 이전 검사와의 비교, 이를 통한 결론 및 감별 진단, 추 가 검사에 대한 제언이 포함된다. 대한임상초음파학회에서는 상복부 초음파 검사를 시행한 경우 이러한 기본 항 목이 포함된 상복부 초음파 검사 표준 판독소견서를 아래 그림 1과 같이 재정한 바 있다.<sup>5</sup>

#### 3. 초음파 검사 판독소견서 요건

국내외 학회 가이드라인을 종합하여 초음파 검사 판독소견서의 요건을 정리하자면 다음과 같다.

1) 양식(Style)

양식은 기본 항목을 포함하여 만들되 간결하고 요점만 간단히 포함되도록 하는 것이 좋다. 불필요한 항목은 효율을 떨어트리고, 의뢰의와 검사의 간의 정보 전달에 방해가 될 수 있다. 표준 서식을 참고하여 기관별로 양식 을 표준화 하여 사용하도록 한다.

## 2) 용어(Terminology)

적절한 해부학적 용어와 초음파 용어를 사용할 수 있다. 다만, 판독소견서에 약어의 사용은 자제하도록 하며

# 오해의 소지가 있는 전문적인 초음파 용어(ex. Transonic, Echogenic etc.) 등은 배제한다. 판독소견서에 '정 상(normal)'의 용어는 모든 장기가 충분히 검사되지 않은 상황에서는 자제하도록 한다.

		상복	ŧ부	초음ī	파 검시	⊦ 표 ਰ	는 판도	소견	서				췌장					
인적사항													췌장 이상	□ No □ Yes				
등록번호		성명			성별	남/여	나이		생년월일		, ,	,	기타(기술)	*췌관 확장 여부 및 크기 등 7	술			
건사 및 시설	숙												비장					
검사일시	1	년	년 월 일										비장 종대	□ No □ Yes	비장 장경(Diameter)			cm
		 일반	산 미정말										기타(기술)					
검사구분	진단			_ 0 년 _ 1 간	□간 □담낭/담도		낭/담도	람도 □췌장		미바	장	_	<u>2. 색도플러 초음파(선택적</u>	)	·			
	기본	□단순!		미단쉰							Portal vein diameter	mm Portal vein velocity cm/sec						
													Portal blood flow	mL/min	· · ·			
검사 의사			면허번		번호							Portal vein flow direction	ection Hepatopetal Hepatofugal					
													Hepatic vein waveform	Triphasic	Biphasic		🗆 Monop	hasic
검사 소견													Hepatic artery	Pulsatile index(PI),		Resistive	index(RI)	
<u>1. 회색조 초</u>	음파												Splenic vein diameter	mm	Splenic vein velocity		cm/sec	
갼 (Liver)	간 (Liver)				lomal Slight Coarse				- Coomo				Splenic vein blood flow	mL/min				
긴 걸걸 (Pai	dularitu)		mal		Nodular	Jaise		Coarse				_	간 종괴 있는 경우, 종괴 내부의 도플러 소견					
긴 표현 (NO 가봐기 (Bri	obtross)		mal		Mild		Moderate		C Source			_						
12 -27 (312	e)											_	3. 관챀 상태					
간 중괴 (Mass)						Size (Lamost)					3. 편을 경매	□ Fair □ Limited			Poor			
			Location				Size (Laigest) Gil			cm		2.1			<u> </u>			
Portal vein thrombosis      □ No      □ Yes      4. 최종 진단 및 기술																		
기타(기술)		*중과의		, 개우, 크	기등의 4	유가 기술							*Final impression					
다나/다드																		
	담석				□ No □ Yes				mm									
담당 이상		8종					□ Yes				mm		A KACU A					
		벽비후		□ No		□ Yes				mm								
담낭 이상 소	-견 (기술)	*Sludg	e, cor	met tail s	ign, 병변	개수 등	의 기술											
담관 확장 및	! 이상	g □ No □ Yes 담관 넓이(Diameter) mm							mm									
기타(기술)		*담관 0	"담관 이상 소견 등의 상술															
() 대한임성	낭초음파혁	비회									내고	의원	() 대한임상초음파악회					내과의원

그림 1. 대한임상초음파학회에서 제시한 상복부초음파 검사 표준 판독소견서

# 3) 측정(Measurement)

모든 측정은 정상 수치 범위를 참고하여 보고하도록 한다. 또한 이전 검사와 비교하여 병변의 크기 변화는 수 치와 함께 보고한다. 장기의 이상적인 크기 변화 (ex. Hepatomegaly, Splenomegaly) 역시 수치와 함께 보고 하는 것이 좋다.

# 4) 제한점(Limitation)

검사의 질에 영향을 줄 수 있는 모든 임상적 제한점(ex. High body mass index, Poor sonic window)을 기록해야 한다. 기술적 혹은 임상적 제한점을 모두 언급하되, 어떠한 장기의 검사가 제한 적이었는지 기술하고 가능하면 그 이유도 같이 기술하여 추후 검사 진행에 참고가 될 수 있도록 한다. (ex. "The pancreas is obscured by bowel gas and not seen adequately enough to assess. The gallbladder is contracted as the patient is not fasted therefore the presence of small gallstones cannot be confirmed or excluded with confidence".)

# 5) 결론(Conclusion)

의뢰의가 검사를 의뢰하게 된 임상적 물음에 답을 제시할 수 있는 결론이 있으면 기술한다(ex. "The

gallbladder is very tender and cholecystitis is the likely cause of the right upper quadrant pain".). 감 별 진단이 있다면 기술하고 추적검사 혹은 추가검사가 필요한지 기술한다. 잠재적으로 악성의 가능성이 있다면 충분히 강조하고 추가검사를 즉각 권유한다.

# 6) 전달(Transmission)

최종 보고서는 검사 종료 후 최소 24시간 이내에 보고되어야 하며, 응급상황 시에는 보다 빠른 전달이 될 수 있도록 조치한다.

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Abdominal Ultrasonography (USG) Training Course for Certified Trainer (Session I) (\*K)

# Advances in Ultrasound Diagnosis for Chronic Liver Diseases

#### Hitoshi Maruyama

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Diagnosis of chronic liver diseases is a key process in the daily medical care, because of the high incidence in Asia. Non-invasive and repeatedly-available tools are preferred to reduce the burden of the patients.

Ultrasound (US) offers real-time evaluations for an anatomical structures and hemodynamics non-invasively. It may be the most frequently used imaging tool in the practical management of patients with chronic liver diseases. Furthermore, with the development of digital imaging technologies and the availability of microbubble contrast agents, contrast-enhanced US may now be the definitive primary modality for detailed evaluation. Efforts have been directed at finding the benefits of this technique for the severity of liver disease in order to decrease the requirement for invasive procedures involving a radiation exposure. With these backgrounds, this presentation shows the recent progress in the application of US as the non-invasive diagnostic tool of chronic liver diseases.

# Assessment of Liver Fibrosis Based on Ultrasonography

#### Soo Young Park

Department of Internal Medicine, Kyungpook National University, Daegu, South Korea

# 만성 간질환 환자의 초음파 소견

박수영

경북대학교 의과대학 내과학교실 소화기내과

Ultrasonography is a widely performed diagnostic procedure which can identify the varying stages of chronic liver disease from minimal liver fibrosis to cirrhosis. Although ultrasonography is a useful diagnostic tool with readiness, easy availability, and inexpensiveness, diagnostic performance of ultrasound is limited by low specificity and operators-dependency. The present session will describe features of ultrasound in patients with different stage of chronic liver disease and tips for assessment of fibrosis in these patients.

Keywords: Ultrasound, Chronic liver disease, Fibrosis, Cirrhosis, Hepatitis

# 서 론

초음파 검사는 비용이 저렴하며 비침습적이며, 연부조직의 미세한 변화를 잘 표현할 수 있어 만성 간염, 간경 변 등의 미만성 간질환과 간세포암종 등의 국소 간병변의 진단에 있어서 선별 검사로 널리 이용된다. 초음파의 역할은 크게 간실질의 거친 정도, 간 표면상태, 간 내 결절성 변화, 비장의 크기 등으로 간질환의 진행 정도의 판 단에도 도움을 준다. 이 외 초음파 검사로 국소 병변의 발견과 발견된 병변의 특성화가 가능하다. 본 강좌에서 는 만성 간질환 환자에서 간섬유화의 정도를 초음파로 확인할 수 있는 소견 및 그 한계에 대해 알아보고자 한다.

# 만성 간염

다양한 원인에 의해 6개월 이상 간세포 괴사 및 염증이 진행하는 경우 보통 만성 간질환으로 정의한다. 간 조 직 검사 상 문맥부의 염증 세포 침윤, 문맥 주변의 간세포 괴사, 간소엽 내의 간세포 파괴 및 국소 괴사 등이 나 타나며, 심한 경우 가교상 괴사(bridging necrosis), 간소엽의 붕괴 그리고 섬유화를 동반한다. 이러한 만성 간 염 환자에서 초음파 소견은 초기 섬유화 과정에서는 즉 조직학적인 형태학적 변화가 보이기 전에는 정상 초음파 소견으로 보일 수도 있다. 그러나 장기간 지속된 염증시 간실질 에코가 전반적으로 증가하며 거칠게(coarse) 보 이며, 문맥 혈관벽 에코의 현저한 감소가 나타난다(그림 1). 그러나 이과 같은 소견은 매우 주관적일 수 있으며, 간실질 에코만으로 판정했을 경우 만성 간염의 민감도 및 특이도는 60% 이하이며 간경변증, 지방간 등 다른 미 만성 병변들과 중복되는 소견이 많아 감별 진단이 용이하지 않다. 간혹 간십이지장 인대를 따라 임파절 종대가 보이기도 한다. 만성 간염 환자에서의 주기적인 초음파 검사의 역할은 간경변으로의 진행 여부를 평가하고 병발 할 수 있는 간 내 결절성 병변을 조기 발견하는데 의의가 있다.



그림 1. 동일한 환자에서 만성 B형 간염 진행에 따른 초음파 소견. (A) 2003년 내원 당시 간초음파 소견. 간실질이 세밀하게 거칠며 분명한 간 내 혈관(간정맥)을 관찰할 수 있으며 간표면이 부드럽다. (B) 2007년 초음파 소견. 간실질이 에코가 더욱 거칠어 졌으며 혈관벽의 비후가 관찰된다. (C) 2013년 초음파 소견. 매우 거친 간실질 에코를 확인할 수 있으며, 재생 결절이 관찰된다. 간표면의 굴곡이 간경변증으로의 진행을 시사한다.

만약 간실질 전반에 걸친 만성적이며 비가역적 손상으로 초래되는 3단계 이상 섬유화가 진행된 경우, 즉 병리 학적으로 반복되는 조직손상 반응에 의해 간세포의 미만성 괴사 및 재생, 이로 인해 세포를 지탱하던 섬유조직 의 밀집 및 증식으로 남은 간 실질이 재생 결절로 치환되는 경우를 진행성 섬유화 단계라 총칭한다. 간경변증으 로 진행시 재생 결절의 크기에 따라 3 mm를 기준으로 minconodular cirrhosis, macronodular cirrhosis, mixed cirrhosis 등으로 분류하기도 한다.

진행성 간섬유화 단계 또는 간경변증에서 보이는 간실질의 고에코는 지방간에서 보이는 고에코 소견과 구분 되지 않을 때도 있어 "지방-섬유화 패턴(fatty-fibrotic pattern)"이라는 하나의 용어로 묶어 표현하기도 한다. 즉 병리적으로도 미만성 간질환의 초음파 소견들이 서로 중첩되어 있는 경우도 흔하다. 그러므로 초음파 상 간 표면의 불규칙성, 간 전체 용적의 감소 및 미상엽의 비후 등이 보이면 간경변증이라 기술하여도 무리가 없다.

진행성 섬유화 단계 - 간경변증 시 간 초음파 소견은 간 우엽, 특히 우후분절과 좌엽 내분절의 크기가 줄고 미 상엽과 간 좌엽의 외분절이 커지면서(간 용적의 재분배) 전체 간 용적 감소 및 넓어진 간 내 틈새(intrahepatic fissure), 울퉁불퉁한 간 표면, 거친(coarse) 고에코의 무수한 재생성 결절 또는 이형성 결절의 동반, 문맥 고혈 압의 이차적 소견인 주문맥의 확장(>13 mm), 측부 혈관, 복수, 위장관벽 비후, 비장 종대 등이 특징적이다.

재생 결절(regenerating nodule)은 간경변으로 생긴 재생 결절을 보통 호칭하는데, 그 크기가 보통 1 mm에 서 10 mm 사이다. 일반적으로 작은 재생 결절은 초음파 상으로 보이지 않는다. 재생 결절의 크기가 5 mm 이 상은 되어야 초음파 검사에서 보인다. 초음파에서 촘촘히 배열된 재생 결절과 주위의 섬유화로 거친 에코를 보 이는 경우가 대부분이나 자세히 보면 경계가 불분명한 작은 저에코 결절을 발견할 수 있다. 초음파 검사에 보이 는 결절의 크기가 비교적 균일하게 1 cm 미만으로 간 전체에 퍼져 있는 경우가 일반적인 경우이나, 재생 결절의 크기가 다양하여 1 cm 이상 되는 결절이 보일 때 이 결절이 재생 결절인지 간세포암종인지 구분되지 않는 경우 가 많다. 일반적으로 결절의 크기가 큰 경우 간세포암의 가능성을 생각하여 컴퓨터 단층촬영이나 자기공명영상 을 통해 반드시 간세포암을 감별 진단하여야 한다.

이형성 결절(Dysplastic nodule)은 대개 1-1.5 cm이다. 간경변증 환자에서 이형성 결절과 재생 결절을 감별 하는 것은 쉽지 않다. 다만 이형성 결절은 크기가 좀 더 크게 보이는 경우가 많다. 초음파 검사에서 다른 수많 은 재생 결절보다 현저히 크게 보이는 결절이 한두 개 있는 경우 이형성 결절이나 간세포암을 의심할 수 있다 (그림 2). 특히 결절의 크기가 2 cm 이상인 경우 간세포암의 가능성이 높으며 1-2 cm인 경우 구별이 불가능하 다. 이형성 결절 속에 있는 지방성분 때문에 고에코를 보이는 경우가 있으나 재생 결절도 지방성분을 포함하고 있으면 고에코로 보여 이도 이형성 결절의 감별에 크게 도움이 되지 않는 경우가 많다. 그러므로 처음으로 이형

성 결절을 발견하는 경우 반드시 역동영상(dynamic imaging)을 이용하여 간세포암을 감별 진단해야 한다. 간경변증이 매우 심한 경우 간실질의 수축으로 간이 쪼그라들고, 표면에 굴곡이 생기며, 무수한 재생 결절과 섬유화로 인하여 초음파 검사가 어렵다. 간초음파 검사는 특성 상 판독이 매우 주관적이며, 검사자에 따라 결과 가 다를 수 있다는 점을 항상 유의하여, 간질환의 섬유화 정도를 판단하여야 한다. 또한 항상 환자의 임상적 특 징, 검사실 결과, 간탄성도 검사 등 다른 간접적으로 환자의 섬유화 정도를 판단 할 수 있는 검사 결과를 인지하 여 종합적으로 판단하여야 한다.



그림 2. 만성 B형 간염 환자에서 간 내 이형성 결절. (A) 거친 간실질 에코를 동반한 만성 B형 간염 환자에서 1.5cm의 저에코 병변(화살표)이 관찰된다. (B) 감별진단을 위해 시행한 컴퓨터 단층 촬영에서 동맥기 조영 증강되지 않는 결절이 관찰된다.

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DAY 3: Saturday, June 16, 2018 (10:10-12:10) EAST TOWER / ROOM A [2F]

# Abdominal Ultrasonography (USG) Training Course for Certified Trainer (Session II) (\*K)

Chairs: Hong Soo Kim (Soonchunhyang Univ.) Won Young Tak (Kyungpook National Univ.)

# Ultrasonography Education Plan of Korean Association of Internal Medicine

#### Joong Sik Eom

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# 엄중식

가천대학교 의과대학 길병원 감염내과

2013년 전공의 정원 감축 정책이 시작된 이후 내과 전공의의 근무 환경이 더욱 열악해지고 원격진료 도입 논의를 비롯한 외 부 환경의 변화로 인하여 내과의 미래가 불투명해지면서 내과 전공의 지원이 급격히 감소하고 내과 전공의 정원을 채우지 못 하는 수련병원이 속출하는 상황이 발생하였다. 이에 대한내과학회는 전공의 지원 감소를 극복하기 위한 대책의 일환으로 숙원 중의 하나인 내과 전공의 수련 혁신을 이루기 위한 노력을 본격적으로 시작하였다.

내과 전공의 표준 수련프로그램을 제시하고 수련 프로그램을 역량 중심으로 구성하였으며 수련병원의 역량을 강화하기 위한 방안을 제시하였다. 실제로 내과 전공의 수련기간을 3년으로 단축하는 큰 변화가 이루어졌으며 이에 따른 내과 전공의 수련교 과과정을 전면 개정하였다. 개정된 수련교과과정에서 2-3년차 기간 동안 각종 초음파 검사(복부, 갑상선, 골관절 등) 참여 50 건 이상으로 규정하였고 '각종 초음파 검사 참여는 1) 각 수련병원이 시행하는 프로그램 또는 2) 대한내과학회에서 인정하는 교육 과정에 전체 수련기간 동안 3회 이상 참여한 경우 대체 인정한다'고 제시하였다. 또한 대한내과학회 전공의 수련핵심역 량을 발간하면서 술기 역량을 제시하면서 복부 초음파 검사, 심초음파 검사, 갑상선 초음파 검사 등은 지도 전문의 평가가 필 요한 술기로 지정하였고 세부 지침을 제시하였다. 해마다 내과 전공의 수련 병원의 평가와 전공의 정원 결정에 활용하는 전공 의 지도감독 보고서에서 초음파 검사의 진료 실적을 입력하여 보고하도록 되어 있고 전공의 기록에서도 전공의가 참여한 초 음파 검사를 전산 입력하도록 구축되어 있다.

앞으로 대한내과학회는 내과 전공의 수련과 관련하여 교육 전용 초음파 기기를 의무적으로 보유하고 초음파 검사 지도 전문 의의 인증과 역량 강화를 위한 기준을 신설하는 것에 대한 논의를 진행 중이다. 또한 전공의에 대한 초음파 검사 교육 체계가 완전히 구축된 이후에 초음파 검사 역량을 평가하기 위한 도구나 시스템을 개발하여 도입할 예정이다.

초음파 검사는 내과 질환을 진료하는데 점점 더 필수적인 장비가 될 것으로 예측된다. 따라서 전공의 기간 중 충분한 교육과 수련을 받아서 일정 수준 이상의 역량을 갖추어야 한다. 이를 위하여 대한내과학회는 적절한 교육 수련 기반을 만들고 평가 시 스템을 도입하기 위한 노력을 기울이고 있다.

# Current State of Ultrasound Training Programs in Japan: How Should We Manage Ultrasound Training for Residents?

#### Shinji Okaniwa

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# 1. Introduction

These days, Japanese doctors prefer non contrast CT to US for the first imaging. Even gastroenterologists can neither perform US nor interpret US findings properly. So, sonographers are primarily engaged in US instead of doctors.

# 2. Aspects of Adult Education

Before start training, we have to know the difference between school education which is teacher-directed learning and adult education which is self-directed and mutual learning. Educators should use a variety of different methods depending on the trainees' skill level. So, trainers should listen to trainees' aims, consider their experiences and try to have trainees to identify and resolve problems by themselves. Regarding training methods, interactive experience-based methods are preferable to lectures.

# 3. Popular Training Methods in Japan

In addition to classroom lectures, hands-on trainings and live demonstrations are usually employed as interactive experience-based training methods in Japan.

## 3.1 Hands-on Trainings

Usually, target organs are the liver, biliary tract and pancreas. Each trainer instructs only one of them at each station. Trainees learn how to visualize those 3 organs moving between 3 different stations. With this style, trainees can take same instruction at every station and perform US on 3 different volunteers. Furthermore, the mental burden of trainers may be reduced and employment of volunteers tends to be easier. To understand anatomical structures, hands-on trainings on phantoms are more effective especially for beginners and residents.

## 3.2 Live Demonstrations

Usually, target organs are the liver, biliary tract, pancreas and kidney. In the beginning, demonstrators give small lectures regarding how to visualize the targets, pitfalls and practical solutions. After those lectures, demonstrators perform US explaining points of scanning methods. In the case of large halls, US images and scanning maneuvers should be exhibited on the screen simultaneously. Live demonstrations are suitable for intermediate level trainees.

#### 3.3 Other Interactive Resources

Some learning resources having QR codes printed enable trainees to see motion pictures by mobile phone at

anytime and anywhere. Some of those are very entertaining and popular with Japanese trainees.

# 4. Action Taken by the Japanese Society of Ultrasonics in Medicine (JSUM)

Until 2016, there weren't enough training programs and courses for residents. Therefore, most of residents lost opportunities to perform US, which led to a lack of interest in US. In order to resolve this problem, the educational committee of JSUM has been holding a small-scale hands-on workshop for residents (SHWR) in each regional area of Japan since July 2016.

The SHWR is usually held in the evening (5:00-8:30 PM) on weekdays as extracurricular training. Junior and senior residents regardless of having the membership of JSUM can attend for free. In the beginning, trainers give lectures on important points regarding acute abdomen and US screening skills for the liver, pancreatobiliary system, GI-tract with live demonstrations. After those lectures, trainees are divided into small groups (4-6 persons) and get hands-on trainings moving between 3 different stations (liver, pancreatobiliary, GI-tract). It's very tough task for trainers to assist every trainee on how to visualize the target organ within the limited time (5-6 minutes per person) and have them feel satisfied with those sessions.

In addition to the development of trainers (facilitators) and standardized textbooks, management of regional disparities and expenses are key issues which need to be dealt with.

# 5. Action Taken by the Japanese Society of Gastrointestinal Cancer Screening (JSGCS)

In Japan, sonographers are primarily engaged in US cancer screening. Unlike doctors, sonographers require several kinds of lectures including anatomy and cancer screening in addition to technical skill trainings. In 2014, JS-GCS and JSUM published the Manual for Abdominal Ultrasound in Cancer Screening and Health Checkups. This manual explains important US findings for differential diagnoses and the categorized criteria for each US finding. Familiarizing themselves with this manual, sonographers are expected to improve their diagnostic accuracy and detect carcinomas in its early stage.

# 6. Conclusions

The current US training programs in Japan could be applied to those of the KASL. We should collaborate regarding further updates of the US training programs for trainees.

# Experience and Current Status of Ultrasonography Education Program for Residents

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# 전공의를 위한 복부 초음파 교육 현실 및 경험

정 재 연

아주대병원 소화기내과학교실

# 1. 아주대병원 소화기 초음파 검사실 운영 현황

- 1) 소화기내과 전용 초음파 검사실이 내시경실 바로 옆에 위치
- 2) 소화기내과에서 시행하는 복부 초음파검사는 상복부 초음파검사를 의미하며, 소화기내과, 소화기센터 및 간센터 소속 외과(위장관외과, 간외과, 췌담도외과), 소화기내과 협진을 시행한 타과 환자에서 처방. 이외의 타과는 영상의학과 초음파 검사를 처방함. 소화기내과도 필요시 선택적으로 영상의학과 초음파 검사 처방
- 3) 초음파 기기 2대와 간섬유화스캔(Fibroscan<sup>®</sup>) 1대를 구비: 가능한 당일 Fibroscan<sup>®</sup>을 이용한 검사는 9시 30분 전까지 마치고, 초음파 기기 2대를 이용하여 초음파 검사를 시행

# 2. 복부 초음파 교육 현황

- 1) 이론 교육 (3월-5월, 각각 1시간씩 이론 강의)
  - (1) 복부초음파 기기 사용법
  - (2) 정상 및 간질환 초음파 소견
  - (3) 췌담도 질환 초음파 소견
- 2) Live demonstration

내과 학생 실습기간인 2월-5월까지 매 2주마다 월요일 오전 초음파 검사시에 외래 환자 2-3명에 대해 live demonstration을 통해 초음파 영상 구현법에 대해 설명

- 3) 소화기 연수강좌 프로그램(연 1회)에 복부초음파 세션 포함 ± 핸즈온 코스
- 4) 초음파실에 4년차 내과전공의(2019년부터는 3년차)를 한 명씩 배정하여 한달 동안 초음파 검사 참여. 스 케쥴 관리는 4년차 자체적으로, 현재 회진파트와 상관없이 일정 조정

# 3. 복부 초음파 실습 내용

1) 4주 동안의 교육 내용

- 1주차: 초음파 기기 사용법 및 기본 조작법, 좋은 영상을 얻기 위한 환자의 협조 및 자세 터득, 복부 기본 스캔 법, 병변과 artifact 구별
- 2주차: 정상 간의 해부학적 구조, 담낭, 신장, 비장 영상 구현

3주차: 췌장 및 CBD 영상 구현

4주차: 초음파검사 실행가이드라인의 모든 영상 구현

# 2) 외래 환자: 흔한 양성 병변 및 간질환 초음파 소견 습득

Diffuse liver disease, fatty liver, liver cirrhosis, hepatic cyst, hemangioma, GB stone, GB polyp, GB adenomyomatosis, renal cyst, renal stone 등

# 3) 입원 환자: 악성 병변 및 급성 담도계 질환, 복수 등 소견 습득

Hepatocellular carcinoma, 간암의 TACE 후 소견, bile duct cancer, CBD stone, cholecystitis, ascites (marking for ultrasound-guided paracentesis)

# 4. 초음파 검사 실제 과정

- 초음파실에 있는 2대의 초음파 기기에 각각 전공의와 전임의가 먼저 검사를 시작하며, 1차 검사 후 당일 담
  당 스탭이 확인 검사를 시행함
- 전공의 / 전임의가 검사 전 EMR로 환자 파악
  파악 사항: 주치의, 초음파 시행 이유, 마지막 영상 검사 소견(초음파 또는 CT)
- 2) 전공의 / 전임의가 먼저 검사를 시행한 후 당일 초음파실 담당 스탭이 확인검사를 할 때 사전 파악한 사항 및 전공의 / 전임의가 1차 검사로 파악한 검사소견을 구두로 기술
- 3) 담당 스탭이 검사 후 최종 검사 결과를 구두로 기술
- 4) 전공의 / 전임의가 초음파검사 결과지 작성. 스탭이 처음부터 시행한 경우는 스탭이 결과지 작성

# 5. 초음파실 숙지사항(전공의 / 전임의 교육용)

- Probe를 소중히 다룰것
  Probe가 바닥에 떨어지지 않게 주의할 것. 망가지면 수리 혹은 교체 비용이 고가이므로 항상 probe 거치 대에 잘 꽂아 놓아야 함. Probe를 환자 몸 위에 올려놓고 자리를 뜨지 말 것
- 2) 환자에게 예의를 지킬 것
  "제가 먼저 보고 교수님이 한번 더 확인하실 겁니다"라고 미리 고지하면 환자가 덜 불안해 함. 환자 앞에서
  "잠 모르겠다" 등의 얘기를 할 때는 신중하게 할 것. 환자가 항상 대화를 듣고 있다는 사실을 잊지 말것
- 3) 환자 확인하기 환자 이름 확인 및 복부 초음파 안내장 이름과 초음파 기기 환자 이름이 같은지 확인. 초음파를 시행한 환 자의 안내장은 옆에 따로 두어 혼동되지 않도록 할 것. 절대 결과지가 바뀌지 않도록 주의할 것
- 4) 초음파 관련 서적이나 동영상 등을 통해 사전에 공부를 하고 검사에 참여할 것

# Role of Artificial Intelligence for Ultrasonography Practice and Training in Future

## Jeong Won Ryu

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기계학습 분야는 1950년대 인간의 신경세포의 기능을 모사해서 Perceptron이 개발된 이래로, 대규모 데이터베이스를 활용 한 추론 엔진과 인공 신경망으로 인공지능에 대한 연구가 진행되어 왔다. 곧, 인공지능이 완성될 거라는 부푼 기대로 50년에 걸친 연구를 수행해 왔지만, 필기체 인식 정도의 단순 기능만 가능하고 2000년대 초반까지는 큰 진전이 없는 인공지능의 겨 울에 머물러왔다. 최근 10년 동안, 제프리 힌튼 등의 선구자들의 연구에 힘입어 인공 신경망 중에서 특히, deep learning 이 라 불리는 다층 신경망에 대한 연구가 급속도의 진전을 이루어 의료 영상 진단, 로봇, 자연어 처리 등 많은 분야에서 두각을 보 이고 있다. 이러한 기계 학습의 전반적인 역사와, 지도학습, 비지도학습, 강화 학습 그리고, 진화 학습 등의 대표적인 인공지능 알고리즘을 설명한다.

현재까지 Fundoscopy, CT, X-ray, Mammo, 초음파 등의 의료 영상 분야에 적용된 인공지능의 사례를 설명하고, 초음파 분야에 있어서 인공지능의 적용 가능성을 살펴본다.

# Current Changes of National Health Insurance System Policy for Reimbursement of Ultrasonography

#### Hyung Joon Kim

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# 상복부 초음파 보험 급여화 관련 국가 건강보험 정책의 최근 변화

# 김형준

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The reform plan, an election pledge of President Moon, features health insurance coverage for all treatments and medications \_ except for cosmetic surgery \_ including charges for MRIs, ultrasound, hospital room and nursing care, which are not covered by the current formula.

Basically, Moon Jae-in Care is necessary for the improvement of medical services and the guarantee of the people's rights to full health care. Even though insurance fees are lower than the OECD average, the medical expenses not covered by the insurance are almost double the OECD cost. The state-led insurance plan will also cover costs of abdomen ultrasonography in this April. The aim of this article was to review the current changes of national health insurance system policy for reimbursement of ultrasound.

작년 8월 정부는 의료비 부담을 낮추고 고액의료비로 인한 가계부담을 줄이기 위한 "건강보험 보장성 강 화대책"을 발표하였다. 정부는 그간 건강보험 혜택을 확대하기 위해 지속적으로 노력해왔지만, 건강보험 보 장률이 지난 10년간 60% 초반에서 정체되어 있는 등 국민이 체감하는 정책효과가 미흡한 것이 이번 대책 을 발표하게 된 배경이었다고 밝혔다. 우리나라는 건강보험이 적용되지 않는 비급여의 비중이 높아, 국민들이 직접 부담하는 의료비가 선진국에 비해 매우 높다. 정부 발표에 의하면, 가계직접부담 의료비 비율은 36.8%로 OECD 평균(19.6%) 대비 1.9배이며(2014년 기준), 멕시코(40.8%)에 이어 두 번째로 높은 수준이다. 이는 결국 중증질환으로 인한 고액 의료비 발생 위험에 대비하는 책임이 많은 부분 개인에게 맡겨져 있다고 판단하여 정부는 보장성 강화대책을 수립하여 30.6조원을 투입하고, 의료비 부담에 대한 국가책임을 강화할 계획이다. 이번 대책은 이전과 달리 '비급여의 점진적 축소'가 아니라 '의학적으로 필요한 비급여를 완전히 해소'하는 전환을 추진한다. 미용, 성형 등 일부를 제외하고 모든 의학적 비급여는 신속히 급여화하되, 다소 비용·효과성 이 떨어지는 경우는 본인부담을 차등 적용하는 '예비급여'로 건강보험에 편입·관리할 예정이다. 그 일환으로 MRI, 초음파 등 치료에 필수적 비급여는 모두 급여 또는 예비급여를 통해 급여화('17-'22)하고 미용·성형 등 치료와 무관한 경우에만 비급여로 남는다. 이에 2018년 4월1일부터 상복부초음파 검사를 필두로 초음파 검사 가 2020년까지 단계적으로 전면 급여화될 예정이다. 간·담낭·담도·비장·췌장의 이상 소견을 확인하는 상복부 초음파 검사는 그간 4대 중증질화(암, 심장, 뇌혈관, 희귀 난치) 의심자 및 확진자 등만 제한적으로 보험 적용이 됐다. 하지만, 이번 급여화 확대로 B형·C형간염, 담낭질환 등 상복부 질환자 307만여 명의 의료비 부담이 평균 6-20만원에서 2-8만원 수준으로 경감될 것으로 전망된다.

상복부 초음파는 일반적으로 상복부 질환이 의심될 경우 검사하는 일반 초음파와 간경변증, 간세포암, 간이 식 등 중증환자 상태를 검사하는 정밀 초음파로 구분된다. 즉, 일반 초음파는 의사의 판단 하에 상복부 질환자 또는 의심 증상이 발생해 검사가 필요한 경우 보험이 적용되고, 정밀 초음파는 만성간염, 간경변증 등 중증 질환 자에 대해 보험이 적용된다. 정밀 초음파는 간세포암종 또는 악성 종양 환자 중 간 전이 의심, 간 이식 수술 전· 후 상태 평가(이하 기존 급여대상자), 간경변증, 만 40세 이상 만성 B형 또는 만성 C형간염 환자 등에서의 간암 감시검사를 대상으로 한다. 이후 새로운 증상이 있거나, 증상 변화가 없더라도 경과 관찰이 필요한 고위험군 환 자의 경우 추가 검사에 대해서도 보험이 적용된다. 고위험군 환자는 간경변증, 만 40세 이상 만성 B형 및 만성 C형간염, 담낭용종 고위험군 환자 등이다. 그 밖의 단순한 이상 확인이나 처치 시술에 보조되는 단순 초음파는 소수의 경우만 실시돼 사회적 요구도가 낮고 의학적 필요성 판단이 어려운 점을 고려해 본인부담률 80%를 적용 한다. 또한 급여화 이후 6개월-2년간 상복부 초음파 검사 적정성을 의학계와 공동 모니터링하고 필요 시 보완 대책을 마련해 나갈 예정이다.



Figure 1. 초음파 급여화 계획

#### Table 1. 등재 비급여 연도별 해소계획

추진연도	주요 분야 대상	예시
'17-'18년	노인, 아동, 여성 등 취약계층	·신경인지기능검사, 선천성 대사이상 선별검사 등
'19년	만성·중증질환(간질환)	·다빈치 로봇수술, 만성질환 교육상담료 등
'20년	안과질환·기타 중증질환	・눈의 계측검사(백내장), 폐렴균┌HIV 현장검사 등
'21-'22년	척추·통증 치료	• 대뇌운동피질자극술 등

#### Table 2. 상복부 초음파 급여 고시

#### 세부인정사항

 상복부 질환이 있거나 의심되어 <u>의사가 직접 시행한 경우</u> 다음과 같이 요양급여함. 다만, <u>의사가 동일한 공간에서</u> 방사선사를 실시간으로 지도, 진단하는 경우 포함

가. 산정요건

(가) 일반 또는 (나)정밀초음파: 다음의 영상을 획득, 검사의가 판독소견서를 작성 보관. 표준영상의 범위를 아래와 같이 권고, 제한적 초음파는 문제되는 부위 위주로 영상을 획득, 판독소견서를 작성·보관.

1) 표준영상의 범위

가) 일반

간우엽의 횡스캔, 늑간스캔, 간좌엽의 종스캔, 횡스캔, 간정맥의 늑간하 스캔, 간우엽의 상부, 우간하부와 우측신장피질의 관상면 스캔, 담낭의 장축, 간외담관의 종스캔, 비장의 장축스캔, 췌장두부, 체부·미부의 횡스캔

나) 정밀

표준영상과 우간문맥을 포함한 간우엽의 늑간스캔과 우간정맥을 포함한 간우엽의 늑간스캔, 좌우간문맥 분지의 횡스캔 포함 2) 판독소견서

가) 인적사항, 검사명, 일시, 판독의사(면허번호), 검사소견, 결론, 판독일시, 의료기관명칭

나) 간실질의 에코, 간종괴 유무, 담낭이상 여부, 담관확장 여부, 비장종대 여부, 췌장이상 여부, 이상이 있는 경우 세부내용 기술.

#### 나. 산정방법

1) 상복부 질환 경과관찰 시 인정, 산정횟수 초과하는 경우 본인부담률 80%

가) 진단을 위하여 시행한 경우 일반1회, 다만, 30일 초과하고 최초 진단과 다른 질환이 의심되어 시행한 경우에는 별도 산정 나) 간경변증, 만40세 이상 만성 B형간염, 만40세 이상 만성 C형간염 환자, 간암감시검사 시행 경우 -정밀 연 2회

다) 경과관찰이 필요한 <u>담낭용종 -일반 연 1회</u>

<u>2) 진단초음파 영상과 비교목적으로 시행 시 제한적 초음파를</u> 산정하며, <u>초회부터 본인부담률 80%적용.</u>

- 3) <u>일부 부위 확인이나 장기크기 측정</u> 등을 시행한 경우 <u>단순초음파</u> 산정, 초회부터 본인부담률을 80% 적용. 다만, 동일 날, 동일 목적으로 수회 시행하더라도 해당 항목의 소정점수를 1회 산정함.
- 2. 암, 심장질환, 뇌혈관질환, 희귀난치성 질환 대상자 및 의심자, 「초음파 검사의 급여기준」을 우선 적용하되, 「초음파 검사의 급여기준」에서 별도로 정하지 아니한 경우는 「상복부 초음파 검사의 급여기준」을 적용함.

#### Table 3. 상복부초음파 검사 급여화 관련 Q&A

□ 급여대상 및 급여범위

질의	답변
<u>'의사가 동일한 공간에서 실시간으로 방</u>	의사는 방사선사와 물리적으로 동일한 공간에 입회하여 실시간으로 지도하고 환자
<u>사선사의 촬영</u> 하는 영상을 동시에 보면	상태를 진단하여야 함(모니터 등 다른 공간에서의 진단 및 지도는 요양급여 불가)
서 지도하고 진단하는 경우'의 의미	의사는 검사의 지도 및 실시간으로 진단하고 판독한 의사임.
<u>건강검진으로</u> 시행한 초음파검사에서 질	진료의사가 상복부 질환이 의심하여 시행한 것이 아니고, 환자의 희망에 의하여
환이 진단된 경우	시행한 건강검진이므로 비급여임.

#### □ 산정요건

질의	답변								
			해보하저	산정요건					
	구분		에누익석 부위확인	영상	판독 소견서	기타			
진단 제한적	진단 초음파	일반, 정밀	전부 확인 (간, 담낭, 담도, 비장, 췌장)	5개 장기 영상 모두 구비	별도 구비	표준 영상항목 시행토록 권고			
단순초음파의 구분	진단 초음파	제한적	문제되는 부위 위주로 확인	문제되는 부위 위주로 구비	별도 구비	진단초음파 이후 경과관찰			
	기본 초음파	단순 ( /  )	일부부위 확인	필요시 구비	진료기록부등 검사 결과 기재				
판독소견서는 진료기록부에만 기재해도 수가산정 가능한가?	제한적초음파를 포함한 진단초음파는 판독소견서를 별도로 작성하고 보관하여야 함.								
# □ 산정방법

질 의	답 변
단순초음파 산정방법	(단순초음파(1)) 진찰 시 보조 역할을 하는 초음파 ① 수술 또는 시술 후 혈종 확인 ② 종물 또는 종양 크기 확인 ③ 수술부위 피부 위치 표시 ④ 장기크기 측정 등(ex 비장크기 측정 등)
	(단순초음파(II)) ① 분해부학적 부위 상태를 모두 확인하는 것이 아니라, 일부만을 확인하기 위하 여 시행 ② 처치·시술 진행 시 보조역할로 시행하는 초음파 - 천자부위 위치확인 - 카테터 삽입부위 위치확인
도플러 가산은 언제 산정하나?	간 이식 전·후 상태 평가, 간 또는 췌장 종양의 상태 확인, 혈관기형이 있거나 출혈 이 의심되어 도플러 검사를 시행하는 경우 소정점수의 10%를 가산함.
'상복부 질환이 의심되어 진단을 위해 시행한 경 우 상복부 진단초음파-일반 1회의 의미	상복부 질환이 의심되는 에피소드당 1회 급여 인정을 의미함. 다만, 30일 이내에는 다른 증상으로 내원하더라도 같은 에피소드로 간주. * 평생 또는 연간 개념 아님
30일 이내에 초음파(일반)를 다시 시행하는 경우	또는 일반의 제한적초음파로 산정하며, 본인부담률은 80%로 적용.
<u>2주 전</u> 우측 상복부 통증으로 초음파시행 후 담 석으로 진단 받은 환자가 고열, 우측 상복부 통증 으로 <u>내원하여 담낭염이 의심되어 시행한</u> 경우	<u>30일 이내에 내원하여 다른 질환을 의심하여 시행하더라도 본인부담률 80%로</u> <u>적용함.</u>
<u>4개월 전 우</u> 상복부 통증으로 초음파 시행 후 담 석으로 진단 받은 환자가 담낭염이 의심되어 초 음파(일반) 시행한 경우	<u>30일 이후</u> 다른 질환이 의심되어 시행한 경우 <u>급여함.</u>
초음파검사를 시행한 진료의사의 <u>의학적 판단</u> <u>에 대한 기재 필</u> 요여부	진료의사의 <u>의학적 판단 근거는 진료기록부 또는 판독소견서에서 확인</u> 되어야 함.
고시 시행일('18.4.1.) 이전 상복부 질환으로 진 단받아 비급여로 초음파 검사비용을 부담하던 환자가 경과관찰을 위해 '18.4.1.이후 초음파 시 행시	고시 시행일을 기준으로 간경변증, 만40세이상 만성 B형감염, 만40세이상 만성 C 형간염 환자의 간암감시목적으로 시행하는 경우와 담낭용종 환자는「초음파검사의 급여기준」따르며, 이외의 질환으로 경과관찰을 하는 경우에는 1회 급여, 이후는 본 인부담률 80%로 적용
	 산정요건 <sup>*</sup> 에 따라 진단초음파 또는 진단의 제한적초음파, 단순초음파로 산정하며, 본인부담률은 80%로 적용함.
<u>연단위 횟수</u> 적용 기준	<u>매년 1월 1일부터 12월 31일까지</u> 로 함.

질 의	답 변
<u>40세 미만의 간경변증 환자가 간암감시검사</u> 를 시행한 경우	간경변증 환자는연령구분 없이 <u>초음파(정밀) 연 2회 급여</u> 하며, 횟수를 초과하여 간암감시검사가 필요한 경우 본인부담률 80%로 적용함.
<u>40세 미만의 만성 B형 또는 C형간염 환자</u> 가 초 음파 시행 시	40세 미만의 만성 B형 또는 C형간염 환자가 초음파검사가 필요한 경우 <u>초음파(일반)</u> 1회 급여하며, 경과관찰이 필요한 경우에는 본인부담률 80%로 적용함.
자가면역성 간염 같은 희귀난치 환자경과관찰 시	자가면역성 간염은 희귀난치성질환자에 해당되며, 「초음파검사의 급여기준」에 따라 급여함
<u>간경변증으로 간</u> 초음파(정밀)을 정기적으로 받 는 환자가 <u>복통으로 담낭염이 의심되어 상복부</u> <u>초음파 검사 시</u>	간경변증의 간암감시목적으로 시행한 경우 (정밀) 대상이나, 이외 질환이 의심되어 시행한 초음파는 (일반) 으로 산정함.
<u>복수를 천자하기</u> 위해 천자 부위 위치 확인	간질환 으로 인해 발생한 복수천자 시행 시 보조역할을 한 초음파검사는 단순초음 파(II) 본인부담률 80%로 산정

# 결 론

금년에 시작한 상복부 초음파급여화는 합리적인 안이 도출되기 전에 먼저 시행된 아쉬운 점이 있다. 하지만, 급여화 이후 6개월-2년간 상복부 초음파 검사 적정성을 의학계와 공동 모니터링하고 필요 시 보완 대책을 마련 해 나갈 예정이다. 향후, 제한된 의료재정으로 국민건강을 위하여 상복부 초음파의 급여화를 어떤 방식으로 정 착을 하고 보상을 할 것일지 의료계와 정부, 관련 단체들의 지혜를 모아야 하는 것이 현 시대의 상생을 위한 코 드일 것이다.

The Liver Week 2018

DAY 3: Saturday, June 16, 2018 (08:30-09:50) EAST TOWER / ROOM C [2F]

# Educational Program of Abdominal Ultrasonography (USG) Practice (\*K)

Chairs: Young Soo Moon (Inje Univ.) Young Seok Kim (Soonchunhyang Univ.)

# Optimal Scanning of Abdominal Ultrasonography and Trouble Shootings

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#### 김 문 영

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#### Ⅰ. 초음파 검사 준비

초음파 검사는 장내가스, 환자의 체형 및 호흡조절 등 환자 요인에 의하여 좋은 영상을 얻는데 제한을 받게 된 다. 그러므로 검사자는 환자의 체위, 호흡조절, 기기의 조작, 다양한 스캔법의 활용을 통하여 좋은 영상을 얻기 위해 노력하여야 한다.

마른 체형의 환자일 경우에 탐촉자와 피부의 원활한 접촉을 위해 충분히 젤리를 사용하거나 곡선형의 탐촉자 를 사용하는 것이 도움이 된다. 비만한 환자일 경우에는 가급적이면 여러 방향에서 스캔을 하면서 압박을 가하 여 탐촉자와 관찰하고자 하는 병변의 거리를 최소화하며, 심부를 관찰할 때는 초음파의 주파수를 낮추어 관찰 한다.

경우에 따라 환자를 좌측와위를 취하게 하거나 심호흡을 하게 함으로써 간을 늑골 아래로 내려오게 하여 관찰 을 용이하게 할 수 있다. 또한 간경변증 등의 질환으로 간이 위축된 경우에는 좌측와위나 우측와위를 취하게 하 는 것이 도움이 될 수 있다.

초음파에 방해가 되는 장내가스를 제거하기 위해 적절하게 탐촉자를 압박하여 사용하여야 하며 sweep, tilting, rotation등의 다양한 방법으로 탐촉자를 움직임으로써 간초음파 시 사각지대를 최소화 할 수 있다. 환자에게 좌위 혹은 반좌위를 취하게 하여 가스를 이동시키거나, 간좌엽이나 비장을 음향창으로 이용하여 촬영할 수 있다. 폐음영에 가려져 관찰에 제한이 있는 S8 부위의 경우 환자에게 복식호흡을 하게하면 횡격막이 아래로 내려오게 되어 관찰에 도움이 된다.

또한 하모닉 영상을 사용하거나 게인, SGC (sensitivity gain control) 등의 기기 조작을 통하여 영상의 질을 향상시킬 수 있다.



그림 1. Couinaud 분류에 의한 간의 해부



그림 2. 간의 초음파 모식도

# II. 간의 정상 해부학 및 스캔법

간의 간엽과 구역을 나눔으로써, 간에 국소병변이 생겼을 때 위치, 범위에 대한 기술이 용이하고, 다른 영상 진 단법 간의 비교 및 추적검사 때의 전, 후 소견의 비교에 유리하다.



그림 3. 실제 초음파 영상

# 1. 간엽과 구역(Hepatic Lobe and Segment)의 해부

1) Couinaud의 방식에 의한 구역 구분

1954년 Couinaud가 발표한 간문맥(portal vein)과 간정맥(hepatic vein)의 주행을 기본으로 간엽과 구 역을 구분하는 방법이 널리 쓰인다. 간문맥은 우문맥(RPV)과 좌문맥(LPV)으로 나누어지고, 우문맥은 우전 문맥(RAPV)과 우후문맥(RPPV)으로 나눈다. 문맥은 간구역의 중심(intrasegmental=within segment)으 로 주행한다. 간정맥은 우간정맥(RHV), 중간정맥(MHV), 좌간정맥(LHV)이 있고, 중간정맥은 간을 우엽과 좌 엽으로 나누며, 우간정맥은 간우엽을 전구역(anterior segment)과 후구역(posterior segment)으로, 좌간 정맥은 간좌엽을 내측구역(medial seg.)과 외측구역(lateral seg.)으로 나눈다. 즉, 간정맥은 간구역의 사이 (intersegmental=between segment)로 주행하여 간구역을 나눈다(표1).

표	1	

Couinaud		Anatomic segment	
I(S1)	Caudate lobe	Caudate lobe	
II(S2)	Left lateral cogmont	Left lateral superior segment	
III(S3)		Left lateral inferior segment	
IV(S4)	Left medial segment	Left medial segment	
V(S5)	Right antorior cogmont	Right anterior inferior segment	
VIII(S8)		Right anterior superior segment	
VII(S7)	Right postarior cogmont	Right posterior superior segment	
VI(S6)		Right posterior inferior segment	

2) 인대(ligament)와 열(fissure)에 의한 구역 구분

간은 인대와 열에 의해 구역구분이 된다. 인대와 열은 초음파 상에서 고에코의 선상 구조로 보인다(표 2).

₩2

열(Fissure)	구분	참고		
주엽열(main lobar fissure)	우엽과 좌엽구분	transverse scan에서 혜성꼬리 모양, 담낭의 위치		
간원삭(ligamentum teres)	S3과 S4구분	umbilical vein의 흔적으로 falciform ligament로 연결		
정맥관삭(ligamentum venosum)	S1(caudate lobe)과 S2구분	매우 짧아서 간문부와 분리되어 보이지 않음		



그림 4. 정맥관삭



그림 5. 간원삭

# 2. 간내 맥관 해부

간문부에서는 간동맥(hepatic artery), 간문맥(portal vein), 담관(bile duct) 즉, portal triad와 간정맥 (hepatic vein)의 4가지 관상구조물(tubular structure)이 주행하고 있다. 하지만 정상 간내에서 간동맥과 담 관은 거의 관찰이 어렵다. 그래서 초음파 검사를 하면서 가장 중점을 두어야 하는 관상구조물은 간정맥과 간문 맥이라 하겠다.

간정맥은 횡경막 하에 있는 하대정맥(IVC)으로 유입이 된다. 그래서 횡격막으로 갈수록 직경은 증가되고 호흡 에 의해서 직경의 변화가 일어나는 것을 볼 수 있으며(valsalva법 후 직경 증가), 혈관벽의 에코가 없다.

하지만 간문맥은 초음파상 혈관벽의 에코가 강한(hyperechoic) 구조물로 나타난다. 지방간(fatty liver)이 있 을 시에는 상대적으로 문맥혈관벽의 에코가 감소하게 보인다. 그리고 간문맥은 간문부(portal hepatis)에서 간 으로 유입되므로 간문부로 갈수록 직경이 증가된다.

# 3. 정상 간의 에코정도(Echo patterns)

1) 우측 신장과 비교 : 간의 에코 정도는 신장의 실질과 같거나 약간 높다.

초음파상에서 신장의 실질이라 함은 흔히 피질(cortex)을 가지고 이야기 한다. 실제적으로 신장실질은 피질 (cortex)과 수질(medullar)로 나누어지는데, 초음파 상에서 피질과 수질의 에코정도가 다르다. 피질은 수질보 다 고에코이고, 수질은 신동(renal sinus)의 주변으로 저에코 구조물로 묘사된다.

2) 비장과 비교 : 비장과 같거나 증가된 에코(iso or hyperechoic)로 관찰된다. 비장은 병변이 많지 않은 장기이므로 비교하기가 쉽다.

3) 췌장과 비교 : 췌장과 같거나 약간 낮다.

췌장은 피막이 없는 장기(noncapsule)로서 외부 요인에 의해 내부에코의 변화가 다양하다. 고령, 알코올 환자나 비만인 경우에 상대적으로 고에코 소견을 보인다.



a: 신장과 비교

b: 비장과 비교 그림 6. 정상 간의 echo patterns c: 췌장과 비교

# 4. 간의 기본적 스캔 방법

초음파는 탐촉자의 빔이 통과하는 장기의 단면을 묘사하게 되는데, 장기는 3차원적이다 보니 여러 개의 스캔 방향을 가지고 3차원적인 장기의 모습을 영상화하는 노력이 필요하다. 그리고 어느 장기 검사를 하든지 두 방 향 이상에서 검사를 하는 습관도 중요하다. 간의 기본적 스캔방법 중에는 횡단주사(transverse scan), 종단주사 (longitudinal scan), 늑골궁하주사(subcostal scan), 늑간주사(intercostal scan)가 있다.

#### 1) 횡단주사(Transverse scan)

간좌엽(Lt. lobe)을 검사하는 방법으로 주로 심와부(epigastrium)에 탐촉자를 위치시켜 몸의 장축과 수직이 되도록 하는 검사이다.



그림 7. Transverse scan

2) 종단주사(Longitudinal scan)

횡단주사에 수직으로 탐촉자가 위치하는 검사법으로 간좌엽의 첨부(margin)을 묘사하여 간좌엽 종대를 평가 하기에 좋은 검사법이라 할 수 있다.



그림 8. Longitudinal scan

#### 3) 늑골궁하주사(Right subcostal scan)

탐촉자가 늑골궁하(subcostal margin)에 위치하는 검사법으로, 간우엽을 묘사하는 방법이다. 탐촉자의 각도 를 머리쪽(cephalad)으로 주면 간정맥이 보이고, 각도를 다리쪽(caudal)으로 주면 간의 하방향이 보인다. 이렇 게 탐촉자의 각도를 머리쪽, 다리쪽으로 달리 주면서 3차원적인 장기의 구조물을 묘사할 수 있다. 또한 우간문 맥(Rt. main PV)을 찾아 S5-S8 까지의 구역을 관찰할 수 있다.



그림 9. Right subcostal scan

#### 4) 늑간주사(Right intercostal scan)

간우엽을 묘사하는 영상으로써, S5-S8 까지의 간구역을 관찰할 수 있다. 그리고 이 주사 방법은 담낭의 목 (neck)부분을 묘사할 수 있는 방법이기도 하다.



그림 10. Right intercostal scan

# Ⅲ. 담낭(Gallbladder)

#### 1. 담낭의 정상 해부

담낭은 간 우엽과 좌엽 사이에 위치하는 타원형의 장기이며 간장과 함께 복막에 싸여 있고 담낭의 약 3분의 1은 결합조직에 의해 간 하면의 담낭와에 고정되어 있다. 담낭의 크기는 장경이 8 cm 이하, 단경이 4 cm 이하, 용량이 30-50 ml 정도이다. 담낭벽의 두께는 3 mm 이하이나 담낭 경부의 두꺼운 부분에서는 정상에서도 3 mm 정도가 된다. 담낭벽은 조직학적으로 점막층, 근층, 장막층의 3층으로 되어있으며 담낭관의 길이는 3-4 cm이고 나선형의 모양을 취하고 있다.

담낭의 상방에는 간의 우엽, 우엽문맥, 중간 간정맥 등이 있으며 후방에는 우측신장이 하면과 내측으로는 횡 행 결장, 십이지장구부 및 위전정부가 위치하여 이들 위장관의 공기 음영이 담낭의 초음파 관찰을 방해하기도 한다. 담낭을 저부의 정점에서 담낭관(cystic duct) 이행부까지 장축으로 3등분하면 저부(fundus), 체부(body), 경부(neck)로 나눌 수 있다. 담낭관은 간외담관에 합류하여 총담관(commom bile duct)을 형성한다.

June 16 (Sat)



그림 11 . Anatomy of GB

# 2. 담낭의 기본적 스캔방법

실시간으로 관찰이 가능한 초음파는 담낭 질환의 일차적 선별검사로 널리 쓰이고 있다. 담낭 초음파는 최소한 6시간 이상 금식한 후에 검사를 시행해야 담낭이 충분히 팽창되어서 정확한 관찰이 가능하다. 환자는 앙와위 자 세에서 검사를 시작하며, 좌측와위로 눕히면 늑골에서 내측으로 이동하여 주름을 펴지게 하고 가스를 밀어내는 효과가 있어 더 잘 보이게 할 수 있다. 또한 숨을 깊게 들이마신 후 참게 하거나 앉는 자세가 담낭이 아래로 내려 오게 하여 도움이 될 수 있다.

# 1) 우늑골궁하 스캔(Rt. subcostal scan)

우늑골궁하 스캔은 심호흡기에 스캔하는 것이 원칙이지만 적당히 호흡의 정도를 변화하면서 스캔할 필요가 있다.



그림 12. Subcostal scan

2) 우종단 스캔(Rt. longitudinal scan) 우종단 스캔은 복부 중앙에서 우측으로 탐촉자를 이동시키면서 스캔한다.



그림13. Longitudinal scan

담낭은 우측중앙쇄골선에서 간하면에 위치하며 경부는 문맥우측분지에 인접하여 위치한다.

#### 3) 우늑간스캔(Rt. intercostal scan)

우늑간 스캔은 제 7늑간을 중심으로 각 늑골사이를 통하여 담낭을 관찰한다. 이때는 호기상태가 도움이 되며 담낭의 경부가 잘 관찰된다. 또한 비만한 환자나 간경변으로 간이 위축된 환자의 담낭 관찰에 도움이 된다.



그림 14. Intercostal scan

#### 3. 담낭의 정상 초음파 소견

담낭벽은 규칙적이고 평활하며 경계가 뚜렷하다. 정상 담낭벽의 두께는 3 mm이하이며 담낭벽은 식사를 한 후에는 4-7 mm 로 비후되어 내강쪽에서 고.저.고에코의 3층 구조를 보이기도 한다. 담낭은 담즙으로 차있어 무 에코 소견을 보인다. 어떤 경우에는 담낭의 저부가 주름이 잡힌 'Phrygian cap'으로 담낭내강을 충분히 검사하 기가 힘들다. 이때는 환자 체위를 바꿔서 검사하면 충분한 검사가 이루어지는 경우도 있다. 굴곡된 담낭은 마치 담낭 내에 격벽이 존재하는 것처럼 보이기도 하며 골곡의 튀어나온 부분이 담석처럼 보이기도 한다. 이때는 종 단 스캔이나 횡단스캔을 하면 감별이 가능하다.

#### 4. 정상 담낭에서 보이는 허상

1) 반향허상(reverbration artifact)

복벽 등에 의한 반사에코 때문에 담낭내강에 생긴 줄무늬허상으로 스캔방향이나 스캔면을 바꾸어야 한다.





#### 2) 측엽허상(Side lobe artifact)

결장이나 십이지장내 가스가 담낭 내에 측엽에 의한 허상을 만든다. 이때 측엽에 의한 허상을 담즙앙금으로 오인할 수 있다. 이때는 탐촉자를 부채살 모양으로 조금씩 움직이면서 실시간으로 관찰하는 것이 필요하다.



그림 16. 측엽허상

3) 담낭경부에서 단면상의 두께에 의한 허상

초음파 영상은 두께가 3-5 mm의 조직 절편으로부터 얻어 진 에코를 두께가 없는 한 화면에 압축하여 맺어놓은 상으로 초음파 화상의 두께는 진동자로부터의 거리에 따라 다소 변화 한다. 이와 같이 초음파 영상은 일정 공간내의 각 점이 동일 평 면 내에 있는 것으로 나타나게 되기도 하고 탐촉자에서 멀리 있는 동일거리내의 두 개의 선상 구조가 1개의 선으로 나타나 기도 한다.

### 4. 초음파에서 담낭이 잘 보이지 않는 경우

- 1) 담낭 내강을 채우는 담낭의 질환
- 2) 음식물 섭취 후
- 3) 담낭관 상부의 담도 폐쇄
- 4) 선천성 기형 또는 이소성담낭
- 5) 급성 간염 같은 간기능 장애를 가져오는 질환
- 6) WES (wall-echo-shadow) 징후(그림 18)

# Ⅳ. 담관(Biliary trees)

#### 1. 담관의 해부

간내 담관은 문맥(portal vein)을 따라 거의 나란히 주행 한다. 좌우 간내 담관은 간문부(porta hepatitis)에서 합류하 여 총간관(common hepatic duct)이 되고 총간관은 더욱 하 방으로 내려와서 담낭관과 합류하여 총담관(common bile

duct)이 되어 췌장두부내를 지나 십이지장 유두부(ampulla of Vater)로 개구된다. 좌우 간내담관 이하의 담관 은 문맥 복측의 다소 내측하방을 따라 주행한다. 초음파 검사에 의한 담관직경의 계측은 전후직경으로 간내 담 관의 2-3차 분지는 1 mm정도이고, 좌우간내담관은 2 mm 정도이며, 간외담관의 직경은 4 mm 정도이다. 담관 은 간문부 부근에서는 문맥의 전면, 즉 복측에 위치하지만 간좌엽의 문맥제부(umbilical portion)에서는 서로 교차하여 복측지(하지)는 문맥의 배측에, 배측지(상지)는 복측으로 주행하게 된다. 초음파 검사 상 문맥 좌지의 수평부(horizontal portion)와 나란히 주행하는 좌측간관을 측정하였을 때 4 mm 이하를 정상으로 볼 수 있다. 간내 담관계에서는 정상인에서도 관강구조를 잘 관찰할 수 있다. 젊은 정상인에서는 담관내강이 잘 보이지 않는 경우가 많으나 고령자가 되면 내강이 자주 관찰되는데 이는 전신적 변화에 따라 담도의 조직도 경화성 변화를 일



그림 17. 단면상의 두께에 의한 허상



그림 18. WES 징후

으킨 것으로 볼 수 있다. 따라서 간외 담관은 그 직경이 7 mm 이하 인 경우, 담낭절제술을 받은 경우 1 cm까지 정상범위로 본다.

#### 2. 담관의 기본적 스캔방법

간내 담관과 상부 총관은 앙와위에서 오른쪽을 조금 들어준 자세 나 좌측 측와위 상태에서 검사하며, 총 담관을 잘 관찰하기 위해서 는 배를 불룩하거나, 좌측사위를 하는 것이 좋다.

간내 담관과 간외담관의 상단부는 실시간 스캔장치로서 용이하 게 임의의 단층상을 얻을 수 있고 관상구조의 주행에 따라 추적 관 찰이 가능하다.

#### 1) 심와부 횡단스캔(Transverse scan)

간좌엽의 간내담관이 장축방향으로 나타나며 촤측간내담관과 좌 측문맥을 관찰할 수 있으며 담관과 문맥과의 초음파상 해부학적 위 치관계가 명료하여 간내담관의 확장유무의 진단에 매우 도움이 된다.

2) 우늑골궁하 스캔(Right subcostal scan)

문맥의 수평부를 관찰하여, 좌측 간내 담관을 관찰 할 수 있다.

#### 3) 우계늑부사 스캔(Right oblique scan)

우늑간에서 연속적으로 시행하면 주행에 따라 근위부 간외담관 (proximal extrahepatic duct)을 찾을 수 있는데, 근위부 간외담 관은 문맥과 나란히 주행한다.

이 영상은 총간관에서 췌장두부의 상부 총담관까지 간외담관을 분석하는 영상으로 간문맥의 늑골하사위영

그림 21. Right oblique scan

상에서 시작하여 췌장두부까지 간십이지장인대를 거쳐 스캔을 하 면 주문맥 앞쪽의 총간관과 총담관을 볼 수 있다. 이때 탐촉자를 90도 돌리면 총간관과 총담관을 길이방향으로 볼 수 있다.

#### 4) 우늑간 스캔(Right intercostal scan)

우늑간 스캔에서 우측문맥과 나란히 주행하는 우측간내담관을 잘 관찰 할 수 있으며, 우간내담관의 확장을 평가하는 영상이다.

#### 5) 췌두부 영상

원위부 총담관을 분석하는 영상으로 췌두부 뒤쪽으로 관찰되는

06/128 13Hz

그림 23. 췌두부 영상



그림 22. Right intercostal scan

CBD



그림 19. Transverse scan

그림 20. Right subcostal scan

CBC

원위부 총담관을 관찰한다.

# V. 췌장(Pancreas)

# 1. 췌장의 해부

췌장은 상복부에 비스듬히, 가늘고 길게 위치한 장 기로서 우측은 십이지장내측면(medial portion)과 접하고, 체부는 제 1 또는 제 2 요추 전방을 지나며 미부는 비장에 접하게 된다.

췌장은 두부, 경부, 체부, 미부로 구성되는데, 상장 간막정맥(superior mesenteric vein)이 두부와 체부 의 경계가 되며 상장간막정맥의 바로 앞에 위치한 부



그림 24. 췌장 병변의 놓치기 쉬운 부위

분이 경부이다. 체부와 미부는 척추의 좌측면을 기준으로 구분한다. 두부는 십이지장에 의해 우측면이 둘러싸여 있고 뒤쪽에는 하대정맥(inferior vena cava)이 있다. 구상돌기(uncinate process)는 상장간막정맥의 뒤쪽으 로 갈고리처럼 돌출한 조직이며 두부의 일부이다. 체부의 앞쪽에는 소낭(lessor sac)과 위의 유문부(pylorus)가 있다.

# 2. 췌장의 기본적 스캔방법

췌장은 긴 장기이므로 두부, 체부, 미부로 나누어서 췌장 전체를 검사한다. 췌장의 전면에는 위와 횡행 결장 등의 소화관이 있으므로 탐촉자로 압박하여 가스를 제거하거나 소화관 자체를 압박하여 밀어낼 필요가 있다. 또 체위변화를 하거나 호흡을 조절하여 소화관을 이동시키는 것도 중요하다. 먼저 숨을 들어 마신 상태에서 간 좌엽 외측구역의 횡행 주사를 시행한다. 탐촉자를 점차 아래쪽으로 이동시켜서 복부 대동맥위에 있는 상장간막 동맥의 횡단상을 관찰하고 그 복측에 비정맥이 횡방향으로 관찰되는 부위를 찾는다. 비정맥이 관찰되면 그 복 측에 췌장실질이 있다. 보통 체형의 피검자에서는 간의 배측에 췌장체부가 횡단상으로 보이고 고도의 마른 체 형의 피검자에서 간이 관찰되는 근방에 복벽 직하에서 보인다. 비교적 비만한 피검자에서는 간과 위의 횡단상이 관찰되는 하방에 보이므로 간과 위의 가스상이 보이지 않는 아래까지 탐촉자를 이동할 필요가 있다. 숨을 들여 마신 상태에서 잘 보이지 않는다면 숨을 편하게 쉬는 상태에서 같은 방법으로 탐촉자를 조작하여 찾는다.

초음파 검사 시 췌장의 미부와 두부의 하부, 구상돌기 부위를 놓치는 경우가 많다. 현실적으로 체부만 관찰하고 두부와 미부는 전혀 관찰하지 않는 검사자와 병원도 적지 않다. 췌장은 전장 15-16 cm길이로 가늘고 긴 장 기이므로 체부, 두부, 미부로 구분하여 관찰하는 것이 중요하다.



그림 25. 췌장 전체의 관찰

(SMA: superior mesenteric artery, IVC: inferior vena cava, Ao: aorta, CHA: common hepatic artery, SV: splenic vein, CHA: common hepatic artery, GDA: gastroduodenal artery)

# Ⅵ. 표준영상의 범위

2018년 보건복지부 고시에 의한 표준영상의 범위는 다음과 같으며 검사소견에는 간실질의 에코, 간종괴 유 무, 담관확장 여부, 담낭 이상 여부, 췌장이상 여부, 비장종대 여부를 포함해야 하며 이상이 있는 경우 세부내용 을 상세히 기술하도록 되어 있다.



1) 간우엽의 횡스캔



3) 우간정맥을 포함한 간우엽의 늑간스캔



5) 간좌엽의 종스캔



7) 간정맥의 늑간하 스캔



2) 우간문맥을 포함한 간우엽의 늑간스캔



4) 좌우 간문맥 분지의 횡스캔



6) 간좌엽의 횡스캔



8) 간우엽의 상부



9) 간외담관의 종스캔



11) 우간하부와 우측신장피질의 관상면 스캔



13) 췌장두부의 횡스캔



Educational Program of Abdominal Ultrasonography (USG) Practice (\*K)

10) 담낭의 장축



12) 비장의 장축 스캔



14) 췌장체부, 미부의 횡스캔

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# Differential Diagnosis of Liver Mass Detected by Ultrasonography

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복부 초음파는 비침습적이며 간단하게 진단적 검사를 시행할 수 있으며 조영제를 사용하지 않기 때문에 조영제 부착용이 있 는 환자나 신기능이 저하된 환자에서도 유용하게 사용된다. 간종괴는 이러한 초음파검사 중 종종 접하게 되는 중요한 소견 이며, 실제 일차적인 간 종괴의 발견 및 진단에 있어서 복부 초음파검사는 매우 유용하다. 간 종괴는 그 성상에 따라서 고형 (solid) 종괴와 낭성(cystic) 종괴로 나눌 수 있으며, 생물학적 특성에 따라 양성과 악성으로 분류할 수 있는데, 특히 양성과 악 성의 감별진단은 복부 초음파검사에서 매우 중요하다. 양성 종양은 고형 종괴로는 혈관종(hemangioma), 국소결절성과형성 (focal nodular hyperplasia), 간선종(hepatic adenoma) 등이 대표적이며, 낭성 종괴로는 단순성 간낭종(simple hepatic cyst), 간농양(liver abscess)과 간손상에 의해서 발생하는 간혈종(hepatic hematoma) 등이 있다. 악성 종양은 고형 종괴 로는 간세포암종(hepatocellular carcinoma), 간내담관암(intrahepatic cholangiocarcinoma), 전이성 간암(metastatic liver cancer) 등이 대표적이다. 복부 초음파검사만으로 간 종괴의 양성과 악성의 감별에는 제한이 있지만, 양성과 악성 간종 괴의 특징적인 복부 초음파 소견을 이해하면 복부 초음파의 간종괴 진단을 효과적으로 시행할 수 있다.

# Tips for Sonographic Diagnosis in Pancreatobiliary Diseases: Natural Course of Pancreatic Carcinoma and Ultrasound Scanning Maneuvers

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# 1. Introduction

As US is simple and less invasive, it is widely used for the mass screening. However, it can be difficult to visualize the entire pancreatobiliary system due to complicated anatomy, obesity and overlying gas. To pick up pancreatic carcinoma (PC) in early stage, we should know its natural course and US findings of high-risk individuals (HRI). We should also master not only basic scanning methods, but some special maneuvers especially for HRI.

# 2. Natural Course of PC and Important US Findings

PC is notorious for its poor prognosis and its dismal prognosis is considered as a result of late diagnosis in the natural course of PC. According to some analyses, it takes about 11.7 years from the initiating carcinogenesis until development of the parental clones, about 6.8 years to the development of metastatic subclones within the primary PC and about 2.7 years until death of the case. These results suggest we have a golden opportunity of a couple years to detect PCs in earlier stage.

US is expected to be a first-step imaging and play a key role in the diagnosis of PC. The targets of US are not only solid mass lesions, but US findings of HRI including main pancreatic duct (MPD) dilatation (duct diameter > 2 mm) and pancreatic cysts (size > 4 mm). Furthermore, the magnified image of high-frequency US transducers might detect localized stenosis of MPD, focal dilatation of branch ducts and faint hypoechoic area surrounding MPD. Those findings may correspond to the localized pancreatitis accompanied with the PC in situ.

# 3. Basic Scanning Methods

#### 3.1 Head

We usually employ both supine and left decubitus positions. Both the uncinate process and groove's area are pitfalls. The duodenum, extra hepatic bile duct (EHBD), superior mesenteric vein (SMV) and vena cava (VC) are useful landmarks. Since the angle of the head and the body is almost perpendicular, the probe should be rotated counterclockwise from the transverse to the longitudinal section. To trace the entire pancreatic head above the VC, you should move the probe downward to the transverse part of the duodenum. Furthermore, the uncinate process which lies posterior to the SMV should be scanned by the longitudinal section. To track the entire EHBD, the probe should be moved as if we are writing an inverse letter C in the left decubitus position.

#### 3.2 Body

We usually employ supine positions. The superior mesenteric artery, splenic vein, left adrenal gland and left kid

ney are good landmarks. As the pancreatic body is slightly oblique from the lower right to the upper left, the probe should be rotated to the same angle. To pick up HRI, we should measure the diameter of the MPD on the magnified image.

#### 3.3 Tail

As the pancreatic tail extends quite far posteriorly, we employ both epigastric transverse and left intercostal scanning to visualize the entire tail. The focus should be adjusted deeper to get good images. To visualize the splenic vein and pancreatic tail using the spleen as an acoustic window, we should move the probe just a few intercostal spaces ventrad from the point we can visualize the left kidney at the left intercostal scanning.

# 4. Special Maneuvers Especially for HRI

As positions of the pancreas change inside the body depending on the posture, we should employ several positions to visualize the entire pancreas instead of only compressing strongly by the probe.

#### 4.1 Right lateral decubitus position

As the pancreatic tail moves into the shallower part of the abdomen in this position, you can delineate the lesion in the tail with high-frequency US transducer and linear probe.

#### 4.2 Semi-Fowler and sitting position

As liver moves in front of the pancreas and GI tracts moves to caudad in this position, you can use the liver as an acoustic window to visualize the pancreatic body and tail more clearly. This position is also useful for elderly people who can't stop breathing well.

#### 4.3 Liquid-filled stomach method

If the basic scanning methods and position changing are not useful, the liquid-filled stomach method should be employed. After drinking 200-300 ml of liquid, the pancreatic tail sometimes becomes clearly recognizable up to the end of the tail. We usually employ a sitting and right anterior oblique position.

#### 5. Conclusions

Based on our experience, understanding of the US findings of HRI and adopting various maneuvers will enable us to visualize the pancreas in wider range and pick up PCs in its early stage.

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### 하보니<sup>®</sup>정(레디파스비르 90 mg, 소포스부비르 400 mg)

[호등·효과] 이 약 또는 이 약을 다른 약물과 방용하여 성인의 유전자형 14.56형 만성 C형간염 치료 [통법·용령] 관장 투여 용량은 음식물과 함께 또는 음식물 없이 음식 섭취와 관계없이 1일 1회 1정 경구 투여임. (환자의 상태에 따른 투여 기간은 하가사형을 참죄) [경고] 1. C 형 간염 바이러스바다ሪ// K형 간염 바이러스바다ሪ// 동청 간염 취직 유럽 작품 하다 작업 작용 형바이러스제로 치료 중 또는 치료 완료했으나 Hox 지료를 받지 않은 환자에서 Hox 재활성화 보고가 있었음. 2 이 약은 소포스부바리를 합유하고 있는 다른 약물과 방용 투여해서는 안됨. 3 이미오다르과 방용 시 증상성 서맥, 아미오다란을 이 약과 방용하는 경우 증상성 서맥 및 몇 건의 심박조율기 삽입을 필요로 하는 사례에 대한 사판 후 보고가 있었음. 4 임신 및 리바비리고의 방용: 이 약을 리바비리고 방용하는 경우 기임기 여성 또는 남성 파트너는 리바비린 하가사형의 권고와 같이 치료 중 또는 치료 후 일정 기간 동안 효과적인 형태의 피안법을 사용해야 한 5. 특정 HV 형례트로바이러스세 요법과 함께 사용: 테노프파트 디소프될 수 파르산된 및 약동화 증징채리토나비르 또는 코비시스타트를 함유하고 있는 HV 오법과 함께 사용 위증의 위험을 증가시키고 [금7] 1. 이 약의 주성분 또는 이 약의 다른 성분에 패면법용이 있는 형자 2 로수비스타된 또는 세인트존스워트(Hypericum perforatum)를 방용 투여하는 환자 3. 이 약은 유당을 합유하고 있는 HV 오법과 함께 사용 위증의 위험을 증가시키고 [금7] 1. 이 약의 주성분 또는 이 약의 다른 성분에 패면법용이 있는 형자 2 로수비스타된 또는 세인트존스워트(Hypericum perforatum)를 방용 투여하는 환자 3. 이 약은 유당을 합유하고 있으므로, 갈락 보스로 합러하여 하거나켜 구락성증 및 황료근육 해증의 위험을 증가시키고 [금7] 1. 이 약의 주성분 또는 이 약의 다른 성분에 파면법용이 있는 형자 2 로수비스타된 또는 세인트존스워트(Hypericum perforatum)를 방용 투여하는 환자 3. 이 약은 유당을 합유하고 있으므로, 갈락 물소스 불내성(galactose inderance), Lapp 유당분위함과 관련 이 이 약을 다른 약물의 하가 현황 작고 있는 지난 방원 것 그 푸너 너소된 인수 전원트 문제 기 있는 특성하여 사용되고, 함과 방용하여 사용되고로, 감각 약물에 대한 리가사형 참고 5. 리바비란과 방용 시 업부 및 그 파트너 또는 심인트존스시킬 누성지 않고 갖가 나고 물 작품 2 소자 부바리로 함과 2 성능 사용이 이 외으로 관계 관람 위험 이 약의 인구로과 방용 용 시 증상성 셔맥이 이 의 인원 (P불성호적용) 이 약은 레디파스바르와 소프스부바르를 주성분으로 합유하고 있기 때문에 이들 성분에 대해 확인되고 있을 구 두 6 시상반응) 1. 가장 흔한 이상반응어, 이상 경험은 두통, 파로였음, 2. 사단 후 사용에서 아미오다론과 방 용 시 증상성 셔맥이 이 의 인원 (P불성호적용) 이 약은 레디파스바르와 소프스부바르 취용 분위 되었 및 기 때문과 이 가 형성 사용 약을 사용하여 또 일 약 위 사용 방생할 방송 수 사용으로 우료, 가지 한 약 만을 지원 것 하는 것 이 약 위험 관리 있는 것 같아 유리 같아 것 이 약 위험 관 관계 위험 관계 것 이 약 우 이 이 받았는 방생 수 있는 강력한 우용 유리하는 경우에는 인부 또 인신하고 있을 가려하여 이 약의 이 인원 이 인한 이 인원 이 인원 이 인한 이 인원 이 만을 리하지 않은 가지 정확을 참고 2. 모두, 신성하고 있는 가방 위원 전원 전 약을 상호적으로 이 약 위해 방용해서는 안된 [입부 및 수유부] 1. 임산 이 약을 리바비린 것 않을 지원하는 것 위에 대한 추가 정보는 리바비린 하가사형을 참조, 2. 모두, 수은 신성이 사진 약과 사용 정확으로 받았을 수 있는 것 같아 약 여 것 같아 밖에 관 하나 것을 소프스부비르 것 같고, 고유 수유 신성하고 있는 것을 것 것 같아 관계 것 같아 안된 [요약 및 수요 있는 연구 사용 및 관련 관계 전원 가 여 약 위험 것 이 약 이 약

※ 처방하시기 전에 자세한 사항은 허가시항 전문(www.gllead.co.kr 또는 http://drug.mlds.go.kr)을 참조하여 주시기 바랍니다. 위 문구에 포함되지 않은 허가시항 변경이 하기일자 이후에 있을 수도 있습니다(작성일자: 2017.08.08).







**알마겔(Almagate)**은 Al과 Mg가 포함된 독특한 이중격자 구조를 통해, **신속하고 지속적인 제산 작용**을 발휘합니다.<sup>1,2</sup>



*자르는 방향* 

일반의약품

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1. Beneyto JE et al. Arzneimittelforschung. 1984;34(10A):1350-4. 2. Balanzo C et al. Arzneimittelforschung. 1984;34(10A):1375-7

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**알마겔<sup>®</sup> 한탁액 /에프현탁액 [성분·함량] 알마겔 현탁액: 1포(15mL) 중 알마게이트 1g, 알마겔 에프 현탁액: 1포(15mL) 중 알마게이트 1.5g [성상]점성이 있는 백색의 방향성 현탁액 [효승·효과] 다음 질환의 제산작용 및 증상의 개선: 위·신이지장궤양, 위염, 위산과다, 속쓰림, 구역, 구토, 위통, 신트림 [용법·용량] 상인 및 12세 이상의 소아: 알마게이트로서 1회 1~1.5g을 1일 3회, 식후 30분~(시간에 경구 복용한다. 필요 시 취침 전에 1회 더 복용할 수 있다. [사용상의 주의사항] 1. 다음과 같은 사람은 이 약을 복용하지 말 것 1) 이 약 또는 이 약의 구성 성분에 대해서 과민반응이 있는 환자 2) 알츠하이대병 환자 3) 치질 환자 4) 체액 저류(무기) 환자 5) 임신 증주 환자 6) 실사 환자 7) 잔난더지 않은 소화가란 출혈 환자 2. 이 약을 복용하지 말 것 1) 이 약 또는 이 약의 구성 성분에 대해서 과민반응이 있는 환자 2) 알츠하이대병 환자 3) 치질 환자 4) 체액 저류(무기) 환자 5) 임신 증주 환자 6) 실사 환자 7) 잔난더지 않은 소화가란 출혈 환자 2. 이 약을 복용하는 동안 다음의 약을 복용하지 말 것 1 비르라이클리계 항생물일(함께 복용 시 흡수를 억제할 수 있음) 3. 다음과 같은 사람은 이 약을 복용하기 전에 의사, 치과의사, 약사와 상의할 것 1) 다른 약물을 복용하고 있는 사람: 이 약의 흡착적용 또는 소화관 내 체액의 마 상승에 의해 함께 복용하는 약물의 흡수· 배널에 영향을 줄수 있으므로 신중히 복용한다. (1)비스테로이드 소염진통제(NSAID), 궤양 치료제, 디기탈리스제제, 클로르프로마진, 란소프라졸, 프레드니슬론, 페니실린, 퀴놀론, 첼(Fe)염 제제: 흡수를 감소시킬 수 있으므로 2~3시간 간격을 두고 복용한다. (2)날리실산염: 신장의 배설을 증가시킨다. 2) 신정애 환자: 마그네슘 또는 알루미늄 이온이 오랜기간 동안에 걸쳐 공판에 촉적될 수 있다. 심한 신장애 환자에게는 권고되지 않는다. 3) 신체 하여자, 인 함량이 낮은 식이요법 실시자, 소화흡수 장애가 있는 사람: 이 약의 알루리늄 염이 인 흡수를 감소시키므로 장기간 복용할 경우, 혈증 인산염 함량 감소 및 뼈의 무기질 참수 양을 받수 있는 시 가장한 한 전하지 않는다. 3) 신체 하여자, 인 함량이 낮은 식이요법 실시자, 소화흡수 장애가 있는 사람: 이 약의 알루마늄 염이 인 흡수를 감소시키므로 장기간 복용할 경우, 혈증 인산염 함량 감소 및 뼈의 무기질 참수 사람은 시 약을 받수 있는 소 소치가 관 같은 소화기관 같은 소화기관 같은 소하고 받은 승이 있는 환자 6) 임부 또는 임신하고 있을 가능성이 있는 현자 6) 입부 도 임신하고 있는 가장이 있는 여성 및 수유부 4. 다음과 같은 경우 이 약의 복용을 즉각 중지하고 의사, 치과의사, 약사와 상의할 것, 상태 시 가능한 한 첨부문서를 소지할 것, 1) 소화기계: 이 약을 복용하는 동안 텐비 또는 실사 2) 2주 정도 복용하여도 증상의 개선이 없을 경우 5, 기터 이 약의 복용 시 주의할 사항 1) 소화기관 수용 일상 지 것 1 가 관련 약 처음 전 위 주의 감조 1, 0 소개할 것, 1) 소량의 주의사항 1) 어린이 속이 닿지 않는 곳에 보관할 것, 2) 역자들을 원래 용기에서 깨내 다든 용기에 보관하는 것은 의약품 오용에 따른 사고 발생이나 의약품 물질 지 것 2) 아락에 위원 20 수 있는 위원 4. 다음 사람 전 위 수 목한 적용 적용 성용 이 용 1 용량을 잘 지 길 것 2) 2아라 전에 전 1 수 있 감정 수 있는 1 가능한 한 첨부문서를 조지의 것, 5 위상 동안을 전 지 것 1 수 있는 것 2 주 약품 오용에 따른 사고 발생이나 의약품 물질 지 않 1 등 일 수 있으므로 원리 위 위에 가 1 분은 의 감정 2, 2 가 정도 전 바라고 것 2 의 약품 것 1) 여러 전 모 분용하여 5 것이 가 여는 것 같은 것 1 가 관 것 2 가 품 운 전 것 2) 자 1 가 관 한 것 1 가 관 한 것 1 가 관 분용 전 2) 관 하고 되도록 습기가 적은 소 수 되는 것 2) 약품 조에 가** 

알마겤



# **viekirax® + exviera®** HCV treatment for GT1b patients



Regardless of RAS 12-WEEK %

### ACHIEVED IN GT1b PATIENTS

WITHOUT CIRRHOSIS OR WITH COMPENSATED CIRRHOSIS AND REGARDLESS OF P/R TREATMENT EXPERIENCE FROM RBV-FREE GROUP IN PHASE 3 TRIALS <sup>1,2</sup>

P/R=pegylated interferon with ribavirin; RBV=ribavirin SVR12=sustained virologic response 12 weeks post-treatment RAS=resistant associated substitute

REFERENCES

1. Viekirax Tablet Prescribing Information (Revised as of Jan 30 2018)
 2. Exviera Tablet Prescribing Information (Revised as of Jan 30 2018)

ANNOUSE CHIRD SYN	(Partaphysic Milonawi)						
cindications. Ombitasviriparitapreviolitonavir is indicated in combination with other medicinal products for the treatment of genotype 1 and/or genotype 4 of chronic hepatitis C infection in adults.							
<dosage administration="" and=""> Ombitasvin/parksprevin/itonavir should be used in combination with other medicinal products for the treatment of hepatitis C infection. Refer to the prescribing information of the medicinal products that are used in combination with ombinavivaationavir/itomavir.</dosage>							
The recommended regard to fat or calor	dosage is presented in Table 1. This drug and databusir should be taken with food without is contents.						
Table 1. Recommen	ided dosage						
6-1-1-1	The recommended oral dose is two orrbitativitypartaprevisitionavir 12:5/75/50 mg tablets once daily lin the moming) and one databasir 250 mg tablet twice daily (moming and						

	ribevirin in	certain patient populations (see Table 2).				
Genotype4	The record	The recommended oral dose is two orabitarrit/partapre-initionari 12.5/75/30 mg tablets once daily (in the morning) in combination with ritarritin (see Table 2).				
able 2. Treatmen	t Regimen an	d Duration by Patient Population				
Patient Pop	t Population **	Treatment	Duration			
Genotype 1a, with compensate	d cimhosis	ombitassit/paritaprevio/itionasir and dasabusir + nbavinin'	24 weeks			
Genotype 1a, without cirrhosis		ombitassin/paritaprevio/itionasir and dasabusir + nbavinin'	12 weeks			
Genotype 1b.						

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o dose adjustment of ornibiasviriparitupreviri/tionsvir or dasabusir is required in patients with mild, moderate, or exercised impairment or end-tage-resol disease and ulyris. For patients that require inbuilt, under to the ribaviri scaling information for information segariting use in patients with senal impairment. Keed Dese sides of dissolution is missed, the prescribed dose can be taken within 6 hours of the scheduled time for the transmission. The paraled alonc entrollation is paralely taken or more share 6 hours has an exclusion is caused alonce entrollation is done should NDT be taken and the parient should take the not per the sould ording schedule.

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#### Patients using earning energience of the provided standard, such as estabilized and conjugated estragens used in hormone explorement theorigs had a rate of AL elevision similar to this can be accessing any estragens (198). Hepsile, bloostory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated threads.

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12-year proven real-world efficacy & safety since 2007\*



Refernces 1. PC Wang et al. European Journal of Gastroenterology & Hepatology 2017, 29:946-950 2. IT Wu et al, Clinical Microbiology and Infection (2017)1-6 3. M Vigano et al. Digestive and Liver Disease 49S (2017) e19e42 4. 바라크루드 제품설명서 (개정년월일: 2017년 6월 21일)

[원료약품의 분량] [0.5mg] 1정(206mg) 중 엔테카비르(별규) 0.53mg (엔테카비르무수물로서 0.5mg) [1.0mg] 1정(412mg) 중 엔테카비르(별규) 1.06mg (엔테카비르무수물로서 1.0mg) [시럽 0.05mg/mL] 100mL 중 엔테카비르(별 규) 5.3mg (엔테카비르무수물로서 5.0mg) [주의] 제품 설명서의 사용상의 주의사항 참조 [효능·효과] 활동성 바이러스의 복제가 확인되고, 헐청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)과 2세 이상의 소아 환자의 만성 B형간염 바이러스 감염의 치료 [용법·용량] 1. 성인(16세 이상)의 권고 용량: 1일 1회 엔테카비르로서 0.5mg (시럽제의 경우 10mL) 경구투여. 라미부딘 저항성 환자, 즉, 라미부딘 치료에 도 불구하고 B형간염 바이러스의 지속적 증식을 경험하였거나, 라미부딘 저항성 변이가 있는 16세 이상의 환자: 1일 1회 공복시 엔테카비르로서 1mg (시럽제의 경우 20mL) 2. 소아의 권고 용량: 제품 설명서 참조 \* 신부전 환자의 용량 조절 및 자세한 내용은 제품설명서를 참조하십시오.



### TARGETED DELIVERY OF TENOFOVIR, FOR TODAY AND TOMORROW

- Vemlidy is a novel, targeted prodrug of Tenofovir for the treatment of chronic hepatitis B in adults<sup>1,2</sup>
- TAF (25mg) is 1/10 the dose of TDF (300mg) 1,3,4,5
- Reduces systemic exposure, with 89% lower plasma concentration of tenofovir compared to Viread <sup>1,3,4,5</sup>
- 0% detectable resistance at 48 weeks<sup>4,6</sup>
- Non-inferior to Viread in antiviral efficacy at 48 weeks<sup>4,6</sup>
- Less impact on renal and bone safety parameters as compared to Viread at 48 weeks<sup>2</sup>
- Median change from baseline in eGFR was -1.2 mL/min and -5.4 mL/min for VEMLIDY and TDF groups, respectively
- Mean % change from baseline in hip and spine BMD at Week 48:
   VEMLIDY vs TDF : -0.2% vs -1.9% (Total Hip), -0.6% vs -2.4% (Lumbar Spine)

[Marketing authorization holder] Gilead Sciences International Ltd (Granta Park, Abington, Cambridge, CB21 6GT, UK) [Manufacturer] Patheon, Inc. (2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9) [Importer] Gilead Sciences Korea Ltd., West Tower 15F, Center 1, 26, Euljiro 5-gil, Jung-gu, Seoul, Korea [Distributor] Yuhan, Inc. [Date of Preparation] 01 November 2017 \* Please refer to full prescribing information (<u>www.gilead.co.kr</u> or <u>http://drug.mfds.go.kr</u>) before prescription for detailed information. This abridged PI might not include some latest information after the date above.

ing is not expliminated to be coalimistation with degradination of the oliviving - ferolovin area analyse relation to be coalimistation of the coalimistat

**COMPOSITION:** Each tablet contains Tenofovir alalenamide fumarate (n-house specification) 28.04mg (Equivalent to 25mg Tenofovir alalenamide) **INDICATION:** This drug is indicated for the treatment of drug is indicated for the treatment of this drug is one tablet taken orally once daily, with food, 2. Dosage Adjustment in Patients with Pertait Impairment: No dosage adjustment of this drug is one tablet taken orally once daily, with food, 2. Dosage Adjustment in Patients with Hepatic Impairment: No dosage adjustment of this drug is one tablet taken orally once daily, with food, 2. Dosage Adjustment in Patients with Hepatic Impairment: No dosage adjustment of this drug is orderedano, in patients with decompensated (onlid-byg) & or. Openation and merring **PRECAUTION IN USE:** 1. Advance 3. Dosage Adjustment in Patients with Hepatic Impairment: No dosage adjustment for this drug is redirected on the patient of child-byg) & or. Openation and merring **PRECAUTION IN USE:** 1. Advance 3. Dosage Adjustment of this drug are developed and the patients with genetic problems such as galactose informance **PRECAUTION IN USE:** 1. Advance 1. Advance 3. Dosage Adjustment of this drug are based on Week 48 pooled data from 1298 subjects in two randomized, double-bline, active-controlled and Study 10. In addu subjects with from 2.9 Examples in two randomized, double-bline, active-controlled and Study 10. In addu subjects with from 2.9 Examples in two randomized, double-bline, active-controlled and Study 10. In addu subjects and the from 2.9 Examples is the contained and the subject on the patients with decompensated in the subject on the mathematice of the subject on the subject on

References: 1. Murakami E, et al. Implications of Efficient Hepatic Delivery by Tenofovir Alafenamide (GS-7340) for Hepatitis B Virus Therapy. Antimicrob Agents Chemother. 2015;59:3563-3569. 2. VEMLIDY prescribing information, Glead Korea, May 2017. 3. Lee WA, et al. Selective Intracellular Activation of a Novel Prodrug of the Human Immunodeficiency Virus Reverse Transcriptase Inhibitor Tenofovir Leads to Preferential Distribution and Accumulation in Lymphatic Tissue. Antimicrob Agents Chemother. 2005;49:1398-906. 4. Chan HLY, et al. Tenofovir alafenamide versus tenofovir disports tifundate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:185-95. 5. Agenval K, et al. Wenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection: a trandomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:196-206.





in adults. DOSAGE AND ADMINISTRATION: 1



## Besivo, Your New Partner for the Treatment of Chronic Hepatitis B

New hope for chronic hepatitis B patients

### Antiviral effect of Besivo®

 Besivo was non-inferior to TDF in treatmentnaïve CHB patients in terms of antiviral efficacy.

### Tolerance of Besivo®

- Besivo had no drug-resistance mutation for 48 weeks.
- Improvement of nephrotoxicity, BMD decrease and liver histology by Besivo®
- Patients with Besivo experienced a significantly lower BMD decrease compared to TDF
- Patients with Besivo experienced a significantly lower creatinine increase compared to TDF
- The proportion of subjects who improved hepatic necrosis score<sup>\*</sup> in Besivo was statistically significantly higher than that in TDF

Study design: Clinical trial results of treatment-naïve chronic hepatitis B patients receiving besifovir(n=94) and TDF(n=93) for 48 weeks \*Ishak modified HAI (hepatic activity index) necroinflammatory score BMD, bone mineral density; TDF, tenofovir disoproxil fumarate



Reference 1. Besivo Phase III Clinical Trial. Protocol No. ID\_BVCL011 Clinical Study Report

### Besivo<sup>®</sup> Tab. (Besifovir dipivoxil maleate 183 mg [Besifovir dipivoxil 150 mg])

[Indication and Usage] Treatment of chronic hepatitis B in adults [DOSAGE AND ADMINISTRATION] One tablet containing 150 mg besifovir dipivoxil once daily orally with or without food in adults. When taking this medicine, take 660 mg of L-Carnitine together to prevent a decrease in serum L-Carnitine level. [WARNINGS AND PRECAUTIONS] 1) Lactic acidosis or prepended with steatosis, including fatal cases, have been reported with the use of nucleoside analoga alone or in combination with other antiretrovirias. Treatment should be suspended in any patient who developes clinical or laboratory findings suggestive of lactic acidosis or pronounced hepattoxicity (which may include hepatomegaly with seedosis, including fatal cases, have been reported with the use of nucleoside analoga alone or in combination with other antiretrovirias. Treatment should be suspended in any patient who developes clinical or laboratory findings suggestive of lactic acidosis or pronounced hepattoxicity (which may include hepatomegaly and steatosis even in the absence of marked transminase elevations). 2) Discontinuation of anti-HBV therapy may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Besivo should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B threapy may be warranded. 3) HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with Besivo is not recommended or HIV/HBV co-infected patients.

ES-BR06-1801

ETC

## **MULTIPLE PATIENT TYPES**<sup>1</sup> **POWERFUL CURE**

of G1b<sup>s</sup>TN patients achieved cure\* with 12 weeks of ZEPATIER<sup>\*1,3,a</sup> Of the overall treatment-naïve (TN) patient population with G1 or G4 infection achieved SVR12 with 12 weeks of ZEPATIER<sup>\*</sup>, no RBV <sup>3,a</sup>





**INDICATION:** ZEPATIER<sup>®</sup> is indicated for the treatment of chronic hepatitis C (CHC) genotypes 1 or 4 infection in adults.<sup>1</sup>

a. Study Design: C-EDGE TN was a randomized, double-blind, placebo-controlled trial in treatment-naive subjects with genotype 1 or 4 infection with or without compensated cirrhosis. Subjects were randomized in a 3:1 ratio to: ZEPATIER for 12 weeks (immediate treatment group: n=306) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group: n=102).<sup>1</sup> The primary endpoint was SVR12.<sup>1,3</sup>

\* Cure of hepatitis C virus (HCV) infection=sustained virologic response, the primary end point in all studies, defined as HCV ribonucleic acid (RNA) less than the lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR12).<sup>12</sup> G=genotype; RBV=ribavirin.

§ Includes genotype 1 subtypes other than 1a or 1b.1

References: 1. Zepatier\* Prescribing Infomation. MSD Korea. 2. European Association for the study of the Liver. Recommendations on treatment of hepatitis C 2015 J Hepatol. 2015;63:199-236. 3. Zeuzem S et al. Ann Intern Med. 2015 Jul 7:163(1):1-13

### 제파티어<sup>®</sup> 정(엘바스비르/그라조프레비르) 주요 안전성 정보

### ※ 처방하시기 전 더 자세한 사항은 제품설명서를 참고하시기 바랍니다.

[효능효과] 성인에서 유전자형 1형 및 4형 만성 C형 간염의 치료 [용법용량] 제파티어 정은 엘바스비르 50 mg와 그라조프레비르 100 mg의 2가지 성분을 포함하는 복합제이다. 권장용량은 성인에서 1일 1회 1정으로, 음식과 관계 없이 경구투여 한다. (간경변이 없거나 대상성 간경변을 포함한 만성 C형 간염의 치료를 위한 권장 치료요법 및 치료기간은 제품설명서를 참고.) 1. 경고 1) B형 간염 바이러스 재활성화 위험 2) ALT 상승 위험 증가 3) 리바비린 병용으로 인한 위험 4) 약물상호작용으로 인한 약물이상반응의 위험 또는 치료효과의 감소 2. 다음 환자에는 투여하지 말 것 1) 엘바스비르, 그라조프레비르 또는 제파티어 정의 성분에 과민한 환자 2) 중등도 또는 중증의 간장애 환자(Child-Pugh B 또는 C) 3) 유기음이온전달단백질 1B1/3 (organic anion transporting polypeptide 1B1/3, OATP1B1/3) 억제제와 시토크롬 P450 3A (CYP3A)의 강한 유도제 및 에파비렌즈와 병용투여하지 않는다. 4) 리바비린과 병용할 경우, 리바비린의 투여 금기사항이 제파티어 정과의 병용요법에도 적용된다. 5) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. 3. 다음 환자에는 신중히 투여할 것 유전자형 1a형에 감염된 환자에서 제파티어 정을 투여 전 M28, Q30, L31 또는 Y93 위치의 HCV NS5A 유전다형 검사를 고려해야 한다. 기저시점에서 M28, Q30, L31 또는 Y93 위치의 HCV NS5A 유전다형이 있는 경우 제파티어 정과 리바비린을 병용하여 16주 요법을 고려할 수 있다. **4. 이상반응:** 1) 임상시험에서의 경험: C-EDGE TN 임상시험에서 제파티어 정으로 12주간 치료한 치료 경험이 없는 만성 C형 간염 환자의 5% 이상에서 보고된 약물이상반응(모든 중증도)은 피로(11%), 두통(10%) 이었다. C--EDGE COINFECTION 임상시험에서 제파티어 정으로 12주간 치료한 환자 중 5% 이상에서 발생한 약물이상반응(모든 중증도)은 피로(7%), 두통(7%), 오심(5%), 불면증(5%) 및 설사(5%) 이었다. C-EDGE TE 임상시험에서 제파티어 정으로 12주 또는 제파티어 정과 리바비린을 병용하여 16주간 치료한 이전 페그인터페론/리바비린 치료 경험이 있는 만성 C형 간염 환자의 2% 이상에서 보고된 약물이상반응(중등증 또는 중증)은 피로(5%), 과민성(1%), 복통(2%), 우울증(1%), 설사(2%) 이었다. C-SALVAGE 임상시험에서 제파티어 정을 리바비린과 병용하여 12주간 치료받은 환자 중 2% 이상에서 보고된 중등도 또는 중증의 약물이상반응은 피로(3%) 및 불면증(3%) 이었다. C-SURFER 임상시험에서 4기 또는 5기 만성 신질환을 가지면서 제파티어 정으로 12주간 치료한, 치료 경험이 없거나 페그인터페론/ 리바비린 치료경험이 있는 만성 C형 간염 환자의 5% 이상에서 보고된 약물이상반응(모든 중증도)은 구역(11%), 두통(11%), 피로(5%) 이었다.





## Second-line systemic therapy for HCC<sup>‡</sup> proven to significantly improve OS<sup>1</sup> STIVARGA® (regorafeenib) BRAEAAK BRAEAAK SURVIVAL BARRIERS

### Please refer to the full product information for details

<sup>1</sup>HCC patients in RESORCE trial: BCLC B or C patients who could not benefit from resection, local ablation or chemoembolization<sup>1</sup> BCLC, Barcelona Clinic Liver Cancer; RESORCE, REgorafenib after SORafenib in patients with hepatoCEllular carcinoma ; HCC, hepatocellular carcinoma ; OS, Overall Survival

References 1. Bruix J, Qin S, Merle P, et al; on behalf of the RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo controlled, phase 3 trial [published online December 5 2016]. Lancet. 2016. doi: 10.1016/S0140-6736(16)22433-9.

10.1016/S0140-6738(1632485-36. [Product Name] Stivargs® tablet 40 mg (Regorafenib) [Active ingredient] 1 tablet (472.00 mg) contains active ingredient - regorafenib 14.99 mg (as for regorafenib 40.00 mg). [Indications] 1. Treatment of patients with metastatic colorectal cancer who have been previously treated with imatinib and suntimb. 3. Hepatocellular carcinoma (HCC) who have been previously treated with imatinib and suntimb. 3. Hepatocellular carcinoma (HCC) who have been previously treated with imatinib and suntimb. 3. Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. [Desage and Administration] The recommended dose is 160 mg regorafenib (14 tablets of Sivarge 40 mg), taken orally once daily for 3 weeks on therapy followed by 1 week of therapy to comprise a cycle diversed with imatinib and suntimb. 3. Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. [Desage and Administration] The recommended dose is 160 mg regorafenib (14 tablets of Sivarge 40 mg), taken orally once daily for 3 weeks on therapy followed by 1 week of therapy to comprise a cycle diversed osc. Treatment should be taken on the same day to another abare day to another the same day to another abare day to another the same day to another abare day to another to the full product information. [Precautions in use] 1. Varing 1] Severed drug-induced liver input with table at the all outcome occurred in Silvarge are to be applied in d/m (mo teable) steps. The lowest recommended day dos is 80 mg. For dose modifications are to be applied in d/m (mo teable) steps. The lowest recommended day dos is 60 mg regoratenib table and trends tables are topper services and the same days to another the same day to another the same day to another the same day to another days in the same days to another table. The maximum dially dos is 80 mg. Therease the same day is another days in the same day to another days in the same day to another days in the same days to another days in the same days to another days





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ETC	■200mg	Tab.:	- Gallstones: 200-250mg t.i.d. - Primary biliary cirrhosis(PBC) : 200-300mg t.i.d.
ETC	■300mg	Tab.:	<ul> <li>Preventtion Gallstones During Weight Loss : 300mg b.</li> <li>Primary biliary cirrhosis(PBC) : 300mg t.i.d.</li> </ul>



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Gastroenterology | Volume 148 Number 7 June 2015 Published results of phase III clinical trial

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6

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### Product Information

Description | Reddish brown colored hard gelatin capsule containing yellowish brown colored powder |Composition | Reddish brown colored hard gelatin capsule containing yellowish brown colored powder |Composition | Each capsule contains Carnitine Orotate 150mg (73.8mg as orotic acid, 76.2mg as carnitine), Liver Extract Antitoxic fraction 12.5mg, Adenine HCI 2.5mg, Pyridoxine HCI 25mg, Riboflavin 0.5mg, Cyanocobalamin 0.125mg, Biphenyl dimethyl dicarboxylate 25mg|Indication | 1) General therapeutics for the following hepatic disease - Acute, Subacute and Chronic Hepatitis, Hepatic cirrhosis, Fatty liver, Drug or chemical induced hepatitis 2) Acute, chronic hepatitis involving high transaminase value IDosage & Administration | Usually, each time 2 capsules, 2~3 times a day as adult dosage. Dosage unit can be changeable depending on symptom or age of patient. |Special caution | 1) Severe state of chronic hepatitis 2) Severe state of hapatic cirrhosis | General caution | 1) Rarely skin rash can be represented, in this case general antihistamin therapy will be required. 2) In severe case, sometimes intermittent jaundice can be occur in this case, discontinue administration and follow physician's instruction. | Insurance Code | 693900080Drug price | 431 KRW / 1 cablPacking Unit | 100, 300 caps. (bottle) / 100 caps. (PTP)Storage | Tight closed container, room temperature (1~30°c) in dry place. Expiry - 60 months from Manufacturing date.

### Diagnostic Codes

CELLTRION PHARM

B15-19/Iral hepatitis K70.0Alcoholic fatty liver K71.0Toxic liver disease K73.0Chronic persistent hepatitis, NEC K74.0Hepatic fibrosis K75.8Other specified inflammatory liver disease, Nonalcoholic steatohepatitis K77.0Liver disorders in disease classified elsewhere





## 

CKD



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References J. Kramer BK, et al. Transpl Int. 2016 Mar;29(3):307-14. doi: 10.1111/tri.12716. Epub 2015 Dec 11.





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Eisai

### 용법/용량

- ▶ 위궤양, 십이지장궤양 : 통상 성인에게 라베프라졸나트륨으로서 1일 1회 10 mg을 경구 투여합니다. 증상에 따라
- 1일 1회 20 mg을 경구 투여할 수 있습니다. 통상 위궤양에는 8주까지, 십이지장궤양에는 6주까지 투여합니다. ▶ 미란성 또는 궤양성 위식도역류질환: 1일 1회 10 mg 또는 20 mg을 4~8주간 투여합니다. 프로톤펌프억제제 (PPI, proton pump inhibitor)를 8주간 투여 후에도 치료되지 않은 경우, 추가로 8주간 10 mg 또는 20 mg을 1일 2회 경구 투여할 수 있습니다. 단, 20 mg 1일 2회 투여는 중증의 점막 손상이 확인된 환자에 한합니다.
- ▶ 위식도역류질환의 증상 완화: 1일 1회 10 mg을 투여합니다. 4주간 투여 후에도 증상이 조절되지 않는 경우, 추가 진료가 필요합니다. 증상이 소실된 후에는, 필요시 10 mg을 1일 1회 투여하는 on-demand 요법을 사용하여 이후에 나타나는 증상을 조절할 수 있습니다.
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- ▶ 졸림거 엘리슨 증후군 : 성인에 대한 권장 초회량은 1일 1회 60 mg 입니다. 투여량은 개개 환자의 필요에 따라 1일 120 mg까지 조절 가능합니다. 100 mg 용량까지는 1일 1회 투여가 가능하며, 120 mg 용량은 60 mg씩 1일 2회로 나누어 투여합니다. 졸림거 엘리슨 증후군 환자들은 이 약을 1년까지 투여한 경험이 있습니다.
- 간장애 환자 : 간경변 환자에서 간성뇌증의 이상반응이 보고되었습니다. 따라서 신중히 투여하여야 합니다. • 소아 : 소아에 대한 안전성이 확립되어 있지 않습니다.
- •고령자 : 간기능이 저하되어 있는 경우가 많으므로 신중히 투여합니다.

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#### Hepsera Safety Information

- Hepseta Satety Intormation
  1. 32 11 이 면 27 원 공량을 최처하여 투여해서는 안됨. 21 치료 중단 후 심각한 급성간업 연화가 보고된 바 있으므로 주의감계 모니티킹하여야 한. 30 이 약의 장기 투여로 신특성이 생길 수 있음. 이 약으로 치료를 시작하기 전에 모든 환자들을 크레아니틴 청소율을 계산하는 것이 권장되며, 신기능을 모니티링 해야 함. 치료 초기 또는 치료 도중에 신기능 부록을 나타내는 환자들은 광량 조점이 물요할 수 있음. 41 HU H상을 약기 위해 이 약으로의 치료를 시작하게 전에 모든 환자에 대해 HV 향해 테스트를 실시해야 한. 2. 37 11 아테프 H이 또는 이 약의 다른 실전에 패인증이 있는 환자 21 감독도 모두 관람 관람 가 같다. 물 부도당 갈락로으스 흡수 30% 등의 유전적인 문제가 있는 환자 3. 다음 환자들에 나온히 투약할 것: 라마부터 내성 많은 같은 환자를 대공으로 간이시 전후을 비교했을 때 사이클로스포란과 타크로리루스와의 병용투여, 치료조가 신기능부족, 고열요, 등뇨, 장기 이식 등을 포함한 위험요소를 지닌 환자들에게서 신기능의 변화가 발생. 따라서, 신기능에서의 이러한 변화들에 대해 이 약이 미치는 영황은 평가하기가 여러움. 4. 이상반응 11 48주간 이용편감 치료를 받은 만성 명함 간점 환자 및 대상성간질환 환자 522명을 대상으로 한 두 시험에서 3% 이상 보고된 이상반응은 무력증, 두통, 복통 등이었으며, 1% 이상 보고된 실험시적 검사수치 이상은 ALT, 혈뇨, AST 등이었음. 실험실적 수치 이상이 이 약 치료로 및 위약군에서 비슷한 빈도로 발생하였으나, 간이미노기 전이 효소의 상승은 위약군에서 대주주 발생하였다. 이 약을 연장 투여한 이후, 크레아티닌의 증가가 부적용으로 나타났음.

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✓ 간경변환자의 Nutrition status 개선<sup>4</sup>

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[제품명]테노리드 정 [분류번호]62%기타의 화학요법제) [원료약품의 분량] 1정 중 테노포비르디소프록실 245mg [성상] 연한 피란색의 이몬드 모양의 필름코팅정 [효능・효과] 1, HV-1감염 : 성인 및 12세 이상의 소아에서 HIV-1감염의 치료(다른 항례트로바이러스제제와 병용투여) 2, 만성B형간염 : 성인 및 12세 이상 소아의 만성B형간염을 치료한다. [용법·용량] 음식 섭취와 관계 없이 1일 1회 1정 투여, \*신집애 환자 : 이 약을 중등도-중증의 신집애 환자에게 투약할 경우 약물 노출이 유의하게 증가했다. 따라서 기저 크레아티닌 청소율이 (50mL/min인 환자의 경우 〈표1〉을 참고하여 이 약 의 복용 간격을 조절해야 한다. [저장방법] 기밀용기, 실온(1~30°C)보관 [포장단위] 30정/병

〈표1〉 크레아티닌 청소율에 따른 복용 간격 조절

	크레아티닌 청소율(mL/min) <sup>a</sup>			형애 트서 하다	│ <sup>8</sup> 이상(제자방) 체중을 이용하여 계산한다. │ <sup>D</sup> 오비너저이르 1주의에 양 4175 도안이 2히 형애 트서이르 기저하여	K-Inn
	≥50	50 30-49 10-29	· 즐곡 구곡 원시	일주일에 한 번 투여한다. 이 약은 투석이 끝난 후 투약해야 한다.		
권장되는 245mg 복용 간격	24시간마다	48시간마다	72-96시간마다	7일마다 또는 투석 약 12시간 후 <sup>b</sup>	* <b>소비자 상담전화(080–082–1234)</b> 로 문의하십시오, www.samjinpharm.co.kr	HOLAINE PHARMAG