

## Abstracts

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### Acute Liver Failure

#### A01 - Acute liver failure

Abstract #91

#### Does sepsis-like performance in hepatitis B virus related acute-on-chronic liver failure accord with the existed definition of sepsis?

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**Aim:** Early diagnosis of sepsis is the key to improving the survival rate of patients with hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF). However, it is still unknown that whether sepsis with HBV-ACLF fit into the conventional diagnostic criteria of sepsis. Therefore, it is urgent to identify the clinical feature of sepsis with HBV-ACLF so as to performing the timely and effective prevention and treatment. Our aim was to investigate the potential clinical parameters for the diagnosis of HBV-ACLF with sepsis.

**Methods:** A retrospective study was conducted in 43 patients with HBV-ACLF and sepsis who underwent orthotopic liver transplantation. Immunohistochemistry (IHC) staining, routine hematoxylin-eosin (HE) staining and Gordon Sweet's reticulin staining were performed in this study. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TbIL), cholinesterase (CHE), albumin (ALB), prothrombin activity (PTA), blood routine examination were detected. The results being chosen at admission and before transplantation were analyzed.

**Results:** TbIL had a significant increase ( $563.5 \pm 191.8 \mu\text{mol/L}$  vs.  $383.9 \pm 157.6 \mu\text{mol/L}$ ,  $438.3 \pm 154.7 \mu\text{mol/L}$ ,  $P = 0.031$ ) and ALT significantly decreased ( $81.6 \pm 66.4 \text{ U/L}$ ,  $754.5 \pm 1084.7 \text{ U/L}$ ,  $120.6 \pm 102.5 \text{ U/L}$ ,  $P = 0.005$ ) in sepsis group before liver transplantation. When sepsis appeared in patients with HBV-ACLF, the ratio of PLT to WBC count before liver transplantation was much lower than it at admission ( $4.6 \pm 2.0$  vs.  $16.1 \pm 7.2$ ,  $P = 0.000$ ).

**Conclusions:** The clinical parameters of sepsis in patients with HBV-ACLF should be reset. When sepsis appeared, TbIL and WBC count remarkably elevated, while PLT significantly decreased. The ratio of PLT/WBC and  $(\text{WBCBLT}/\text{WBCCA})/(\text{PLTBLT}/\text{PLTAA})$  could remind us the occurring of sepsis in patients with HBV-ACLF.

Abstract #160

#### Withdrawal of Nucleoside Analogs Leads to Poor Prognosis in HBV-Related Acute-on-Chronic Liver Failure

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**Objectives:** HBV-related-acute on chronic liver failure (HBV-ACLF) accounts for 80% of all ACLF cases in China, and fewer than 50% of HBV-ACLF patients recover spontaneously. HBV reactivation due to withdrawal of Nucleoside Analogs (NAs) therapy is now the most important intrahepatic reasons leading to HBV-ACLF in China. Here, we focused on the prognosis of HBV-ACLF caused by NAs withdrawal and the relationship between plasma HBV-DNA level and oxidative stress, which has been shown mediate inflammation during liver failure.

**Methodology:** We analyzed plasma samples (collected at time of hospital admission) and clinical data from 200 patients included in the HBV-ACLF Group from January 2013 to November 2017. We compared data with those from all patients enrolled in the study, as well as from healthy individuals with no evidence of liver disease (healthy controls) of similar ages. Plasma levels of HBV-DNA were measured using Roche Cobas and SOD were measured using a polyclonal antibody and colorimetric assay.

**Results:** HBV-ACLF patients in NAs withdrawal group showed increased mortality rate compared to those in NAs treated group ( $69.95$  vs  $46.71$ ). Elevated HBV-DNA and SOD levels were found in NAs withdrawal group ( $6.49 \pm 0.24$  vs  $4.79 \pm 0.14$ ,  $P < 0.01$ )  $\text{Log}_{10}$  (HBV-DNA), ( $446.1 \pm 30.69$  vs  $390.0 \pm 12.47$ ,  $P < 0.05$ ). A level of SOD above  $428 \text{ U/mL}$  was associated with a statistically significant increase in risk for mortality in HBV-ACLF patients.

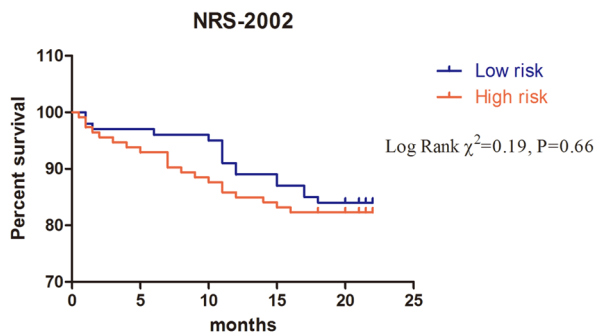
**Conclusion:** A one-time measurement of plasma SOD level can be used to assess prognosis of HBV-ACLF patients. Withdrawal of NAs leads to reactivation of HBV and then elevated oxidative stress in HBV-ACLF patients.

**Table 4** Relationship between nutrition risk screening tools among different MELD score.

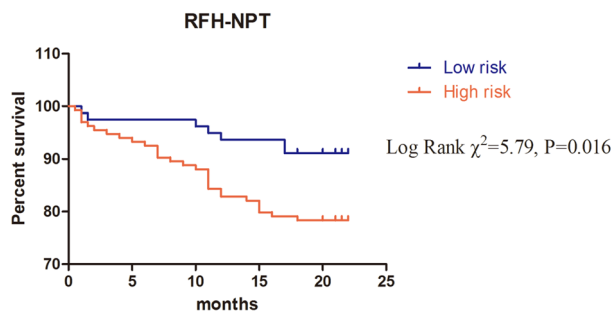
MELD	RFH-NPT	NRS-2002		Total	P
		Low risk	High risk		
≤10	Low risk	62	5	67	0.004
	High risk	20	67	87	
	Total	82	72	154	
10~20	Low risk	7	1	8	0.021
	High risk	9	25	34	
	Total	16	26	42	
20~30	Low risk	2	2	4	0.50
	High risk	0	8	8	
	Total	2	10	12	
>30	Low risk	0	0	0	-
	High risk	0	5	5	
	Total	0	5	5	

**Figure 1**

Kaplan–Meier curves of survival analysis for the patients stratified as low risk and high risk using the NRS-2002 scale.

**Figure 2**

Kaplan–Meier curves of survival analysis for the patients stratified as low risk and high risk using the RFH-NPT scale.

**Abstract #345****Fgl2 regulates liver fibrosis progression and reversal by promoting profibrotic infiltrating macrophages maintenance**

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**Introduction:** Fibrinogen-like protein 2 (Fgl2) is known as a crucial inflammatory regulator. However, its contribution in the pathogenesis of liver fibrosis remains unclear.

**Objectives:** We aimed to investigate the molecular mechanism underlying the involvement of Fgl2 in macrophages function in the pathogenesis of liver fibrosis.

**Methods:** Twenty patients with HBV-induced fibrosis were recruited. FGL2 levels were determined via enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction. Genetic ablation of the Fgl2 gene in rodent models were used to evaluate the phenotype of monocyte/macrophages in the liver by using flow cytometry. Administration of muramyl dipeptide (MDP) was used to alleviate fibrosis in fgl2<sup>-/-</sup> mice. Blood circulating monocytes were further analyzed. We sought investigation on macrophage-dependent regulation of hepatic stellate cells (HSCs) by using primary HSCs and HMs coculture system in vitro. The expression of fibrogenic factors in HSCs were evaluated.

**Results:** We identified increased Fgl2 expression was associated with high grade of liver fibrosis in chronic Hepatitis B patients and experimental models. Genetic ablation of the Fgl2 alleviated fibrosis progression and promoted reversal during the resolution, which was linked to a restorative phenotype of macrophage in Fgl2<sup>-/-</sup> mice. Moreover, administration of MDP alleviated fibrosis in fgl2 deficient mice, which was associated with coordinated an increased Ly6Clow phenotype. Fgl2 depletion in macrophages significantly dampened the activation of primary HSCs in vitro in response to macrophage-dependent stimulation.

**Conclusion:** Fgl2 regulates liver fibrosis by maintaining profibrotic phenotype in resident and infiltrating macrophages, thereby providing novel insights into therapeutic strategy for fibrosis treatment.

**Abstract #446****Combination treatment with epigallocatechin gallate and silibinin restored antioxidant defense mechanisms and prevented N-nitrosodimethylamine induced hepatic fibrosis in rats**

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**Introduction:** Hepatic fibrosis is the result of exuberant wound healing response to a persistent stimulus. Epigallocatechin-3-gallate (EGCG) and silibinin are powerful antioxidants present in green tea and milk thistle, respectively. Oxidative stress and reactive oxygen species (ROS) play significant role in the pathogenesis of hepatic fibrosis.

**Objectives:** Evaluate the combination effect of EGCG and silibinin to prevent experimentally induced liver injury and fibrosis in rats.

**Methodology:** N-nitrosodimethylamine (NDMA) was used to induce liver injury and fibrosis. A group of animals received 0.2 mg EGCG/100 g body weight orally 2 h prior to NDMA administration. Another

group received silibinin 2 mg/100 g body weight and the next group received both EGCG and silibinin in combination. Alanine transaminase (ALT), aspartate transaminase (AST), osteopontin, collagen type IV, TGF- $\beta$ 1, and hyaluronic acid (HA) were measured in serum. Glutathione, glutathione peroxidase, and malondialdehyde were determined in the liver. Collagen type I,  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), 4-hydroxy-2-nonenal (4-HNE), and osteopontin were stained on liver sections.

**Results:** Serum ALT, AST, osteopontin, collagen type IV, TGF- $\beta$ 1, and HA were significantly decreased after EGCG and silibinin treatment. While glutathione and glutathione peroxidase significantly increased in the liver tissue, malondialdehyde levels markedly decreased indicating improved antioxidant status. Furthermore, staining depicted remarkable decrease in collagen type I,  $\alpha$ -SMA, 4-HNE, and osteopontin after EGCG and silibinin treatment with a synergistic effect after the combination therapy.

**Conclusion:** The data indicates both EGCG and silibinin are effective to protect liver from oxidative stress and ROS induced liver injury and subsequent hepatic fibrogenesis.

Abstract #587

### The Role of CX43 in Human Menstrual Blood-Derived Stem Cell's suppression in activating hepatic stellate cell

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**Introduction:** Liver fibrosis is a reversible wound healing response to acute or chronic hepatocellular injury from various etiologies. Activation of hepatic stellate cell plays a pivotal role in the development of liver fibrosis. Human menstrual blood-derived stem cells (MenSCs), also known as menstrual blood-derived mesenchymal stem cells, are reported to protect liver from injury. Connexin43(CX43) is a ubiquitous gap junction protein expressed in a wide variety of tissues and organs that regulates cellular functions such as cell growth, differentiation, migration, metabolism and so on.

**Objectives:** The aims of the study were to verify the hypothesis that CX43 participates in activation of hepatic stellate cell. The protective effect of MenSCs against liver fibrosis was regulated by CX43 expression.

**Methodology:** In this study, we investigated differential expression in LX2 (an immortalized hepatic stellate cell line) that were cocultured with MenSCs. Gap26, an inhibitor of CX43, was added to clarify the communication between LX2 and MenSCs. CX43 Cell proliferation was tested by CCK8. Protein secretion in culture supernates were tested by ELISA and protein expression of cell were tested by western blotting.

**Results:** MenSCs suppressed proliferation of LX-2 cells and the secretion of  $\alpha$ -SMA and TGF- $\beta$ 1. Expression of CX43 in LX2 increased when cocultured with MenSCs. Inhibition of CX43 suppressed the protective effect of MenSCs against liver fibrosis. MAPK signal pathway maybe the possible function method.

**Conclusion:** MenSCs suppressed the activation of hepatic stellate cell. Gap junction communication based on CX43 maybe the possible approach that MenSCs protected liver against fibrosis.

Abstract #792

### Non-heavy drinking and worsening of non-invasive fibrosis markers in nonalcoholic fatty liver disease: A cohort study

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The effect of modest alcohol consumption on fibrosis progression in the general population with NAFLD remains unclear. We examined the association of non-heavy alcohol consumption with worsening of non-invasive fibrosis indices in a large-scale, low-risk population with non-alcoholic fatty liver disease (NAFLD). A cohort study was performed in 58,927 Korean adults with NAFLD and low fibrosis scores who were followed for a median of 8.3 years. Non-, light, and moderate drinkers were defined as 0 g/day, 1–9.9 g/day, and 10–29.9 g/day (10–19.9 g/day for women), respectively. Progression from low to intermediate or high probability of advanced fibrosis was assessed using non-invasive indices including NAFLD fibrosis score (NFS) and FIB-4. Parametric proportional hazards model was used to estimate the multivariate-adjusted hazard ratios and 95% confidence intervals. During 347,925.4 person-years of follow-up, 5630 subjects with low FIB-4 progressed to intermediate or high FIB-4. The multivariable-adjusted HRs (95% CI) for worsening of FIB-4 comparing light-drinkers and moderate-drinkers with non-drinkers were 1.06 (0.98–1.16) and 1.29 (1.18–1.40), respectively. Similarly, using NFS, corresponding HRs (95% CI) comparing light-drinkers and moderate-drinkers with non-drinkers were 1.09 (1.02–1.16) and 1.31 (1.23–1.40), respectively. Furthermore, the association of moderate drinkers with worsening of either FIB-4 or NFS remained significant after introducing alcohol use and confounders treated as time-varying covariates.