Background and Aims: Plasma levels of Von Willebrand factor (VWF) are increased in cirrhotics with endotoxemia, severe portal hypertension, liver dysfunction, and independently predict clinical outcome. Acute bacterial infections, a life threatening complication of cirrhosis, further contributes to increase VWF, whose impact on the hemostatic balance has never been addressed by ad hoc clinical studies. We wondered whether acute bacterial infections may lead to a pro-hemostatic imbalance in cirrhosis that worsens prognosis.
Methods: We prospectively collected clinical and laboratory data of 83 patients hospitalized for decompensated cirrhosis and screened for acute bacterial infection. Baseline examinations included the main pro-(FVIII) and anti-coagulants (antithrombin, AT, protein C, PC), VWF, d-dimer, and Factor II (FII). Endogenous Thrombin Potential (ETP) allowed testing for the *in vitro* thrombin generation in platelet-poor plasma and thromboelastography to assess for whole blood hypercoagulability. Intra-hospital mortality and complications such as organ dysfunction were collected.
Results: There were 54 infected and 29 infection-free patients, the mean MELD score was 18.6 ± 6.8 *vs* 15.0 ± 5.9 ($p = 0.018$), and the VWF 627 ± 329 *vs* 436 ± 152 ($p = 0.003$), respectively. Infection was associated with high levels of FVIII, d-dimer and low levels of AT, PC, FII. By multivariable analysis FVIII ($p = 0.031$) and VWF ($p = 0.023$) were associated with infection, independently of MELD. In infected patients VWF levels correlated with FVIII ($R = 0.658$, $p < 0.001$), significantly influencing *in vitro* hypercoagulability when measured by thromboelastography (high maximum clot firmness, MCF, low clotting formation time, CFT, $p < 0.05$), not by ETP. These results suggest a pro-hemostatic imbalance involving pro- and anti-coagulant factors and platelets. During hospitalization, 24 patients experienced a complication, 10 of them died, MELD score being a strong predictor of outcome. Interestingly, high levels of FVIII significantly increased the risk of severe outcome as predicted by MELD ($p = 0.005$) in association with a pro-hemostatic imbalance measured by thromboelastography.
Conclusions: Acute bacterial infections lead to increased plasma levels of VWF and FVIII that drive a pro-hemosttaic imbalance resulting in worsened prognosis in cirrhotic patients.

THU-400
CRITICAL ROLE OF HEPATOCYTE DEATH IN THE PATHOPHYSIOLOGY OF ACUTE ON CHRONIC LIVER FAILURE: ASSOCIATION BETWEEN THE EXTENT OF HEPATOCYTE DEATH AND TYPES OF PRECIPITATING EVENT

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Background and Aims: Acute on chronic liver failure (ACLF) usually develops from a precipitating event on the basis of established cirrhosis. Current pathophysiological hypothesis for ACLF is that precipitating events may primarily cause acute liver injury, subsequently trigger inflammation response and eventually lead to multiple organ failures. The aim of the study was to investigate the role of hepatocytes death in such process.
Methods: 66 ACLF patients were identified from a prospective cohort of 117 patients with acute decompensated cirrhosis (ADC) admitted to Rui-Jin hospital from February 2013 to August 2014. 50 healthy volunteers (HC) and 50 patients with compensated cirrhosis (CC) were enrolled as controls. Precipitating events were categorized into hepatic alone, extra-hepatic alone and mixed events (hepatic and extra-hepatic). Hepatocyte death was assessed by the serological measurements of cell death biomarkers, M30-antigen (hepatocytes apoptosis) and M65-antigen (hepatocytes total death).
Results: Among those with ACLF, 18 were precipitated by hepatic event alone (Hepatic-ACLF), 19 by extra-hepatic event alone (Extrahepatic-ACLF) and 23 by both hepatic and extra-hepatic events (Mixed-ACLF). Another 6 had no obvious precipitating event. Median serum M30-antigen in ACLF was 10.5-fold ($p < 0.001$), 2.6-fold ($p < 0.001$), and 1.7-fold ($p < 0.001$) higher than in HC, CC and ADC. Serum M65-antigen in HBV-ACLF was 31.5-fold ($p < 0.001$), 3.3-fold ($p < 0.001$), and 3.2-fold ($p < 0.001$) higher than in HC, CC and ADC. Both M30- and M65-antigen significantly correlated with the severity scores of cirrhosis, CTP (both $p < 0.001$) and MELD (both $p < 0.001$). ROC analysis revealed that both serum M30-antigen (AUC 0.71, $p < 0.001$) and M65-antigen (AUC 0.78, $p < 0.001$) could well discriminate ACLF from ADC. Mixed-ACLF demonstrates the highest level of serum hepatocytes death (M30: 19.6-fold of HC, M65: 85.9-fold of HC) followed by that from Hepatic-ACLF (M30: 9.8-fold of HC, M65: 32.2-fold of HC) and Extrahepatic-ACLF (M30: 5.6-fold of HC, M65: 16.8-fold of HC). Serum M30- and M65-antigen from Extrahepatic-ACLF was relatively low and even close to that from ADC (M30: 6.2-fold of HC, M65: 9.9-fold of HC).
Conclusions: Markedly elevated hepatocyte death is crucial for the development of ACLF. Hepatic rather than extra-hepatic precipitating event is the primary reason for massive hepatocyte death. However, extra-hepatic injury may help exaggerating the extent of hepatocyte death in ACLF.

Clinical trials in progress

THU-480
MULTICENTRIC PROSPECTIVE STUDY OF VALIDATION OF ANGIOGENESIS POLYMORPHISMS IN HCC PATIENTS TREATED WITH SORAFENIB. INNOVATE STUDY

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Background and Aims: Preclinical data suggested that significant HCC growth is dependent on angiogenesis, and an increase in tumour dimension may induce vascular endothelial cell proliferation.
SNPs in VEGF,VEGFR,HIF1α, angiopoietin2 and eNOS genes have also been correlated to tumour neoangiogenesis through different biological mechanisms.
In the ALICE-2 study patients (PT) receiving sorafenib were tested for HIF-1α,VEGF-A and VEGF-C SNPs.
At multivariate analysis rs12434438 of HIF-1α,rs2010963 of VEGF-A and rs4604006 of VEGF-C have been confirmed as independent factors for PFS and OS. At the combined analysis of significant SNPs the presence of 2 favourable alleles of VEGF compared to only 1 or to none favourable alleles, identifies three populations with different PFS (respectively: 10.8 vs. 5.6 vs. 3.7 months, $p < 0.0001$) and OS (respectively: 19.0 vs 13.5 vs 7.5 months; $p < 0.0001$). Furthermore the presence of GG genotype of rs12434438 (HIF-1α)select a population with a particularly poor outcome independently from the clinical effect of the two VEGF SNPs(PFS: 2.6 months,$p < 0.0001$; OS:6.6 months,$p < 0.0001$).
In ePHAS study PT homozygous for a specific haplotype (Ht1:T-4b at eNOS-786/eNOS VNTR) showed a lower median PFS(2.1vs6.2 months, $p < 0.0001$)and OS(5.0vs14.9 months, $p < 0.0001$)compared to other genotypes. The multivariate analysis confirmed specific haplotype as the only independent prognostic factor.

On the basis of these premises we want to validate in a prospective study the potential role of VEGF,VEGFR,HIF-1, Ang2 and eNOS SNPs in PT with HCC treated with sorafenib.
Methods: This is a prospective non pharmacological study. The study population consisted of PT with advanced-stage HCC and PT not eligible for locoregional treatments or liver transplantation. The primary aim of the study is to validated the prognostic or predictive role of *eNOS,Ang2,HIF-1, VEGF and VEGFR* SNPs in relation to clinical outcome of PT treated with sorafenib.

THU-481
PROGNOSIS OF ACUTE LIVER FAILURE PATIENTS DUE TO DIFFERENT ETIOLOGY TREATED WITH ARTIFICIAL LIVER

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Background and Aims: Acute liver failure (ALF) is one condition that is characterized with encephalopathy and coagulopathy which can lead to multiorgan system failure. ALF has high mortality rate and requires immediate efficient and effective treatment. Nowadays, liver transplant has become the most effective treatment so far. Due to the limited availability and donor resources, many researches have been studied to develop a new technique of treatment. Artificial liver has many functions, such as for detoxification, correction of coagulopathy, suppression of inflammation, and promotion of liver cell regeneration. This could be an alternative procedure to prolong the survival time of ALF patients. The aim of this study is to determine the survival time of ALF patients treated with artificial liver.
Methods: The data will be collected from ALF patients with different etiology in our hospital from 1st January 2006–31st December 2015 for survival rate analysis. Patients with ALF who received artificial liver treatment will become the experimental group. ALF patients which do not receive artificial liver treatment will become the control group. The survival rate from both the groups within twenty eight days will be compared. Parameters of the laboratory results include: INR, ammonia, hepatic enzymes, serum bilirubin, serum creatinine are monitored in this study. This study uses Li's artificial liver system (Li-ALS) which pair low-volume plasma exchange (low-volume PE) with plasma filtration adsorption (PFA).
Conclusions: This study is expected to determine the effectiveness of artificial liver in prolonging survival time and in decreasing the mortality rate from ALF.

THU-482
ENDURANCE-3: A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY TO COMPARE EFFICACY AND SAFETY OF ABT-493/ABT-530 TO SOFOSBUVIR CO-ADMINISTERED WITH DACLATASVIR IN ADULTS WITH HCV GENOTYPE 3 INFECTION

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Background and Aims: Hepatitis C viral (HCV) infection is a global health problem affecting over 170 million people worldwide. HCV genotype 3 (GT3) infection is commonly found in Latin America (5% > 30%), Europe (20% > 40%) and Asia (30% > 45%), and affects 12% of HCV patients in the United States. Studies have shown that the combination of sofosbuvir (SOF) and daclatasvir (DCV) achieved 12-week sustained virologic response (SVR12) in 96% of HCV GT3-infected, treatment-naive patients without cirrhosis following a 12-week treatment regimen. Currently, 2 next-generation direct-acting antiviral agents (DAA), ABT-493 (identified by AbbVie and Enanta), an HCV NS 3/4A protease inhibitor and ABT-530, an NS5A inhibitor, are being developed for the treatment of all 6 major HCV genotypes. In a phase 2b study (M14-868 Part 1), promising efficacy and safety results were obtained in GT3-infected patients receiving ABT-493 and ABT-530 for 12 weeks. In this phase 3 study, the efficacy and safety of ABT-493 and ABT-530 combination will be confirmed in treatment-naive non-cirrhotic HCV GT3-infected patients and directly compared to the standard-of-care SOF + DCV regimen.
Results: This is a Phase 3, randomized, open-label, active-controlled, multicenter study. Patients will be randomized approximately 2:1 across 2 arms. Arm A will enroll approximately 230 HCV GT3-infected, treatment-naïve patients without cirrhosis who will receive ABT-493/ABT-530 300 mg/120 mg QD for 12 weeks. Arm B will enroll approximately 115 HCV GT3-infected, treatment-naïve patients without cirrhosis who will receive SOF 400 mg + DCV 60 mg QD for 12 weeks. Patients who complete or prematurely discontinue the treatment will be followed for 24 weeks after their last dose of study drugs to evaluate efficacy and the emergence and persistence of viral variants. The first primary objective of this study is to demonstrate non-inferiority of the ABT-493/ABT-530 regimen compared to SOF + DCV by analyzing the percentage of patients achieving SVR12 following 12 weeks of treatment with ABT-493/ABT-530. Additionally, pharmacokinetics of the study drugs will be analyzed in the study.

THU-483
PHARMACOKINETICS OF THE ANTIFIBROTIC DRUG PIRFENIDONE IN CHILD PUGH A AND B CIRRHOTIC PATIENTS COMPARED TO HEALTHY AGE-MATCHED CONTROLS

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Background and Aims: Pirfenidone (**PF**) has demonstrated anti-inflammatory and anti-fibrogenic effects in experimental models of cirrhosis and also in open trials with humans affected with hepatic fibrosis caused by different etiologies. Since the EMA and FDA authorization for **PF** usage in the treatment of patients with Idiopathic Pulmonary Fibrosis, this novel antifibrotic agent is currently in phase II and III clinical development for the treatment of other fibrotic diseases including liver, skin, renal, cardiac and multiple sclerosis. Considering the wide variation in liver function in patients with cirrhosis we aimed to evaluate PF pharmacokinetics.
Methods: A total of 24 subjects (9 men and 15 non pregnant women), aged 58 ± 12 entered the trial; 8 subjects had cirrhosis Child Pugh A, and 8 Child Pugh B and 8 were age-matched healthy volunteers, with no fibrosis result (F0) by using a non invasive validated serologic test (Fibrotest™, Bio Predictive). All volunteers received orally two 600 mg tablets of a slow release formulation of PF, in the morning and in fasted state. Subjects remained in a phase I clinical study unit throughout treatment and for 36 hours after PF administration. Serial blood samples were collected prior to dosing (0 hour) and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 30 and 36 hours after dosing. Analysis was done with mass spectrometry.
Results: Cirrhosis was alcohol related in 6, HCV in 6, Autoimmune in 2 and NASH related in 2 patients. Main pharmacokinetic parameters per group revealed the following results:

PK parameters	Non Cirrotics (Healthy-F0) N = 8	Child Pugh A Cirrhotics (N = 8)	Child Pugh B Cirrhotics (N = 8)
AUC 0-t (μg/mL*h)	57.8 ± 24.0	210.6 ± 43.2	205.4 ± 60.0
AUC 0-α (μg/mL*h)	62.1 ± 23.3	231.6 ± 59.3	287.2 ± 165.5
C max (μg/mL)	6.6 ± 2.6	12.4 ± 0.9	11.7 ± 3.3
T max (h)	4.1 ± 0.8	5.0 ± 0.7	4.4 ± 0.3
T ½ (h)	4.8 ± 0.7	8.6 ± 2.1	7.4 ± 3.6