EASL- 2016

ABSTRACTS ON ACLF

INDEX

	MECHANISMS AND POSITIVELY CORRELATE WITH THE DISEASE OUTCOME IN ACUTE-ON-CHRONIC LIVER FAILURE	
FRI-108	NUCLEOSIDE ANALOGUES IMPROVE THE SHORT-TERM PROGNOSIS OF CHRONIC HEPATITIS B PATIENTS WHEN THEY SUFFERED AN ACUTE-ON-CHRONIC LIVER FAILURE	61
SAT-039	INCIDENCE, PREDICTORS AND OUTCOMES OF ACUTE ON CHRONIC LIVER FAILURE IN OUTPATIENTS WITH CIRRHOSIS	62

PS015

MER TYROSINE KINASE REGULATES THE ACTIVATION OF MYELOID CELLS AND INNATE IMMUNE RESPONSES IN ACUTE-ON-CHRONIC LIVER FAILURE

A. Singanayagam[1,2,3], E. Triantafyllou[1,2,3], V.C. Patel[2], C. Bernsmeier[2], C. Weston[3], S. Curbishley[3], C. Willars[2], W. Bernal[2], G. Auzinger[2], M. Heneghan[2], A. Dhar[1], D. Adams[3], M. Thursz[1], J. Wendon[2], C.G. Antoniades[1,2,3]. [1]Department of Digestive Diseases, Imperial College London; [2]Institute of Liver Studies, King's College Hospital, London; [3]Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom E-mail: asinganayagam@yahoo.co.uk

Background and Aims: Central to the pathogenesis of acute-on-chronic liver failure (ACLF) is immuneparesis and monocyte dysfunction, which accounts for the susceptibility to infection and increased mortality. Mer tyrosine kinase (MerTK), expressed on monocytes/macrophages dampens innate immune responses to microbial stimuli. We determined functional and migratory characteristics of circulating and tissue-derived myeloid cells expressing MerTK.

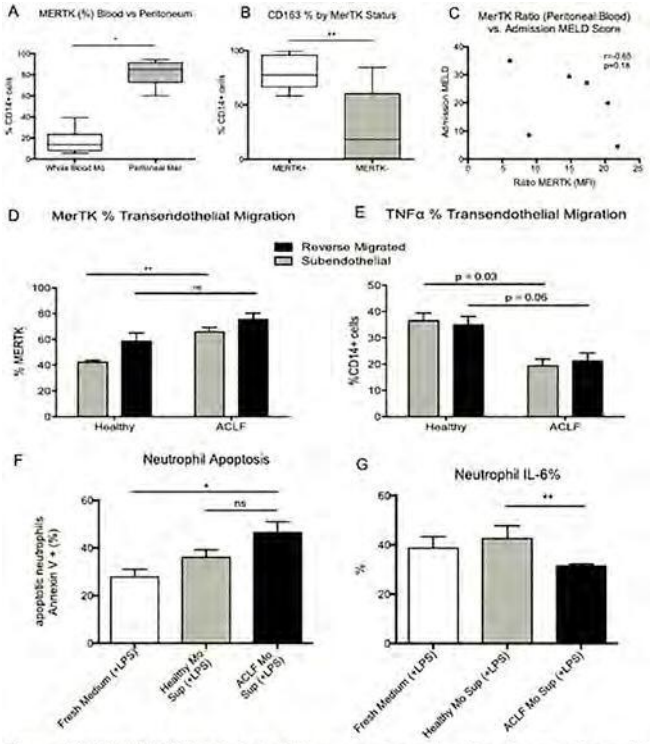


Figure. (A) MerTK (%) Matched circulating monocytes and peritoneal macrophages (B) CD163 expression by MerTK status (C) Reduced peritoneal macrophages: circulating monocyte MerTK (MFI) ratio correlates with admission MELD score (D) MerTK% increased in ACLF vs. healthy in migrated (subendothelial) and even greater in reverse migrated monocytes (E) TNFa% decreased in ACLF vs. healthy. When neutrophils conditioned in supernatants from LPS-stimulated monocytes in ACLF plasma, increased apoptosis (F) and decreased neutrophil IL-6 production (G).

Methods: Using flow cytometry, immunophenotype and functional responses (LPS-induced TNFα/IL-6 production) of peritoneal macrophages

(pMφ) in ascites and circulating monocytes were measured in patients with ACLF (n = 10). pMφ pathogen uptake was assessed using a phagocytosis assay (n = 4). Migratory characteristics of circulating monocytes were assessed using a transendothelial migration (TEM) assay in healthy control (HC) (n = 6) and ACLF (n = 6).
Effects of ACLF-derived monocytes on neutrophil function were assessed after culture of healthy neutrophils in supernatants derived from LPS-stimulated monocytes using Annexin V and LPS-induced TNFα/IL-6 production (n = 8).
Results: pMφ exhibit an anti-inflammatory ($MerTK^{high}CD163^{high}$) phenotype. Compared with circulating monocytes, MerTK expression is markedly elevated (82.1% vs. 16.6%, p = 0.03). pMφ:blood monoyte MerTK ratio inversely correlated with MELD score (r = −0.65, p = 0.18). In ACLF, circulating MerTK-expressing monocytes had reduced TNFα secretion compared to MerTK negative (6.32% vs. 24.9%, p = 0.094). Phagocytosis was preserved in pMφ (p = 0.03). LPS-stimulated TNFα (p = 0.4) and IL-6 (p = 0.228) secretion was attenuated. Compared to HC, monocytes in ACLF had higher MerTK expression (65.7% vs. 42.4%; p = 0.002) and lower TNFα secretion (48.6% vs. 25.3%, p = 0.03) after TEM; MerTK expression inversely correlated with TNFα secretion (r = −0.49, p = 0.05). Compared to HC, neutrophils cultured with supernatants from LPS-stimulated circulating monocytes in ACLF demonstrated increased apoptosis (46.5% vs. 36.2%, p = 0.28) and reduced TNFα (23.5% vs. 29.7%, p = 0.35) and IL-6 (31.4% vs. 42.6%, p = 0.01) secretion.

Conclusions: Our data shows progressively enhanced MerTK expression as monocytes enter and then exit tissues, signified by lower tissue:circulation ratio, associated with impaired activation of circulating and tissue-specific myeloid cells in ACLF, and higher MELD scores. This highlights the regulatory role of MerTK-signalling in innate immune responses. Future work is required to elucidate this novel mechanism of immuneparesis to develop immunotherapeutic targets.

PS033

THE DECISION FOR LIVER TRANSPLANT IN ACUTE ON CHRONIC LIVER FAILURE (ACLF) - FIRST WEEK IS THE CRUCIAL PERIOD - ANALYSIS OF THE APASL ACLF RESEARCH CONSORTIUM (AARC) PROSPECTIVE DATA OF 1021 PATIENTS

A.K. Choudhury[1], M.K. Sharma[1], R. Maiwal[2], P. Jain[3], M.A. Mahtab[4], Y.K. Chawla[5], S.S. Tan[6], Q. Ning[7], H. Devarbhavi[8], D.N. Amarapurkar[9], C.W. Kim[10], S.S. Sadiq[11], A.S. Butt[11], C. Eapen[12], H. Ghazinyan[13], C. yu[14], A. Sood[15], G.H. LEE[16], Z. Abbas[17], G. Shiha[18], L.A. Lesmana[19], D.A. Payawal[20], K.A. Dokmeci[21], G.K. Lau[22], S.K. Sarin[1], APASL ACLF Working party. [1]Hepatology and Liver Transplant; [2]Hepatology; [3]Dept of Research, Institute of Liver and Biliary Sciences, New Delhi, India; [4]Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; [5]Hepatology, Pgimer, Chandigarh, India; [6]Selayang Hospital University of Malaya, Malaysia, Malaysia; [7]Department of Infectious Disease, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [8]St John Medical College, Bangalore; [9]Bombay Hospital & Medical Research Centre, Mumbai, India; [10]Division of Hepatology, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, South Korea; [11]Aga Khan University Hospital, Karachi, Pakistan; [12]Hepatology, CMC, Vellore, India; [13]Nork Clinical Hospital of Infectious Diseases, Armenia, Armenia; [14]Hepatology Institute Capital Medical University, Beijing, China; [15]CMC, Ludhiana, India; [16]Department of Gastroenterology & Hepatology, National University Health System, National University of Singapore, Singapore, Singapore; [17]Sindh Institute of Urology and Transplantation, Karachi, Pakistan; [18]Egyptian Liver Research Institute and Hospital, Egypt, Egypt; [19]Digestive Disease & Oncology Centers, Medistra Hospital, Jakarta, Indonesia; [20]Fatima Medical University Hospital, Manila, Philippines; [21]Ankara University School of Medicine, Ankara, Turkey; [22]Institute of Translational Hepatology, Beijing, China
E-mail: ashok@aclf.in

Background and Aims: ACLF is associated with rapidly progressive liver failure with high short-term mortality. Early identification and intervention for acute insult, aggressive critical care, support for organ failures and timely consideration of liver transplant may improve survival. We investigated the predictors of outcome and the dynamic changes to define the ideal timing of liver transplantation. Methods: The patients diagnosed to have ACLF as per APASL definition were recruited from 40 centres across Asia Pacific. The data was prospectively collected on a predefined format in the database from October 2012 to July 2015 Clinical events, laboratory parameters, disease severity score, organ failures were analysed at baseline and their dynamic changes at D4 and D7 to predict the 28 and 90 days survival outcome.

Results: Of the 2312 enrolled patients, complete follow up data of 1021 was available till last follow-up and was analyzed. The mortality was 11.3%, 22.1% and 43.5% respectively within 4, 7 and 28 day of admission. At

presentation, age (HR 1.10, 95 CI = 1.00–1.02), total bilirubin (HR 1.03 95 CI = 1.02–1.04), creatinine (HR 1.23 95 CI = 1.18– 1.27), INR (HR 1.31 95 CI = 1.25–1.35), HE grade (HR 2.32 95 CI = 2.05– 2.63), Lactate (HR 1.18 95 CI = 1.15–1.21) were independent predictors of 28 days mortality. Absence of new onset HE or AKI within first 4 days, a decline in total bilirubin by 0.43 mg/dL, creatinine by 0.31 mg/dL, INR by 0.34 by day 7 predicted survival ($p < 0.001$). Bilirubin <20.5 mg/dL, Creatinine <0.94 mg/dL, INR <2.18 and MELD score <27 at any time point in first week was associated with 100% survival. A bilirubin of >22 mg/dL, HE Grade –III or IV, INR >2.5, with either creatinine of >1 mg/dL or lactate 1.5 mmol/lit at baseline or persistence of same at D4 or D7 leads to 100% mortality within 28 days.

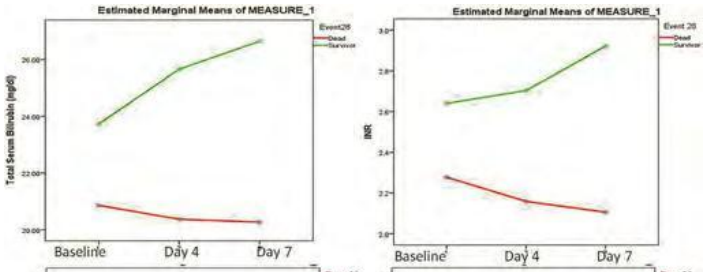


Fig-1.Trend of Parameters in first week as predictor of 28 days Survival.(GEE model, All Graph p<0.001)

Conclusions: ACLF is a serious condition with high short term mortality. The baseline parameters and their change in first week of diagnosis could identify the patient with universal fatality. Emergent live donor LT or special allocation policy for DDLT should be explored in the first week.

PS061

POLYMORPHISMS IN THE INTERLEUKIN (IL)-1 GENE CLUSTER INFLUENCE THE INFLAMMATORY BURDEN IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE

J. A. Quiles[1], E. Titos[1,2], M. Casulleras[1], C. López-Vicario[1], B. Rius[1], A. Lopategi[1], A. de Gottardi[3], M. Bernardi[4,5], I. Graziadei[6], H. Gronbaek[7], P. Ginès[2,8], V. Arroyo[5,9], J. Clària[1,10]. [1]Department of Biochemistry and Molecular Genetics (CDB), Hospital Clinic; [2]CIBERehd, Barcelona, Spain; [3]University of Berne, Berne, Switzerland; [4]EASL-CLIF Consortium; [5]European Foundation for the Study of Chronic Liver Failure (EF-CLIF), Barcelona, Spain; [6]Innsbruck medical University, Innsbruck, Austria; [7]Aahrus University Hospital, Aahrus, Denmark; [8]Liver Unit; [9]Unit Liver, Hospital Clinic; [10]Department of Physiological Sciences I, University of Barcelona, Barcelona, Spain
E-mail: joalcara@clinic.ub.es

Background and Aims: Acute-on-Chronic liver failure (ACLF) is an increasingly recognized entity encompassing multiorgan failure in patients with cirrhosis. Recent findings suggest that immune dysregulation predisposes decompensated cirrhotic patients to a cycle of adverse events culminating in uncontrolled systemic inflammation and ACLF progression. Although the exact mechanisms leading to inflammation-driven ACLF remain to be elucidated, systemic inflammation is influenced by multiple genes regulating the innate immune response. In this study, we analyzed the impact of inflammation-related polymorphisms on the appearance of ACLF.

Methods: Two hundred seventy-nine cirrhotic patients (178 with ACLF and 101 without ACLF) from the CANONIC study of the CLIF consortium were genotyped for SNP polymorphisms in genes coding for IL-1beta (rs1143623, G/C), IL-1 receptor antagonist (IL-1ra) (rs4251961, T/C), SOCS3 (rs4969170, G/A), NOD2 (rs3135500, G/A), CMKLR1 (rs1878022, T/C) and IL-10 (rs1800871, G/A) by allellic discrimination TaqMan assays. Serum cytokine levels were measured by fluorescent bead-based (Luminex) immunoassays.
Results: Among the six SNPs analyzed, we identified two polymorphisms belonging to the IL-1 gene cluster (IL-1beta, rs1143623 and IL-1ra, rs4251961) in strong association with ACLF. Homozygous C carriers in the rs1143623 SNP showed lower serum levels of IL-1β in parallel with reduced markers of systemic inflammation (i.e. IL-1alpha, IL-6, C-reactive protein and white blood cells count). Also, heterozygous TC carriers of the

rs4251961 SNP had lower serum levels of IL-1beta, IL-1alpha, IL-6, IL-8 and IL-10. Under different inheritance models, both genotypes were protective factors for presence of ACLF (rs1143623; OR: 0.34, $p < 0.05$ and rs4251961; OR: 0.60, $p < 0.05$). Notably, a higher frequency of both variants was seen in patients without ACLF (80%) than in those with ACLF (20%).

Conclusions: Common functional polymorphisms in genes coding for IL-1beta and IL-1ra play a role as protective factors in the inflammatory process related with the development of ACLF in decompensated liver cirrhosis patients.

THU-279

METHACETIN BREATH TEST IS SUPERIOR TO MELD IN PREDICTING MORTALITY IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE: RESULTS OF A PHASE II CLINICAL TRIAL

A.K. Choudhury[1], A. Bhardwaj[2], C.K. Kedarisetty[1], Y. Ilan[3], S.K. Sarin[1].
[1]Department of Hepatology; [2]Department of Clinical Research, Institute of Liver and Biliary Sciences, New Delhi, India; [3]2Gastroenterology and Liver Units, Department of Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel
E-mail: doctor.ashokchoudhury@gmail.com

Background and Aims: Background: Acute on chronic liver failure (ACLF) is associated with progressive liver failure leading to high mortality. The clinical, biochemical and disease severity score, their change (change) were not validated for outcome prediction and management decision. Quantitative liver function tests, like ^{13}C-Methacetin breath test (MBT) could enable the assessment of liver function and may predict the recovery or deterioration of liver failure. Aim: To assess the clinical utility of serial MBT in patients of ACLF for prediction of short and long-term mortality.

Methods: Outcome was examined with regard to standard clinical criteria and MBT results. MBT was performed using BreathID® continuous online after 8-hours of fasting. The patient need to ingest 75 mg of Methacetin, followed by breath analysis. The tests were repeated weekly, twice for 4 weeks. The 3 consecutive decline (>20%) in percentage dose recovery (PDR) peak values or 2 consecutive declines in Cumulative PDR at 20 minutes (cPDR20) values (>30%) were correlated with both short term (i.e. 28 days) and long term (i.e. 90 days) survival and disease severity score. A MELD score <15, MBT on discharge with PDR peak >5%/h were considered as criteria for survival.

Results: Total of twenty four ACLF patients were recruited (13 alcohol, 4 HEV and 7 others; 20 Males; ages 19 to 65 years with a mean MELD score at admission of 17.5 ± 6.9), 22 fulfilled the criteria for long-term and 11 for short-term analysis. Of the 11 patients, the short-term survival prediction algorithm was in agreement in 90.9% (95%CI: 58.7–99.8%), as compared to MELD, where there was agreement in survival for 72.7% (95%CI: 39.0–94.0%) of the patients. Of the 22 patients followed for one year, the last MBT at discharge predicted survival in 4 out of 5 (80% PPV). MELD predicted survival for 14 patients (86% PPV). An improvement of the MBT had a high predictive value for one year survival (29% improvement in

survivors versus 10% decline among nonsurvivor), in contrast to MELD where the improvement in survivors was 20% versus 23% respectively.

Conclusions: The ^{13}C-MBT provides a rapid, real time, easily non-invasive assessment for liver function in patients of ACLF unaffected by non-liver confounding factors. This suggests the use of MBT may be a valuable tool for early prognostication and prioritization for liver transplantation.

THU-290

ACUTE ON CHRONIC LIVER FAILURE SECONDARY TO DRUGS: CAUSES, OUTCOME AND PREDICTORS OF MORTALITY

H. Devarbhavi[1], A.K. Choudhury[2], V.V. Reddy[3], M.K. Sharma[2], R. Maiwall[2], P. Jain[4], M. Al-Mahtab[5], Y.K. Chawla[6], S.S. Tan[7], Q. Ning[8], S.S. Hamid[9], C.E. Eapen[10], H. Ghazinyan[11], Z. Duan[12], A. Sood[13], G.H. Lee[14], Z. Abbas[15], G. Shiha[16], L.A. Lesmana[17], D.A. Payawal[18], G. Kumar[4], S.K. Sarin[2], APASL ACLF Working party. [1]ST John Medical College, Bangalore; [2]Hepatology, Institute of Liver and Biliary Sciences, New Delhi; [3]Hepatology, ST John Medical College, Bangalore; [4]Research, Institute of Liver and Biliary Sciences, New Delhi, India; [5]Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; [6]Hepatology, PGIMER, Chandigarh, Chandigarh, India; [7]Hepatology, Selayang Hospital University of Malaya, Malaysia, Malaysia; [8]Hepatology, Institute of Infectious Disease, China; [9]Hepatology, Aga Khan University Hospital, Karachi, Pakistan; [10]Hepatology, CMC, Vellore, India; [11]Hepatology, Nork Clinical Hospital of Infectious Diseases, Armenia; [12]Hepatology, Hepatology Institute Capital Medical University, Beijing, China; [13]Hepatology, CMC, Ludhiana, India; [14]Hepatology, Department of Gastroenterology & Hepatology, National University Health System, National University of Singapore, Singapore, Singapore; [15]Hepatology, Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan; [16]Hepatology, Egyptian Liver Research Institute And Hospital, Egypt, Egypt; [17]Hepatology, Digestive Disease & Oncology Centers, Medistra Hospital, Jakarta, Indonesia; [18]Hepatology, Fatima Medical University Hospital, Valenzuela MetroManila, Valenzuela, Philippines

E-mail: ashok@aclf.in

Background and Aims: Acute hepatic decompensation in patients with chronic liver disease carries significant short term mortality. Although a number of precipitating events may trigger acute on chronic liver failure (ACLF) the impact of drugs on outcome has not been studied. We evaluated drugs as precipitating factors in ACLF in a prospectively enrolled cohort of patients from the AARC consortium.

Methods: ACLF was defined as per APASL criteria (Hepatol Int 2009;3:269). ACLF-APASL research consortium (AARC) includes 24 centres from Asia-pacific region. We investigated the influence of drugs, both antituberculosis therapy (ATT) and non ATT (complementary and alternative medicines (CAM), methotrexate, interferons, others) as acute precipitants in causing ACLF. We studied their baseline clinical, laboratory characteristics including 4 and 7 day values and its impact on mortality. Univariate and multivariate analysis was carried out including Cox proportional regression analysis and a Kaplan Meier analysis curve.

Results: Of the 2224 patients enrolled in AARC, drugs constituted 6.5% (N = 145) as precipitating events. Complete data was available for 136 patients. Anti-tuberculosis therapy (ATT) and non-ATT constituted 62 (46%) and 74 (54%) cases respectively of which 36 (58%) and 47 (63.5%) died. The

majority of underlying chronic liver diseases were secondary to cryptogenic and alcoholic liver disease (>80%). Characteristics between survivors vs non survivors were as follows: Hemoglobin: 11.7 vs 10.8 (p = 0.02), WBC count (9.6 vs 13.5, p = <.001), serum creatinine (SCr) (0.9 vs 1.6, p = 0.002, International normalized ratio (INR)) (2.3 VS 3, p = <0.001, presence of ascites (p = 0.04)) and encephalopathy (p = 0.006). On multivariate analysis the following factors were associated with survival: SCr and (INR) p < .0001(at baseline), INR, serum lactate (S Lac) and serum alkaline phosphatase on day 4 (p < .01) and S Lac on day 7 (p = .002). Using Cox regression analysis SCr and INR were the best predictors of mortality (p < .0001) (Hazard ratio 1.4 and 1.5 respectively). The overall median survival time was 23.5 days (range 12.6–34.7), which was shorter for non ATT drugs compared to ATT drugs (22 vs 31 days).
Conclusions: Drugs as precipitating events constitute 6.5% of cases in ACLF of which ATT and CAM are the commonest causes. Mortality is significant (61%). Presence of encephalopathy, ascites and elevated serum creatinine, INR, and serum lactate are predictors of survival.

THU-315

URINARY MICRO-ALBUMIN LEVEL AND ITS MODIFICATION STATUS SERVE AS AN NON-INVASIVE MARKER FOR OUTCOME PREDICTION IN ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) PATIENTS

S. Hussain[1], S. Das[1], J.S. Maras[1], S.M. Shasthry[2], S.K. Sharma[1], S.K. Sarin[2]. [1]Department of Molecular and Cellular Medicine;
[2]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India
E-mail: shabirhussain.86@gmail.com

Background and Aims: Serum albumin modification and functionality in ACLF patients is well known. Reliable and non-invasive method to determine systemic albumin (Alb) status is yet not known. We investigated urinary micro-albumin (μA) as a putative indicator of circulatory Alb phenotype.

Methods: Urine samples from patients with alcohol related ACLF (n = 100), chronic liver disease (CLD, n = 20), chronic kidney disease (CKD, n = 10), acute liver failure (ALF, n = 10) and healthy control (HC, n = 40) were subjected to micro-albumin (μA), ischemia modified albumin (IMA), IMAr, advanced oxidation protein products (AOPP), advanced glycation end-products (AGEP), Albumin-binding capacity (ABiC) determination. All ACLF patients were treated with corticosteroids and steroid response was assessed at day 4 and 7 (Lille score <0.45 as response) in plasma and urine samples.

Results: Urinary μA levels were highest in CKD patients[338 mg/dL], whereas it was significantly higher in ACLF [50 mg/dL] as compared to CLD[28 mg/dL], ALF [6 mg/dL] or HC [0.17 mg/dL] ($p < 0.05$). The level of IMA and IMAr was significantly higher in ACLF as compared to CKD or HC, with both levels being similar and highest in CLD and ALF
($p < 0.05$). AOPP was significantly more in ACLF as compared to CKD,
CLD, ALF or HC ($p < 0.05$). AGEP were increased in CLD and ALF as compared to CKD, ACLF or HC ($p < 0.05$). Functionality of Alb measured as ABiC was reduced in ACLF and CKD as compared to
CLD, ALF or HC ($p < 0.05$). Temporal analysis of ACLF highlighted a decrease in oxidative modification in μA that corroborated with increase in ABiC levels. ACLF patients Non-responders to steroids (NR) had increased urinary μA levels than responders (R) at D0, Day4 or Day7 ($p < 0.05$) (AUROC = 0.7; $p < 0.05$). NR showed increased AGEP and decreased AOPP levels ($p < 0.05$). Concomitantly ABiC was increased in NR as compared to R ($p < 0.05$), suggesting that AOPP formation results in reduction of the Alb

drug binding capacity. Urinary μA significantly correlated with MELD and SOFA score in ACLF patients ($r = 0.3$, $p < 0.05$).

Conclusions: Urinary μA can be used as a reliable and simple non-invasive biomarker for outcome prediction in ACLF alcoholic patients.

THU-319

MOLECULAR ELLIPTICITY OF CIRCULATING ALBUMIN-BILIRUBIN COMPLEX IS A RELIABLE PROGNOSTIC MEASURE OF SEVERITY OF ACUTE ON CHRONIC LIVER FAILURE (ACLF)

S. Das[1], J.S. Maras[1], S. Hussain[1], C. Sudarshan[2], S.M. Shastry[3], S.K. Sharma [1], P. Balaram[4], S.K. Sarin[5]. [1]Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi; [2]Molecular Biophysics Unit, Indian Institute of Science, Bangalore; [3]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi; [4]Molecular Biophysics Unit, Indian Institute of Science, Bangalore; [5]Department of Molecular and Cellular Medicine and Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India
E-mail: suri.sukanta@gmail.com

Background and Aims: Interaction of bilirubin with albumin results in an optically active albumin-bilirubin (A-B) complex, measured using circular dichroism (CD) spectroscopy. In liver failure patients, specially ACLF, high bilirubin and low albumin are generally seen and this may affect formation of A-B complexes. We investigated the correlation of variability in A-B complex with the severity and albumin functionality in ACLF patients, in two phases; discovery (DP) and validation phase (VP).

Methods: Albumin/bilirubin (A/B) ratio was determined in plasma samples of ACLF [n = 90; 40 enrolled during DP and 50 during VP], cirrhosis [n = 60; 30DP and 30VP], and healthy controls [HC, n = 30; 15DP and 15VP] and CD spectra of A-B complexes were recorded. The optical activity of A-B complex (in term of molecular ellipticity) was estimated from the CD spectra, which was then correlated with the severity and outcome in ACLF patients. Further, the plasma samples were subjected to determination of albumin binding capacity (ABiC) and correlated with molecular ellipticity.

Results: The A/B ratio was reduced in ACLF (1.33) as compared to cirrhosis (12.66) and HC (107) ($p < 0.01$). Molecular ellipticity of A-B complex was found to be highest in ACLF (2.47 mdeg), compared to cirrhosis (1.1 mdeg) and HC (0.67 mdeg) ($p < 0.01$). Molecular elipticity significantly correlated with MELD, CTP and SOFA scores ($p < 0.05$, $r2 > 0.3$). ROC analysis showed AUROC of 0.74 ($p < 0.01$, 95% CI “0.633–0.856”), cut-off of 1.5 mdeg at “86–87” sensitivity-specificity for molecular ellipticity, which correlated significantly with mortality ($p < 0.05$, $r2 > 0.3$). KM curve analysis elucidated an increase in the overall mortality or 1 month mortality in ACLF patients with molecular elipticity >1.5 medg (log rank <0.01). In addition, binding capacity of circulatory albumin (ABiC) was found to be

significantly reduced ($p < 0.001$) in ACLF(54.4%) as compared to cirrhosis (74.3%) and HC (96.1%), inversely correlating with molecular ellipticity of A-B complex ($p < 0.05$, $r2 > 0.3$).

Conclusions: Molecular ellipticity of A-B complex in plasma correlates with severity and outcome of ACLF patients. Increased interaction between bilirubin and albumin molecules in ACLF patients is an additional mechanism for reduced functionality of albumin and can serve as a reliable marker of outcome in ACLF patients.

THU-320

IRREVERSIBLE MODIFICATION OF CIRCULATING ALBUMIN IN ACUTE ON CHRONIC LIVER FAILURE (ACLF) TRIGGERS NEUTROPHIL BURST VIA INDUCING GENES ASSOCIATED TO CYTOKINE RELEASE AND CELLULAR STRESS

S. Das[1], J.S. Maras[1], S. Hussain[1], P. David[1], S.M. Shasthry[2], N. Trehanpati[1], S.K. Sharma[1], T.P. Singh[3], S.K. Sarin[4]. [1]Department of Molecular and Cellular Medicine; [2]Department of Hepatology, Institute of Liver and Biliary Sciences; [3]Department of Biophysics; [4]Department of Molecular and Cellular Medicine and Department of Hepatology, All India Institute of Medical Sciences, New Delhi, India
E-mail: suri.sukanta@gmail.com

Background and Aims: Circulating milieu in ACLF patients is associated with increased systemic oxidative stress and concurrent immune cell activation. Neutrophil respiratory burst results in generation of ROS and RNS. Circulating albumin has ROS and RNS scavenging properties. Modifications in the albumin structure may result in its inability to curb oxidative stress. We examined the contribution of modified circulating albumin in neutrophil activation, production of intracellular stress and associated altered molecular pathways.

Methods: Albumin was purified from plasma of alcoholic ACLF (n = 10), cirrhosis (n = 10) and healthy controls (HC, n = 10). Plasma oxidative stress was measured by advanced oxidative protein product (AOPP). Neutrophils from healthy subjects was incubated with albumin purified from study groups and commercially available albumin (5% HSA). Intracellular ROS production was measured by FACS dihydrorhodamine (DHR) test. Cell supernatant was subjected to measurement of neutrophil activation markers; MPO and NGAL. Neutrophils isolated from study groups were subjected to RT-PCR based expression analysis for a panel of 83 genes associated with oxidative stress, neutrophil activation, ER stress, apoptosis, cell adhesion, chemokine and interleukin modules.

Results: The purified albumin was 95% pure. Plasma levels of AOPP were found to be significantly higher ($p < 0.05$) in ACLF [151.1 μmol/L] as compared to cirrhosis [86.15 μmol/L] or HC [27.40 μmol/L]. Intracellular ROS was found to be highest in healthy neutrophil incubated with ACLF-albumin [MFI = 2,500] as compared to cirrhosis-albumin [MFI = 1,200] or HC-albumin [MFI = 1,000] ($p < 0.01$).

Commercial albumin did not demonstrate significantly different

ROS levels in healthy neutrophils. ACLF-albumin treated cell supernatant had significantly higher ($p < 0.05$) MPO and NGAL levels [53.4, 31.4 ng/mL] as compared to that from cirrhotic [45.4, 10.9 ng/mL] or HC [26.9, 5.1 ng/mL]. RT-PCR analysis revealed increased gene expression (>2FC, $p < 0.05$) in all modules [oxidative stress(79%), neutrophil activation (100%), ER stress (30%), apoptosis
(58%), cell adhesion (50%), chemokine and interleukin (57%)] in neutrophils of ACLF as compared to cirrhosis.
Conclusions: The present study provides evidence that albumin in
ACLF patients is not only oxidatively modified but also acts as a potent mediator for induction of neutrophils during ACLF.

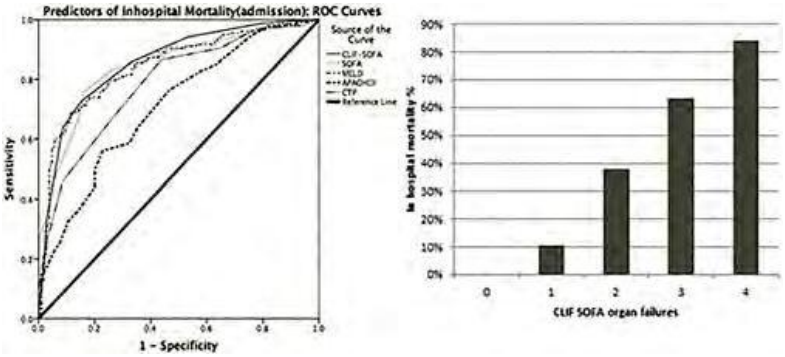
THU-028

ASSESSMENT OF PROGNOSTIC SCORES IN ACUTE ON CHRONIC LIVER FAILURE PATIENTS ADMITTED TO CRITICAL CARE UNITS: A CANADIAN COHORT STUDY

E. Sy[1], J. Ronco[1], C. Karvellas[2]. [1]Critical Care Medicine, University of British Columbia, Vancouver; [2]Critical Care Medicine, University of Alberta, Edmonton, Canada
E-mail: cjk2@ualberta.ca

Background and Aims: Cirrhotic patients with organ failure/critical illness (acute on chronic liver failure ~ACLF) are at risk for imminent death. The chronic liver failure–sequential organ failure assessment (CLIF-SOFA) was developed recently and has not previously been validated in North American patients.
Methods: We retrospectively examined 274 ACLF patients (mean age 55 years; 50% alcohol) that were urgently admitted between 01/2000 and 12/2011 to ICU at Vancouver General Hospital, Canada. The abilities of liver (Model for end-stage liver disease ~MELD; Child Pugh ~CTP) and critical illness/organ failure scores (APACHEII, SOFA) were compared with CLIF-SOFA in predicting patient outcomes.

Results: Of 274 cirrhotic patients, 270 had at least 1 organ failure defined by CLIF-SOFA (n = 1, 48; n = 2, 90; n = 3, 90; n = 4 or more, 38). On admission, patients had mean (standard deviation) scores of APACHE II 24 (7), MELD 26 (11), CTP 11 (2), SOFA 15 (4) and CLIF-SOFA 12 (3). Overall in-hospital mortality was 60%. ICU admission for GI bleeding portended a better outcome then other indications (hospital mortality 46% vs. 64%, p = 0.011). CLIF-SOFA and SOFA scores on ICU admission predicted patient mortality with area under the receiver-operating curve (AUROC) values of 0.86 and 0.85, respectively. These AUROC values were higher than those obtained from admission MELD (0.84), CTP (0.79) and APACHE II (0.71). At 48 hours post-admission, SOFA (AUROC 0.94) outperformed MELD (0.88). The number of organ failures (OF) defined by CLIF-SOFA correlated strongly with in-hospital mortality (1 OF ~ 17%, 2 OF ~ 53%, 3 OF ~ 80%, 4 or more OF ~ 89%, Log rank p < 0.001).



Conclusions: CLIF-SOFA and SOFA scores within the first 72 hours of ICU admission perform well in predicting in-hospital mortality. Reason for ICU admission (GI bleeding) impacted mortality. Increasing number of OFs as defined by CLIF-SOFA correlated with significant increased mortality.

THU-331

USE OF NON-SELECTIVE BETA BLOCKERS (NSBB) IN CIRRHOTIC PATIENTS WITH BACTERIAL INFECTIONS IS ASSOCIATED WITH LOWER FREQUENCY OF SEPSIS, BUT NOT OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) OR SURVIVAL. RESULTS OF A PROSPECTIVE STUDY

G.H. Pereira[1], C. Baldin[1], L. Victor[1], J. Piedade[1], L. Guimarães [1], T. Rocha[1], Z. Veiga[1], F. Fernandes[1], E. Ahmed[1], J.L. Pereira[1]. [1]Liver Unit, Bonsucesso General Hospital, Rio de Janeiro, Brazil
E-mail: ghspereira@gmail.com

Background and Aims: Use of NSBB has deleterious effects in decompensated cirrhosis. Bacterial infections are associated with Sepsis and ACLF, and NSBB trough reduction in systemic inflammatory response, could have beneficial effects. There are few data respect use of NSBB in patients with bacterial infections and their correlation with SIRS and ACLF. Our objective was to evaluate the frequency of complications of cirrhosis, incidence and clinical course of ACLF and SIRS in patients with and without NSSB use.
Methods: Cirrhotic patients prospectively included in a large database were analyzed. Bacterial infections and sepsis were diagnosed at hospitalization. ACLF was diagnosed and staged according to CLIF C OF score. Dose and type of NSSBB used within last 3 months was recorded. Frequency of complications of cirrhosis, sepsis and ACLF were compared between groups.
Results: 163 patients were included (57 ± 12 years, 64% male, MELD 18 ± 6, child C 54%). The most common type of infection was SBP and skin infections (37 and 38 patients). One hundred four patients were currently using NSSB. Patients taking NSBB more commonly had previous variceal bleeding, ascites and hepatic encephalopathy. At study inclusion, prevalence of complications of cirrhosis, liver and kidney function parameters were similar between patients taking NSBB or not. However, the frequency of ascites and hepatic encephalopathy throughout hospital stay was higher in patients taking NSBB (90 vs. 79%, 60 vs. 43%, $p < 0.05$). Use of NSBB was associated with lower heart rate (76 ± 12 vs.85 ± 15, $p < 0.001$), leukocyte count (7.5 ± 4.5 vs. 9.7 ± 7.6, $p = 0.04$) and frequency of sepsis (21 vs. 42%, $p = 0.03$). Frequency of ACLF was similar between groups (38 vs. 27%, $p = 0.2$), as well as CLIF-CF OF score and frequency of

grade 2–3 ACLF. Patients taking NSBB had lower frequency of liver and coagulation failure, but higher frequency of kidney and cerebral failure. In – hospital and 3-month survival for patients taking NSBB and not was 67 and 59% versus 69 and 63% (p = ns).

Conclusions: In patients hospitalized with bacterial infections, NSBB use is associated with higher frequency of complications of cirrhosis. Patients with NSBB had a blunted inflammatory response, as evidenced by lower frequency of sepsis. NSBB does not reduce ACLF frequency or severity, but their use correlates with distinct types of organ failure. Use of NSBB in cirrhotic patients with bacterial infections does not modify prognosis.

THU-332

LIPOCALIN-2 GENE AND ITS PROTEIN NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN ARE BIOMARKERS OF ACUTE-ON-CHRONIC LIVER FAILURE

I. Graupera[1–3], M. Coll[2], M. Llopis[2], X. Ariza[1–3], E. Solà[1–3], P. Huelin[1–3], C. Solé[1–3], E. Pose[1–3], C. Millán[2], R. Moreira[1–3], G. de Prada[4], D. Blaya[2], D. Rodrigo[2], L. Perea[2], B. Aguilar[2], P. Sancho-Bru[2,3], P. Ginès[1–3]. [1]Liver Unit, Hospital Clinic; [2]Institut d'Investigacions Biomediquès August-Pi-Sunyer (IDIBAPS); [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED); [4]Hospital Clinic, Barcelona, Spain
E-mail: igraupe@clinic.ub.es

Background and Aims: LCN2 gene is up-regulated in experimental models of liver injury and its product, Neutrophil gelatinase-associated lipocalin (NGAL), has been found elevated in plasma and urine in patients with cirrhosis. Acute-on-chronic liver failure (ACLF) is a syndrome that occurs in cirrhosis characterized by organ failure
(s) and high short-term mortality. There are no biomarkers of ACLF. The aim is to investigate whether LCN2 is up-regulated in ACLF and
NGAL could be a biomarker of ACLF.
Methods: LCN2 expression was assessed in liver biopsies from 46 patients with chronic liver diseases encompassing the whole spectrum of liver disease, from pre-cirrhotic stage to ACLF. Plasma and urine NGAL and plasma Interleukin-6 were also measured in the same subset of patients. In addition, LCN2 gene expression was assessed in liver biopsies from 6 healthy donors obtained at the time of living donor liver transplantation.

Results: LCN2 gene expression increased with progression of liver disease and remarkably, patients with ACLF had a striking increase in hepatic LCN2 gene expression compared to all other groups (fc 63 ± 35 vs 3.8 ± 5;$p < 0.001$, patients with and without
ACLF). LCN2 gene expression directly correlated with parameters of liver function such as bilirrubin, INR and MELD score($r = 0.68$; $p <$
0.001) and also with plasma IL-6 levels ($r = 0.65$; $p < 0.001$). Plasma and urine levels of NGAL were increased in ACLF vs. no ACLF patients
(647 (227-897) vs. 112 (75–152) ng/mL and 147 (19–1160) vs. 24 (15–39) μg/g creat, respectively; $p < 0.05$). Moreover, plasma and urine
NGAL correlated with LCN2 gene expression ($r = 0.52$ i $r = 0.34$, respectively; $p < 0.05$).

Conclusions: There is a remarkable overexpression of LCN2 gene in the liver in ACLF syndrome. LCN2 gene expression correlates with hepatic function, inflammation and levels of plasma and urine NGAL. These results suggest that NGAL could be a biomarker of ACLF.

THU-334

IN-HOSPITAL MORTALITY RELATED TO HEPATIC ENCEPHALOPATHY IS INDEPENDENT OF ACUTE-ON-CHRONIC LIVER FAILURE AND VARIES SIGNIFICANTLY ACROSS NORTH AMERICA: NACSELD EXPERIENCE

J.S. Bajaj[1], K. Reddy[2], P. Tandon[3], G. Garcia-Tsao[4], F. Wong[5], P. Kamath[6], S. Biggins[7], M. Fallon[8], B. Maliakkal[9], P. Thuluvath[10], R. Subramanian[11], H. Vargas[12], J. Lai[13], L. Thacker[1], J. O'leary[14] and NACSELD. [1]Virginia Commonwealth University, Richmond; [2]University of Pennsylvania, Philadephia, United States; [3]University of Alberta, Edmonton, Canada; [4]Yale University Medical Center, New Haven, United States; [5]University of Toronto, Toronto, Canada; [6]Mayo Clinic School of Medicine, Rochester; [7]University of Colorado, Denver; [8]University of Texas, Houston; [9]University of Rochester, Rochester; [10]Mercy Medical Center, Baltimore; [11]Emory University Medical Center, Atlanta; [12]Mayo Clinic, Scottsdale; [13]University of California, San Francisco; [14]Baylor University Medical Center, Dallas, United States

E-mail: jasmohan@hotmail.com

Background and Aims: Hepatic encephalopathy (HE) is a part of acute-on-chronic liver failure (ACLF) but its competing impact with ACLF on in-hospital mortality is unclear. Aim: 1. Define the contribution of HE with/without ACLF on in-hospital mortality in NACSELD (North American Consortium for Study of End-stage Liver Disease) 2. Define regional variations in HE outcomes

Methods: Cirrhotic inpatients were followed till discharge/in-hospital death. Pts were divided by West-Haven criteria (0, 1–2 & 3–4) for HE but ACLF was defined as ≥2 (3–4 HE, ventilation, dialysis or shock). Survival was compared between gps (no HE/no ACLF, 1–2 HE/no ACLF, 1–2 HE/ACLF, 3–4 HE/no ACLF, 3–4 HE/ACLF) & by region using logistic regression. Regions are Gp 1(NE US), Gp 2 (SE US), Gp 3 (SW US) & Gp 4 (Canada).

Results: 1522 pts (age 57, MELD 17, 57% prior HE, 38% on rifaximin, 40% infected) were included. During the hospitalization, 517 had HE (372 1–2, 145 grade 3–4) &104 developed ACLF. HE survival): Grade 3–4 vs. Grade 1–2 & no-HE pts had higher MELD (22 vs 18/18, $p < 0.0001$), ACLF (46% vs 10/4% $p < 0.001$), diabetes (43% vs 40%/33%, $p = 0.03$) &in-hospital mortality (27% vs 5%/4%, $p < 0.0001$). 3–4 HE In-hospital mortality was highest(OR 3.3, $p < 0.0001$) independent of MELD, WBC &non-HE organ failures. HE/ACLF interaction: Both HE +
ACLF gps had higher admission MELD/WBC, greater % SIRS/infections,
& highest unadjusted in-hospital mortality (Table). While unadjusted in-hospital mortality was higher for ACLF + HE groups vs. no-ACLF/HE gps

(all p < 0.001) & in those with higher HE grade + ACLF compared to lower grades with ACLF (p = 0.01), when adjusted for organ failures, age, WBC, infections & SIRS on regression, only HE grade remained significant (grade 3–4 HE/ACLF vs 1–2 HE/ACLF OR 4.0 p = 0.04). Regional comparison: 533 were in Gp 1, 374 in gp 2, 375 in gp 3 & 281 pts in gp 4. Demographics, MELD score, %SIRS/prior HE, & infections/ACLF were similar between regions. Rifaximin use was lowest (6% gp 4 vs. 50%, 39% & 44% in gps 1–3, p < 0.0001), while admission creatinine (2.3 vs. 1.4, 1.3, 1.5, p = 0.003) & in-hospital mortality were highest (10% gp 4 vs. 6%, 5%, 5% in gps 1–3, p = 0.05) in Gp4. The high gp 4 mortality was significant on regression (adjusted OR gp 4 compared to gp 1:5.6, vs gp 2 OR: 6.3, vs gp 3: 7.1, p < 0.0001).

*p<0.01, **p<0.0001	No HE No ACLF (n=1005)	HE 3-4 No ACLF (n = 78)	HE 1-2 No ACLF (n=335)	HE 1-2 ACLF (n=36)	HE 3-4 ACLF (n = 68)
MELD on admission**	17	19	18	24	26
WBC count on admission**	4.4±6.2	4.4±7.1	4.2±6.0	6.0±7.3	8.7±10.6
Diabetes*	33%	49%	41%	31%	34%
Infection during admission**	35%	37%	45%	74%	78%
Shock during admission**	2%	1%	2%	53%	63%
Dialysis during admission**	3%	0%	3%	61%	51%
Ventilation during admission**	4%	1%	5%	78%	76%
SIRS during admission*	24%	10%	21%	40%	34%
Prior HE on admission**	47%	73%	78%	78%	68%
Rifaximin on admission**	31%	48%	49%	53%	53%
In-hospital mortality	2%	8%	3%	22%	49%

Conclusions: HE is a significant determinant of in-hospital mortality with or without the presence of ACLF. There is considerable regional variation within North America with HE-related in-hospital mortality.

THU-349

HBV ASSOCIATED CIRRHOTIC PATIENTS MEETING APASL ACUTE-ON-CHRONIC LIVER FAILURE CRITERIA HAVE HETEROGENEOUS OUTCOME AND SHORT TERM SURVIVAL RATE

H. Li1, L.-Y. Chen1, Q. Xie2, N.-N. Zhang1, S. Yin1, S.-J. Wang1.

1Department of Gastroenterology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University; 2Department of Infectious Disease, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

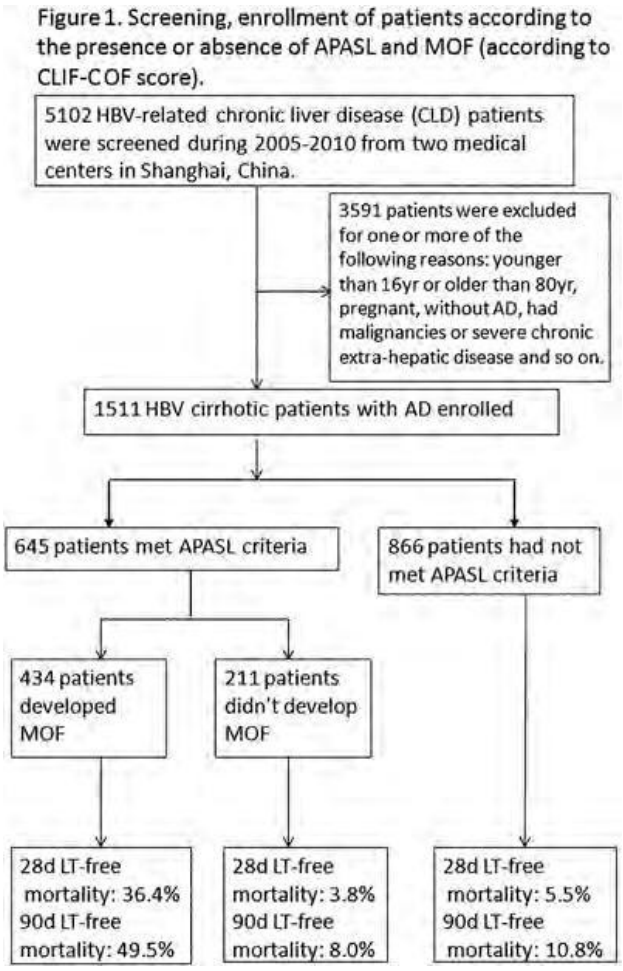
E-mail: jinniuzuo400@126.com

Background and Aims: Multiple organ failure (MOF) and submassive hepatic necrosis (SMHN) and are clinical and pathological characteristics separately for HBV associated acute-on-chronic liver failure (ACLF) patients. However, if APASL diagnostic criteria (TB >5 mg/dL, INR > 1.5) could accurately distinguish ACLF patients from HBV associated cirrhotic patients with acute decompensation (AD) is still controversy. The aim of the current study is to identify whether APASL criteria recruited HBV associated cirrhotic patients belong to a homogenous cohort or not.

Methods: 1511 consecutive hospitalized HBV associated cirrhotic patients with AD from two medical centers between 2005 and 2010 in Shanghai, China were included. Among them 280 (19%) patients underwent liver transplantation (LT). MOF (meeting any of ACLF grade I, II or III according to CLIF-OFs), short-term mortality and LT patients' pathological feature were used to evaluate the population.

Results: According to APASL criteria for ACLF, 37.5% (567/1511) patients met at enrollment and 5.2% (78/1511) developed to meet it within 28-days. Among all above 645 patients, 67.3% (434/645) had MOF at admission or developed within 28-days. However, 32.7% (211/ 645) patients had not suffered MOF within 28-days after enrollment. The 28 and 90-day mortality of APASL MOF patients were 36.4% and 45.9% respectively. APASL non-MOF patients had a 28 and 90-day mortality of 3.8% and 8% respectively ($p < 0.001$ vs APASL MOF). APASL patients with MOF displayed more accelerated deterioration of serum levels of total bilirubin, creatinine, INR, as well as MELD, CLIF-OF scores than non-MOF patients determined at 1, 7 and 14 days after hospital admission ($p < 0.05$ for all parameters). White cell count was significantly higher in MOF patients than non MOF patients ($10.1 \pm 6.9 \times 109$ vs $6.5 \pm 4.0 \times 109$, $p < 0.001$). 136 (22%) meeting APASL criteria patients received LT. The

percentage of the pathological feature of SMHN positive was 86% (63/73) in MOF patients, which was significantly higher than that in non MOF patients ($p < 0.001$).



Conclusions: The data argue strongly that the diagnostic criteria for HBV associate ACLF should not follow APASL criteria because there are two groups in APASL criteria recruited patients for significantly different clinical aspect, pathogenesis, outcome and short term survival rate.

THU-351

A MORE INTENSIVE REGIMEN OF ALBUMIN DYALISIS IMPROVES SURVIVAL IN PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE. RESULTS FROM AN INDIVIDUAL-PATIENT DATA META-ANALYSIS

L.I. Samaniego1,2, C. Olmedo2, M. Pavesi3, J. Torner3, M.-V. Catalina1,4,

T. Hassanein5, U. Heemann6, F. Nevens3,7, F. Larsen8, R. Jalan3,9, A. Albillos3,4,10, H. Schmidt11, R. Moreau3,12, V. Arroyo3,13,

R. Bañares1–4. 1Liver Unit; 2Instituto de investigación sanitaria, Hospital General Universitario Gregorio Marañón, Madrid; 3European Foundation for the study of Chronic Liver Failure (EF-CLIF), Barcelona; 4CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; 5Southern California Liver Centers, Coronado, United States; 6Department of Nephrology, Klinikum rechts der Isar der Technischen Universität, München, Germany; 7Department of Hepatology, University Hospitals KULeuven, Leuven, Belgium; 8Department of Hepatology, Rigshospitalet, Copenhagen, Denmark; 9Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom; 10Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal, Madrid, Spain; 11Department of Transplantation Medicine, Universitätsklinikum Münster, Münster, Germany; 12Centre de Recherche sur l'inflammation, Hôpital Beaujon, Paris, France; 13Liver Unit, Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

E-mail: lisamaniego@gmail.com

Background and Aims: Several randomized clinical trials (RCT) and meta-analysis failed to show any impact of MARS therapy on survival in patients with acute on chronic liver failure (ACLF). However, the effect of the time under MARS therapy on survival has not been evaluated. The aim was to evaluate the safety and efficacy of MARS therapy and the impact of treatment duration on survival through an individual patient-data meta-analysis.

Methods: Individual data of participants in RCT with MARS in ACLF were obtained. Severity of ACLF according to CLIF score was retrospectively calculated. We identified outcome variables (30-day mortality, effect on hepatic encephalopathy (HE) and hepatorenal syndrome (HRS)), safety variables and other variables that could potentially impact survival (MELD score, ACLF grade, duration of MARS therapy). A Cox-regression model was developed to identify predictive variables of survival.

Results: We collected individual-patient data from 3 out of 4 RCT, comprising 285 patients (95.6% of all patients included in the RCT), 147 (51.57%) patients received MARS therapy. In two RCT the primary

criterion for inclusion was the presence of ACLF (215, 75.4%) and in the third RCT it was the presence of refractory HE (70, 24.6%). Median age (IQR) was 48.9 (26.7–78.8) years. Alcohol was the most frequent etiology of liver disease (214; 75.1 %). Median MELD score was 29.2 (24.4–35.7) points. One-hundred and six (36.5%) patients presented HE grade III or IV and 104 (36.5%) HRS. ACLF-grade 3 was present in 30.9%. The median number of organ failures was 2 (1–3). Resolution of HE at day 4 was more frequently observed in MARS treated patients (OR: 0.63 CI95% 0.42–0.97). Overall survival was similar between patients treated with or without MARS. However, patients who received 4 or more MARS (73, 25.6%) sessions showed a better survival (Breslow 4.6 p = 0.032). Baseline characteristics were similar between patients who received less than 4 MARS sessions and patients who received 4 or more MARS sessions. In multivariate analysis, only age (HR 1.03 CI95% 1.01–1.05), MELD (HR 1.07 CI95% 1.04–1.10) and duration of MARS therapy (>4 sessions, HR 0.50 CI95% 0.28–0.87) were predictors of survival. Incidence of adverse events between groups was similar, although there was a trend to a higher rate of coagulopathy in MARS group.

Conclusions: A more intensive regimen of MARS therapy is associated with a higher survival in patients with ACLF. This concept may be useful for the development of new clinical trials.

THU-363

ACUTE-ON CHRONIC LIVER FAILURE: THE RELATIONSHIP WITH UNDERLYING LIVER DISEASE SEVERITY AND PORTAL HYPERTENSION

M.Y. Kim1, Y.L. Lim1, S.K. Baik1, Y.O. Jang1. 1Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea

E-mail: drkimmy@yonsei.ac.kr

Background and Aims: Recently, acute-on-chronic liver failure (ACLF) is considered as main prognostic event in cirrhotic patients. Portal hypertension (PHT) and basal liver disease severity have been accepted as main prognostic factors in the development of acute decompensation which is essential precondition of ACLF and cirrhosis related mortality. The aim of this study is evaluation about the relationship between basal PHT, liver disease severity with the future ACLF development.

Methods: During 30.8 months (0.2–177.5 months) of median follow up period, 755 cirrhotic patients (male 638, 84.5%) have been prospectively followed for the development of liver related events. Baseline hepatic venous pressure gradient (HVPG) was performed to all patients at enrolment. The diagnosis of ACLF was based on EASL/AASLD criteria (ACLF-E/A) and APASL (ACLF-A) criteria. The first episode of ACLF was decided as an index ACLF in patients who showed multiple and repeated ACLF events. Cox proportional hazard model was applied for the uni- and multivariate analysis of the predictive factors for the ACLF developments.

Results: During the follow up period, 170 (22.5%) and 138 patients (18.3%) developed more than once of ACLF-E/A and ACLF-A respectively. Each ACLF related mortality was developed in 95 patients (12.6%) and 55 (7.3%) respectively. In the univariate analysis, Child-Pugh score(CPS), MELD score, HVPG, medium to large EV, ascites, cystatin C, total bilirubin (TB), albumin (Alb), INR, platelet count, spleen size were significant with both ACLF-E/A and ACLF-A developments ($p < 0.05$). Especially, in the multivariate analysis using model of CPS, MELD and HVPG, all three parameters showed significant predictive value for the both ACLF type (for ACLF- E/A, CPS, MELD, HVPG hazard ratio (HR) = 1.139 ($p = 0.015$), 1.061 ($p = 0.016$), 1.040 ($p = 0.013$) respectively/ for ACLF-A, HR = 1.155($p = 0.014$), 1.085($p = 0.002$), 1.046(0.010)) (age, sex, alcohol and non-selective beta blocker compliance adjusted). However, in the analysis models using TB, Alb, INR, cystatin-C instead of CPS or MELD score, cystatin-C (ACLF

E/A) and INR (ACLF-A) showed constant predictive values with TB, Alb, and HVPG was not significant.

Conclusions: Our data suggests that the risk of ACLF is closely related with underlying liver disease severity and PHT.

THU-368

TLR-10 SINGLE NUCLEOTIDE POLYMORPHISM IS ASSOCIATED TO POOR SHORT TERM SURVIVAL IN CIRRHOTIC PATIENTS WITH ACUTE ON CHRONIC LIVER FAILURE PRECIPITATED BY BACTERIAL INFECTIONS

P. Caraceni1, M. Domenicali1, M. Baldassarre1, F.A. Giannone1, E. Marasco2, M. Pavesi3, V. Mantovani2, P. Angeli4, A. Gerbes5,

R. Moreau6–8, R. Jalan9, P. Ginès10, V. Arroyo3, M. Bernardi1, on behalf of CANONIC Study Investigators of the EASL-CLIF Consortium.

1Department of Surgical and Medical Sciences; 2Center for Applied Biomedical Research (CRBA), University of Bologna, Bologna, Italy; 3EF-CLIF, Barcellona, Spain; 4Unit of Internal Medicine and Hepatology, Dept. of Medicine, DIMED, University of Padova, Padova, Italy;

5Liver Centre Munich, Med Klinik 2, Klinikum of the University of Munich, Munich, Germany; 6Inserm, U1149, Centre de Recherche sur l'Inflammation (CRI), UMRS1149, Université Paris Diderot; 7Département Hospitalo-Universitaire (DHU) UNITY, Service d'hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris; 8Laboratoire d'Excellence Inflamex, ComUE Sorbonne Paris Cité, Paris, France; 9Royal Free Hospital, London, United Kingdom; 10Liver Unit, Hospital Clínic, IDIBAPS and CIBERehd, Barcellona, Spain

E-mail: paolo.caraceni@unibo.it

Background and Aims: Bacterial infections are a frequent complication of cirrhosis. In this setting the activation of toll-like receptors (TLRs) often triggers an enhanced inflammatory response leading to multi-organ failure and high mortality. Single nucleotide polymorphisms (SNPs) of TLRs family genes can modulate the intensity of immune response. The present study aimed at exploring the relationship between specific SNPs of the TLRs family known to be associated with a poor outcome of bacterial infections in other clinical settings and short-term survival of patients with acutely decompensated cirrhosis and bacterial infections, with and without acute on chronic liver failure (ACLF).

Methods: We assessed 19 SNPs of TLRs family (TLR1, TLR2, TLR4, TLR9, TLR10 and toll interacting protein), chosen for their association with poor outcome of bacterial infections, in DNA samples from 835 hospitalized cirrhotic patients enrolled in the CANONIC study. Genotyping was performed using the Sequenom MassARRAY technology. Basal clinical and laboratory parameters and 28-day survival were also recorded.

Results: Only the TLR10 polymorphism rs4129009, was significantly associated with the overall 28-day mortality (OR 1.632, CI 1.041– 2.560, p = 0.031). After grouping patients according to the presence of bacterial infection (n = 313) at hospital admission or during the hospitalization, the rs4129009 was significantly associated to 28-day mortality only in patients with bacterial infections (OR 2.3 CI 1.3–4.2; p = 0.004) related to the risk allele G. Multivariate analysis showed that the relative contributions of rs4129009 and bacterial infection to short term survival was independent from the severity of cirrhosis. When patients were divided according to the presence of ACLF (n = 264) at inclusion or during hospitalization, the rs4129009 was associated to 28 day-survival mainly in patients with ACLF, irrespective of ACLF grade (OR 1.7 CI 1.0–2.9; p = 0.050). Finally, survival analysis showed that patients with bacterial infections carrying the G allele of rs4129009 had a significantly shorter survival than patients with either SNP or bacterial infection alone.

Conclusions: The presence of the TLR10 polymorphism, known to enhance the inflammatory response, negatively affects survival of patients with acutely decompensated cirrhosis and bacterial infections. This effect is mainly observed in those who developed ACLF.

THU-382

LECITHIN-CHOLESTEROL ACYLTRANSFERASE ACTIVITY AND APOLIPOPROTEIN A1 LEVELS PREDICT PROGRESSION TO ORGAN FAILURE IN ACLF PATIENTS AND 3 MONTH MORTALITY FOLLOWING ACUTE CIRRHOSIS DECOMPENSATION

S. Samra1, K.L. Thomsen1,2, A.F.B. DaSilva1, R. Sawhney1, H. Jones1,

J. Owen1, R.P. Mookerjee1. 1UCL Institute of Liver and Digestive Health, University College London, London, United Kingdom; 2Department Of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus C, Denmark

E-mail: karethom@rm.dk

Background and Aims: Lecithin cholesterol acyltransferase (LCAT) is secreted by the liver and esterifies plasma cholesterol, a vital step regulating HDL levels and cell membrane cholesterol. LCAT activity is thought to decrease with increasing liver disease severity and similar data exists for HDL levels but this has not been evaluated in acute-on-chronic liver failure (ACLF). The aim of this study was to determine LCAT activity and HDL levels in acute cirrhosis decompensation (AD) and determine their prognostic utility and relationship with progression of organ failure.

Methods: Patients admitted to Royal Free London with acute cirrhosis decompensation were included and characterised by clinical disease severity scores (including ACLF) and standard biochemistry. Admission plasma was assessed for LCAT activity [percent cholesterol esterification (%CE)], apolipoprotein A1 (ApoA1) and HDL and their relationship with subsequent clinical outcomes.

Results: 72 acute decompensated cirrhosis patients were included: age 50 (24–75) yrs; 46 male; 55-alcohol; 9-viral; 2-PBC; 4-NASH; 2-AIH. 43 patients fulfilled ACLF criteria (grades 1–3) at baseline or within 72 hours of inclusion (mean MELD 27.5 ± 1.1); the remainder (AD: n = 29) had no organ failure (mean MELD 15.4 ± 0.8). 24 patients died within 3 months of admission; encephalopathy was the most common organ failure. %CE was reduced in ACLF patients and was lowest in ACLF 2–3 cf. ACLF 1 (1.7 ± 0.5 vs 3.8 ± 0.8 $p < 0.02$) and correlated with MELD (spearman rank: $r = -0.5$; $p < 0.0001$). This was mirrored by significantly lower ApoA1 levels in ACLF patients cf. AD patients (0.41 ± 0.04 vs. 0.6 ± 0.06, $p < 0.001$) which progressed from grade 1 to 2/3 (0.5 ± 0.2 vs 0.34 ± 0.2 g/L; $p < 0.001$). Similarly, HDL levels were significantly lower in ACLF vs AD patients (p <

0.01). ROC curve analysis showed ApoA1 as a good predictor of 3 month mortality (AUC 0.82; C.I. 0.72–0.91), highest in patients with values <0.5 cf. values ≥0.5 g/L (54 vs. 6%; p < 0.001). %CE also had predictive utility for mortality with AUROC 0.74 (C.I. 0.59–0.89).

Conclusions: Our data show for the first time that reduced LCAT activity and corresponding ApoA1 levels (reflecting mature HDL) define progression to organ failure following acute cirrhosis decompensation and predict 3 month mortality. This provides a potential mechanistic insight into organ failure in ACLF and justifies a rationale for intervention given current trials of recombinant therapy for primary LCAT deficiency.

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

Z. Cao1, Y. Wang1, L. Chen1, X. Xiang1, Y. Liu1, J. Lu1, L. Lin1, Q. Xie1,

H. Wang1. 1Department of infectious diseases, Rui-Jin hospital affiliated to Shanghai Jiao-Tong University School of medicine, Shanghai, China

E-mail: estherlucifer@163.com

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.

THU-384

PORTAL HEMODYNAMICS PREDICTS THE OUTCOME IN SEVERE ALCOHOLIC HEPATITIS PRESENTING AS ACUTE-ON-CHRONIC LIVER FAILURE

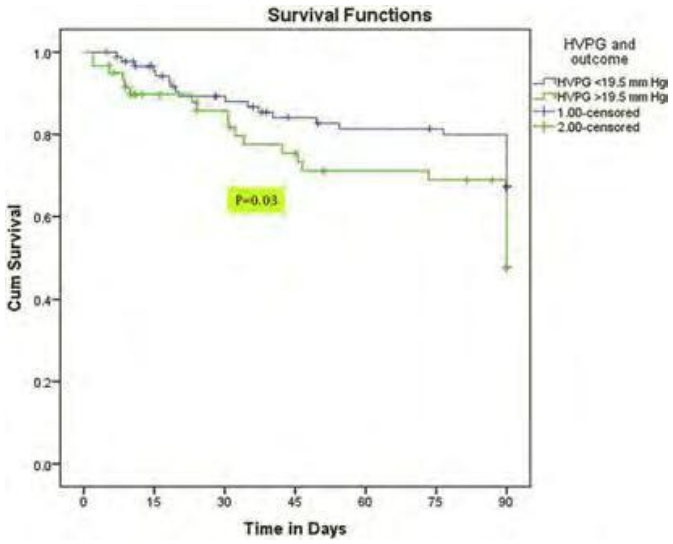
A.K. Choudhury1, M.K. Sharma1, R. Maiwal2, P. Jain3, M.A. Mahtab4, Y.K. Chawla5, S.S. Tan6, Q. Ning7, H. Devarbhavi8, D.N. Amarapurkar9, C.W. Kim10, S.S. Sadiq11, A.S. Butt11, C. Eapen12, H. Ghazinyan13, C. Yu14, A. Sood15, G.H. LEE16, Z. Abbas17, G. Shiha18, L.A. Lesmana19, D.A. Payawal20, K.A. Dokmeci21, G.K. Lau22, S.K. Sarin1, and APASL ACLF Working party. 1Hepatology and Liver Transplant; 2Hepatology; 3Dept of Research, Institute of Liver and Biliary Sciences, New Delhi, India; 4Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; 5Hepatology, PGIMER, Chandigarh, India; 6Selayang Hospital University of Malaya, Malaysia, Malaysia; 7Department of Infectious Disease, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 8St John Medical College, Bangalore; 9Bombay Hospital & Medical Research Centre, Mumbai, India; 10Division of Hepatology, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, South Korea; 11Aga Khan University Hospital, Karachi, Pakistan; 12Hepatology, CMC, Vellore, India; 13Nork Clinical Hospital of Infectious Diseases, Armenia, Armenia; 14Hepatology Institute Capital Medical University, Beijing, China; 15CMC, Ludhiana, India; 16Department of Gastroenterology & Hepatology, National University Health System, National University of Singapore, Singapore, Singapore; 17Sindh Institute of Urology and Transplantation, Karachi, Pakistan; 18Egyptian Liver Research Institute And Hospital, Egypt, Egypt; 19Digestive Disease & Oncology Centers, Medistra Hospital, Jakarta, Indonesia; 20Fatima Medical University Hospital, Manila, Philippines; 21Ankara University School of Medicine, Ankara, Turkey; 22Institute of Translational Hepatology, Beijing, China

E-mail: ashok@aclf.in

Background and Aims: During acute-on-chronic liver failure (ACLF=, the progressive liver failure is associated with rise in portal pressure. Development of variceal bleed, sepsis and organ failures often related to the severity of portal hypertension in addition to the inciting acute injury. The aim is identify the changes in portal and systemic hemodynamics in patients of ACLF caused by Severe Alcoholic Hepatitis (SAH) or other etiologies and their influence on organ failure and survival

Methods: ACLF patients as by APASL were enrolled into the AARC database and followed prospectively for initial 90 days. Clinical events, laboratory parameters, disease severity score, survival were compared for the acute insult i.e. SAH against other etiologies. Median stiffness (KPa), Transient elastography (Fibroscan™), Transjugular portal hemodynamic parameters (HVPG), cardiac catheterization [mean Pulmonary Artery pressure (MPAP), PCWP, and formula based systemic hemodynamic variables [SVRI,PVRI,

Cardiac Output (CO),Cardiac Index (CI)] were compared in SAH against other acute insults in predicting AKI, sepsis, organ failure, variceal bleed and survival.



Results: 308 patients (150 SAH, 158 other etiologies) with TJLB were analyzed. At baseline the MELD, SOFA, bilirubin, creatinine, mortality (51.5% vs 48.5%,p = 0.29) were comparable. SAH group were younger [(40.8 + 8.7) vs. (46.6 + 12.8) years, p < 0.001] with higher portal pressure i.e. HVPG [(18.5 + 5.0) vs. (16.7 + 5.1) mm of Hg, p = 0.003] and lower Hb [(10.6 + 1.7) vs. (11.3 + 1.9) gm/dL. p = 0.001]. HR, MAP, CO, CI, SVRI, PVRI were comparable in both the groups. LSM, HVPG, PCWP, MPAP, variceal grade, INR, serum Na were predictors of 90 days mortality. In multivariate analysis HVPG [OR = 1.02, 95CI (1.01–1.13),p = 0.01], MPAP [OR = 1.04, 95CI(1.03–1.12) were independent predictor of mortality. HVPG > 17.2 mm Hg correlate to variceal bleed (p = 0.03), AKI (p = 0.09) and sepsis (p = 0.07) within 15 days. HVPG correlated to low platelet (p = 0.02) and presence of RCS (p = 0.003) but not to the grade of varices, TNF-alpha, CRP and Ferritin. The HVPG > 19.5 mm Hg was associated with mortality 28% vs. 42%, p=

Conclusions: SAH is associated with higher portal pressure than other etiologies irrespective of variceal grade and is an independent predictor of mortality. Presence of RCS on varices or low platelet, not the inflammatory markers correlate to portal hemodynamics.

THU-401

INCREASED TLR2 EXPRESSION IN PERIPHERAL CD4+T CELLS PROMOTES TH17 CELLS RESPONSES AND IS ASSOCIATED WITH DISEASE AGGRAVATION OF HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

J. Liu1, C. Xu1, X. Zheng1, M. Lu2, D. Yang1. 1Department of Infectious Disease, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 2Institute for Virology, University Hospital of Essen, University of Duisburg-Essen, Essen, Germany

E-mail: jialiu77@hotmail.com

Background and Aims: Interleukin (IL)-17-producing CD4+ T cells (Th17) have been shown to play crucial roles in the pathogenesis of hepatitis B virus (HBV)-associated acute-on-chronic liver failure (ACLF). However, the mechanism underlying the enhanced Th17 responses in these patients remains largely unclear. There is growing evidence that Toll like receptors (TLRs) play a critical role in regulating Th17 differentiation. In current study, we investigated TLRs expression in peripheral T cells and their roles in Th17 cell differentiation and disease aggravation in ACLF patients.

Methods: 18 healthy subjects (HS), 20 chronic HBV-infected (CHB) patients and 26 ACLF patients were enrolled in the study. The mRNA levels of TLR1-10 in PBMCs of different subjects were measured by real-time PCR. The expression of TLR2 and TLR4 in peripheral CD4+ and CD8+ T cells were analyzed by flow cytometry. The correlation of T cell TLR2 and TLR4 expression with the frequency of Th17 cells and disease aggravation was evaluated in ACLF patients. The ability of TLR2 and TLR4 ligands stimulation on inducing peripheral Th17 differentiation in ACLF patients was analyzed by flow cytometry and ELISA.

Results: Compared to HS and CHB patients, ACLF patients showed a distinct TLRs expression pattern in PBMCs. Upregulation of TLR2 and TLR4 expression in peripheral CD4+ and CD8+ T cells was observed in HBV infected patients, and ACLF patients showed significantly increased TLR2 and TLR4 expression than CHB patients. Higher TLR2 but not TLR4 expression was observed in ACLF patients with HBeAg seroconversion than patients without, indicating the presence of HBeAg may play a role in regulating TLR2 expression. The TLR2 expression in CD4+ T cells was correlated with the frequency and the response of Th17 cells as well as the clinical markers for disease aggravation in ACLF patients. Moreover, TLR2

ligands stimulation promoted Th17 cell differentiation and response in PBMCs of ACLF patients.

Conclusions: Increased TLR2 expression in peripheral CD4+T cells may promote Th17 cell response and is associated with disease aggravation in ACLF patients. Our results elucidate a new mechanism underlying the enhanced Th17responses and may be used to design new immunotherapeutic strategies in ACLF patients.

THU-419

URINARY METABOLOMIC ANALYSIS OR EARLY PREDICTION OF SEPSIS IN ACUTE-ON -CHRONIC LIVER FAILURE PATIENTS

J.S. Maras1, S. Das2, Md.S. Hussain2, A. Chaudhary3, S.M. Shasthry3, S. Sharma1, C. Junot4, R. Moreau5, S.K. Sarin6. 11Molecular & Cellular Medicine; 2Molecular & Cellular Medicine; 3Hepatology, Institute of Liver & Biliary Sciences, New Delhi, India; 4Laboratoire d'Etude du Métabolisme des Médicaments, DSV/iBiTec-S/SPI, CEA-Saclay, MetaboHUB-Paris, 91191 Gif-sur-Yvette; 5Centre de Recherche Biomédicale Bichat-Beaujon, Paris, France; 6Molecular & Cellular Medicine, 2Hepatology, Institute of Liver & Biliary Sciences, New Delhi, India

E-mail: jassi2param@gmail.com

Background and Aims: Sepsis is often associated with poor outcome and is leading cause of mortality in acute-on-chronic liver failure (ACLF) patients. Role of sepsis as precipitating event is still in dilemma. However, early identification of sepsis, differentiating it from non-infectious systemic inflammatory response might improve the outcome in ACLF. The aim is to study the role of urinary metabolites in early detection and prediction of sepsis in patients of ACLF.

Methods: Urine samples from ACLF patients developing sepsis within one week (SEP; n = 11) was compared to ACLF-no-sepsis (No-SEP; n = 49) for their urinary metabolome profile (UPLC-MS/MS) at presentation and at D7. Metabolite signature differentiating sepsis at presentation was compared to D7. Top 1% Metabolite significant at D0 and D7 were only used as biomarker candidates and was subjected to ROC analysis, biomarker model building. Prediction accuracy for biomarker panel was calculated and tested in the cohorts.

Results: 315 features were validated by MS2 experiments. At D0 6% (21) metabolites were significant between SEP:No-SEP($p < 0.05$) of them 66% (14) was downregulated while 33% (7) was upregulated in SEP. Downregulated metabolites were of steroid or monosaccharide derivatives. While upregulated were Sugar-acid or Tricarboxylic-acid derivatives. At D7 9% (28) metabolites were significant. Of them 71% (20) were upregulated and 28% (8) were downregulated in SEP:No-SEP. Upregulated metabolites were alkaloids, phenyl, fatty acid, bile acid derivatives while down regulated metabolites were Benzamides, fatty-acid and

Tricarboxylic-acids derivatives. PLS-DA analysis significantly segregated SEP:No-SEP. VIP score for top 10% metabolites were calculated and top 1% of these were used as biomarkers candidates. At D0 upregulation of L-fucose, 4 gaunodinobutanioc acid and Estrone sulfate highlighted Importance > 0.8 combined AUROC > 0.8 ($p < 0.05$) prediction accuracy >90% while at D7 down regulation of hydroxy-indoleleactyl acid, creatine and 3-hydroxypentanoic acid highlighted importance >0.8 and combined AUROC > 0.85 ($p < 0.05$) and prediction accuracy >.85%. Panel of urinary metabolites significantly correlated with severity and mortality at baseline and day 7 ($r2 > 0.3$, $p < 0.05$).

Conclusions: The urinary metabolite composition in sepsis is distinct and is dynamic in patients of ACLF. The study identified the key metabolites that can be considered as biomarkers in predicting sepsis with high confidence and may serve as potential clinical tools.

THU-107

BETTER SURVIVAL IN PATIENTS WITH HEPATITIS E VIRUS C.F. TO OTHER ACUTE INSULTS CAUSING ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) – APASL-ACLF RESEARCH CONSORTIUM (AARC) DATABASE

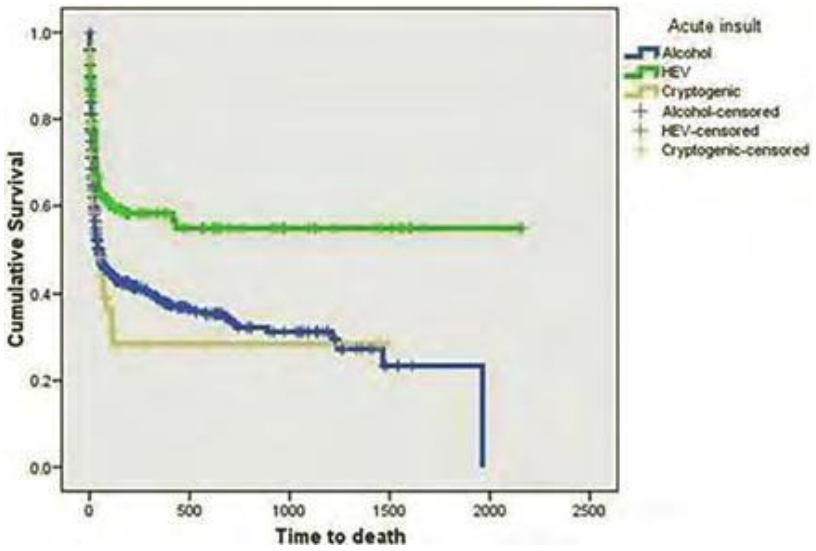
A. Goel1, C.E. Eapen1, A. Choudhary2, M.K. Sharma2, R. Maiwall2, M. Al Mahtab3, Y.K. Chawla4, S.-S. Tan5, Q. Ning6, H. Devarbhavi7, D.N. Amrapurkar8, C.W. Kim9, S.S. Hamid10, A.S. Butt10, H. Ghazinyan11, Z. Duan12, C. Yu12, A. Sood13, G.H. Lee14, Z. Abbas15, G. Shiha16, L.A. Lesmana17, D.A. Payawal18, A. Kadir Dokmeci19, M.F. Yuen20, G.K. Lau21, Md.F. Karim22, J.D. Sollano23, S.K. Sarin2 and APASL-ACLF working party. 1Hepatology, Christian Medical College, Vellore; 2Institute of Liver and Biliary Sciences, New Delhi, India; 3Bangabandhu Sheikh Mujib Medical university, Dhaka, Bangladesh; 4PGIMER, Chandigarh, India; 5Selayang Hospital University of Malaya, Malaysia, Malaysia; 6Department of Infectious Disease, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 7St John Medical College, Bangalore; 8Bombay Hospital & Medical Research Centre, Mumbai, India; 9Division of Hepatology, Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, South Korea; 10Aga Khan University Hospital, Karachi, Pakistan; 11Nork Clinical Hospital of Infectious Diseases, Armenia, Armenia; 12Hepatology Institute Capital Medical University, Beijing, China; 13Christian Medical College, Ludhiana, India; 14Department of Gastroenterology & Hepatology, National University Health System, National University of Singapore, Singapore, Singapore; 15Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan; 16Egyptian Liver Research Institute And Hospital (ELRIAH), Cairo, Egypt; 17Disease & Oncology Centers, Medistra Hospital, Jakarta, Indonesia; 18Fatima Medical University Hospital, Valenzuela MetroManila, Manila, Philippines; 19Ankara University School of Medicine, Ankara, Turkey; 20Queen Mary Hospital, Hong Kong, Hong Kong; 21Institute of Translational Hepatology, Beijing, China; 22Department of Hepatology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh; 23University of Santo Tomas, España Blvd, Manila, Philippines

E-mail: drashishgoel@cmcvellore.ac.in

Background and Aims: The current study aims to analyse impact of acute insult on short term mortality in ACLF patients.

Methods: AARC, consisting of multiple tertiary centers spread across Asia-Pacific regions, maintains an online database for prospectively accruing data on patients with ACLF, defined as per APASL criteria. The patients were managed as per individual institutional protocols. We compared short term survival in ACLF patients with acute insult caused by alcohol (group 1), Hepatitis E (group 2) and no identifiabe cause (cryptogenic, group 3).

Results: From July 2007 to April 2015, ACLF patients with acute insult which was alcohol related (group 1, n = 801, age: 41.9 ± 9.1 years, male: 782, MELD score: 29.4 ± 8.4), Hepatitis E related (group 2, n = 180, age:47.8 ± 13.6 years, male:148, MELD:28.3 ± 7.1) and cryptogenic (group 3, n = 118, age:47.2 ± 14.5; male: 80, MELD: 28.7 ± 10) were recruited. Short term mortality data was available in 978 (89%) of study patients with follow up duration of 182 (±329) days in group 1, 340 (±514) days in group 2 and 182 (±392) days in group 3. On Kaplan Meier analysis, the median survival in group 1 was 45 days (95% C.I:20–70 days) and group 3 was 47 days (95% C.I:16–78 days). In group 2, 63% survived the follow up period. Overall, group 1 had worse survival as compared to group 2 (p-value: < 0.001) and similar survival as group 3 (p-value: 0.4) (see Figure). Cumulative survival at 1 week was – group 1: 0.77 (0.018); group 2: 0.88 (0.03) and group 3: 0.7 (0.06). The proportion of patients with decreasing trend of MELD score over 7 days was similar in all groups (224/407 v/s 51/102 v/s 21/41; p-value: 0.6). On Cox proportional hazards model, controlling for baseline MELD score, as compared to group 1, group 2 had significantly lower hazard ratio (0.64, 95% C.I: 0.48–0.86, p- value:0.003); in contrast, group 3 had similar hazard ratio (1.2, 95% C. I: 0.84–1.7, p-value:0. 3) to group 1.



Conclusions: In this study conducted in 58 centres, across 18 countires, etiology of acute insult has a significant impact on prognosis of ACLF patients – those with Hepatitis E virus related acute insult tend to have better short term survival compared to those with alcohol related/cryptogenic acute insults. Further studies are needed to analyse the mechanisms of injury by different acute insults in ACLF.

THU-128

CLINICAL EPIDEMIOLOGICAL INVESTIGATION OF DEATH CAUSES IN PATIENTS WITH HBV-ACLF

X. Liu1, J. Hu1, J. Chen1, H. Su1, H. Yang1, L. Xiao1, J. Tong1. 1Liver Failure Treatment and Research Center of 302 Military Hospital, Beijing, China

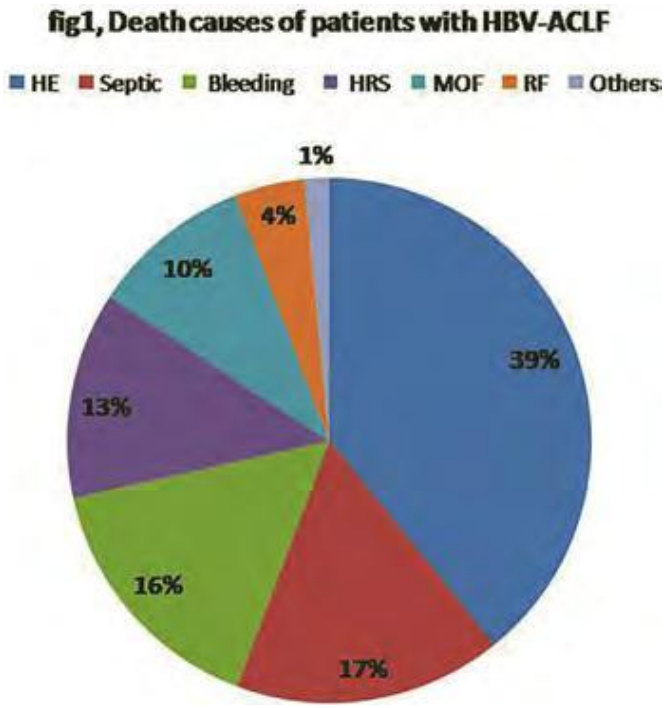
E-mail: hjh@medmail.com.cn

Background and Aims: Hepatitis B Virus associated Acute on Chronic Liver Failure (HBV-ACLF) is a serious disease with rapid and progressive liver failure leading to high mortality. The aim of this study is to retrospectively investigate the causes of death and clinical epidemiological characteristics of patients with HBV-ACLF.

Methods: 1156 patients with HBV-ACLF hospitalized in 302 military hospital in recent three years were enrolled, 393 of whom had died within six months after onset and were investigated the death causes and clinical epidemiological characteristics. The data of death causes were collected from the patients' death certificates which were established clinically by chief physicians.

Results: The mortality of HBV-ACLF was 34.00% (393/1156) in this group patients. Clinical epidemiological study showed that the median death age was 47ys (range:18 to 79ys) and sex ratio was male to female 5.55 to 1. Of 393 patients, 219 (55.7%) had a positive family history of HBV infection, including 82 from mother' family, 47 from father's family, 60 from sisters or brothers and 30 from their children. The top three leading precipitating factors of liver failure were physical or mental exertion, withdraw NAs anti-viral therapy, and infection. Pre liver diseases were investigated and found that 25.70% (101/393) patients with CHB, 21.88% (86/393) with compensated cirrhosis and 52.42% (206/393) with decompensated cirrhosis. Serum HBV markers were detected and the results showed there were 14.25% patients with undetectable HBVDNA level (<100 IU/mL). The patients with eAg+/eAb- accounts for 36.88%, eAg-/eAb+ accounts for 55.47% and others accounts for 17.65%. The incidence of complications in this group was very high, they were ascites (94.40%), hyponatremia (73.79%), Hepatic encephalopathy(66.92%), spontaneous bacterial peritonitis (51.40%), infection other than SBP (48.60%), hydrothorax (36.64%), acute kidney injur (31.81%), and gastrointestinal bleeding (29.01%). However, hepatic encephalopathy was the leading cause of death, accounting for 39.19% (154 cases), then followed by septic shock

16.54% (65 cases), gastrointestinal bleeding 15.78%, Hepatorenal syndrome 12.72%, Multiorgan failure 9.93% , respiratory failure 4.33% and there was 1.53% died of other causes. (Fig 1).



Conclusions: The mortality of HBV-ACLF was 34.00% in this group patients. Hepatic encephalopathy was the leading cause of death. Others in turn were septic shock, gastrointestinal bleeding, Hepatorenal syndrome, Multiorgan failure, and respiratory failure.

THU-170

MYELOID-DERIVED SUPPRESSOR CELLS ARE CLOSELY ASSOCIATED WITH DISEASE PROGRESSION IN PATIENTS WITH HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

Y. Zeng1, C. Lin1, L. Lu2, Y. Liu1. 1Department of Infectious Disease, Third Affiliated Hospital of Sun Yat-sen University, Guang Zhou; 2Department of Infectious Disease, First Affiliated Hospital of Kun Ming Medical School, Kun Ming, China

E-mail: zengyingfu@163.com

Background and Aims: The leading cause of liver failure in China is usually considered as hepatitis virus (mainly considered as HBV) infection. MDSCs are a heterogeneous subset of immature myeloid cells with the potent ability to suppress T cell responses via several mechanisms, the shortage of L-arginine can inhibit T-cell proliferation through decreasing their expression of CD3 ζ-chain. The frequency and possible role of MDSCs are rarely studied in HBV-related ACLF patients.

Methods: 25 HBV-related ACLF patients (Diagnosed according to Chinese guidelines) were enrolledin HBV-ACLF group, 15 of which were in early stage, 10 in middle to advanced stage. 32 CHB patients were enrolled as CHB group (Diagnosed according to EASL clinical practice guidelines).18 healthy volunteers were admitted as healthy controls (HC). Blood samples were obtained in our study, the frequency of MDSCs and CD3 ζ-chain expression in CD8 + T cells were detected by flow-cytometry. MELD score of each ACLF patient was calculated by previously described equation. 8 patients with ACLF were followed up for 4 weeks, MDSCs frequencies of each patient was determined every week. Baseline clinical data including biochemical parameters and virological parameters of all patients were collected at the day when they were hospitalized or enrolled in outpatient clinic.

Results: MDSCs frequencies in peripheral blood mononuclear cells (PBMCs) were significantly increased in HBV-ACLF patients when compared with HC and CHB group. HBV-ACLF patients in middle to advanced stage had a higher frequency of MDSCs than those of early stage. According to 4-week observation of ACLF patients, the peripheral MDSCs remained at high levels in the nonsurvival group, whereas the survival group displayed a gradual decline. CD3 ζ-chain expression was significantly down-regulated in CD8 + T cells of HBV-related ACLF patients. Correlation analysis showed that MDSCs frequencies were positively correlated with ALT, TBIL, INR levels

and MELD score. ALB, PTA levels and CD3ζ chain expression levels in CD8 + T cells were negatively correlated with MDSCs frequencies. Besides, we found that the MDSCs frequencies were not correlated with serum HBV DNA levels and HBeAg status.

Conclusions: Peripheral MDSCs are closely associated with disease progression in patients with HBV-related ACLF, and they may serve as a possible predictor for short-term outcome. MDSCs may suppress T-cell >function through decreasing the expression of CD3 ζ-chain in CD8 + T cells.

THU-172

CLINICAL CHARACTERISTICS AND LONG-TERM OUTCOME OF ACUTE KIDNEY INJURY IN PATIENTS WITH HBV-RELATED ACUTE-ON-CHRONIC LIVER FAILURE

X. Shi1, Y. Wang1. 1Southwest Hospital, Chongqing, China
E-mail: 812432411@qq.com

Background and Aims: Acute kidney injury (AKI) is a common complication in patients with decompensated cirrhosis, and also an important cause for poor outcome. So far, study for AKI in patients with HBV-related acute-on-chronic liver failure (ACLF) is still lacking. This study analyzes the clinical characteristics and long-term prognosis of AKI in patients with HBV-related ACLF.

Methods: A total of 1167 patients with HBV-related ACLF from January 2010 to January 2015 were enrolled retrospectively, and then they were divided into AKI group (n = 308) and non-AKI group (n = 859). The patients were followed up to investigate clinical characteristics, long-term overall survival (OS) and risk factors.

Results: Incidence rate of AKI was 26.4% in patients with HBV-related ACLF. TBIL, INR, sCr and MELD scores were higher in AKI group than that in non-AKI group. Patients in AKI group and non-AKI group had 30-day OS of 44.8% and 70.3%; 90-day OS of 17.9% and 55.4%; and 1-year OS of 15.6% and 51.2%, respectively, with significant differences in all of three parameters ($p < 0.001$). Significant differences were observed in 30-day, 90-day and 1-year OS between subgroups with different AKI stages. Incidence rates of ascites, spontaneous bacterial peritonitis, upper gastrointestinal bleeding, infection and hepatic encephalopathy were higher in the AKI group than that in non-AKI group ($p < 0.001$). High WBC, ALT and MELD score were risk factors for 30-day mortality, whereas hepatic encephalopathy, high MELD score and low PLT were risk factors for 90-day mortality. There was good agreement between KDIGO and AKIN criteriain staging AKI in patients with HBV-related ACLF (Kappa = 0.807, $p < 0.001$).

Conclusions: AKI is associated with poor outcome in ACLF patients, particularly with increased short-term mortality. Both KDIGO and AKIN criteria can be used for staging AKI in Chinese patients with HBV-related ACLF.

FRI-008

SYSTEMIC INFLAMMATORY RESPONSE PROFILE IN ACUTE-ON-CHRONIC LIVER FAILURE AND ITS RELATIONSHIP WITH PROGNOSIS

C. Sole1,2,3, E. Sola1,2,3, M. Morales-Ruiz2,3,4, G. Fernàndez5, P. Huelin2,3,6, I. Graupera2,3,6, R. Moreira2,3,6, G. De Prada2,3,6, X. Ariza2,3,6, E. Pose2,3,6, N. Fabrellas6,7, S. Kalko5, W. Jiménez3,4,8, P. Ginès2,3,6. 1Liver Unit, Hospital Clínic, Universitat de Barcelona; 2Institut d'Investigacions Biomediquès Agust Pi i Sunyer (IDIBAPS); 3Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD); 4Biochemistry and Molecular Genetics Department, Hospital Clínic, Universitat de Barcelona; 5Bioinformatics Core Facility, IDIBAPS-CEK, Hospital Clínic, Universitat de Barcelona; 6Liver Unit, Hospital Clínic, Universitat de Barcelona; 7Escola Universitària d'Infermeria, Universitat de Barcelona; 8IDIBAPS-CEK, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

E-mail: csolem@clinic.ub.es

Background and Aims: The physiopathology of acute-on-chronic liver failure (ACLF) is unknown. It has been related to the existence of systemic inflammatory response, but information is very limited. AIMS: To investigate the systemic inflammatory response profile in ACLF and its relationship with prognosis.

Methods: Prospective study including 64 patients with cirrhosis (26 with ACLF). Systemic inflammatory response profile was analyzed by measuring plasma biomarkers of inflammation (cell adhesion and migration leukocyte molecules, cytokines, chemokines and growth factors) by a multiplex kit (Procarta® Immunoassay Kit).

Results: ACLF was significantly related with abnormal levels of 12 inflammatory biomarkers, specially markers of leukocyte adhesion and migration, endothelial factors, and chemokines related to recruitment of lymphocytes Th1, NK cells and monocytes-macrophages: VCAM-1, VEGF-A, Fractalkine, MIP-1alpha, Eotaxin, IP-10, RANTES, GM-CSF, IL-1beta, IL-2, ICAM-1 and MCP-1. Biomarkers showing the strongest relationship with the presence of ACLF were VCAM-1 and VEGF-A (AUCROC 0.8 for both; $p = 0.001$). The relationship between ACLF and inflammatory biomarkers was independent of bacterial infections. There was a significant relationship between some of the inflammatory biomarkers and 3-month mortality, particularly VCAM-1, ICAM-1, MIP-1alpha, IP-10 and GM-CSF (AUCROC > 0.7; $p < 0.05$). Three-month survival of patients with VCAM < 1.9 μg/mL and VCAM ≥ 1.9 μg/mL (median value in the whole series) were 85% and 55%, respectively ($p = 0.02$). VCAM-1 and ICAM-1 were independent

predictive factors of 3-month mortality. A principal component analysis (PCA) confirmed that the inflammatory profile of patients with ACLF was markedly different from that of patients with cirrhosis without ACLF. Data were integrated in Ingenuity Pathway Analysis (IPA) and showed that inflammatory markers significantly expressed in ACLF patients were enriched in leukocyte migration and chemotaxis pathways. IRF3 (Interferon Regulatory Factor 3) was the transcription factor most significantly related with the biomarkers studied.

Conclusions: ACLF syndrome is characterized by marked systemic inflammatory response with activation of adhesion and migration leukocyte molecules and abnormalities in cytokine and chemokine levels. This inflammatory response profile is independent from presence of bacterial infections and correlates with short-term mortality.

FRI-362

ALTERED GUT MICROBIAL PROFILE IS A PROPONENT OF BACTERIAL TRANSLOCATION IN ACUTE-ON-CHRONIC LIVER FAILURE

V.C. Patel1, L.E.X. Leong2, G. Koller3, S. Knapp4, G. Lai4, A. Singanayagam5, C. Bernsmeier6, M.J.W. McPhail4,6, D.L. Shawcross1, C.G. Antoniades4, M. Thursz4, J.A. Wendon1, G.B. Rogers2, K.D. Bruce3.

1Institute of Liver Studies & Transplantation, King's College Hospital, King's College London, London, United Kingdom; 2Infection & Immunity Theme, South Australian Health & Medical Research Institute, Adelaide, Australia; 3Institute of Pharmaceutical Science, King's College London; 4Section of Hepatology, St. Mary's Hospital, Imperial College London; 5Institute of Liver Studies & Transplantation, King's College Hospital; 6Institute of Liver Studies & Transplantation, King's College Hospital, London, United Kingdom

E-mail: vishal.patel@nhs.net

Background and Aims: Gut dysbiosis is implicated in the pathogenesis of acute-on-chronic liver failure (ACLF) where alterations in gut microbiota (GM) pathogenicity have been proposed to lead to increased bacterial translocation (BT). Increased BT in association with gut barrier dysfunction may result in elevated circulating levels of bacterial-derived components. This in turn can potentiate a pro-inflammatory milieu with adverse clinical outcomes. We determined GM composition in faeces from ACLF patients, and measured circulating levels of whole blood (WB) bacterial DNA (bDNA) used as a surrogate for BT.

Methods: Patients with ACLF (n = 38) and decompensated cirrhosis (DC)(n = 46) were compared to stable cirrhosis (SC) and healthy controls (HC)(n = 32). Whole blood (WB) for bDNA and faecal samples for GM analysis were obtained concomitantly. After DNA extraction from faeces, GM analysis was performed by amplifying and sequencing the V4 region of the 16S rRNA gene using Illumina MiSeq platform. Operational taxonomic unit assignment was performed using Quantitative Insights Into Microbial Ecology. After DNA extraction from WB, real-time qPCR with a TaqMan probe targeting a 380 bp region of bacterial 16S rRNA gene was used to quantify bDNA (in pg/mL (median (IQR))).

Results: CLIF-SOFA scores (median (IQR)) were SC 4 (3–5); DC 5 (4– 7); ACLF 9 (8–11); $p < 0.0001$. Circulating WB bDNA levels in ACLF (7.03 (6.96); $p = 0.0001$) were elevated significantly as compared to SC (2.78 (1.70)), but without significant differences in DC (4.51 (2.35))

(Fig. 1). bDNA levels were also similar in HC (1.62 (0.93)) and SC. A significant difference in GM diversity measured by PERMANOVA where $p < 0.01$ is significant was observed in ACLF ($p = 0.0011$) and DC ($p = 0.0069$) as compared to SC. No significant differences in GM diversity were detected between SC and HC ($p = 0.019$), as shown in Fig. 2A. A positive correlation was evident between potentially pathogenic Enterococcus in ACLF, with a relative decrease in potentially protective fermentative Clostridiales (Fig. 2B).

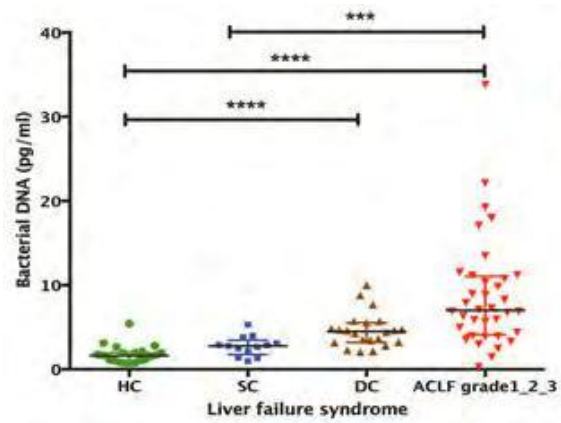


Figure 1: **Scatter plot showing circulating WB bDNA levels by study cohort.** Significant changes ($P<0.001$) in circulating WB bDNA levels are noted between HC and SC in comparison to ACLF. Of note no difference was detected between the different grades of ACLF by CLIF-EASL criteria.

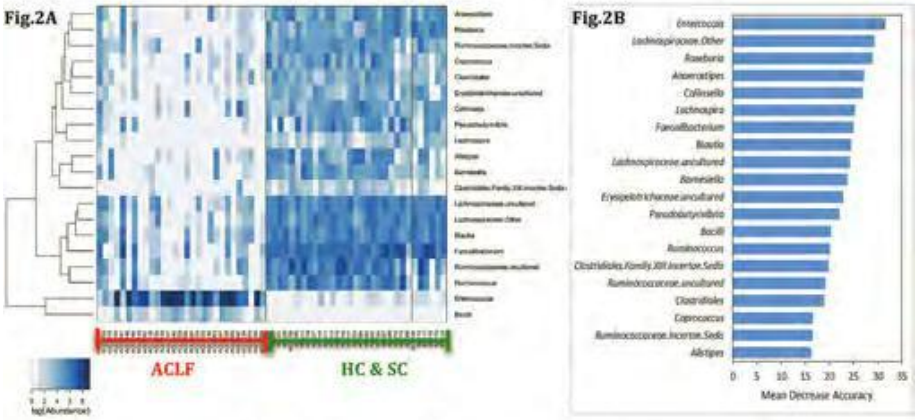


Figure 2A (left): **Heatmap of gut microbial taxa** that differentiate HC and SC cohorts (right of plot) from ACLF (left of plot). *Figure 2B (right):* **Relative abundance of the top 20 most important taxa are plotted as 'mean decrease accuracy'**, with the taxon with highest decrease accuracy indicating those taxa that separate most effectively the ACLF and HC/SC cohorts into distinct classes.

Conclusions: Significantly higher levels of circulating WB bDNA levels, a robust marker of gut BT, was found in ACLF as compared to SC and HC. Similarly, the GM of ACLF differed most markedly from that of SC and DC. We propose that this altered, more pathogenic GM composition drives BT in ACLF. Subsequent mechanistic insight from GM studies over the role of endotoxin tolerance, immuneparesis and infection susceptibility may lead to the identification of potential therapeutic targets in ACLF.

FRI-210

NEUTROPHILS INDUCE EARLY HEPATOCYTE DEATH BY CONTACT DEPENDENT AND INDEPENDENT MECHANISMS AND POSITIVELY CORRELATE WITH THE DISEASE OUTCOME IN ACUTE-ON-CHRONIC LIVER FAILURE

A. Khanam1, N. Trehanpati1, P. Riese2, A. Rastogi3, C.A. Guzman2, S.K. Sarin4. 1Dept. of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India; 2Dept. of Vaccinology and Applied Microbiology, Helmholtz Centre for Infection Research, Braunschweig, Germany; 3Dept. of Histopathology; 4Dept. of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

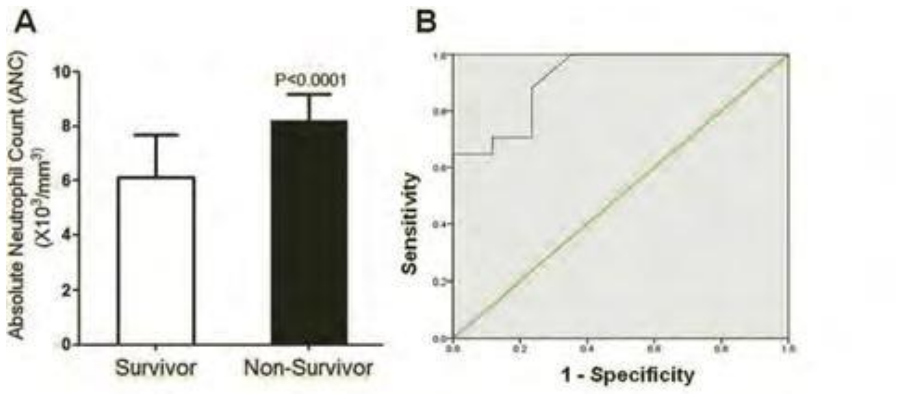
E-mail: arshigbpant@gmail.com

Background and Aims: Neutrophils serve as a biomarker of organ dysfunction in acute liver failure. However, the mechanisms of on-going liver injury in acute-on-chronic liver failure (ACLF) remain unknown. We investigated the mechanisms of CXCR-1 and CXCR-2 expressing neutrophil mediated cell death and further hepatic damage in ACLF (alcohol related n = 19) and hepatitis B related n = 17) and compared with chronic hepatitis B (CHB n = 42) and healthy controls (HC n = 18).

Methods: CXCR-1 and CXCR-2 expressions on neutrophils were measured by flowcytometry, immunohistochemistry and RT-PCR. Absolute neutrophil count (ANC) was detected in ACLF survivors and non-survivors and correlated with the disease outcome and mortality. In vitro co-culture assays were performed to determine the mechanisms of hepatic injury and cell death.

Results: In ACLF, marked increase in CXCR-1 and CXCR-2 expressing neutrophils was seen;more so near necrotic areas of liver. ANC was significantly increased in ACLF patients having higher bilirubin (>20 mg/dl; $p < 0.03$), MELD score (≥30; $p < 0.04$) and coagulation failure (INR > 2.5; $p < 0.02$). Importantly, ACLF non-survivors had significantly higher ANC than those who survived [AUROC for ANC [0.92 (95% CI 0.828–1.00, cut-off 75.5); $p < 0.0001$] with the cut-off of >75.5, sensitivity of 88% and specificity of 76% predict disease severity, outcome and mortality in ACLF (Figure 1A,B). Co-culture of neutrophils with HepG2 and HepG2.2.15 cells significantly induced cell death through early apoptosis and necrosis in contact dependant manner. In fact, increased intrahepatic caspase-3 and receptor-interacting-protein kinase-3 was found in ACLF. Importantly, blockade of CXCR-1 and CXCR-2 with SCH527123 antagonist significantly

reduced cell death. Culture of HepG2 and HepG2.2.15 cells with neutrophil supernatant resulted cell death due to inflammatory mediators indicating contact independent mechanism of cell death. The production of these inflammatory mediators was significantly diminished after CXCR-1 and CXCR-2blockade; notably, reactive oxygen species (ROS) production was completely inhibited.



Area	Std. Error	Significance	Cut-off	Sensitivity	Specificity
0.92	0.045	P< 0.0001	75.5	0.88	0.76

Conclusions: ACLF non-survivors had high ANC which efficiently predicted disease outcome and mortality. High CXCR-1 and CXCR-2 expressing neutrophils induce hepatocyte death by early apoptosis and necrosis in contact dependent and independent manner. CXCR-1 and CXCR-2 blockade abrogated cell death and further hepatic injury and these could be used as novel therapeutic targets in management of ACLF.

FRI-108

NUCLEOSIDE ANALOGUES IMPROVE THE SHORT-TERM PROGNOSIS OF CHRONIC HEPATITIS B PATIENTS WHEN THEY SUFFERED AN ACUTE-ON-CHRONIC LIVER FAILURE

C. Ye1, J. Lu1, L. Li1. 1State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

E-mail: yechao850606@163.com

Background and Aims: This study was conducted to evaluate the effect of nucleoside analogues treatment in improving the short-term prognosis of chronic hepatitis B (CHB) patients that suffered from an acute liver failure, and to investigate the factors to predict the mortality in patients with HBV-related acute-on-chronic liver failure (ACLF).
Methods: There were 248 CHB patients hospitalized with ACLF. Among these patients, only 49 patients were given nucleoside analogues treatment (NAs group) while 199 patients were used as control groups (no-NAs group). All patients were followed up for 3 months and data collected including clinical and lab data. This study integrated Child-Turcotte-Pugh (CTP), model for end-stage liver disease (MELD), MELD-Na scores for assessing the short-term mortality and difference between these two groups. Logisitic regression was used to determine independent predictors associated with short-term mortality.

Results: Patients in NAs group showed a lower level of serum total bilirubin (TBiL), BUN, creatinine, MELD and MELD-Na scores as compared to no-NAs group. The mortality in NAs group (11/49, 26.5%) was lower than no-NAs group (81/199, 38.7%) ($p = 0.018$). Multivariate analysis suggested that elder age, high serum TBiL, low serum sodium, low MELD and MELD-Na scores had better short-term prognosis of patients with HBV related ACLF.

Conclusions: CHB patients with NAs treatment demonstrated an improved short-term mortality in 3 months when they suffered from ACLF. But only age, serum TBiL, serum sodium, MELD and MELD-Na scores were independent factors to predict the short-term mortality in patients with HBV-related ACLF.

SAT-039

INCIDENCE, PREDICTORS AND OUTCOMES OF ACUTE ON CHRONIC LIVER FAILURE IN OUTPATIENTS WITH CIRRHOSIS

S. Piano1, M. Tonon2, C. Pilutti1, E. Vettore1, M.L. Stanco1, F. Morando1, S. Rosi1, A. Romano1, E. Gola2, A. Sticca2, S. Fasolato1, P. Angeli1.

1Regional Center for Hepatology, Unit of Internal Medicine and Hepatology, Department of Medicine; 2Department of Medicine, University of Padova, Padova, Italy

E-mail: salvatorepiano@gmail.com

Background and Aims: Acute on chronic liver failure (ACLF) is the most life-threatening complication of cirrhosis. Prevalence, and outcomes of ACLF have been recently described in hospitalized patients with cirrhosis. However, no data is currently available on the prevalence and the risk factors of ACLF in outpatients with cirrhosis. The aim of this study was to evaluate incidence, predictors and outcome of ACLF in a large cohort of outpatients with cirrhosis.

Methods: Consecutive patients admitted to the outpatients clinic of the University Hospital of Padova from 2003 to 2014 were included in this study and followed up until death and/or liver transplantation for a mean of 48 months. Data on development of hepatic and extrahepatic organ failures were collected during this period. ACLF was defined and graded according to the EASL-CLIF Consortium definition.

Results: 416 patients (69% male, mean age 55 years old) with cirrhosis were included in this study. At inclusion, most of them had ascites (57%) and oesophageal varices (64%). HCV and alcohol were the most common etiologies (36% and 35%, respectively). Mean MELD score and Child Pugh score were 12 and 7.6, respectively. During the follow up 106 patients (26%) developed ACLF, 53 grade 1, 28 grade 2 and 25 grade 3. The probability to develop ACLF was 14%, 29% and 48% at 1 year, 5 years and 10 years, respectively. In the multivariate analysis, age (HR = 1.04; $p = 0.001$), baseline mean arterial pressure (HR = 0.96; $p < 0.001$), presence of varices (1.66; $p = 0.041$) and MELD score (1.23; $p < 0.001$) were found to be independent predictors of development of ACLF at 5 years. As expected, the development of ACLF was associated with a poor prognosis, with a 3-month and 1-year probability of transplant free survival of 57% and 46%, respectively. Three-month probability of survival had a stepwise decrease

with ACLF grade (79%, 48% and 13% for grade 1, grade 2 and grade 3, respectively).

Conclusions: Outpatients with cirrhosis have a high probability to develop ACLF. Simple variables such as age, MELD, MAP and presence of varices may help to identify patients with a high risk to develop ACLF and to plan a close program of surveillance and prevention in these patients.