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ABSTRACTS ON ACLF

INDEX

50

Predictive factors for the development of acute-on-chronic liver failure in hospitalized decompensated cir-rhotic patients

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Acute-on-chronic liver failure (ACLF) is often precipitated by an event that disturbs systemic or regional hemodynamics, lead-ing to significant deterioration of liver function with one or more extra-hepatic organ failures, associated with high mor-bidity and mortality.. Identifying predictors of ACLF is critical to develop preventive strategies. . Aim: To identify predictors for ACLF development in hospitalized cirrhotic patients.. Meth-ods: We compared cirrhotic inpatients who developed ACLF >48 hours after admission (ACLF+) with those who did not (ACLD-) from the North American Consortium for the Study of End-Stage Liver Disease, consisting of 16 tertiary-care hepatol-ogy centers that prospectively enrolled non-elective admitted cirrhotic patients . . Those admitted with ACLF were excluded. . ACLF is defined by the presence of ≥2 organ failures: 1) cir-culatory- need for vasopressor support; 2) renal- initiation of dialysis; 3) cerebral- Grade III or IV hepatic encephalopathy; 4) respiratory- need for ventilation. . Results: Inpatients with ACLF+ vs. . ACLF- were similar (mean± SD) in age (55. .7±8..3 vs.. 57..6±10..5 years), male sex (65 vs.. 63%) alcoholic (30 vs.. 30%) and diabetes (37 vs.. 34%).. The ACLF+ group was more likely to be admitted with infections, hence their higher white cell count, and was more likely to have systemic inflamma-tory response syndrome (SIRS) when compared to ACLF- group

(Table 1).. Amongst the ACLF+ group, 51, 23 and 7 patients had 2, 3 and 4 organ failures respectively, with no signifi-cant differences between the ACLF subgroups. . Independent predictors for ACLF development included a high admission MELD, presence of SIRS, and hospitalization in <6 months (all p<0. .05). . In-hospital and 30-day mortality were significantly higher in the ACLF+ vs.. ACLF- patients (41% vs.. 3%, and 53% vs.. 7% respectively) (p<0..0001).. Conclusions: Sicker admitted cirrhotic patients with a previous admission in < 6 months are more likely to develop ACLF, especially when inflammation is present, likely related to infections. . Hospitalized cirrhotic patients with high MELD need to be monitored closely for the development of ACLF, especially if infection is present..

*mean SD

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216

Predicting 90-day mortality following liver transplanta-tion in patients with Acute-On-Chronic Liver Failure: a decision-tree model from the French national liver trans-plantation system, the OPTIMATCH study

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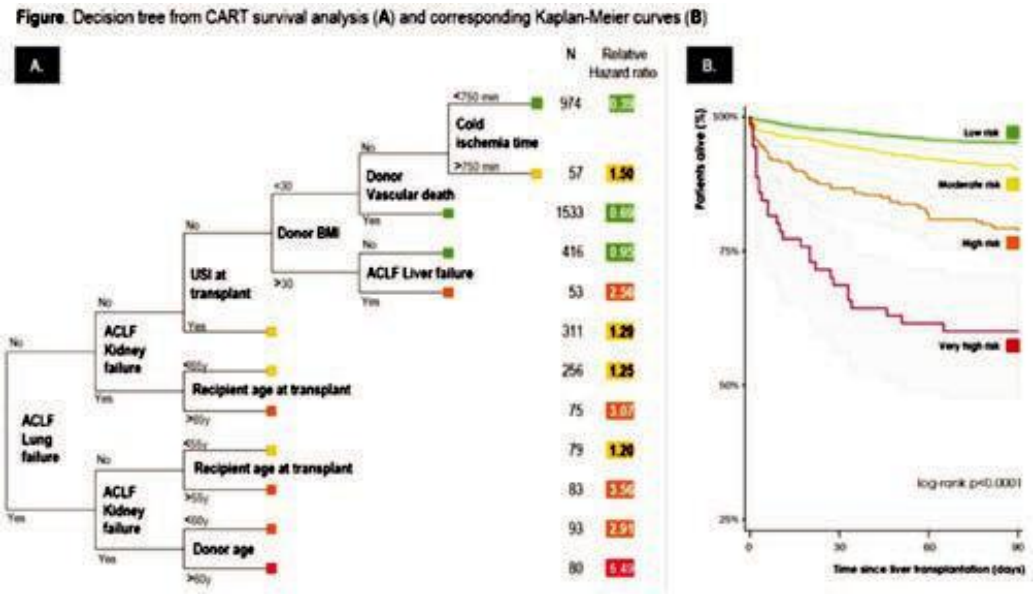
Introduction Cirrhotic patients undergoing an initial liver trans-plantation (LT) have a 1-year survival exceeding 85%.. Some cirrhotic patients present at least one of the 6 failures defin-ing Acute-On-Chronic Liver Failure (ACLF): respiratory, kidney, liver, coagulation, encephalopathy and circulation. . The aim of this study was to build a decision-tree algorithm for pre-dicting 90-day mortality in transplanted patients, by assess-ing the independent prognostic contribution of ACLF.. Methods All patients transplanted between 2008 and 2014 (N=4789) were included as part of the OPTIMATCH study, yielding 4010 patients with complete data for the present analysis.. Data col-lected comprised clinical and biological features at the time of LT for recipients and their donors, assessing ACLF status according to ACLF/CANONIC criteria to categorize patients.. A survival Classification and Regression Analysis (CART) algo-rithm was applied to build the prognostic model for 90-day mortality.. Results 1657 patients (41%) met the CANONIC cri-teria of ACLF with at least one organ failure (1: 20. 3%;. 2: 12..6%; 3 and more: 8..4%).. Overall 90-day mortality rate was 7..6%, with corresponding rates of 5..4%, 7..2%, 10..2% and 20..1% in patients with 0, 1, 2, 3 and more organ failures, respectively.. Decision-tree modelling identified 12 subgroups further classified in 4 increasing risk classes (Figure), highlight-ing the prognostic importance of respiratory failure and acute renal failure at the time of LT, as well as strong interactions between donor and recipient features.. Conclusion From a large nation-wide data base including the 6 organ failures defined by the ACLF as covariables, the unsupervised CART algorithm demonstrated that

the 90-day mortality is mainly determined by ventilator support and/or acute renal failure at the time of LT.. Interestingly, the matching of candidates with ACLF or in USI

at the time of LT, to young (<60y) or non-obese donors may decrease the 90-day mortality and avoid futile transplantations..



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267

Combining Chronic Liver Failure-Sequential Organ Failure Assessment(CLIF SOFA) criteria with Asia-Pacific Association for the Study of Liver (APASL) criteria pre-dicts short term mortality of Acute on chronic liver fail-ure (ACLF) better than APASL criteria alone

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Background: ACLF is a new entity used to describe patients with acute complication of cirrhosis with organ failure(s). . In contrast to acute decompensation of compensated cirrhosis, ACLF has a high 1 and 3 month mortality.. Aims: To see if appli-cation of CLIF SOFA criteria in patients diagnosed as ACLF by APASL criteria improves prediction of short mortality (at 28 days and 90days).. Methods: This study, a single center pro-spective observational study included 100 ACLF patients as per APASL definition, admitted in an University hospital in South India.. These patients were reclassified into ACLF and no ACLF groups using CLIF SOFA criteria.. Results: Alcohol was the most common cause of chronic liver disease (62%) followed by Hep-atitis B(19%) and Nonalcoholic steatohepatitis(12%). . Active alcoholism was the most common precipitating event in 53 (53 %),followed by infection 31 (31 %).. There as more than one precipitating event in 24 (24 %).. Out of the 100, 72 patients were classified as ACLF by both CLIF SOFA and APASLcriteria (Group A) and 28 patients had ACLF by APASL criteria only (Group B).. Bacterial infection (p value 0..024) and coagulation failure (59..7 % vs 7..1 % p <0..001) was significantly higher in Group A.. Mortality at 28 days and 90 days was higher in Group A (44..4% vs 7..1%, p <0..001 and 63..9% vs 32..1%, p<0..004).. As per CLIF SOFA ACLF definition, the 72 patients were graded as ACLF grade 1, 11..1 % (n=8), ACLF grade 2, 38..9 % (n=28), ACLF grade 3, 50 % (n=36).. In these ACLF patients, the most common organ failure was cerebral failure (80. 6%). followed by liver failure (70. 8%),. coagulation fail-ure (59..7%), renal failure (16..7%), renal dysfunction (22..2%), cardiac failure (22..2%) and respiratory failure (12..5 %).. 28 day mortality in patients with no ACLF, ACLF grade 1, ACLF grade 2 and ACLF grade 3 as per CLIF-SOFA criteria was 7..1 %, 25 %, 25% and 63..9% and 90 day mortality was 32..1%, 37..5 %, 57..1 % and 75 % respectively..

Compared to patients without ACLF, ACLF patients as per CLIF-SOFA criteria had significantly higher international normalized ratio (INR), serum creatinine, total leucocyte count, Child-Pugh and MELD score, lower serum sodium and Hepatic encephalopathy (p value <0..05) .. Conclusions: According to our study clinical profile of ACLF in our population is similar to the western population with active alcoholism and infection being most common precipitat-ing event.. Combining CLIF-SOFA criteria with APASL definition of ACLF is better than APASL definition alone in predicting 28 day and 90 day mortality..

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268

Characteristics and outcomes of patients with Hepatitis B virus (HBV) related Acute-on-Chronic Liver Failure (ACLF) by a new classification according to the severity of underlying liver disease

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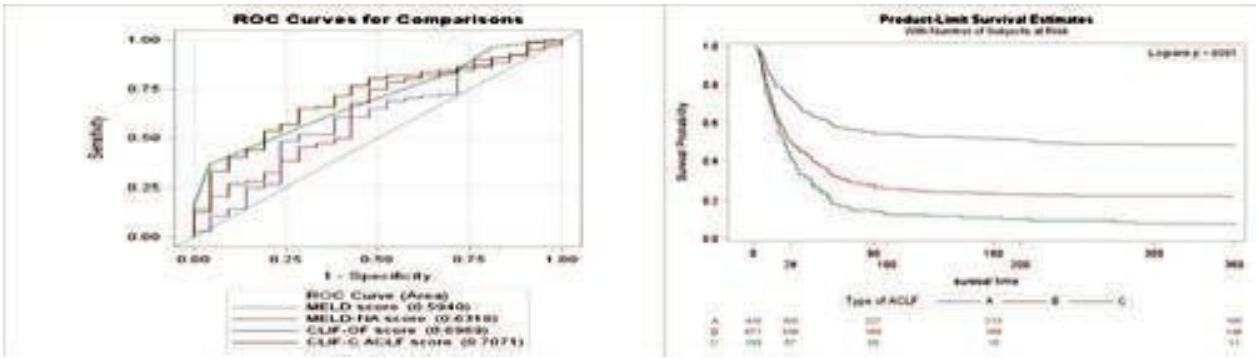
Background:A new definition and classification for ACLF was proposed including the entire spectrum of chronic liver dis-eases and categorized them as type A(non-cirrhotic), type B(cirrhosis),and type C(decompensated cirrhosis). .We aimed to analyze the characteristics and outcomes of patients with HBV related ACLF according to the new classification.. Methods:1,240 patients with HBV related ACLF defined by Asian Pacific Association for the Study of the Liver criteria were ana-lyzed.. Precipitants, response, organ failure, and transplant-free survival rates were evaluated and compared between patients with the 3 types. . Results:Reactivation of HBV was the most prevalent precipitant in patients with type A (81..8%) compared to patients with type B (73..4%) and C(41..5%)(P<0..001)..Sepsis and ischemic were more common precipitants in patients with type C(22. .2% and 24. .4%) compared to patients with type A(6..0% and 0..2%) and B(13..4% and 1..8%)(P<0..001).. MELD-Na score and CLIF Consortium ACLF score (CLIF-C ACLFs) were higher in patients with type C in comparison with others (P<0..001).. The CLIF-C ACLFs showed a higher ability in predicting 90-day transplant-free mortality compared to other scores in patients with Type C (AUROC=0..7071, P=0..021).. Infections (including spontaneous bacterial peritonitis and pneumonia) were higher in patients with type C(63..7%) than in patients with types A (36. .1%) and B (54. .4%)(P<0. .001). . Kidney failure was the most common organ failure, with the higher incidence of 14..8% in patients with type C compared to patients with type A(1. 4%). and B(5. 8%)(P<0. . 001).. The. 28-d(72..2%, 48..9% and 41..4% for types A, B and C, respec-tively P <0..001), 90-d(54..4%, 27..3% and 15..8% for types A, B and C, respectively P <0..001), and the 1-year transplant-free survival rate(48..5%, 22..2% and 7..5% for types A, B and C, respectively P <0..001) were different by ACLF subtype.. ACLF subtype and CLIF-C ACLFs were both independent risk factors in

predicting 28d, 90d, and 1 year transplant-free survival rates in patients with HBV related ACLF(P<0. .001). . Conclu-sion:The new ACLF classification according to the severity of underlying liver disease was clinically useful because different injury, response, and organ failure could be predicted, which also suggests different management strategies and different outcomes..

CLIF-Cs in predicting 90d mortality in typeC and K-M analysis according to ACLF type



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274

Incidence, risk factors and outcomes of acute kidney injury (AKI) in patients with acute-on-chronic liver fail-ure (ACLF) of underlying cirrhosis

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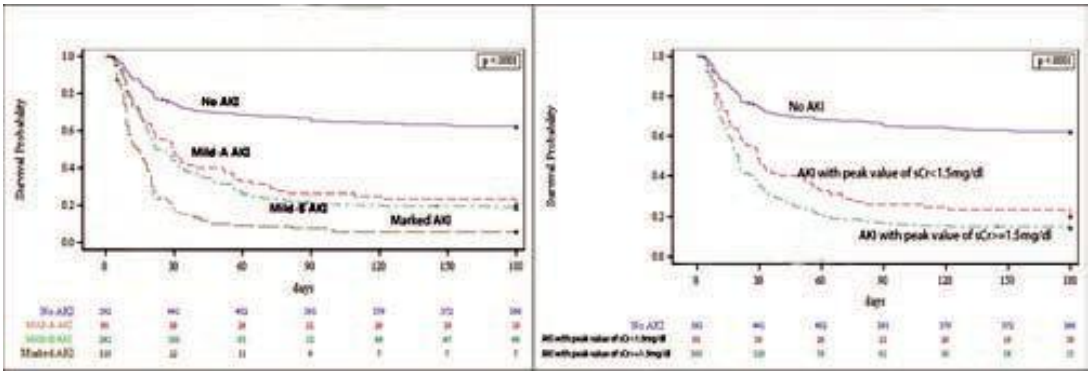
Background and aims: Acute kidney injury (AKI) is a life-threat-ing complication in patients with acute-on-chronic liver failure (ACLF) of underlying cirrhosis. . However, the characteristics of AKI in these patients have not been clarified.. Our aim was to determine the incidence and risk factors of AKI and the association between AKI severity and 180-day transplant-free survival.. Methods: We performed a retrospective cohort anal-ysis of patients with ACLF of underlying cirrhosis in a single center from January 2009 through December 2014.. AKI was defined by the criteria proposed by International Club of Asci-tes (ICA).. The incidence and risk factors of AKI development and its relationship to 180-day transplant-free survival rates were evaluated.. Results: Of 1,032 patients with ACLF of under-lying cirrhosis, 121 (11..72%) had AKI at admission, and 319 (30..9%) developed to AKI during hospitalization.. We estab-lished a logistic regression model including 4 independent fac-tors with AKI development: MELD score (odds ratio [OR], 1..1; 95% confidence interval [CI], 1..07-1..14), presence of ascites (OR, 3..80; 95% CI, 2..13-6..78), sepsis/ infection (OR, 2..25; 95% CI, 1. .66-3. .03), and acute variceal bleed (OR, 1. .78; 95% CI, 1..00-3..19).. The AUROC of the model in internal and external validations were 0..95 and 0..85, respectively.. Patients with mild-A AKI had a higher 180-day transplant-free survival rate (23..8%) than patients with mild-B AKI (19..0%) or marked AKI (5..9%) (all P < 0..001).. AKI patients with a peak value of sCr <1..5 mg/dl had a higher 180-day transplant-free survival rates compared to those with a peak value of sCr^1..5 mg/ dl (23..8% vs..14..7%, P < 0..001).. In the competing risk test, counting liver transplantation as competing risk for survival-development of AKI, end-stage ACLF, present of HE, sepsis/ infection, PLT counts), and MELD score were the predictors of 180-day overall survival rates.. Conclusions: We developed a clinical risk model for predicting development of AKI with

great accuracy.. Combining the ICA-AKI criteria and the peak value of sCr with 1..5mg/dl provides a good prognostic method for patients with ACLF of underlying cirrhosis..

Kaplan-Meier's analysis according to AKI stage and peak sCr value



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276

Vaildation of Prognostic Scores to Predict Short-term Mortality in Patients with Acute-on-Chronic Liver Failure

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Background and Aim The Chronic Liver Failure - Sequential Organ Failure Assessment score (CLIF-SOFAs), CLIF consortium organ function score (CLIF-C OFs), CLIF-C acute-on-chronic liver failure score (CLIF-C ACLFs) were developed to define ACLF and to predict mortality of ACLF patients. . This study aimed to validate the CLIF-SOFAs, CLIF-C OFs and CLIF-C ACLFs in Korean ACLF patients and compare the prognostic accuracy of prognostic scoring systems. . Methods This study included 252 ACLF patients who satisfied either Asian Pacific Associa-tion for the Study of the Liver [APASL] ACLF Research Consor-tium (AARC) or European Association for the Study of the Liver CLIF-C criteria at admission from January 2013 to December 2013 in 21 university hospitals.. The diagnostic performances of CLIF-SOFA, CLIF-C OF, CLIF-C ACLF, Model for End-stage Liver Disease (MELD), MELD-Na, and Child-Pugh scores for short-term mortality were compared by area under the receiver operating characteristics (AUROC) curve . . Hosmer-Lemeshow test was used to assess the goodness-of-fit.. Results Among total 252 patients, 196 patients were according to CLIF-C defini-tion and 93 patients were according to AARC definition.. Thir-ty-four patients satisfied both definitions simultaneously. . The AUC of CLIF-SOFAs, CLIF-C OFs and CLIF-C ACLFs for 28-day and 90-day mortality were significantly higher than MELD, MELD-Na, and Child-Pugh scores in ACLF patients according to CLIF-C definition (all Ps < 0..05), but there were no significant differences in ACLF patients according to AARC definition.. In the CLIF-C ACLF patients, CLIF-SOFA score had highest AUC value for 28- day and 90-day mortality (0. .890 and 0.

.863), and followed by CLIF-C ACLF (0..880 and 0..825) and CLIF-C OFs (0. .871 and 0. .850). . Hosmer-Lemeshow tests for 28-day and 90-day mortality of CLIF-SOFAs, CLIF-C OFs, and CLIF-C ACLFs did not show a significant lack of fit in both CLIF-C ACLF group and AARC ACLF patients (all Ps > 0..05).. Conclusions CLIF-SOFAs, CLIF-C OFs and CLIF-C ACLFs are useful scoring systems to provide accurate information on short-term mortality in ACLF patients according to CLIF-C definition.. However, these scoring systems did not show the superiority in predicting short term mortality compared with MELD, MELD-Na, and Child-Pugh score in ACLF patients according to AARC definition..

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566

Acute on chronic liver failure from Wilson disease: Out-come and predictors of mortality in 61 patients

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Background: Acute on chronic liver failure (ACLF) is an emerg-ing entity with unique pathogenesis and outcome that is differ-ent from decompensated cirrhosis.. Patients with Wilson disease (WD) often present acutely with jaundice, ascites, encepha-lopathy or coagulopathy despite underlying cirrhosis. . WD is a prototypical example of type B ACLF (Gastroenterology 2014;147:4) There is no study that has analyzed the outcome and predictors of mortality in patients with WD presenting with ACLF.. Methods: Sixty-one patients with WD who fulfilled crite-ria for ACLF were identified from a WD registry of 264 patients (1997-2016).. ACLF was defined as per APASL.. (Hepatology Int 2009;3:269).. All patients had jaundice (bilirubin>5 mg/dl) and coagulopathy (INR >1..5) which was complicated by asci-tes and or encephalopathy within 4 weeks.. Outcome assessed at 3 months was either death or liver transplantation.. Descrip-tive statistics, chi-square test and student t test were carried out to determine differences between survivors and non survivors followed by Cox-regression analysis to determine predictors of mortality.. Results: There were 36 males and 25 females with a mean age 14. 4. years. . Ascites and encephalopathy were present in 55 (90..2%) and 29 (47..5%) patients respectively.. Forty-four patients died and two underwent transplantation (75..4%): 74% with ascites and 96..5% with encephalopathy.. The differences between survivors and non survivors are shown in table. . Cox regression analysis identified encephalopathy (Hazards ratio, HR 3. 7),. INR (HR 1. 14),. serum protein (HR 0..84), total bilirubin (HR 1) and log WBC (HR 0..87) as risk fac-tors for mortality.. No precipitant could be identified for acute deterioration.. Conclusions: Patients with ACLF from Wilson dis-ease have high mortality (75%) and should be expeditiously worked up for liver transplantation.. Encephalopathy (not asci-tes alone) is significantly associated with mortality..

Comparison of interval variables according to outcome

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1045

IL10 associated downstream signalling pathways play a central role in severe monocyte dysfunction during acute-on-chronic liver failure.

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Objective: Acute-on-chronic liver failure (ACLF) is character-ized by rapid deterioration of liver function in cirrhosis which often precipitates organ failure.. ACLF is associated with severe immunodysfunction where immune activation and paresis often co-exist.. This dysregulated immune state leads to severe monocyte dysfunction that may precipitate bacterial infections.. Although ACLF as disease entity has attracted much attention, little is known about the molecular mechanisms responsible for altered monocyte function in this condition. . Design: We studied 64 patients with biopsy proven alcoholic liver disease (n=19 decompensated cirrhosis, n=23 alcoholic hepatitis, n=22 ACLF) and 7 controls. . Blood was obtained at admis-sion for biochemical tests, gene expression of PBMC's, flow cytometry and functional monocyte assays and plasma was used to determine cytokine/chemokine levels.. In addition we isolated CD14pos monocytes from 4 donors and 5 well-char-acterized ACLF patients and determined gene expression by NextGen sequencing to characterize key molecular factors associated with monocyte dysfunction using pathway analysis.. Additionally functional assays were performed with healthy or ACLF monocytes in the presence or absence of normal or ACLF serum.. Results: We observed decreased expression of HLA-DR, TLR2 and TLR4 within the classical monocyte subset and ele-vated numbers of IL10 producing intermediate monocytes in ACLF.. Functional analysis of total PBMC and isolated CD14pos monocytes showed severely impaired phagocytosis and oxida-tive burst in ACLF.. Increased IL10 gene expression by PBMC's and elevated IL10 plasma levels in ACLF were associated with decreased survival at 3 and 6 months. . Pathway analy-sis revealed significant downregulation of genes associated with immunological processes such as monocyte phagocytosis, cytokine-cytokine interactions and response to bacterial infec-tion.. Importantly, culturing healthy monocytes in ACLF serum induced an ACLF dysfunctional phenotype..

Conversely, cultur-ing ACLF-monocytes in healthy plasma reversed the ACLF phe-notype and restored phagocytosis.. Finally, our data indicated a central role for IL10 in the molecular pathways associated with ACLF.. Conclusion: ACLF is associated with severe immune dysfunction.. Inducing an ACLF signature in healthy monocytes using ACLF serum-containing media and reversing monocyte dysfunction of ACLF monocytes using normal serum containing medium suggests a circulating factor promotes this syndrome.. IL10 associates with more severe immune dysfunction and poor survival in ACLF while expression analysis suggests a crucial role for IL10 as driver of this condition..

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1221

Acute-on-chronic alcohol exposure using the 'NIAAA model' concomitantly damages the liver and lung

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Background.. The liver is a primary target of alcohol toxicity, but chronic alcohol abuse can damage several other organs, including the lung.. In fact, previous studies have shown that chronic ethanol exposure increases the incidence, severity, and mortality of sepsis-induced acute lung injury (ALI).. Furthermore, recent work by this group has indicated that liver injury caused by alcohol may contribute to lung pathology. . To date, most animal models investigating the role of alcohol in ALI require administration of an exogenous inflammatory stimulus (e. g.. ,. LPS); whether or not alcohol exposure is sufficient to induce pulmonary changes is unclear.. The 'NIAAA' model of acute-on-chronic alcohol exposure is a recently developed model that appears to better recapitulate alcoholic (steato)hepatitis.. The impacts of this liver model on lung pathology have not been explored; the goal of this study was to therefore char-acterize simultaneously the effects of acute-on-chronic alcohol on the liver and lung.. Methods. 10 W male C57Bl6/J mice were exposed to alcohol on the NIAAA protocol: 10 days liquid diet, followed by a bolus gavage (5 g/kg). . Animals were sacrificed 9 or 24 hours after the gavage, and liver and lung tissue, plasma, and bronchoalveolar lavage fluid (BALF) were collected for analysis.. Injury was determined biochemi-cally and histologically.. Inflammatory cytokine and chemokine production were also quantitated.. Results. As expected, acute-on-chronic alcohol feeding caused significant steatohepatitis, characterized by increased plasma AST/ALT, as well as fat and neutrophil accumulation. . Interestingly, acute-on-chronic alcohol exposure also caused transient lung injury.. Similar to liver, this injury was characterized by a predominantly neutro-philic inflammatory response in lung tissue and BALF.. Indices of the pulmonary inflammasome were also elevated by acute-on-chronic alcohol in the lung, analogous to previous findings in the liver..

Conclusions.. Taken together, these data indicate that the newly developed NIAAA model of alcoholic (steato) hepatitis also develops concomitant lung damage.. These results indicate, for the first time, that alcohol exposure is sufficient to induce pulmonary inflammatory injury and emphasize the parallel (and potentially interdependent) damage between the liver and the lung after alcohol exposure.. This work was sup-ported, in part by NIH grants R01AA021978 (GEA, PI) and R01AA013353 (JR, PI)..

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1233

Alterations of the gut microbiome in the acute-on-chronic model of alcoholic hepatitis correlate with liver damage, steatosis and inflammation

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Purpose: Increasingly, intestinal microbiome changes are recognized for their profound influence on various disease processes. . Several studies reveal that in alcoholic liver dis-ease, microbiome shifts may play a pathogenic role in dis-ease progression. . In a field that relies heavily on models to simulate human alcoholic disease, we sought to analyze the microbiome changes in the recently published acute-on-chronic (NIAAA) model of alcoholic hepatitis (AH).. Methods: 6-8 week-old C57BL/6 female mice received 10d of 5% ethanol (EtOH) in Lieber DeCarli liquid diet followed by EtOH gavage (5g EtOH/kg body weight) or pair-fed diet (PF) followed by sugar gavage.. Some EtOH and PF mice received a p.o. cocktail of antibiotics to decontaminate gut microbes. . Cecal stool DNA was extracted and Illumina 16S sequencing was completed using QIIME and LEfSe analysis. . Results: Mice treated with antibiotics showed protection from key measures of AH includ-ing hepatic cytokine increases, steatosis and neutrophil infiltra-tion highlighting the importance of gut microbiota.. From stool of non-antibiotic treated mice, we measured α diversity using

PD_whole _tree, chao1, observed_ otus and shannon. . Each quantifies diversity within a sample and compares that diver-sity between groups.. We observed no differences in α diver-sity between PF and EtOH mice, indicating that after 10d of alcohol, there is no suppression of α diversity.. Next we exam-ined β diversity, a metric that assesses community dissimilarity, using bray-curtis, unweighted UniFrac and weighted UniFrac.. By these measures, we observed that there were no significant community differences between PF and EtOH. . Finally, LEfSe examines taxonomic changes between groups and revealed enrichment in EtOH mice in phylum Actinobacteria, driven by enrichment in genus Olsenella. . Phylum

Tenericutes was reduced in relative abundance in EtOH mice.. Most dramatic was the reduction observed in phylum Verrucomicrobia driven largely by genus Akkermansia in EtOH mice.. Conclusions: Our results suggest that gut microbes affect the liver following EtOH consumption and that alcohol alters bacterial content in the acute-on-chronic feeding model.. α and β metrics did not differ in our cohort, suggesting that the diversity within and between EtOH and PF mice was not significantly changed.. However, we do observe dynamic changes in specific taxonomies pres-ent within each group.. These changes concur with published evidence of taxonomic shifts at later time points of EtOH admin-istration.. Importantly, our data suggest that the 10d acute-on-chronic model of AH does induce microbiome changes that impact liver inflammation and such dynamic changes may impact human AH..

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The following people have nothing to disclose: Patrick P.. Lowe, Benedek Gyongy-osi, Abhishek Satishchandran, Arvin Iracheta-Vellve, Aditya Ambade, Doyle V.. Ward

1392

Impact of Acute-On-Chronic Liver Failure on 90-day Mortality following Liver Transplantation

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Introduction: Acute-On-Chronic Liver Failure (ACLF) is characterised by organ failures and is associated with a significant rate of mortality within 28-days (23 to 74%), depending on the number of organ failures. The aim of this study was to assess whether ACLF at the time of liver transplantation (LT) were also a prognostic factor in cirrhotic patients and its impact the early outcome (the 90-day mortality). Patients and methods: 350 cirrhotic patients admitted to our Liver ICU between January 2008 and December 2013, and who underwent LT, were enrolled in this study. We used ACLF grades based on analyses of patients with organ failure and assessed according to ACLF/CANONIC criteria (EASL-CLIF consortium) to categorize the cirrhotic patients. A propensity score was applied with an Inverse Probability Treatment Weighting in a Cox model, and a prognostic score of LT futility (90-day mortality) was generated.
Results: The primary indications for liver transplantation were end-stage cirrhosis (n=194; 55%) and cirrhosis with hepatocellular carcinoma (n=156; 45%). 140/350 patients (40%) met the "EASL-CLIF consortium" criteria of ACLF. Overall mortality rate at 90 days post-transplant was 10.6% (37/350 patients). In patients with ACLF, the 3-month, 1 year and 5-year rates of patient and graft survival were 79%, 70%, 60% and 77%, 73 and 58%, respectively; in patients without ACLF it was 96%, 91%, 84% and 94%, 88% and 78%, respectively. The 90-day survival rate for ACLF grade 3 was 60% and 83%, 85% and 96% for grades 2, 1 and 0, respectively. ACLF at the time of LT (HR: 5.78 [3.42 – 9.77], p< 0.001) was an independent predictor of 90-day mortality. Sepsis occurring during the month before LT, high recipient age and male recipient, cause of LT and female donor were also independent risk factors of early mortality. Using the six factors retained in the weighted Cox model, the 90-day mortality risk was calculated according to following equation: Futility Score =1 − 0.9A *Where: A = exp (− 0.28 × (1 if the recipient is male, 0 otherwise) + 0.29 × (1 if the donor is male, 0 otherwise) − 0.29 × (1 if the LT indication is decompensated cirrhosis, 0 if LT is hepatocellular carcinoma on cirrhosis) +*

0.44 × (1 if the recipient has sepsis, 0 otherwise) + 0.40 × (1 if the recipient is older than 57.2 years, 0 otherwise) + 1.75 × (1 if the recipient is ACLF, 0 otherwise).
Conclusion: LT is feasible in cirrhotic patients with ACLF. However, we showed that ACLF was a significant and independent predictor of 90-day mortality, and thus of futile LT. We propose a score, integrating the concept of ACLF, to identify candidate cirrhotic patients in whom LT might be futile.

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1407

Goal Directed Ammonia Lowering Therapy in Acute on Chronic Liver Failure (ACLF) with Hepatic Encephalopathy (HE): A Randomized Trial (ClinicalTrials.gov Identifier:NCT02321371)

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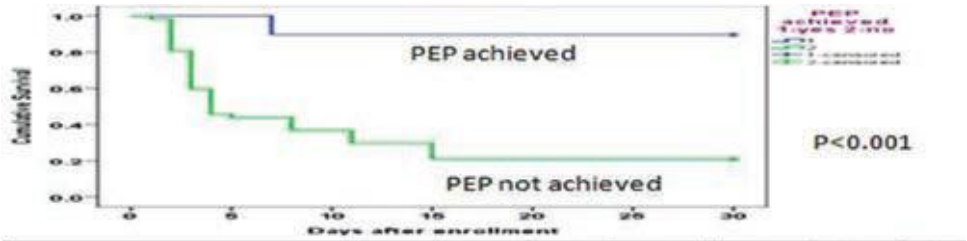
Background and Aims: HE in ACLF is associated with high mortality. There is limited data on the role of ammonia(NH3) and anti-ammonia measures in treating HE in ACLF. We prospectively studied the NH3 dynamics and effects of goal directed ammonia lowering therapy on short-term disease outcome in ACLF patients with grade III/IV HE. Patients and Methods: Of 276 ACLF patients screened between 11.2014 and 12.2015; 86 with grade III/IV HE received aggressive purging with lactulose (100mL followed by 30mL hourly till 4-6 times stool passed) for first 24hr. Patients not achieving NH3 ≤70mg/dL in this period (n=73), were randomized to continued lactulose arm(Gr. A, n=35) or lactulose plus rifaximin arm (Gr. B, n=38). NH3 level was measured 12 hourly for 72hr. Management of sepsis/coagulopathy/shock/GI-bleeding, was done as per standard protocols. Primary end-point (PEP) was to achieve the target NH3 ≤70mg/dL in 72hr. Patients were followed-up till 30 days to see effect on disease outcome(secondary end point).Results: Attainment of PEP[21.1 vs. 22.9%, p=0.423], improvement in grade of HE from III/IV to II/I/0 [39.5 vs. 45.7%, p=0.922] & 30 day mortality[34.2% vs. 42.9%, p=0.582] were not different in Gr A vs. B. However, combining the two groups, patients who achieved PEP in 72 hr (responders;n=29, 13 within 24 hr and 16 in next 48 hr), had lower baseline NH3 (169±43 vs. 216±79, p=0.030), HE grade(grade IV in 0% vs. 26.3%, p=0.002), and MELD (25.7±5.1 vs. 31.2±7.5, p=0.002) in comparison to non-responders. Responders had greater improvement in HE grade III/ IV to II/I/0 [100 vs. 24.6%, p<0.001], and lower frequency of sepsis[10.3 vs. 64.9%, p<0.001] and 30 day mortality[10.3 vs.82.5%, p<0.001;Fig 1, HR=12.8 for nonresponder; 95% CI 3.97-41.49]. NH3 levels correlated with HE grade(R=0.673, p<0.0001). Conclusions: Monitoring and targeting NH3 is important in management of ACLF patients with HE, as patients achieving target NH3 of ≤70mg/dL, have greater likelihood of reversal of HE and improved survival. Additions of rifaximin to lactulose did not help in NH3 reduction or improvement in outcomes/survival. Newer strategies are needed for effective NH3 reduction to reduce mortality in this group



			D2	D3	D5	D7	D11	D15	D30
PEP (n=29)	achieved	At risk	29	29	29	26	26	26	26
		survival %	100	100	100	89	89	89	89
PEP (n=57)	achieved	At risk	46	34	25	25	17	12	12
		survival %	81	60	44	44	30	21	21

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1708

Management Of Refractory Variceal Bleed With Dannis- Ella Stent In Patients With Acute On Chronic Liver Failure

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Background and Aims: Almost, 10% of the bleeding episodes are refractory to combination of vasoactive agent and endotherapy, and are associated with a mortality upto 50%. Severity of liver disease and high portal pressure are mainly responsible for it. TIPS can not be used in these patients due to high MELD score. Self-expandable DE stents could be an effective option for control of refractory variceal bleeds. Patients and Methods: ACLF patients (n=88, mean age 47.3±10.9 yr.) with refractory variceal bleeds received either DE stent (Gr. A, n=35) or continued with repeat endotherapy and vasoactive drug (Gr.B, n=55) Matching by propensity risk score (PRS) was done to avoid selection bias. Competing risk Cox regression analysis was done to identify event specific i.e. gastrointestinal bleed-related death. Results: Majority (78.4%) of the patients were alcoholic with a MELD score of 45.9±20. Patients in the two groups had significant differences with respect to baseline MELD and the CTP scores which were not evident in the PRS matched cohort. Control of initial bleeding (89% versus 37%, $p<0.001$) and bleed related death (26% versus 64%; p=0.006) was significantly lower in the DE stent group as compared to controls. In a multivariate competing risk Cox model, patients who underwent DE stenting had reduced mortality in both the pre-match (p=0.004, HR 0.24, 95%CI 0.09-0.64) and PRS-matched cohorts (p=0.02, HR 0.09, 95% CI 0.01- 0.74).
Conclusions: Self-expandable DE stents are very effective in control of refractory variceal bleeding and improved mortality in patients with severe liver failure.

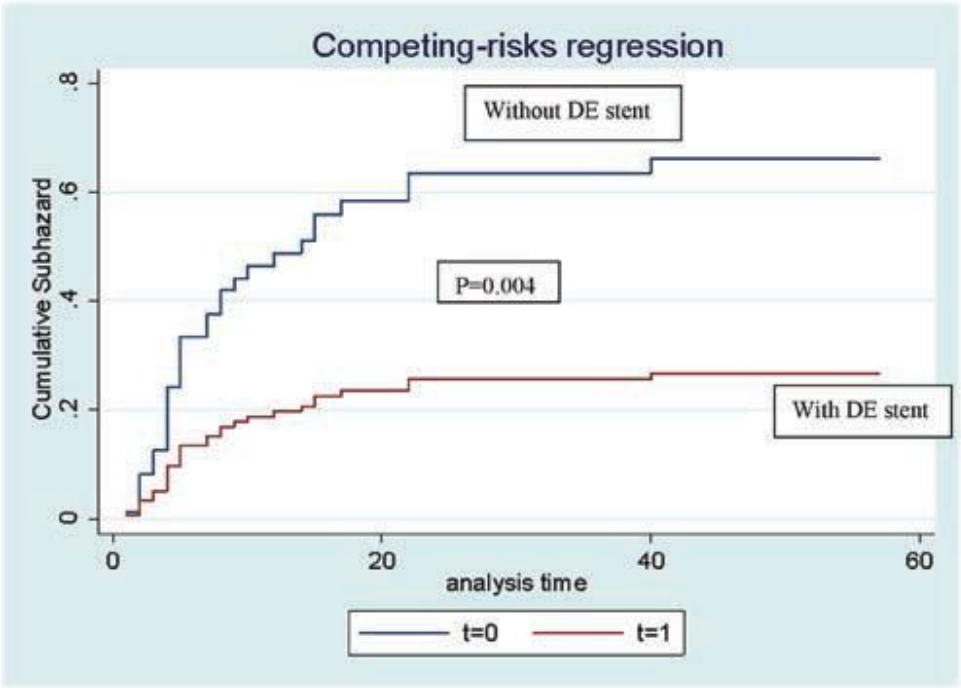

Figure 1a

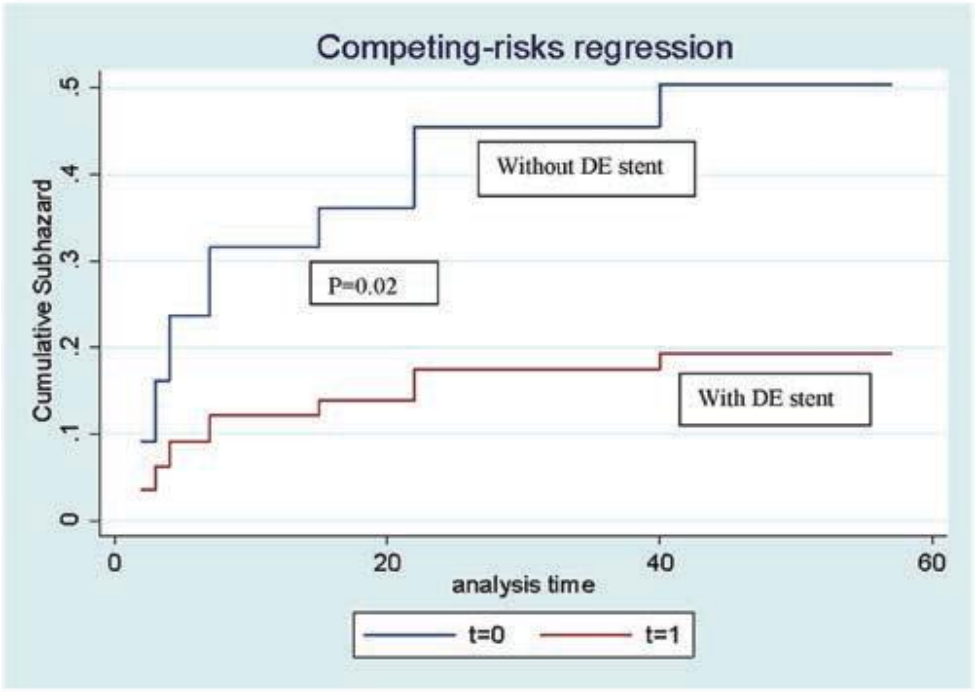

Figure 1b

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2045

Does the presence of cirrhosis influence on the mortality rate in patients with acute on chronic liver failure?

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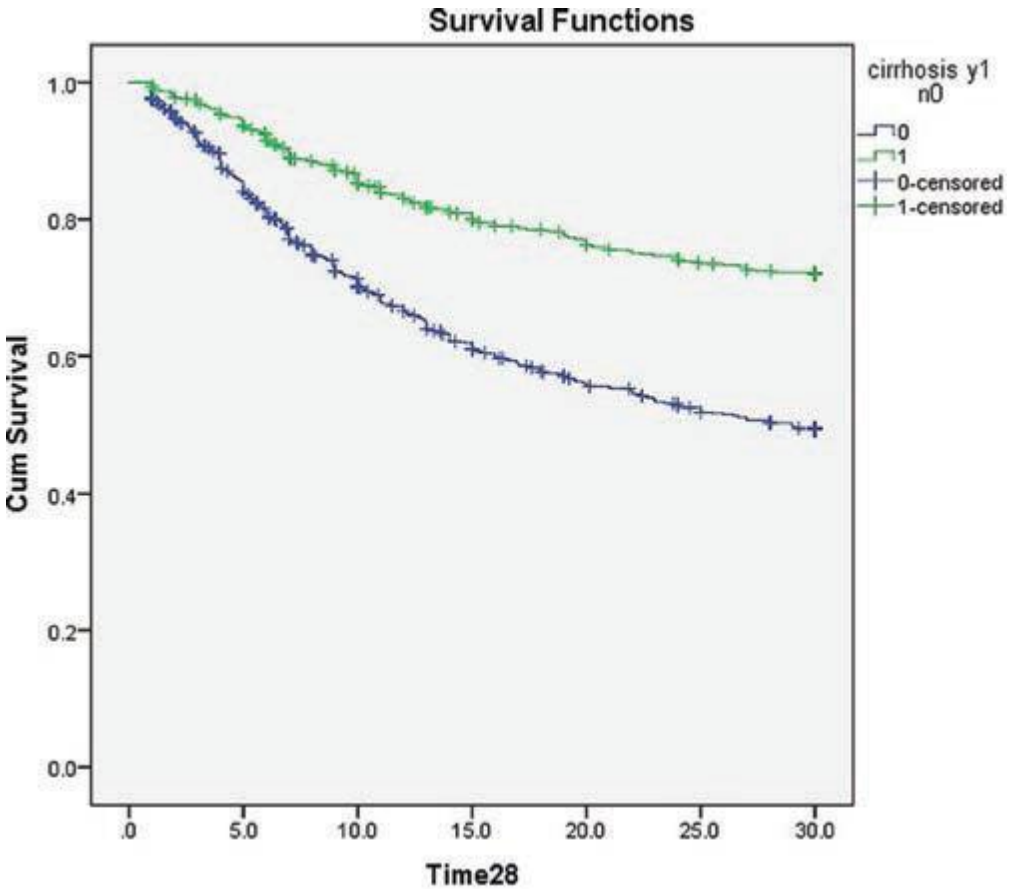
Background: Currently, the APASL Acute-on-chronic liver failure (ACLF) research consortium (AARC) criteria includes non-cirrhotic chronic liver disease; CLD patients due to the evidence of high mortality rate (Sarin SK, Hepatol Int 2014). The basal CLD severity may play important role on outcomes. We aim to compare the 28-day and 90-day mortality rate of ACLF patients with and without cirrhosis. Methods: AARC collected data prospectively from multicenter of ACLF patients during Oct, 2009 to Apr, 2016. Of 1621 patients, 637 of them (39%) were diagnosed as cirrhosis which defines as clinical presentations or biochemical or imaging evidence or histopathological confirmation advanced fibrosis. Baseline characteristics and the 28-day and 90-day mortality were recorded. The Kaplan-Meier ;K-M method was used to compare the mortality rate between two groups. Results: Of a total of 1621 patients, 86.7% were male with mean age ± SD of 44.6±12 years. The most common acute insult were alcohol (48%), HBV reactivation (16%) and hepatitis E infection (7.5%). The baseline MELD score were 29 ± 7 and 52% of patients developed >2 organs failure.

The most frequent organs failure were liver (80%), coagulopathy (35%), and renal failure (23%). The 28-day and 90-day mortality rate were 39% and 50% respectively. Baseline characteristics showed that non-cirrhotic patients had significantly higher MELD score, number of organ failures than those cirrhotic patients. ACLF patient without cirrhosis had significantly higher 28-day and 90-day mortality rate than cirrhotic patients as shown by the K-M survival curve in figure1.

Conclusion: Our data suggests that the 28-day and 90-day mortality rate of ACLF patient without cirrhosis was significantly higher than those with cirrhotic, thus the presence of underlying cirrhosis at baseline should be evaluated due to its influence on mortality.



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The following people have nothing to disclose: Sombat Treeprasertsuk, Kessarin Thanapirom, Roongruedee Chaiteerakij, Ashok Choudhary, Manoj Sharma, Rakhi Maiwall, Viniyendra Pamecha, Richard Moreau, Mamun A. Mahtab, Yogesh K. Chawla, Harshad Devarbhavi, Yu Chen, Zhongping Duan, Deepak N. Amarapurkar, Saeed Hamid, Amna S. Butt, Hasmik Ghazinyan, Guan Huei Lee, Ajit Sood, Laurentius A. Lesmana, Gamal Shiha, Abdulkadir Dokmeci, Shiv. K. Sarin

2046

Long-term prognosis of patients who survived from acute-on-chronic liver failure based on KACLiF cohort

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Background This study aimed to investigate the impact of ACLF on long-term survival after surviving the ACLF events in patients with acute decompensation.. Methods A total of 1177 acutely deteriorated patients who survived more than 3 months were consecutively collected and prospectively followed up in KACLiF study.. ACLF was defined by either EASL CLIF-C or APASL AARC definition.. Survival analysis according to ACLF events and grades were obtained by Kaplan-Meier method. . Results Mean duration of follow up was 18. .2±9. .1 months. . Of patients enrolled, the prevalence of ACLF based on CLIF-C and AARC definitions were 11. .0% (118/1073) and 8. .8% (74/838), respectively. . The survival of CLIF-C ACLF group was shorter than no CLIF-C ACLF group (25..6±1..2months vs.. 30..7±0..4months, p=0..013).. In the subgroup of 515 patients without prior decompensation, survivals were not different between the groups (p=0..289).. Even the experience of grade 2 and higher CLIF-C ACLF did not shorten the survival com-pared to the experience of grade 1 CLIF-C ACLF. . However, in the subgroup of 558 patients with prior decompensation, the survival of CLIF-C ACLF group was shorter than no CLIF-C ACLF group (23..3±1.. 7months vs.. 29..1±0..6months, p=0..020).. Also.. the survivals of grade 2 or higher CLIF-C ACLF patients were shorter than grade 1 and no CLIF-C ACLF patients (19..3±2..6months vs.. 29..0±0..6months, p=0..008).. In the sub-group of 50 patients who experienced grade 2 and higher CLIF-C ACLF, the survival of patients with prior decompensa-tion was shorter than patients without (19. .3±2. .6months vs. . 27..8±1..8months, p=0..026) even though the MELD scores were not different.. However, experience of grade 1 CLIF-C ACLF did not affect the survival regardless of presence of prior decom-pensation.. Meanwhile, survivals of patients were not different

regardless of AARC ACLF (which exclude patients with prior decompensation by definition) experience (p=0..288).. Conclu-sions Long-term mortality after survival from ACLF is dependent on the presence of prior decompensation.. In the absence of prior decompensation, long-term mortality of ACLF patients is not different regardless of ACLF experience according to both CLIF-C and AARC definitions.. In the presence of prior decom-pensation, the experience of grade 2 and higher negatively affects the long-term survival even after the recovery of ACLF.. Therefore, efforts to prevent 1st event of acute decompensation and progression of organ failures may be important to improve the survival of chronic liver disease patients..

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2047

Network Approach to unveil Molecular Pathways driv-ing Cirrhosis progression to Acute-on-Chronic Liver Fail-ure (ACLF)

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BACKGROUND: The molecular pathways driving progres-sion from precirrhotic conditions to cirrhosis and ACLF are not known. . AIM: To develop a new network approach to inves-tigate molecular pathways driving progression from pre-cir-rhotic stages to ACLF.. METHODS: We performed a microarray analysis (Affymetrix Human Genome U219) of human liver biopsies at different stages of disease (5 fibrosis F2-F3, 8 com-pensated cirrhosis, 12 decompensated cirrhosis, and 8 with ACLF; 6 healthy livers were also studied) .. A human protein-pro-tein interactions network was generated from public databases containing all protein interactions with available experimen-tal evidence.. We created 7 specific sub-networks containing proteins related to important biological processes involved in liver disease (oxidative stress, genetic factors, fibrosis, inflam-mation, hepatocyte apoptosis, HSC apoptosis and angiogen-esis).. Using networks as scaffold we added our human gene expression data.. Pathway Enrichment Analysis using Reactome was performed and subnetworks around genes of interest were constructed for network clustering and functional analysis. . RESULTS: PCA analysis revealed that samples clustered accord-ing to the stage of disease.. Fibrosis, inflammation, apoptosis, and angiogenesis were significantly up-regulated in parallel to disease progression. . We found 546 significant differentially expressed genes at different stages.. Pathway enrichment anal-ysis showed that these genes are involved in lipid metabolism, bile acid metabolism, extracellular matrix formation, and fibrin clot formation. . We constructed functional Interaction subnet-work around genes of interest with 175 genes.. The network clustering and posterior functional analysis of the subnetwork showed that genes were clustered into 8 modules.. Out of the 8, 7 modules had significant pathways enriched in either descen-dent or ascendant profiles with disease progression (M0: extracellular matrix, platelet activation and PDGF as ascendant profiles; M1: IL-2, mTOR and pluripotent stem cell signalling; M3: metabolic pathways and bile secretion as descendent pro-files; M4: insulin resistance, AMPk signalling,

adipocytokine and detoxification of ROS, the majority as descendent profiles; M5: extracellular matrix, osteopontin signalling; M6: extracel-lular matrix; M7: drug metabolism, chemical carcinogenesis) CONCLUSION: This is a new methodology based on network approach allowing the identification of key pathways driving cirrhosis progression to ACLF.. Further mechanistic evaluation of identified networks will allow proposing new mechanistic hypothesis for cirrhosis progression and candidate genes for experimental validation..

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2049

Improved short-term survival in patients with Acute-on-Chronic Liver Failure (ACLF) *in extremis* with a combina-tion therapy approach

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Background: ACLF *in extremis* is a subset with a very high MELD and short-term mortality. . Pathophysiology of ACLF is dominated by severe systemic inflammation and aggravated hyperdynamic circulation originating from the gut and lead-ing to multi organ dysfunction. Using. a combination of treat-ments that address major pathophysiologic derangements may improve survival . . Aim: To study the efficacy of combination medical therapy (CMT) using N-acetylcysteine(NAC), probiot-ics and slow infusion of furosemide, albumin with or without terlipressin [SIFA (T)] in patients with ACLF *in extremis* with high CVP and compare it with a similar cohort treated with standard medical therapy (SMT). Methods: ACLF according to APASL, OF according to CLIF-SOFA and MELD ≥35 were included.. After standard blood, urine and ascitic fluid tests a central venous pressure (CVP) catheter was placed..Consecutive patients with CVP ≥10 cmH_2O received CMT(Arm I) using slow infusion of furosemide (2 mg/ hour),albumin (2 gm/ hour; 20-40g/d;(SIFA), NAC and oral probiotics in addition to SMT for complications of ACLF.. Furosemide was stepped up by 2 mg/h every 12 hours for 48 hours based on urinary sodium (UNa^+) excretion.. If UNa^+ still remained <85 mmol/d, terlipres-sin infusion [SIFA (T)] was started at 4mg/24 hrs, (max..up to 8 mg/ 24hr)..Treatment was continued till the patient was clin-ically dry and with UNa^+ >85 mmol/L.. Similar patients during the same period in other unit of the department received SMT; (Arm II) for ACLF and its complications including lactulose,an-tibiotics,large volume paracentesis terlipressin-albumin therapy for HRS and therapy for other complications as per guidelines.. Result:41 patients with ACLF *in extremis* were included from 2013 to 2015..20 received CMT (Arm I) and 21 received SMT (Arm II).. Etiology of cirrhosis and of the acute insults did not differ significantly (p>0. 05).. . Baseline parameters were also similar (p>0..05) for serum creatinine (2..3±1..67 vs.. 2..4±1..7); CTP score (12..8±0..8 vs.. 12..7±1..38); number of OF (2..9±1..4 vs. . 3. 1.±1. 5);CLIF.-SOFA score (12. 3.±1. 9. vs. . 12. 2.±2. 3). and urine output (523±78 vs. . 525±85ml/day). . However, MELD score (39. 50. (36. 25.-40. 00). vs37. 00. (35. 5.-39. 50;. p=0. 03). was higher in group

I..Significant improvement (p<0..05) was seen in urine sodium (27..6±21 to 202±106 mmol/24hrs),UO (523±78 to 2152±815ml/24hrs) and serum creatinine (2..3± 1. 67. vs . . 1. 63.± 0. 9). after treatment in group I while there was no change in group II [serum creatinine (2..4±1..7 to 1. 99.±1. 7);. UO (525±85ml/day to 810±150ml/d)]..28-day survival in Arm I vs..II was 65% (13/20) vs47% (10/21), (p<0..05).. Conclusion: Preliminary data suggestCMT in ACLF *in extremis* may improve survival.. ..

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2051

The combined of Urine Neutrophil Gelatinase-associated Lipocalin and the CLIF-SOFA score in prediction of mortality of patients with acute-on-chronic liver failure

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Background: Acute-on-chronic liver failure (ACLF) causes organ(s) failure with high short term mortality. CLIF-SOFA score is the proposed scoring system for ACLF diagnosis, which composed of six organs failure criteria, including renal failure which is the major organ that related to short term death. We aimed to study the clinical significance of urine Neutrophil Gelatinase-associated Lipocalin (uNGAL), a new biomarker for early detection acute kidney injury (AKI), in combination with CLIF-SOFA score for mortality prediction in ACLF patients. Methods: We enrolled prospectively Thai cirrhotic patients with acute decompensation who were admitted at the King Chulalongkorn Memorial Hospital, Bangkok, during August 1, 2014 to November 30, 2015. The CLIF-SOFA score, clinical history, laboratory profiles and uNGAL were collected within 48 hours. The modified CLIF/uNGAL-56 was developed with using the standard CLIF and/or urine Neutrophil Gelatinase-associated Lipocalin (uNGAL) >56 ng/mL as an additional criterion of acute kidney injury (Treeprasertsuk S, et al. BMC Gastroenterol 2015 Oct 16;15:140.). The 30-day mortality and clinical outcomes were recorded. Results: There were 77 acute decompensated cirrhotic patients enrolled. According to the CLIF-SOFA score, 32 patients (42.6%) had ACLF. According to their baseline characteristics; there was no significant difference in mean age, gender, etiology of cirrhosis, precipitating causes of acute decompensation between both groups. Patients with ACLF had higher MELD score than those without ACLF (26.9 VS 16.6; P<0.001). The 30-day mortality rate of ACLF patients was 43.7% which was significantly higher than those without ACLF (13.3%). By using the CLIF-SOFA, it can predict the 30-day mortality with relative risk (RR) of 3.3 (95%CI 1.4-7.6). With the modified CLIF/uNGAL-56, the 30-day mortality rate was 38.6% and this new score can predict the 30-day mortality with RR of 4.2 (95%CI 1.4-13.3) as shown in table 1. Conclusion: The combined of urine Neutrophil Gelatinase-associated Lipocalin and the CLIF-SOFA score increase the prediction value of

mortality compared to CLIFSOFA score alone in patients with acute-on-chronic liver failure.

Table1: The 30-day mortality rate according to the CLIF-SOFA and the modified CLIF/uNGAL-56 MR; mortality rate

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2053

Protective effects of beta-blockers in patients with acute-on-chronic liver failure including circulatory failure requiring vasopressors

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Background & aims: Recently, several studies have suggested that non selective beta-blockers (NSBB) may have beneficial effects in patients with acute on chronic liver failure (ACLF) through reducing the severity of inflammatory response. . On the other hand, the use of beta blockers remains controver-sial in non-cirrhotic patients with septic shock.. The aim of this study was to explore the impact of NSBB in patients with ACLF and distributive shock requiring vasopressors (norepinephrine).. Patients and methods: Eighty consecutive patients with ACLF admitted from June 2010 to Sept 2015 in a specialized ICU and were retrospectively studied.. All patients had distributive circulatory failure defined by the need for norepinephrine to achieve a target mean arterial pressure of 65mmHg after ade-quate fluid resuscitation. . The study subjects were classified into NSBB+ (receiving NSSB) and NSBB- (not receiving NSBB) groups.. Patients were followed up from admission in the ICU to death, transplantation or last follow-up visit for patients alive without transplant at the end of the study.. Results: The study population included 58 males and 22 females.. The mean age of the study participants was 54 ± 9 years.. Causes of cirrhosis were alcohol in 62%, HCV in 19%, HBV in 6% and others in 16%. . Mechanical ventilation (MV) and renal replacement therapy (RRT) were used in 72% and 49% patients, respectively (including 40% with both MV and RRT in addition to vasopres-sors).. Forty patients out of eighty (50%) were receiving NSBB at admission (NSBB+).. The mean of the MELD score at admission was not significantly different in NSBB+ (29) and NSBB- (32) patients.. No significant difference was found between the 2 groups (NSBB+ vs NSBB-) regarding age (56 vs 52-y), gender (72 % vs 72% males), rate of MV (69% vs 75%), rate of RRT (41% vs 57%), rate of empirical antibiotics before admission (65% vs 52%), and rate of documented infection after admis-sion (85% vs 78%).. The proportion of patients who were trans-planted was not significantly different in the 2 groups (20% vs 7%, p=0..1)..

Transplant free-survival (Kaplan-Meier) was signifi-cantly better in NSBB+ as compared to NSBB- patients (48% vs. . 15% at 28-day, respectively, p=0. 007).. . On multivariate analysis (Cox model including NSBB and MV), only NSBB was significantly and independently predictive of survival (p=0..02).. Conclusion: The results of this series suggest that NSBB intake at admission of patients with ACLF and circulatory failure requiring administration of vasopressors is associated with better outcome, irrespective of the presence or absence of bacterial infection..

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2054

Etiology of chronic liver disease has no impact on the course and outcome of patients with Acute on Chronic Liver Failure

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Introduction: Acute on Chronic Liver Failure (ACLF) leads to higher mortality. . Whether etiology of chronic liver disease influences the course and outcome of these patients is not well understood.. Aims: To compare presentation, course and out-come of patients with ACLF with a known etiology of chronic liver disease (KC) to those with cryptogenic chronic liver dis-ease (CC). . Methods: We retrospectively analysed our data-base of 1631 patients of APASL, ACLF Research Consortium (AARC), and included consecutive patients of ACLF according to APASL definition.. Patients were divided into 2 groups based on whether etiology of chronic liver disease was known (KC) or cryptogenic (CC).. The clinical and laboratory parameters, organ failures, prognostic models and short term mortality rates were compared.. Results: Out of 1631 patients, 1469 patients were eligible for analysis. . 1277 (87%) patients were males and 192 (13%) were females .. Mean age of the patients was 44..9 ± 11..8yrs.. The etiology of chronic liver disease was alco-hol in 862 (58.. 7%), viral hepatitis in 293 (19.. 9%), cryptogenic in 146 (9..9%), non-alcoholic steatohepatitis in 81 (5..5%), auto-immune liver disease in 49 (3..3%) and others in 38 (2..6%) patients.. The most common cause of acute deterioration was alcoholic hepatitis 785 (50..8%) followed by viral hepatitis in 454 (29%),drug induced in 146 (9. .4%), autoimmune flare in 48 (3..1%), spontaneous bacterial peritonitis and sepsis in 24 (1..5%), tropical infections in 6 (0..4%), variceal bleed in 8 (0..5%), Wilsons disease in 7 (0..4%), surgery in 1 (0..1%) and unknown in 67 (4..3%) patients.. We compared 1323 patients in KC and 146 patients in CC group.. The patients were older (49..20±14. .32 vs 44. .38±11. .38yrs, p<0. .001) and females were more common in CC group versus KC group (30. .9% vs 6..5%, p<0..001).. CC had more severe coagulopathy (INR 2. .87 vs 2. .53, p= 0. .009). . There was no difference in inci-dence of ascites (91..3 % vs 86..9%, p=0..09) or encephalop-athy (49..6% vs 52..5%, p=0..51), severity of encephalopathy (p=0.. 88) or the frequency of sepsis (41.. 4% vs 44..1% p=0..53).. There was no difference in the number of organ failures (1..49 vs 1. .68,p=0. .06),CTP, (12 vs 11. .8,

p=0. .24), MELD scores (29. .9 vs 29. .6, p=0. .39),CLIF-SOFA (11. .7 vs 11. .3, p=0. .20) and APACHE II (14. .92 vs 14. .93, p=0. .64) scores. . The 28 day (59% vs 62..1%, p=0..50) and 90 day (48..3 vs 51..1%, p=0. .51) survival between the two groups was similar. . Con-clusion: ACLF is a syndromic entity attributing poor prognosis in patients with chronic liver disease. . Our study shows that patients with cryptogenic chronic liver disease with ACLF behave similarly to those with known etiologies in terms of presentation, course and overall outcome..

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2055

Plasma markers of liver cell death Keratin 18 (K18) and its caspase-cleaved fragment (cK18) are novel biomark-ers to define progression of cirrhotic patients with acute decompensation to acute on chronic liver failure (ACLF) and mortality

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Acute on chronic liver failure (ACLF) is a devastating clinical syndrome that develops in cirrhotic patients suffering acute decompensation (AD).. About 20% will progress to ACLF during hospitalisation. . The CLIF-AD score has limited accuracy and new biomarkers are needed. . Intermediate filament K18 is present in hepatocytes and during apoptosis undergoes frag-mentation (cK18); both are detectable in the plasma.. The aim of this study was to evaluate their potential as biomarkers. . Materials and Methods 376 patients from the CANONIC study cohort with acute decompensation of cirrhosis were included.. 82 presented with ACLF and 294 with AD, of whom 70 pro-gressed to ACLF.. Additionally 44 patients with stable cirrhosis (SC) and 34 healthy volunteers (HV) were included.. Baseline Serum K18 and cK18 were measured by ELISA [M65 EpiDeath (Peviva) and M30 Apoptosense (Peviva) respectively].. Results A stepwise increase in K18 and cK18 level was demonstrated with increasing clinical severity (p<0..001) (see table 1..) and between different severities of ACLF grades (p=0..009).. *Mortal-ity:* Both K18 and cK18 were independent predictors of 28-day and 90-day mortality [K18:HR 1. 36. (95%CI 1. 03.-1. 81).

(p=0. 03),. cK18:HR 1. 46. (95%CI 1. 06.-2. 01)(p=0.. 02)]. and 90-day survival [(K18:HR 1..26 (95%CI 1..01-1..56)(p=0..038), cK18:HR 1..32 (95%CI 0..99-1..75)(p=0..06)].. The addition of K18 to the CLIF-C AD score improved the C-index for predic-tion of 28 day mortality [CLIF-C AD 0. 788. (95%CI 0. 688.-0..888), CLIF-C AD+K18 0..816 (95%CI 0..718- 0..825)] and 90 day mortality [CLIF-C AD 0. 725. (95%CI 0. 653.-0. 797),.

CLIF -C AD+K18 0. 75. (95%CI 0. 675.-0. 913.-0. 825)].. . *Predic-tion of Progression from AD to ACLF*: Both K18 and cK18 were significantly higher in the patients that progressed compared with those who did not (both p<0. 001).. . Their inclusion sig-nificantly improved the predictive ability of CLIF-C AD score (AUROC 0..696 (0..626-0..765) to 0..742 (0..673-0..811).. Con-clusion These data clearly demonstrates a statistically signifi-cant stepwise increase in serum K18 and cK18 with clinical severity of patients with acute decompensation. . Inclusion of K18 values into the CLIF-AD score improves predictive value for progression to ACLF and 28-day and 90-day mortality in patients with AD..

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2059

Natural Course and Outcome in ACLF is Dependent upon the Etiology of Acute Hepatic Insults: Analysis of 368 patients

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BACKGROUND & AIMS: Acute on chronic liver failure (ACLF) is associated with high short-term mortality.. The effect of specific acute hepatic insults on ACLF outcome is not clear.. We aimed to compare the natural course and outcomes in ACLF due to acute hepatic insults.. METHODS: Consecutive 368 ACLF patients at a tertiary care center in India were included.. Etiology of acute hepatic insult and underlying chronic liver disease, and organ failure (OF) data was collected.. Model for end-stage liver dis-ease (MELD), chronic liver failure consortium (CLIF)-C ACLF and acute physiology and chronic health evaluation (APACHE) II scores were calculated.. Predictors of survival were assessed by Cox-proportional hazard model.. RESULTS: Most frequent acute hepatic insult was active alcohol consumption 150 (40. 8%). followed by hepatitis B virus (HBV)- 71 (19. .3%), hepatitis E virus (HEV) superinfection- 45 (12..2%), autoimmune hepatitis flare-17 (4..6%), anti-tuberculosis drugs- 16 (4..3%) and hepati-tis A virus-2 (0..5%); remaining 67 (18..2%) were cryptogenic.. Patients with active alcohol consumption and cryptogenic acute insults had more severe disease. . Median CLIF-C, MELD and APACHE II scores in active alcohol consumers, cryptogenic, HBV and HEV-ACLF were 47..1, 47..4, 42..9, 42..0 (P = 0..002); 29, 29.. 9, 28..9, 25..2 (P = 0..02); 16..5, 18.. 0, 12 and 14 (P < 0..001), respectively.. Frequencies of kidney and brain failures among above etiologies were also higher - 35. .3%, 34. .3%, 23..9%, 11.. 1% (P = 0..009); 26..0%, 22..4%, 15..5%, and 4..4% (P = 0..01), respectively.. Overall mortality rates in the 4 groups were 64..0%, 62..7%, 45..1% and 17..8% (P < 0..001), respec-tively. . In multivariable model analysis, etiology of the acute hepatic insult- alcohol (HR, 3..06; 95%CI, 1..10-8..49, P = 0..03) independently predicted mortality.. CONCLUSIONS: The pheno-typic presentation of ACLF varies with acute precipitating insult.. Active alcohol consumption is associated with higher mortality, whereas HEV superinfection has the best survival..

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2060

NMR based urinary profiling of Lactulose/Mannitol ratio to compare the intestinal permeability in cirrhosis, acute on chronic liver failure (ACLF) patients and normal controls

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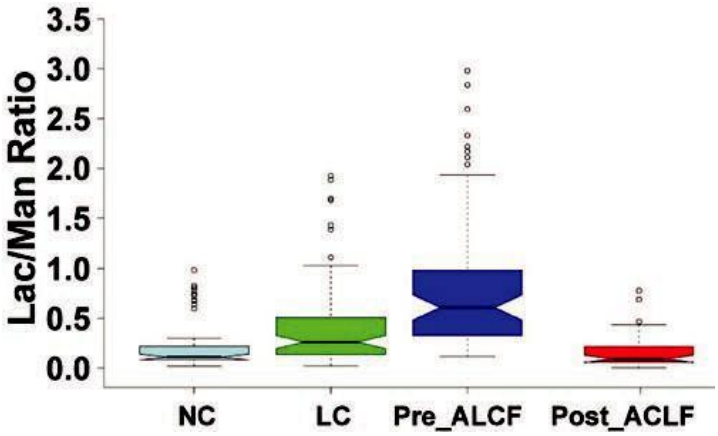
Background: Increased/altered intestinal permeability is com-mon clinical manifestation in patients with cirrhosis and acute on chronic liver failure (ACLF). . Gut dysbiosis has also been implicated in assessing mortality in patients with ACLF.. Aim: The study aims to evaluate the altered intestinal permeability (IP) in healthy controls,cirrhotics and ACLF patients(before and after therapy) Methods: Urinary excretion of lactulose/man-nitol ratio (LMR) is one of the simple and efficient method to assess the intestinal permeability (IP). . Urinary LMR excretion was measured using ^{1}H NMR spectroscopy for 10 healthy controls, cirrhotics and ACLF patients with ascites: ACLF patients were treated with Slow low-dose continuous albumin + Furosemide ± Terlipressin (SAFI± T) and probiotics and after recovery LMR was repeated.. Baseline characteristics of ACLF patients were CLIF SOFA score 10..2±1..7;CTP-12..5±1..4;MELD -29..5±8. 7.. Mean. therapy duration was 14. 3.±7. 2. days. . Post therapy - Urine sodium had increased from 26..4±18 mmol/24 hrs to 264±106 mmol/24hrs and Serum Albumin increased to 3..2±1..1g/dl from 2..4±0..7g/dl (p<0..05).. Results: The urinary LMR excretion was higher in ACLF patients (untreated) com-pared to compensated cirrhotics(CTP A) and normal controls.. In normal controls,median value was 0..11mmol, range 0..02 to 0..3, In cirrhotics median was 0..26mmol, range 0..14 to 1..03) and in ACLF median 0..61; range0..12 -1..93mmol) (p<0..05) and post therapy ACLF, median 0..09; range 0..0 – 0..43mmol).. However, the urinary LMR excretion in improved ACLF patients was comparable to normal controls indicating restored IP after the treatment.. Conclusion:^{1}H-NMR spectroscopy is an efficient analytical tool for the assessment of altered intestinal perme-ability in ACLF and cirrhotic patients with reasonable sensi-tivity and specificity . . ACLF patients' have higher intestinal permeability compared to compensated cirrhotics and controls.. Intestinal permeability decreases

post therapy suggesting that intestinal decongestion and probiotics may have a role in alter-ing gut permeability



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2061

Monocyte HLA-DR expression, neutrophil oxidative burst capacity and cytokine analysis in patients with decompensated cirrhosis with and without acute-on-chronic liver failure (ACLF).

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Background: Patients with acute-on-chronic liver failure (ACLF) have increased risk of infection due to a dysregulated immune response.. Comparative data on the presence of such 'immune-paresis' between patients with ACLF and decompensated cir-rhosis without ACLF is not available.. Aim of the present study was to compare the immunological functions in patients with decompensated cirrhosis with and without ACLF.. Methodology: Ninety six patients with decompensated cirrhosis with (n=38, males=35, mean age=45. 4.±12. 9. yrs) and without (n=38, males=29, mean age=48. 2.±13. 2. yrs) ACLF were included prospectively.. Patients with evidence of current or recent infec-tion (< 1 month) were excluded.. ACLF was diagnosed as per the Asian Pacific Association for the Study of the Liver definition and was graded as per the CANONIC study.. All patients gave a written informed consent and study had the approval of the institute's ethics committee.. HLA-DR expression was studied by ex vivo mean percentage of monocytes expressing HLA-DR and by the mean fluorescence intensity (MFI) of HLA-DR expression.. Neutrophil oxidative burst capacity (NOX) was assessed by in vitro stimulation with phorbol 12-myristate 13-acetate and MFI values of production of reactive oxygen species were analyzed by flow cytometry.. Serum levels of cytokines (IL-1β, IL-6, IL-8, IL10, IL-12, and TNFα) were determined by human cytometric bead array kit. . Results: Even though the values were lower than the historic controls, there was no difference in mean per-centage of monocytes with HLA-DR expression (42..6±26..5% vs. . 43. 1.±20. 9%). (p=0. 95). and MFI of HLA-DR expression (30.. 3±29. 3. vs. . 41. 7.±52. 1). (p=0. 42). amongst patients with and without ACLF.. Both groups of patients had higher NOX and its lower MFI in comparison to historic controls but there was no difference in NOX (149. 9.±89. 4. vs. . 152.

4.±135..4) (p=0. 29). and its MFI (16. 5.±11. 9. vs. . 17. 2.±16. 1). (p=0. 47). amongst patients with and without ACLF.. Patients with ACLF had significantly higher pro-inflammatory cytokines (pg/ml) [IL1β (3..5±2..6 vs.. 0..35±1..12, p<0..0001), IL-6(220..9±611..2 vs.. 16..5±16..5, p<0..0001), IL-8 (781..7±865..1 vs.. 48.. 8±62..0, p<0. .0001), IL-12 (0. .9±1. .1 vs. . 0. .1±0. .2, p<0. .0001), TNFα (3..2±2. .9 vs. . 0. .35±1. .12, p<0. .0001) and anti-inflammatory cytokines (pg/ml) [IL-10(3. 2.±3. 6. vs. 0.. 4.±0. 6,. p<0. 0001]. in comparison to patients with decompensated cirrhosis with-out ACLF. . Conclusion: Patients with decompensated cirrhosis with and without ACLF have similar impairment in HLA– DR expression and neutrophil oxidative burst capacity.. Both pro-in-flammatory and anti-inflammatory cytokines are increased in patients with ACLF in comparison to decompensated cirrhosis without ACLF..

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2063

Alcohol-related acute on chronic liver failure- compari-son of various prognostic scores in predicting outcome

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Background and aims: There is no consensus regarding the best available prognostic score in acute on chronic liver failure (ACLF).. We compared all available prognostic models in pre-dicting outcome in alcohol-related ACLF.. Methods: All consec-utive patients with alcohol-related ACLF admitted in a tertiary care center in India were included.. Admission chronic liver fail-ure (CLIF)- sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE II) score, model for end-stage liver disease (MELD), MELD-Na, Child-Pugh-Turcotte (CTP) score, Maddrey's discriminant func-tion (DF), ABIC score and CLIF-Consortium (CLIF-C) ACLF score were calculated; receiver operator characteristic (ROC) curves were compared with Hanley and McNeil test.. Results: Of the 143 patients with alcohol-related ACLF, 142 (99. 3%). Were males; 90 (62..9%) died over a median (range) hospital stay of 7 (1-45) days. . Grade I ACLF was present in 40 (28%), Grade II in 44 (31%) and Grade III in 59 (41%) patients.. The median (IQR) CLIF-SOFA, APACHE II, MELD, CTP score, DF, ABIC score, CLIF C ACLF score were 9 (6-10), 17 (12-22), 24 (17-31), 12 (10-13), 76. .4 (46. .4-101. .1), 17. .9 (12. .3-27. .9), 27..8 (20..9-34..2) and 38..1 (30..6-45..5) respectively.. On mul-tivariate cox regression analysis, independent predictors of outcome were hepatic encephalopathy (early: HR 3..52, 95% CI 1..51 - 8..17, P = 0..003 and advanced: HR 4..24, 95% CI 1. .48 - 12. .0, P = 0. .007), arterial ammonia (HR 1. .01, 95% CI 1. .00 -1. .02, P < 0. .001) and serum creatinine (HR, 1. .22 95% CI 1..01-1..48, P = 0..033).. The AUROC was highest for CLIF-C ACLF score; with a cut-off score of 44, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 81..5%, 62..5%, 77..9%, 67..6% and 74..3% respectively.. CLIF-C ACLF was significantly better than MELD, MELD-Na, CTP score, DF, ABIC score and Mad-drey's DF (P < 0..05, Hanley and McNeil); however, statistical significance was not seen when compared with APACHE II (P = 0..118) and CLIF-SOFA score (P = 0..358).. Conclusions: Alco-hol-related ACLF has a high (62..9%) mortality over a median hospital stay of 7 days.. Among the

available prognostic scores, CLIF-C ACLF performs better than other prognostic scores..

Disclosures:

The following people have nothing to disclose: .. Shalimar, Ujjwal Sonika, Sau-rabh Kedia, Baibaswata Nayak, Bhaskar Thakur, Subrat K.. Acharya

2086

Renal replacement therapy in acute on chronic liver fail-ure – Outcomes and predictors of survival

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Acute kidney injury (AKI) requiring renal replacement ther-apy (RRT) is the one of most devastated complication in ACLF. The. dialysis in this group throws various challenges due to severe coagulopathy, hemodynamic instability and making them unsuitable for any slow form of dialysis .. We studied the outcomes and predictors of survival in ACLF patients with on dialysis.. Material &Methods: All adult ACLF patients with AKI requiring hemodialysis were enrolled between study period (May 2009 to september 2013) The sustained low efficiency dialysis (SLED) was used as modaility of dialysis. Indication of dialysis was fluid overload, metabolic acidosis, hyperkale-mia and advanced azotemia .. Results: Total 117 patients with ACLF had severe AKI requiring RRT during the study period (May 2009 to september 2013) The study population con-sisted of predominantly males.. Most common acute factor in ACLF patients requiring RRT were -Alcohol (56..5%) followed by hepatitis E (16. .2%) followed by Hepatitis B reactivation (9..4%).. Most common etiologies of underlying CLD were -Alco-hol (63..2%) followed by cryptogenic (13..7%) followed by hep-atitis B (11..1%).. Besides ACLF patients with AKI requiring RRT had severe liver disease (mean MELD 42..3) and high rate of multi-organ dysfunction (Mean SOFA – 12..8).. About 53% of the ACLF patients had some form of intra-dialytic complication.. Double lumen femoral dialysis catheter was the commonest vas-cular access used for RRT.. The average number of days ACLF patient survived after initiation of RRT was 11..6±2..02 days.. On comparison of variables between patients who survived RRT versus those who did not survive by multi-variable step-wise linear regression analysis, the independent predictors of mortality among ACLF patients requiring RRT were – CTP score (Beta- 0.14, standard error – 0.05) and SOFA score (beta – 0.09; standard error – 0.05). Contrary to the expectation, serum creatinine and MELD were not predictors of mortality. The possible reasons why creatinine and MELD score were not good predictors of outcomes as non-survivors had more sarcopenia leading to decreased

creatinine generation and MELD incorporates creatinine in its estimation, therefore did not predict survival ROC curve analysis revealed that, SOFA score has the best area under the curve to predict mortality, and the cut-off of SOFA score that highly predicted mortality was 11..5 Conclusion: ACLF patients with severe AKI requiring RRT have very high mortality – Mean survival 11.6 days on RRT and SLED is the practical mode of RRT among ACLF patients with severe AKI.CTP and SOFA score are independent predictors of mortality among ACLF patients with AKI requiring RRT

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