2017 AASLD SINGLE TOPIC CONFERENCE:
Acute on Chronic Liver Failure: Is it Ready for Clinical Practice?

SEPTEMBER 15–16, 2017
CHICAGO, IL

Program Chairs:
Florence Wong, MD
Jasmohan S. Bajaj, MD, FAASLD
Schedule-at-a-Glance and Meeting Locations
Wi-Fi Network: WESTINCHICAGO-MEETING
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Single Topic Conference

Acute on Chronic Liver Failure: Is it Ready for Clinical Practice?

September 15 – 16, 2017
The Westin Chicago River North
Chicago, IL

Program Chairs: Florence Wong, MD and Jasmohan S. Bajaj, MD, FAASLD

Continuing Education Information

Upon completion of this activity, participants will be able to:

- To discuss the diagnosis and natural history of ACLF
- To understand the pathophysiology of ACLF
- To learn about the therapies for the various organ failures that are part of the syndrome of ACLF
- To develop strategies for the prevention of ACLF

This activity was planned in the context of the following ACGME/IOM/IPEC competencies:

Patient Care, Medical Knowledge and Evidence-based Practice.

Accreditation and Designation Statements

Continuing Medical Education (CME)
The American Association for the Study of Liver Diseases (AASLD) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. AASLD designates this live activity for a maximum of 10.50 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Maintenance of Certification (MOC)
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10.50 MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for granting ABIM MOC credit.

CME Credits
Physicians and other health care professionals seeking AMA PRA Category 1 Credits™ for this live continuing medical education activity must complete an evaluation by Monday, October 16, 2017. A link to the CME and MOC evaluation will be emailed to attendees after the conference.

Certificates will only be issued to those who complete an evaluation by the deadline. CME certificates will be emailed upon successful completion of the evaluation.
ABIM MOC Points
Physicians seeking ABIM MOC points must complete the CME evaluation and the MOC evaluation by Monday, October 16, 2017. Requests for MOC after this date will not be honored. The MOC evaluation is included in the CME evaluation that will be emailed to all attendees, and will remain live until the deadline.

MOC points will be reported to the ABIM by the end of October 2017 for attendees who successfully complete the MOC evaluation.

Disclosures
This live educational activity has been planned in accordance with AASLD and ACCME Standards of Commercial Support by members of the Single Topic Conference faculty and Clinical Research Committee.

As an accredited provider, AASLD requires individuals involved in the planning of continuing medical education (CME) activities to disclose all financial relationships, including those of their spouse or partner, with a commercial interest within the past 12 months. A commercial interest is defined as any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. All conflicts of interest are resolved prior to participation.

Statement on off-label and investigational use: Speakers are asked to make a reasonable effort to identify during their presentation any discussion of off-label or investigative use or application of a product or device.

Financial disclosures will appear at the beginning of each session and are provided below.

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Conference Agenda

Friday, September 15, 2017

7:00 am  Breakfast

Session I: Pathophysiology of ACLF
Moderators: Jasmohan S. Bajaj, MD, FAASLD and Patrick S. Kamath, MD

8:00 – 8:20 am  Introducing the Syndrome of ACLF
Florence Wong, MD

8:20 – 8:45 am  Inflammation in the Pathogenesis of ACLF: Infective Versus Non-infective
Gyongyi Szabo, MD, PhD, FAASLD

8:45 – 9:10 am  Mechanisms Linking Inflammation to ACLF: Is it via Immune Modulation
or via Systemic Circulatory Dysfunction?
Richard Moreau, MD

9:10 – 9:40 am  Q&A

9:40 – 10:10 am  Break

Session II: Clinical Experience in Organ Failures Throughout the World
Moderators: K. Rajender Reddy, MD, FAASLD and Jody C. Olson, MD

10:10 – 10:25 am  Clinical Experience in Organ Failure in ACLF: Asian Experience
Shiv K. Sarin, MD, FAASLD

10:25 – 10:40 am  Acute on Chronic Liver Failure in Cirrhosis: European Experience
Vicente Arroyo, MD, PhD

10:40 – 10:55 am  ACLF: North American Experience
Jasmohan S. Bajaj, MD, FAASLD

10:55 – 11:15 am  Towards a Unified Definition of ACLF
Patrick S. Kamath, MD

11:15 – 11:45 am  Q&A

Noon – 1:00 pm  Lunch

Session III: Predisposing and Precipitating Factors
Moderators: Gyongyi Szabo, MD, PhD, FAASLD and Puneeta Tandon, MD, FRCPC

1:00 – 1:20 pm  Co-morbid Conditions and Aging
Jennifer C. Lai, MD

1:20 – 1:50 pm  Sepsis/Infection
Richard Moreau, MD
1:50 – 2:10 pm  ACLF: Surgery as a Precipitating Factor for Acute on Chronic Liver Failure
Patrick S. Kamath, MD

2:10 – 2:30 pm  Alcohol as a Precipitant of ACLF
Gyongyi Szabo, MD, PhD, FAASLD

2:30 – 2:50 pm  Q&A

2:50 – 3:10 pm  Break

**Session IV: Individual Extra-Hepatic Organ Failures**
**Moderators: Constantine J. Karvellas, MD, SM, FRCPC and Shiv K. Sarin, MD, FAASLD**

3:10 – 3:40 pm  Extra Hepatic Organ Failures: Cardiovascular and Pulmonary Complications
Jody C. Olson, MD

3:40 – 4:05 pm  Individual Extra-Hepatic Organ Failures: Kidney Failure
Florence Wong, MD

4:05 – 4:30 pm  Brain Failure in ACLF
Jasmohan S. Bajaj, MD, FAASLD

4:30 – 5 pm  Q&A

5:30 – 7:00 pm  Poster Reception

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**Saturday, September 16, 2017**

7:00 am  Breakfast

**Session V: Treatment and Prevention of ACLF**
**Moderators: Jennifer C. Lai, MD and Richard Moreau, MD**

8 – 8:20 am  Non-infective Precipitating Factor Treatment
Hugo E. Vargas, MD, FAASLD

8:20 – 8:40 am  Changing Landscape of Sepsis Therapy Including Albumin
Puneeta Tandon, MD, FRCPC

8:40 – 9 am  Prevention of ACLF: Is Pre-emptive Treatment the Appropriate Choice?
Constantine J. Karvellas, MD, SM, FRCPC

9 – 9:30 am  Q&A

9:30 – 10 am  Break
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<td>When is Transplant a Futile Option and Enough is Enough</td>
<td>Jennifer C. Lai, MD</td>
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<td>11 – 11:20 am</td>
<td>Palliative Care Across the Spectrum of Cirrhosis and ACLF Care</td>
<td>Puneeta Tandon, MD, FRCPC</td>
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Noon            | Adjourn                                                                       |
SPEAKER SUMMARIES
Introducing the Syndrome of Acute-on-Chronic Liver Failure

The concept of “acute-on-chronic liver failure” or ACLF was established to describe the frequent episodes of deteriorations in liver function, associated with organ failures and high short-term mortality that occur in decompensated cirrhosis. Therefore, this syndrome describes a stage in decompensated cirrhosis, when patients deteriorate rapidly with liver failure, usually following some precipitating event, instead of the usual steady decline in global liver function observed in patients with decompensated cirrhosis. ACLF was once thought to not occur in patients with stable compensated cirrhosis. We now know that events that can precipitously lead to rapid deterioration in liver function can happen in patients with compensated cirrhosis (Figure). In fact, ACLF can also occur in patients with chronic liver disease without cirrhosis. The key components of ACLF are rapid deterioration of liver function leading to liver failure, multiple extra-hepatic organ failures and high short-term mortality. The concept of ACLF is necessary because patients usually do not die from a gradual destruction of liver cell mass; rather, they die from acute deterioration of their clinical condition, aptly described by the syndrome ACLF. Jalan et al proposed to differentiate the ACLF that occurs in patients with chronic liver disease but without cirrhosis, in patients with compensated cirrhosis, or in patients with decompensated cirrhosis as types A, B and C ACLF respectively.

= precipitating event
Although the concept of ACLF is easy to understand, the definition of ACLF varies throughout different parts of the world. This is because regional differences in the epidemiology of liver disease have led to the design of definitions better suited to describe the disease patterns observed in a particular region. Thus the Asian Pacific Association for the Study of the Liver (APASL)'s definition of ACLF does not include patients with decompensated cirrhosis, as hepatologists in the Asian Pacific region tend to see patients with chronic liver disease who acutely deteriorate from a hepatic insult, be it viral hepatitis, or alcohol or drugs; while hepatologists in the western world tend to see patients with established cirrhosis who deteriorate from an infective episode. Further differentiations amongst hepatologists in Europe and North America in their definitions of ACLF makes it difficult to compare results of studies from different parts of the world, and hampers the design of therapeutic trials and therefore slows the development of effective treatment strategies. Therefore, one of the aims of this symposium is to bring individuals across regions to discuss the merits of the various aspects of the different definitions, with a hope to come to a unifying definition of ACLF, so to allow us to study patients of disparate etiologies, precipitating events and better define treatment strategies. For now, all agree that ACLF is a distinct syndrome that is different from acute liver failure, that there is high 28-day mortality, mostly due to organ failure and sepsis, and that these patients need early assessment for liver transplantation in order to improve their survival.

References
Systemic inflammation is a major characteristic of ACLF indicated by increased CRP, pro-inflammatory cytokines, IL-1β, IL-6, IL-8 and white cell count in these patients. The clinical significance of the systemic inflammation is that unopposed upregulation of the pro-inflammatory cytokine cascade lead to systemic inflammatory response syndrome and multi-organ failure. While specific inducers of the inflammatory response are not always identified, both infectious and non-infectious triggers can result in the same clinical manifestation in ACLF. Pathogen-derived molecular patterns (PAMPs) are the triggers of inflammation when an infectious source is present while host derived damage-associated molecular patterns (DAMPs) induce similar inflammation pathways in sterile inflammation. Inflammation is the host defense response of the innate immune system to PAMPs and DAMPs. PAMPs and DAMPs are recognized by the host immune system via pattern recognition receptor family that includes Toll-like receptors, helicase receptors, Nod-like receptors and others (21994762). The inflammasome is an intracellular multi-protein complex that plays a major role in inflammation. The nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) represent the sensor component of the inflammasome. The inflammasome also contains the adaptor protein apoptosis-associated specklike protein, ASC, and the inflammatory effector molecule Caspase-1. Caspase-1 has enzymatic activity, which, as the effector of inflammasome activation, cleaves pro-interleukin (IL)-1β, pro-IL-18 and pro-IL-33.

Compared to other pro-inflammatory cytokines (TNF-α or IL-6) or chemokines (MCP-1) that are readily induced upon Toll-like receptor (TLR) activation, IL-1β production is more tightly controlled (24332029). TLR stimulation results in IL-1β mRNA production that is rapidly translated into pro-IL-1β that is not secreted from the cell until a second signal is provided that activates the inflammasome, leading to Caspase-1 activation that cleaves pro-IL-1β into the mature form of IL-1β. This mature, 18kD, IL-1β is secreted from the cell into the extracellular space and acts locally or through systemic effects. Interestingly, IL-1β rapidly binds to the IL-1 Receptor (IL-1R) and has strong autoregulatory feedback effects. All of these have major implications in liver inflammation. First, due to the requirement for two signals for activation, inflammasome activation and IL-1β production might not be the initial response to a minimum inflammatory signal. Second, because of the two signals that regulate inflammasome and IL-1β, cumulative danger signals will likely activate the inflammasome even if the signals are low amplitude such as seen in chronic inflammation states. Third, because of its capacity to readily bind the IL-1R and autoregulatory effects, IL-1β has a major role in amplification of inflammation. These mechanism provide various regulatory steps in the control of inflammation as well as may provide explanation of over-activation of the inflammatory cascade in ACLF where cumulative danger signals, often a combination of PAMPs and DAMPs are present. For example, cirrhosis and portal hypertension are associated with “gut leakiness” and changes in the gut microbiome that lead to increased translocation of gut microbial products to the liver where Kupffer cells and recruited macrophages will be activated. During events that precipitate ACLF, hepatocytes and other damaged cells release sterile danger signals such as uric acid, ATP, HMGB-1 that can amplify inflammation triggered by the gut-derived PAMPs. Typically, the
presence of low amplitude of inflammation that is present in compensated cirrhosis is amplified by the culmination of the inflammatory stimuli with the combination of DAMPs and PAMPs. The amplification of immune responses is likely due to the increase both in the number inflammatory pathways and the extent of their activation in ACLF.

References
Mechanisms Linking Inflammation to ACLF: Is it via Immune Modulation or via Systemic Circulatory Dysfunction?

The results of CANONIC study have shown that acute-on-chronic liver failure (ACLF) is associated with a systemic inflammatory response (assessed by white-cell count and plasma C-reactive protein levels) (1). Moreover, this study showed that the higher ACLF grade the higher systemic inflammation intensity (1). Finally, translational studies performed in patients with ACLF revealed that these patients had elevated plasma levels of a broad variety of plasma cytokines (e.g., interleukin (IL)-6, tumor necrosis factor (TNF)-α, showing that full-blown systemic inflammation developed in these patients (2-3). In one study (2), systemic inflammation and ACLF were found to be strongly associated with respect to their course (improvement, no change, or worsening). We have learnt from immunologists and our experience of the acute stage of severe sepsis that an excessive systemic inflammatory response can drive end-organ dysfunction/failure (4). By analogy, excessive systemic inflammation likely explains the development of organ failures in cirrhosis (5-7). However, there are no published studies so far showing that the use of anti-inflammatory interventions results in improvement of ACLF. One cannot exclude that, at least in some cases, systemic inflammation is a correlate rather than a contributor to ACLF. Nevertheless, the ‘inflammation theory’ is to date the best theory to explain the development of ACLF (5) and will be commented here.

Role of Systemic Circulatory Dysfunction (SCD) in ACLF
SCD, a hallmark of cirrhosis, is characterized by high blood flow and vasodilation in the splanchnic and systemic circulations. The intensity of SCD (assessed by measuring plasma concentrations of renin and copeptin) culminates in patients with ACLF (2). It has been hypothesized that inflammation could lead to end-organ dysfunction, indirectly, by promoting SCD.

Involvement of inflammation in the development of SCD
A major breakthrough in our understanding of the pathophysiology of circulatory alterations associated with cirrhosis was the discovery that nitric oxide (NO) produced in the arteriolar wall was the major cause of splanchnic and systemic vasodilation. In 1991, Vallance and Moncada hypothesized that circulating cytokines and/or pathogen-associated molecular patterns (PAMPs, such as lipopolysaccharide [LPS]) could induce the expression of inducible NO synthase (iNOS) in arteriolar wall (8). The enzyme iNOS was known to produce larger amount of the vasorelaxant NO than the constitutive endothelial NOS (eNOS). A pioneer study conducted in cirrhotic rats with ascites by Wiest and colleagues in the Groszmann’s lab, only partially confirmed the Vallance and Moncada hypothesis (9). In this study, vascular response to an α-adrenoceptor agonist was diminished in the superior mesenteric arterial beds of cirrhotic rats, was further blunted in the presence of bacterial translocation (BT) without overt infection (9). BT promoted endothelial NO release in cirrhotic rats via eNOS but not iNOS. eNOS was present in mesenteric vasculature of cirrhotic rats with and without BT, and its expression was enhanced compared with controls. The pro-inflammatory cytokine tumor necrosis factor (TNF)-α was induced in mesenteric lymph nodes (MLNs) by BT and accumulated in parallel in the serum. This TNF-α production was
associated with elevated levels of tetrahydrobiopterin (BH4), a TNF-α–stimulated cofactor and enhancer of eNOS-derived NO biosynthesis and NOS activity in mesenteric vasculature (9). These findings established for the first time a link between BT to MLNs and increased TNF-α production (reflecting systemic inflammation) and elevated BH4 levels enhancing eNOS-derived NO overproduction, further impairing contractility in the cirrhotic mesenteric vasculature.

In 2005, Tazi and colleagues in the Lebrec’s lab investigated vascular biology in aortas from norfloxacin-treated and -untreated cirrhotic rats (10). The fluoroquinolone was given to inhibit BT. Aortic eNOS and iNOS protein expressions, Akt activity, and Akt-dependent eNOS activity were up-regulated in cirrhotic rats. Norfloxacin administration significantly decreased the incidence of gram-negative translocation and proinflammatory cytokine (TNF-α, interferon (IFN)-γ, and IL-6) levels; norfloxacin also decreased aortic Akt activity, eNOS phosphorylation, and NOS expressions and activities. This study identified a signaling pathway in which bacterial translocation induces aortic NOS up-regulation and thus NO overproduction in cirrhotic rats. These results strongly suggested that BT and proinflammatory cytokines play a role in systemic NO overproduction in cirrhosis by the Akt pathway. Together these studies suggest a major role of BT-induced systemic and local inflammation in vascular NO-overproduction and subsequent circulatory alterations associated with cirrhosis.

A Role for inflammation-induced SCD in end-organ failure?

In cirrhosis, splanchnic and subsequent systemic vasodilatation trigger a homeostatic increase in the activity of endogenous vasoconstrictor systems (i.e., renin-angiotensin, and sympathetic nervous systems; vasopressin secretion) resulting in intense vasoconstriction and hypoperfusion in certain vascular beds (11). Hypoperfusion was thought to be the primary mechanism for end-organ dysfunction in cirrhosis. This scenario was used, for example, to explain the development of type 1 hepatorenal syndrome (HRS), which was considered as a functional renal failure caused by renal hypoperfusion (11). However, the reversibility of type 1 HRS with the use of systemic vasoconstrictors (that deactivate the homeostatic cascade leading to renal hypoperfusion) is not universal (11). In addition, results of transjugular kidney biopsies showing features of acute-on-chronic inflammation in kidney-specimens from patients with HRS, challenge the ‘functional’ nature of HRS, at least in some cases (12). Finally, it has been shown that the association of ACLF was closer with systemic inflammation than with SCD, suggesting a preeminence of systemic inflammation over SCD. Together these findings suggest that ‘inflammation-induced SCD’ does fully explain the development of acute end-organ dysfunction in cirrhosis.

Role of Inflammation Independently of SCD

In the context of sepsis, organ failure is a collateral damage of an excessive immune response of the host (4). For example, plasma pro-inflammatory cytokines activate vascular endothelium. Activated endothelium can interact with circulating immune cells and this interaction is the first step for immune-cell migration within tissues. Activated endothelium also contributes to formation of microthrombi by producing tissue factor and by interacting with platelets. Microthrombi formation further impairs microcirculation and tissue oxygenation. In the context of severe alcoholic hepatitis, the mechanisms explaining the development of ACLF are still poorly understood (6). A role endotoxemia (which is likely due to increased translocation of LPS from the gut lumen), and/or increased plasma cytokines levels has been suggested. It is also important to have in mind that the baseline level of immune-cell activation may play a role in the development of ACLF. Peripheral blood mononuclear cells (PBMCs) from patients with stable alcoholic cirrhosis are primed and overexpress certain pro-inflammatory chemokines of the CXCL family (which are potent neutrophil activators) (13). Migration of these primed cells in tissues may result in the release of CXCL chemokines and subsequent deleterious neutrophil tissue infiltration. In cirrhotic patients, constitutive activation of type 1 IFN signaling in PBMCs is associated with poor
prognosis (13), suggesting that these cells exhibit a potential for IFN-mediated immunopathology.

Areas of Future Research
Several questions should be addressed in future studies. One question is the origin of plasma cytokines in ACLF: Are they produced by circulating immune cells or cells (including resident macrophages) within injured tissues? Another question for future study is how systemic inflammation changes during the course of ACLF. It is believed that in ACLF, the first stage of excessive inflammation is followed by a prolonged immune suppression (6). Obviously, longitudinal studies are required. Another question is to know whether the immune response in ACLF is modulated by genetic variations and/or alterations in the microbiome. Finally, it will be important to determine if there are mechanisms other than excessive inflammation that could contribute to end-organ failure in ACLF. Recent experimental studies suggest that sepsis-induced organ failure could be a result of failed organ tolerance rather than immunopathology (4).

References
Clinical Experience in Organ Failure in ACLF: Asian Experience

Acute-on-chronic liver failure (ACLF) is a distinct clinical syndrome, often rapidly progressive, with high 28 days mortality. A consensus definition of ACLF is still wanting. [1-3] The Western (CLIF) definition is all inclusive and involves an acute deterioration of pre-existing chronic liver disease with extrahepatic organ failure and prior decompensation as parts of the definition and sepsis as a precipitant to ACLF. In the Asian definition (APASL ACLF Research Consortium (AARC)), extrahepatic organ failure is not included in definition of ACLF and sepsis is considered a result of liver failure. In the AARC definition, liver failure remains at the core of the syndrome and permits homogeneity of patient population. The prime drivers of patient outcome at different time points are a combination of the critical functional hepatic reserve, and the nature and severity of the acute insult [3].

Alcohol and hepatitis B are the commonest acute and chronic insults seen in ACLF patients in Asia [1,4]. The AARC has more than 56 collaborative centers and has prospectively enrolled >3,400 patients. A cohort of 1,402 patients in whom the 28 day survival was 51.7% and median survival was 26.3 days, was used to develop a dynamic prognostic model. Five baseline variables; total bilirubin, creatinine, serum lactate, INR and hepatic encephalopathy were found as independent predictors of mortality and were used to develop AARC-ACLF score [range 5 -15]. The score was found superior to MELD score and CLIF SOFA score to predict mortality [AUROC 0.80]. The point scores were categorized into grades of liver failure [Gr I: 5-7, II: 8-10 and III: 11-15 points) and the mortality risk can easily be calculated dynamically as with each unit increase in AARC-ACLF score above 10, the risk of death increased by 20%, and a score ≥11 at baseline or persisting in the first week reflected nonsurvival (p=0.001) [4].

Extrahepatic organ failure specially of 3 or more organs, indicates a late stage of the disease and often could preclude the liver transplantation [5-8]. Patients with a MELD of ≥30 and a delta MELD of >4 points in 7 days should be considered for early liver transplantation for better outcomes. The Simple organ failure count (SOFC) is not only simpler but also more discriminative than the CANONIC grading system at both extremes of severity of ACLF. [6] The acute kidney injury in ACLF is more rapidly progressive and less responsive to terlipressin [7]. Early renal replacement therapy and liver dialysis could be useful options in such patients [8]. A TPPM scoring system established by related ACLF was found to be superior to MELD.

Early detection of the syndrome of ACLF, prevention of sepsis, support for preventing organ failure, augmentation of liver regeneration, and the use of bridging therapy with artificial liver support systems in addition to specific treatment (like antivirals or steroids for HBV/alcohol) of the acute insult can improve outcomes of patients without liver transplantation [10,11]. An important tenet of the AARC definition is the concept of ‘golden window’ of 7 days, which precedes sepsis development and organ(s) failure. This window provides an opportunity for immunomodulation with GCSF and other interventions like plasmapheresis. In another large cohort of 6,326 patients, 1-year mortality was higher with hepatic than extra hepatic insults.
The fact that GCSF improves neutrophil function and antigen processing by recruiting dendritic cells to the liver [12] and in turn can prevent/regress the cellular necrosis and improve survival, supports the concept that liver failure initiates SIRS and sepsis. In fact, bilirubinostasis is known to correlate with development of bacterial infections. Results of liver transplantation in patients with ACLF have been nearly comparable to the elective transplants in Asian countries [13].

References
Acute on Chronic Liver Failure in Cirrhosis: The European Experience

In Europe, the term ACLF is applied according to the results obtained in the Canonic study, a European prospective observational follow-up investigation in 1343 consecutive patients admitted to 29 hospitals for acute decompensation of cirrhosis (1). The aim of the study was to provide diagnostic criteria of organ/system failure and of ACLF in patients with cirrhosis through an evidence-based pragmatic approach.

The Canonic Study defined ACLF as a syndrome that develops at any phase during the course of the disease, from compensated to decompensated cirrhosis. It is characterized by acute decompensation (development of ascites, encephalopathy, GI bleeding or any combination of these in patients with or without prior history of these complications), organ/system failure (liver, kidney, brain, coagulation, respiration and/or circulation) and high 28-day mortality rate (>15%).

The prevalence of ACLF in the Canonic study was 30.9%. Similar prevalence of ACLF has been reported in Korea, China, USA and Latin America in patients diagnosed according to the Canonic Criteria. The most frequently affected organs or systems were kidney (55.8% of patients), followed by the liver (43.6%), coagulation (27.7%), brain (24.1%), circulation (16.8%) and the lungs (9.2%). ACLF frequently occurs in closed temporal relationship to a precipitating event, mainly bacterial infections or acute liver injury. However, no precipitating event can be identified in approximately 40%.

ACLF is graded into three stages according to the number of organ failures (ACLF-1: 1 organ failure, ACLF-2: 2 organ failures, ACLF-3: 3-6 organ failures). The prevalence of ACLF-1, ACLF-2 and ACLF-3 among the whole series of patients included in the Canonic study was 15.8%, 10.9% and 4.4%, respectively. Mortality (28-day and 90-day) increases across the ACLF grades (no ACLF: 1.9% and 9.8% respectively; ACLF-1: 23.3% and 40.8%; ACLF-2: 31.3% and 55.2%; ACLF-3: 74.5% and 78.4%).

ACLF is very dynamic (2). It may resolve, improve, follow a steady course or worsen with standard medical treatment. Changes usually occur within few days after diagnosis. Resolution of ACLF is very frequent in ACLF-1 (54.4%), RELATIVELY frequent in ACLF-2 (34.6%) and rare in ACLF-3 (16.0%). In contrast, in many patients with ACLF 2 (51.4%) and ACLF 3 (68%) at diagnosis the grade of ACLF remains steady or worsens. early clinical course of ACLF is an important predictor of prognosis (3).

References
ACLF: North American Experience

ACLF has been defined worldwide using several systems. In the North American sphere, there have been several studies that have studied this syndrome. Given the population in North America, the overwhelming majority of ACLF patients are hospitalized cirrhotic patients rather than those with chronic liver disease.

Most studies in ACLF from North America stem from the North American Consortium for the Study of End-Stage Liver Disease (NACSELD). This consortium was initiated in 2011 and has studied patients in over 21 centers in USA and Canada. The initial 565 patients were only those with an infection, while the remaining 3051 patients have both infected and uninfected precipitants of ACLF.

Using the initial infection dataset, the 30-day mortality in the North American experience was found to be with two or higher of the following extra-hepatic organ failures: respiratory (mechanical ventilation or BiPAP), cerebral (Grade 3-4 hepatic encephalopathy), renal (dialysis) or circulatory (shock). Therefore this definition was used as ACLF and has now been validated with similar 30-day mortality in uninfected and infected cirrhotic patients.

With this definition, Allen et al used the Nationwide Inpatient Sample, which consists of 20% of discharged US-based patients. The authors found that the ACLF defined using the NACSELD increased from 1.5% (n = 5,400) to 5% (n = 32,300) from 2001 to 2011. The inpatient costs increased 2-fold for cirrhosis ($4.8 billion to $9.8 billion) and 5-fold ($320 million to $1.7 billion) for ACLF. In 2011, the cost per hospitalization for ACLF was 3.5-fold higher than that for cirrhosis. The organ failure trends in ACLF showed an increasing proportion of cardiovascular and cerebral and decreasing proportion of respiratory and renal failure.

Using the NACSELD definition, the survival in the prospectively enrolled infected cohort was worse with two (51.3%), three (36%), and all four (23%) organ failures compared to those with no or one organ failure alone. Using the newer cohort, the similar definition of ACLF predicted survival using a training and validation set with a c-statistic of 0.81 and 0.85 respectively regardless of infection. Specifically ACLF is associated with second infections and fungal infections. Individual organ failures such as hepatic encephalopathy and renal failure can independently predict outcomes in addition to other organ failures in the North American experience.

The North American experience shows that the financial burden is increasing and a simple definition of ACLF can predict mortality in this large population.
References
Towards a Unified Definition of Acute on Chronic Liver Failure

The concept of acute on chronic liver failure (ACLF) is an alternate pathway in the natural history of chronic liver disease and cirrhosis. ACLF is characterized by the presence of a precipitating event in subjects with underlying chronic liver disease which leads to rapid progression of liver injury, ending in multiple organ dysfunction and associated with high short-term mortality. Multiple organ failure and increased mortality risk are key to diagnosis of ACLF.

Three separate definitions have been derived from multi-center efforts from the Asia Pacific region, European groups, and North American groups. Each definition includes organ failure, though the characterization of organ failure is different between the separate consortium definitions. In addition, the timing of the precipitating injury, whether infection can be considered as a precipitating factor or not, and definition of chronic liver disease are different across the three iterations. A working definition has been proposed on behalf of the World Gastroenterology Organization: ACLF is defined as a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, and is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months. ACLF is characterized further based on whether it occurs in patients without cirrhosis (type A, example: Reactivation of hepatitis B), compensated cirrhosis (type B, example: Acute alcoholic hepatitis in patients with cirrhosis); or in patients with a history of prior decompensated cirrhosis (type C).

The various definitions of acute on chronic liver failure are given in the Table modified from Asrani SK, Simonetto DA, Kamath PS. Acute on chronic liver failure. Clinical Gastroenterology and Hepatology 2015;13: 2128-2139.

<table>
<thead>
<tr>
<th>Study</th>
<th>ACLF</th>
<th>Components</th>
<th>Survival</th>
<th>Common regional precipitants and underlying disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCELD</td>
<td>≥2 extra-hepatic organ failures</td>
<td>shock, grade 3 or 4 hepatic encephalopathy, need for dialysis, or need for mechanical ventilation</td>
<td>30 day mortality: 27% (1), 49% (2), 64% (3), and 77% (4) extra-hepatic organ failures</td>
<td>Bacterial infection, 16% with nosocomial infection</td>
</tr>
<tr>
<td>Infection related ACLF</td>
<td></td>
<td></td>
<td></td>
<td>Varied etiology of underlying liver disease:</td>
</tr>
<tr>
<td>European Association for the Study of the Liver-Chronic Liver Failure consortium (EASL-CLIF) Consortium</td>
<td>hepatic or extra-hepatic organ failure with &gt;15% 28-day mortality</td>
<td>Grade 1 (1) patients with single kidney failure; (2) patients with kidney dysfunction (1.5-1.9 mg/dL) and or mild to moderate hepatic encephalopathy along with single failure of liver, coagulation, circulation or respiration; (3) patients with hepatic encephalopathy along with kidney dysfunction (1.5-1.9 mg/dL). Grade 2: 2 or more failures Grade 3: 3 or more organ failures.</td>
<td>28-day mortality 22%, 32%, and 77%</td>
<td>Bacterial infection Underlying liver disease: alcoholic liver disease and HCV</td>
</tr>
<tr>
<td>Asia Pacific Association for the Study of the Liver (APASL)</td>
<td>acute hepatic insult manifesting as jaundice (bilirubin &gt;5mg/dL) and coagulopathy (INR &gt;1.5) complicated within 4 weeks of onset by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease</td>
<td>Liver failure</td>
<td>Reactivation of hepatitis B, superinfection with hepatitis E Underlying liver disease: Hepatitis B; alcoholic cirrhosis; Hepatotoxic drugs</td>
<td></td>
</tr>
</tbody>
</table>

References
Co-morbid Conditions and Aging
And
When is Transplant a Futile Option and Enough is Enough

The population of patients with cirrhosis is aging. This is a result of general population trends in aging that are exacerbated by two additional phenomena specific to patients with liver disease.

- The first is the emergence of widely-available treatments for chronic hepatitis C (HCV) in the form of all oral direct-acting antiviral (DAA) regimens. While DAAs have offered individuals a realistic option for cure for chronic HCV, nearly half of these individuals are estimated to have cirrhosis by 2020,(1) meaning that their cure may come too late. Despite eradication of virus, these individuals remain at risk for hepatic decompensation and hepatocellular carcinoma, although these terminal events are developing at older and older ages (2).

- The second is the epidemic of non-alcoholic fatty liver disease (NAFLD), which is emerging as a leading indication for liver transplantation (3). NAFLD typically leads to cirrhosis after decades and decades of ongoing hepatic injury, so patients with NAFLD are frequently diagnosed with cirrhosis at older ages than patients with other chronic liver diseases such a HCV, alcohol, or autoimmune disease (4).

Why does the aging of patients with cirrhosis matter? Because if and when they experience acute hepatic decompensation and develop acute-on-chronic liver failure (ACLF), the combination of aging and aging-related comorbidities (e.g., diabetes, sarcopenia, coronary artery disease) may synergize with the effects of ACLF to adversely impact their outcomes disproportionately to the severity of ACLF itself. In Figure 1, I offer a schematic of how aging and aging-related comorbidities may adversely impact a cirrhotic patient's ability to recover from ACLF.

**Figure 1. Schematic of how aging and aging-related comorbidities (manifesting as low physiologic reserve) may alter the trajectory of recovery in a patient with cirrhosis after an acute decompensating event.**
A patient with high physiologic reserve can withstand an episode of ACLF and recover to the point that he or she may be considered for liver transplantation and, once listed, withstand the wait for a suitable liver offer. A patient with low physiologic reserve, however, has lost the ability to adapt to physiologic stressors. An episode of ACLF will propel him or her into the “zone of adverse outcomes”, where one complication leads to another, resulting in prolonged hospitalization, loss of function, disability, and ultimately death.

Intuitively, it is easy to understand how advanced age and aging-related comorbidities reduce physiologic reserve in all patients, including those with cirrhosis. Indeed, there are data to support that factors such as advancing age, (5 -7) sarcopenia, (8,9) coronary artery disease, (10,11) and diabetes (12) individually contribute to adverse outcomes in decompensated cirrhotic patients, independent of liver disease severity. But how does one quantify the impact of each individual factor – and the sum of all the factors – on a patient’s physiologic reserve for clinical decision-making?

For this answer, we can turn to the field of geriatrics. Geriatricians have long been assessing their patients’ physiologic reserve to inform their day-to-day decisions such as: should this patient undergo elective surgery? Would this patient benefit from cancer screening? What is the risk-benefit ratio of starting warfarin in this patient? Over the last decades, researchers in the field of aging have operationalized older adults’ physiologic reserve with a number of tools to measure the concept of “frailty” – the term referring to a state of decreased physiologic reserve and increased vulnerability to health stressors (13). “Classic” geriatric tools to measure frailty such as the Fried Frailty Index and the Clinical Frailty Scale have been applied to (non-geriatric) patients with cirrhosis and demonstrated strong associations between frailty and clinically relevant outcomes include hospitalizations and mortality (14-16). Similarly, geriatric tools to measure physical function (e.g., Short Physical Performance Battery, gait speed) or disability (e.g., Activities of Daily Living Scale) – both of which are concepts that are integrally related to physical frailty – also predict outcomes in decompensated cirrhotic patient (14, 17-19). More recently, we have developed the Liver Frailty Index, consisting of 3 performance-based measures – grip strength, chair stands, and balance testing – that significantly improves the ability of MELDNa to predict mortality in cirrhotic patients awaiting liver transplantation (20). The Liver Frailty Index calculator is available at: http://www.liverfrailtyindex.ucsf.edu/.

Applying this concept of frailty in clinical hepatology practice, we can now begin to assess a patient’s likelihood that he or she will recover from an episode of ACLF. Let’s take as examples two 68 year old women with cirrhosis, diabetes, and coronary artery disease who differ only in their frailty status – one is “robust” and one is “frail” by the Liver Frailty Index (20) that was assessed during their most recent outpatient clinic visits. Both develop ACLF and are now in the intensive care unit. Their trajectories in response to this episode of ACLF would be predicted to differ (Figure 1). A clinician could conclude that if the robust patient were to undergo liver transplantation, she would experience favorable outcomes, because the reasons that she is currently sick and in the intensive care unit are related to the acute insult and the underlying liver failure, and therefore reversible with liver transplantation. On the other hand, the patient who was frail even before her ACLF presentation is at high risk for remaining frail despite a new liver. With the acute severe stressor of ACLF on top of her frailty, she will not be able to regain enough reserve with a new liver – and quickly enough after receiving it. It is this circumstance in which liver transplantation should be considered futile (Figure 2) (21).
As you can see from this example, what matters is not the patients' advanced age or comorbidities, but how those factors impact their physiologic reserve as manifest clinically by their phenotype of frailty.

References


17. Dunn MA, Josbeno DA, Tevar AD, et al. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. *Am J Gastroenterol*.


Sepsis/Infection

Patients with cirrhosis are susceptible to bacterial infections(1). Twenty-five percent of patients admitted to the hospital for an acute decompensation (AD) of cirrhosis have ongoing bacterial infection(1). On admission, the prevalence of bacterial infection is higher among patients with acute-on-chronic liver failure (ACLF) and among those without ACLF (22%). ACLF triggered by infection is called infection-related ACLF(2). In a recent study(3), severe infections (spontaneous bacterial peritonitis [SBP], pneumonia, severe sepsis/shock, nosocomial infections and infections caused by multi-resistant organisms) were more prevalent among patients with ACLF than among those with AD without ACLF. Patients with ACLF and bacterial infections showed higher grade of systemic inflammation at diagnosis of the syndrome, worse clinical course (ACLF 2-3 at final assessment: 47% vs. 26%) and lower 90-day probability of survival (49% vs. 72.5%) than patients with ACLF without infection. Bacterial infections were independently associated with mortality in patients with ACLF-1 and 2. These findings illustrate the extreme severity of infection-related ACLF.

Pathophysiology of Infection-related ACLF

The reasons why patients with cirrhosis are prone to develop bacterial infections and why some of the infected patients develop ACLF, are still unclear. In cirrhotic patients, alterations in the intestinal barrier results in bacterial translocation. In cirrhosis, neutrophils, which are the first-line, local defense against invading bacteria, often exhibit defective bactericidal activity(4). Because such local defenses are insufficient to contain the bacteria, the immune system engages a systemic-level acute-phase response to combat the spreading bacteria. For example, bacteria in the bloodstream are recognized immediately by monocytes and neutrophils through pattern recognition receptors (PRRs). Activation of these PRRs leads to the secretion of cytokines among others(4). Virulence factors of bacteria can also stimulate cytokine production but via PRR-independent mechanisms(4). An excessive immune response of the host is thought to cause organ failures both through a process named immunopathology and indirectly via the accentuation of systemic circulatory dysfunction(4). However, one cannot rule out that organ failures can develop because of direct tissue damage caused by bacteria(4), or because of an alteration of mechanisms involved in tissue homeostasis (i.e., failed tolerance)(5).

Early Diagnosis of Sepsis

The severity of bacterial infection in cirrhosis indicates that an early diagnosis, treatment, and prognostic stratification of patients with cirrhosis and sepsis are crucial. The systemic inflammatory response syndrome criteria for the diagnosis of sepsis are poorly effective in patients with cirrhosis and bacterial infections. This is why Piano and colleagues conducted a study aimed to evaluate two new tools for assessment of sepsis, Sepsis-3 and quick sequential organ failure assessment (qSOFA)(6). Sepsis-3 was defined as an acute change in SOFA score of 2 points or more. The qSOFA, which was used at bedside, is considered positive when at least 2 among the following criteria are present (alteration of consciousness; respiratory rate of 22/min or more; systolic blood pressure of 100 mm Hg or less). These tools were initially defined in the general population and have not yet been validated in patients with cirrhosis. In the cirrhotic population(6), Sepsis-3 and qSOFA had significantly
greater discrimination for in-hospital mortality than SIRS. Sepsis-3, qSOFA, CLIF-C-AD score and C-reactive protein were found to be independent predictors of in-hospital mortality. Patients with Sepsis-3 criteria had higher incidence of acute-on-chronic liver failure, septic shock and transfer to ICU than those without Sepsis-3. Together, these findings suggest that Sepsis-3 and qSOFA should be used to assess potential severity of patients with cirrhosis and infection.

**Prevention of Organ Failures**  
The use of intravenous albumin has been shown to prevent the development of hepatorenal syndrome and increase survival in patients with SBP treated with cefotaxime(7). The efficacy of albumin administration has not yet been demonstrated in patients with infection unrelated to SBP(8).

**Prevention of Infections**  
The severity of infections in cirrhosis pleads for using strategies that prevent the development of these complications. The use of a fluoroquinolone for the prevention of infection in the context of variceal hemorrhage or in patients who recover a SBP episode, is well established(9). In contrast, the use of antibiotic prophylaxis in patients with advanced cirrhosis without prior SBP episode remains debated(8). Four double-blind, randomized, placebo-controlled clinical trials of fluoroquinolone therapy have assessed survival in patients with cirrhosis and baseline ascitic fluid protein levels of less than 15 g per liter(10-13). However, two of these trials showed that fluoroquinolone administration significantly reduced mortality (10,13), while two others did not find any significant effect on survival(11,12). Moreover, the designs differed in these studies; the primary outcome was either survival(13), SBP(10,12), or Gram-negative bacterial infections(11). Finally, these 4 trials were performed in small series of patients and the severity of cirrhosis of the enrolled patients differed from one study to the other. Further studies are needed.

**References**
Surgery as a Precipitating Factor for Acute on Chronic Liver Failure

Acute on chronic liver failure is a condition associated with increased short-term mortality and involving a precipitating event which may or may not be identified in patients with chronic liver disease and cirrhosis. Surgery in patients with cirrhosis is recognized as being associated with an increased risk of short-term mortality. Surgery in a patient with cirrhosis is perhaps the ideal model to study events in ACLF since the underlying liver condition is well-characterized before the surgery, the precipitating event can be timed, and patients are followed very closely in the immediate postoperative period and for several weeks.

Our own data suggests that the increased risk of postoperative mortality is for 90 days, and following that period mortality risk returns to baseline PMID:17408652. Therefore, the duration of the ACLF “event” is 90 days. The risk for mortality following surgery at 7 days is related to multiple organ failure or American Society of Anesthesia Class 5 (defined as survival not expected with or without treatment). Age, CTP score, and MELD score are significant at 7 days only by univariable analysis. The factors determining mortality at 7 days seem to depend on intraoperative factors since patients with ACLF have a prominent surge reaction when they come off anesthesia.

Mortality at 90 days is associated with MELD score, age >70 years, and ASA Class IV which is decompensated cirrhosis. The postoperative mortality risk in expert hands is independent of the type of procedure, that is, GI, hepatobiliary, or others; orthopedic; or cardiac. Once ASA, MELD and age are factored in it is also immaterial whether the procedure is carried out as an emergency or not. Therefore risk for ACLF related mortality at 7 days post-surgery is related to multiple organ failure, but at 90 days is associated with age, and degree of hepatic dysfunction.

In summary, ACLF is seen following surgery in patients with cirrhosis, specifically decompensated cirrhosis, and is characterized by multiple organ dysfunction. SIRS is an early manifestation in these patients. Seven day mortality is associated with multiple organ failure, and 90-day mortality may be predicted by age, ASA class, and MELD score.

References
1. PMID:17408652
Chronic excessive alcohol use often results in an unrecognized progressive liver damage and fibrosis. In most patients, the presence of ALD may not be diagnosed until an acute clinical event of alcoholic hepatitis that can be severe and life threatening. Such presentation of acute severe alcoholic hepatitis in chronic ALD is a form of ACLF. The pathomechanism of alcoholic liver disease is only partially understood and precipitating factors of acute alcoholic hepatitis, the most severe form of alcoholic liver disease, are yet to be delineated. Poor clinical prognosis in alcoholic hepatitis correlates with increased circulating markers of inflammation and gut bacterial translocation as well as with development of multi-organ failure. These observations indicate that triggers of inflammatory cascade activation and mediators of inflammation and systemic inflammatory response play a major role in precipitation and outcome of ACLF in severe alcoholic hepatitis. Alcoholic hepatitis is characterized by the presence of a cytokine “storm” mediated by key pro-inflammatory cytokines, TNFα, IL-1β, MCP-1, and IL-6. In addition to endotoxin, a component of Gram-negative bacteria, the gut-derived pathogen-associated inflammatory signals that induce cytokines include bacterial DNA and other microbe-derived PAMPs. High alcohol levels in tissues from excessive alcohol use also trigger release of damage-associated molecular patterns (DAPMs) that are sterile inflammatory signals and activate overlapping pathways of inflammation as PAMPs thereby providing amplification of triggers for acute as well as sustained inflammation. Alcohol and its metabolites damage hepatocytes that release DAMPs including uric acid, ATP, HMGB1 that activate and amplify ongoing inflammation. Furthermore, chronic alcohol was shown to sensitize monocytes and macrophages to endotoxin (LPS) stimulation due to a loss of TLR tolerance that otherwise serves as a homeostatic protective mechanisms in severe inflammation. Such alcohol-induced molecular mechanisms can serve as precipitants of an amplified and sustained pro-inflammatory response characteristic of acute alcoholic hepatitis. Additional consideration in ACLF in ALD is the general alcohol-related immunosuppression of these patients that is a result of the effects of alcohol on innate and adaptive immune responses that contribute to impaired host defense fueling susceptibility to infections. Finally, acute alcohol binge may be a trigger for ACLF in patients with cirrhosis and advance liver disease due to other causes than alcohol. Interactions between chronic HCV infection and ongoing alcohol use promote not only fibrosis and progression of liver disease but alcohol-induced cellular damage and inflammation may contribute to precipitation of ACLF in chronic HCV cirrhosis.

References
Acute-on-chronic liver failure is a distinct syndrome occurring in patients with cirrhosis which is characterized by acute decompensation of liver function with associated high short-term mortality and associated extra hepatic organ failures (1). Among these are disorders of the pulmonary and circulatory systems.

Pulmonary complications when they occur are broadly categorized into acute complications (e.g., the acute respiratory distress syndrome (ARDS), pneumonia, or pulmonary edema) and those which are directly associated with liver disease (e.g., hepatopulmonary syndrome and portopulmonary hypertension). Previous studies have demonstrated that patients who require mechanical ventilation have high rates of mortality, however this is often related to the severity of underlying liver disease and not necessarily a feature of a requirement for mechanical ventilation (2). At the present time, there is no evidence to support alternative strategies for management of respiratory failure in patients with cirrhosis as compared to other critically ill patients and typical recommendations are for lung protective ventilation strategies using low tidal volumes (3,4).

What degree of respiratory failure represents a contraindication to liver transplantation is somewhat controversial and is likely dependent on center expertise. In the CANONIC trial, no patient with ACLF and associated respiratory failure (as defined by a PaO₂/FiO₂ ≤ 200 or SpO₂/FiO₂ ≤ 214) underwent transplantation (5). Whether patients who do not meet the above criteria may be safely transplanted routinely remains to be answered.

Circulatory disorders are extremely common in patients with ACLF. The typical hemodynamic state in cirrhosis is that of a hyperdynamic circulation with high cardiac output and low systemic vascular resistance. Additional structural and functional cardiac abnormalities (cirrhotic cardiomyopathy) occur in approximately 40-50% cirrhotic patients (6). In patients with compensated cirrhosis, end-organ perfusion may be maintained in the presence of circulatory abnormalities. However in ACLF, additional insults to cardiovascular integrity result in worsening hypotension with inadequate end-organ perfusion requiring hemodynamic support in the intensive care unit. Assessment of volume status and cardiovascular function can be particularly challenging in the cirrhotic patient due to significant volume overload and abdominal hypertension (ascites).

The optimal method for assessing both volume and hemodynamic status has yet to be determined. Dynamic measures of cardiovascular function such as bedside echocardiography and in appropriate situations use of pulmonary artery catheters may be beneficial in guidance of both fluid and pharmacologic resuscitation end-points (7).

In patients with ACLF and cardiovascular compromise, the point at which liver transplantation cannot be safely considered has not been defined and is again likely related to center
experience, volume, and expertise. The use of vasopressors is not considered an absolute contraindication for transplantation.

References
Individually Extra-Hepatic Organ Failures: Kidney Failure

Acute kidney injury (AKI), defined by the International Ascites Club as an increase in serum creatinine by ≥0.3mg/dL in <48 hours, or a 50% increase from a stable baseline within the past 3 months (1), occurs frequently in cirrhosis, estimated to be 20% of all patients with acute decompensation (2). Therefore, renal failure, an extension of AKI, is also the most common organ failure in patients with acute-on-chronic liver failure (ACLF). Its prevalence in ACLF depends on which definition is used. In Europe, the EASL-CLIF Consortium has defined renal failure as a serum creatinine of ≥2.0mg/dL. Using this definition, renal failure was identified in 55.8% of all patients with ACLF from the CANONIC study (3), 32% of patients from India (4), and 22.5% of patients from China (5). When defined as the need for renal dialysis in the North American Consortium for the Study of End-Stage Liver Disease (NACSELD), the incidence of renal failure in infected cirrhotic patients with ACLF was 15.1% (6). The precipitating event for the renal failure in ACLF could be related to infection, hypovolemia, hepatorenal syndrome, or structural renal damage. It is interesting to note that when the ACLF was triggered by intrahepatic events such as a flare of viral hepatitis, renal failure was a rare complication, occurring in 5% of all patients. When compared to patients with acute decompensation, AKI events in patients with ACLF were more likely to have evidence of structural renal damage, they were more likely to be prolonged and more likely to progress to a more severe stage of renal dysfunction (7). The reason for this difference may be related to the fact that in patients with ACLF, more than 1 mechanism may be involved in the pathogenesis of renal failure. That is, the AKI is unlikely to be related to hemodynamic changes of advanced cirrhosis only. Rather, the presence of inflammation may play an important role in the development of renal failure in ACLF, especially in patients with alcoholic cirrhosis (8). The fact that an anti-inflammatory agent such as pentoxifylline can prevent the development of HRS in patients with alcoholic cirrhosis supports this contention (9). It has been proposed that inflammatory mediators, possibly related to bacterial translocation, or related to the presence of infection, can cause sluggish flow within the renal microcirculation and induce direct renal tubular damage, thereby causing renal failure (10). Therefore, patients who have AKI with ACLF are more likely to require renal replacement therapy, and have less AKI resolution, associated with higher mortality (9). In infected cirrhotic patients who developed AKI, even those who recovered from their AKI event still had a significantly higher 30-day mortality rate compared to patients who did not develop AKI (11). Thus, renal failure carries a significant weight in the determination of cirrhosis in patients with ACLF.

Volume expansion, preferably using colloid solutions, is the first step in the management of renal failure in cirrhosis. Albumin is the most common solution used in the resuscitation of cirrhotic patients with renal failure (12). Albumin not only has oncotic property which is used for volume expansion, its anti-oxidant and scavenging properties can also help to dampen the extent of inflammation in patients with decompensated cirrhosis (13). Patients with pre-renal renal failure but not those with structural renal disease or HRS will respond to volume challenge with improvement of renal function and reduction of serum creatinine. Patients whose renal failure is not responsive to volume challenge should have structural renal disease excluded by searching for urinary casts, proteinuria and contracted kidneys on
Abdominal ultrasound. Hepatorenal syndrome is a diagnosis of exclusion, when all other causes of renal failure have been ruled out. A combination of vasoconstrictors, whether terlipressin or norepinephrine, together with albumin, is the mainstay of treatment for acute HRS (14). Although albumin alone is not effective in the treatment of acute HRS, there is some evidence that the beneficial effect of albumin in combination with vasoconstrictors is dose dependent (15). The combination of midodrine, octreotide and albumin has been shown in a randomized controlled trial to be inferior to terlipressin and albumin (16) in reversing HRS, and therefore should be discouraged. However, in countries where terlipressin is not commercially available, a short course of midodrine, octreotide and albumin can be given, and if there is no response as indicated by a decrease in serum creatinine after 3 days, patients should be switched over to the combination of norepinephrine and albumin (17). Treatment should be started as soon as possible, as a lower pre-treatment serum creatinine is a consistent predictor of response to vasoconstrictor therapy (18). A recent meta-analysis confirmed that the use of terlipressin and albumin was significantly more efficacious in reversing HRS than albumin alone or placebo (relative risk: 2.54, 95% confidence interval: 1.51-4.26) (19). Norepinephrine was also effective in reversing acute HRS, but the trials were small and non-blinded (19). The use of terlipressin was associated with a survival benefit (relative risk: 0.79, 95% confidence interval: 0.63-1.01), but with significant increased risk of adverse events (19).

A suggested algorithm for the management of renal failure in ACLF.
References
Brain Failure in ACLF

ACLF is defined by different prognostic and diagnostic systems\(^1\). However, the importance of brain dysfunction, usually characterized by grades 3 and 4 of hepatic encephalopathy (HE) is common across most classifications. HE due to advanced liver disease is caused by a multitude of factors associated with hyperammonemia, systemic inflammation and the immuno-suppressive nature of cirrhosis\(^2\). However, with the identification and treatment of precipitating factors, HE typically can be treated from a mental status standpoint\(^3\). However, patients with advanced cirrhosis can also be susceptible to mental status changes from several other causes including medications, alcohol intoxication/withdrawal, intra-cerebral bleeding/strokes, and sepsis-associated encephalopathy. These multiple factors can contribute to precipitation of HE or are independent factors behind brain failure and need to be defined and treated accordingly. Progression of HE from earlier grades to grade 3/4 should be prevented and a low threshold for airway protection measures instituted. The four prongs of treatment of suspected HE or altered mental status in a patient with cirrhosis are (i) confirmation that it is indeed HE by performing investigations that would rule out other causes (ii) standard care of the unconscious patient with airway protection and transfer to a monitored unit early if necessary (iii) identification and treatment of precipitating factors, without which the mental status will not recover and (iv) empiric HE treatment using first line lactulose and other treatments as tolerated and locally available\(^3\). The role of rifaximin and IV albumin have been lately defined but need to be studied together and replicated in other centers\(^4,5\). In patients who are not responding to the above measures (persistent HE), reconsideration of the diagnosis of HE, continuing to look for undiscovered precipitating factors and potentially embolize spontaneous spleno-renal shunts in those with a low MELD score may be further options\(^6\).

In ACLF, due to the combination of hepatic and extra-hepatic organ failures, there is an opportunity to study the individual role of brain failure towards the overall prognosis. Two large studies published, from Europe and North America, have defined the role of HE with and without ACLF. In the CANONIC cohort, Cordoba et al found that HE grades, if accompanied by ACLF, conferred a worse prognosis compared to those who did not have ACLF\(^7\). This is an important difference, which can guide future therapeutic studies. In the largest study to date studying HE compared to other extra-hepatic organ failures (EHOF) in cirrhosis and ACLF, the NACSELD cohort evaluated 1560 cirrhotic inpatients\(^8\). The results showed the grade 3/4 HE with >2 EHOFS had the highest 30-day mortality, similar to the European cohort. However, grade 3/4 HE was associated with 30-day mortality independent of other EHOFS, indicating that regardless of other organ failures, brain failure or grade 3/4 HE is an important independent prognostic factor. Apart from defining prognosis, the importance of brain dysfunction and HE looms large when decisions need to be made between end-of-life futility measures and defining fitness for liver transplant\(^9,10\). This is especially relevant if patients still do not recover despite the measures instituted above. Not having the personal input of the patient can be challenging when facing these ethical questions.
Therefore, all efforts to prevent progression of brain failure to coma by pro-active measures are needed in cirrhotic inpatients, regardless of other extra-hepatic organ failures.

References
Patients presenting with ACLF challenge the clinician in that therapeutic options and approaches may be too late on arrival in making significant difference. The investigators in the CANONIC study demonstrated the fluidity of this newly defined condition in ways may highlight practical approaches which are worthwhile contemplating. Their observation that patients who did not meet ACLF diagnostic criteria have low mortality, and that even those patients presenting with more than 1 organ failure can, with diligent care in the ICU be downgraded to lower grade ACLF, should prompt rapid management of those elements which carry the highest risk and that present potential preventive strategies.

One of the single most significant injuries in ACLF is renal dysfunction. While renal failure (defined as serum creatinine ≥ 2 mg/dL) by itself carries significant morbidity risk, less severe acute kidney injury (AKI) has additive impact to the risk of mortality when other organ failures (OFs) are present. Brain dysfunction or failure as evidenced by high grade hepatic encephalopathy (measure by West Haven HE grade 3/4) is again strongly linked singly or in combination with other OFs with high risk of mortality. Since the topic of this discussion centers around triggers of ACLF that are non-infectious, it bears reminding that sterile inflammatory triggers can prompt renal or brain failure.

In the European population, alcoholic liver disease alcoholic cirrhosis (as well as alcoholic hepatitis) is a very common precipitating factor for ACLF, and to a lesser degree surgery and drug induced liver injury. It is therefore imperative that measures be taken to recognize early renal dysfunction and to prevent any nosocomial source for renal injury to prevent escalation of ACLF and allow interventions that may reverse the inciting injury in a timely fashion. In cases where hepatic encephalopathy (HE) complicates the course of ACLF, the situation may be more difficult to manage. As we have already heard during prior presentations, as many as 40% of European ACLF patients can present without any evident trigger for ACLF.

**Renal Failure**

Therapeutic options in this setting of renal failure/injury are well established and their use is predicated upon recognition of renal injury or its precipitating factors. Renal failure is well recognized to compromise the prognosis of alcoholic hepatitis. Treatment options such as pentoxifylline may be only effective in those patients that do not developed hepatorenal syndrome. The institution of renal protective therapies regardless of the cause of ACLF are likely to diminish its morbidity. It is well recognized that the etiology of renal injury carries a significant impact on the prognosis of that injury in patients with cirrhosis. Those recognized to have hypovolemia or intrinsic renal injury have a much better prognosis than those patients with hepatorenal syndrome or sepsis related renal dysfunction. Volume repletion in cases of hypovolemia such as variceal bleeding not only protect renal function but if combined with active interventions such as the use of albumin, may prevent spontaneous bacterial peritonitis and thus further decompensating events that only worsen the outcome of ACLF. There is also indirect evidence that critically ill patients benefit from early initiation of renal replacement therapy, so it stands to reason that in the cirrhotic population hemodialysis should be initiated early in the course of renal failure to minimize the impact on already critically ill patients.
There is already ample evidence that if hepatorenal syndrome is diagnosed, the initiation of terlipressin and the use of albumin to maintain intravascular volume are key in the survival of this patient population. The role of hemodialysis in this group of very sick patients should be limited to those who have an option to go on to liver transplantation, as hemodialysis does not seem to prolong survival in the long-term.

**Hepatic Encephalopathy**

The recognition of hepatic encephalopathy early on in the course of ACLF presentation should prompt recognition of triggers that can be reversed. Unfortunately, there is a subset of patients presenting to hospital with already advanced HE. The promise extracorporeal liver support was embraced very avidly after introduction of several systems. Despite early promise in exploratory studies using the PROMETHEUS and MARS devices, more recent rigorous studies have failed to reveal survival benefit in this patient population and may not justify the high expense incurred in their use in cases of ACLF.

Current strategies in the management of this difficult population require recognition of early presentation of ACLF or the risks for its onset. In cases where infectious triggers are not evident, it is imperative to recognize those triggers that may induce an inflammatory response such as alcoholic hepatitis, drug hepatotoxicity or variceal bleeding bleeding. The clinician also needs to recognize that as many as 40% of patients presenting with ACLF may not have a specific trigger. In all cases, the presentation of renal failure or hepatic encephalopathy may add significant negative prognostic weight and any strategy to mitigate these complications may translate in clinical improvement the patient and survival. In extreme cases, candidacy for liver transplantation may need to be considered, thus consideration of referral to a liver center is of critical importance.

**References**


The Changing Landscape of Sepsis Therapy Including Albumin

Infections are a key driver of acute-on-chronic liver failure. The 2016 Sepsis-3 task force define sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection” and septic shock as a “subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality” (1). A comprehensive review of sepsis therapy is provided in the recent 2016 Surviving Sepsis Campaign Guidelines (2) and covered throughout the ACLF STC presentations. In an attempt to reduce overlap, the current presentation will focus on 4 topics: i) biomarkers for early identification of sepsis and antibiotic de-escalation, ii) the role of albumin replacement, iii) the shift in microbial pathogens and importance of early and appropriate antibiotic therapy and iv) emerging therapies beyond antibiotics.

1) Biomarkers for the early identification of sepsis and antibiotic de-escalation –

Optimally, in the setting of sepsis, biomarkers would clearly facilitate the diagnosis, prognosis or prediction of treatment response. At best, currently, they offer a supportive and supplemental role on top of clinical assessment. The most well-studied of these biomarkers in sepsis have been the white blood cell count, procalcitonin, serum lactate and the C-reactive protein. Sepsis guidelines provide a weak recommendation (low quality of evidence) for the use of procalcitonin levels to shorten antimicrobial therapy duration and discontinue empiric antibiotics in patients who have limited clinical evidence of infection (2, 3). The data to support the use of these biomarkers in cirrhosis is similarly supportive but inconclusive, with recent algorithms incorporating their use to aid in antibiotic selection (4).

2) The role of albumin replacement therapy –

Human serum albumin (HSA) is a diverse molecule with volume expanding and systemic and organ inflammation modulating properties (5). In cirrhosis, the use of HSA reduces mortality in the settings of large volume paracentesis and the treatment of SBP and Type 1 HRS. The results from two RCT’s released at EASL 2017 add to the evolving role of HSA in decompensated cirrhosis (and sepsis prevention) – i) trial by Sola E et al (n=196) - HSA (40 g every 2 weeks) with midodrine vs a double placebo x 1 year and ii) the ANSWER trial by Caraceni P et al (n=440) – standard therapy vs standard therapy plus HSA (40 g twice weekly for 2 weeks, then once weekly for a year). The first trial reported no significant reduction in cirrhosis complications or mortality. The second trial demonstrated a significant reduction in mortality, liver related complications (including SBP and non-SBP related infections), hospitalizations and an improvement in quality of life. Ongoing studies will help to clarify the discordant results. For the general population of patients with sepsis, given the absence of clear benefit over crystalloid solution (6) and considering the expense of albumin, Sepsis guidelines suggest that albumin be used only when patients require substantial amount of crystalloids (weak recommendation, low quality of evidence) (2).
3) The shift in microbial pathogens and the importance of early and appropriate antibiotic therapy with early de-escalation – High rates of antibiotic use (for treatment and prophylaxis) and frequent invasive procedures in hospitalized patients with cirrhosis have led to an increase in infections by multi-drug resistant (MDR) organisms and Gram-positive bacteria (4, 7). The prevalence of these infections differs across countries, reaching rates of up to 37% in North America (4). MDR infections have a significant impact on morbidity and mortality. The major tenants of management include **early and appropriate antibiotics**. Ideally, antibiotics should be provided within 1 hour of recognizing sepsis. In patients with septic shock related to SBP, the risk of in hospital mortality increases by 1.8 times for every hour delay in appropriate antimicrobials (8). Empiric appropriate antibiotic therapy is often broad-spectrum, tailored based on local antimicrobial resistance patterns and predictors of an increased risk of MDR infections (infection by MDR bacteria in the last 6 months, use of β-lactam antibiotics within the last 3 months, long-term norfloxacin prophylaxis, recent exposure to the health care system or residency in a nursing home). Recent guidelines provide recommendations for the choice of empirical antibiotic therapy in light of these risk factors (4, 9). Two recent randomized controlled trials support the empiric use of carbapenem based antibiotic therapy in cirrhotic patients with nosocomial infection (10, 11). A treatment duration of 7-10 days is considered adequate for most infections (2) and patients should be assessed daily for de-escalation of antimicrobial therapy. The optimal duration of the total course will be affected by factors such as the patient’s immune status, the nature of the infecting pathogen and the site of infection.

4) Emerging therapies beyond antibiotics – In order to combat the burgeoning tide of MDR infections, antibiotic stewardship, judicious antibiotic use and infection control policies need to be prioritized at all hospitals. Beyond this, in the general infection literature, other non-antibiotic strategies are being evaluated including modulation of host immunity, antivirulence strategies and phage therapy (12). Although there have been some signals for benefit, none of these therapies have sufficient data to support wide adoption into clinical practice. Similarly, in cirrhosis, although preliminary data exists, non-antibiotic strategies such as pre and probiotics, fecal microbial transplantation, prokinetics, statins, bile acids, beta-blockers and hematopoietic growth factors remain within the investigational realm (4, 7).

**References**


Prevention of ACLF: Is Pre-emptive Treatment the Appropriate Choice?

In ACLF patients, progressive organ failures are associated with significant morbidity and mortality. The role of the hepatologist and the intensivist are to identify potential precipitants and potentially intervene to prevent deterioration and/or further organ failure.

Sepsis is the most common precipitant of ICU admission in ACLF patients. Time delay to appropriate antimicrobial therapy in ACLF patients with septic shock is independently associated with increased mortality (~1.5 times per hour in delay) (1). The new 2017 Surviving sepsis guidelines published by the Society of Critical Care Medicine (SCCM) have identified the following key measures to be performed within 3 hours of the development of sepsis: measure lactate level, obtain blood cultures prior to antibiotics, administer broad spectrum antibiotics and administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L(2). Within 6 hours, apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg(2). Given the widespread use of antibiotics in the setting of SBP prophylaxis and variceal bleeding, the development of resistant organisms is of concern and should be considered when deciding upon empiric therapy in ACLF patients with septic shock (e.g. extended spectrum beta-lactamase, carbapenem). In patients without clinical improvement with initial therapy, consider empiric antifungal therapy and appropriate imaging(3). In non-infected ACLF patients, use of daily chlorhexidine, avoidance of unnecessary vascular catheterizations (removal when no longer necessary) and the use antibiotic-impregnated catheters in those expected to remain >5 days have been demonstrated to reduce bloodstream infection(4).

In ACLF patients with circulatory shock, assessment of volume status can be particularly challenging due to ascites and edema. Dynamic measures of volume and circulatory function such as echocardiography, changes in CVP in response to fluid challenge, and passive leg raise may aid the clinician in management decisions regarding fluids and vasopressors(5, 6). In patients with persistent shock after appropriate correction of volume deficiencies, pharmacological management is indicated. Norepinephrine is the recommended first-line agent as it is associated with fewer adverse events(7). Vasopressin or terlipressin may be used as second-line agents and have demonstrated improvement in hemodynamics in patients with cirrhosis(8, 9). Adrenal insufficiency is common in critically ill cirrhotic patients and should be considered in cases of refractory shock(10). In patients where adrenal insufficiency is suspected, consider hydrocortisone 200 mg IV in 4 divided doses(11). Consider discontinuing non-selective beta blockers in ACLF patients admitted to the ICU with persistent hypotension.

ACLF patients may require intubation/mechanical ventilation for airway protection in the setting of variceal bleeding, hepatic encephalopathy or for respiratory failure. Similar to other critically ill patients, lung protective ventilation strategies utilizing low tidal volume ventilation and use of positive end expiratory pressure (PEEP) to maintain appropriate oxygenation are
recommended(12). In patients with significant acute lung injury, a conservative fluid management strategy may improve lung function and decrease duration of mechanical ventilation(13).

The use of renal replacement therapy (CRRT) may be considered not only in the setting of acute kidney injury but for the ACLF patient with pulmonary edema/fluid overload in ACLF patients being considered for LT. However, in the ACLF patient with a potential indication for RRT, the benefit of ‘early’ or ‘prophylactic’ RRT remains an area of controversy(14).

References
Liver Transplant and ACLF: North American Experience

Acute on Chronic Liver Failure (ACLF) is a clinical manifestation that is distinct from progressive cirrhosis or acute liver failure. ACLF has been variably described in the US, Europe, and Asia but the theme is common in that it is a dramatic event and is associated with significant morbidity and mortality (1,2). The evolution of ACLF is variable and the mortality is related to the severity and number of organ failures. The precipitating events are heterogeneous and vary across the various regions of the World. While infections are a major cause in the Western World, cirrhosis or varying severity of chronic liver disease superimposed with viral illness, medications, and alcohol excess constitute common reasons for ACLF in other parts of the World.

While supportive measures are essential to the care of the patient with decompensated cirrhosis or ACLF, the ultimate and lifesaving intervention is through liver transplantation (LT). There are unique issues and challenges with LT in ACLF. Because of the dramatic presentation and associated multi-organ failure, the “window” of opportunity for LT may be quite narrow and the effort to rescue these patients may turn out to be futile in some cases. The challenge the clinician faces in ACLF is deciding on “when to” and “when not” to transplant these patients.

The liver allocation process in the US is based on Model for End-Stage Liver Disease (MELD) score and therefore not uncommonly patients with ACLF and particularly acute renal failure have a dramatic increase in MELD making them competitive for organ allocation; yet on the other hand associated respiratory and circulatory failure may contraindicate LT because of the known poor outcomes in such cases. In the North American Consortium for Study of End Stage Liver Disease Cohort (NACSELD), Reddy et al noted that infection associated ACLF was a major cause for delisting patients who were on the waitlist for LT (3). Within 6 months, 42% of patients were de-listed and with subsequent poor outcomes while those transplanted did well. Those who were delisted or died, rather than those who underwent transplantation or were awaiting transplantation, had the highest proportion of 3 or 4 organ failures at hospitalization versus those transplanted or those continuing to await LT (38%, 11%, and 3%, respectively; P = 0.004). For those who were delisted or died, underwent transplantation, or were awaiting transplantation, organ failures were dominated by respiratory (41%, 17%, and 3%, respectively; P < 0.001) and circulatory failures (42%, 16%, and 3%, respectively; P < 0.001).

Bittermann et al analyzed UNOS data from 2002 to 2013 on 50,838 non-status 1 single-organ liver transplant recipients and noted a significant interaction (p<0.01) between laboratory MELD score and hospitalization status on three-, six-, and 12-month post-transplant mortality (4). This interaction was most pronounced in patients with a laboratory MELD score <25 transplanted from an intensive care unit (ICU), whose adjusted predicted three-, six-, and 12-month post-transplant mortality approximated those of patients with a MELD score ≥ 30. Compared to hospitalized patients with a MELD score of 30–34, those with a MELD score ≥ 35 in an ICU had significantly increased risk of three-month (OR: 1.54, 95% CI: 1.21–1.97), 6-month (OR: 1.35, 95% CI: 1.09–1.67), and 12-month (OR: 1.25, 95% CI: 1.03–1.52) post-transplant mortality suggesting that transplanting patients in the ICU is associated with suboptimal outcomes and...
that careful consideration be given to LT in such patients in order to optimize the use of an organ.

Carefully selected patients, however, may do well as noted by Bahirwani et al where the survival and renal outcomes were similar in those with and without ACLF (5). In those listed for LT, ACLF was defined as a sudden increase in MELD score by 5 or greater within a month, and such patients did well. Mean MELD score at transplant was significantly different between the groups (ACLF 28.77 vs. non-ACLF 21.23, \( P < 0.0001 \)). On multivariate analysis, ACLF was not significantly associated with eGFR less than 30 mL/min, death, recurrent cirrhosis, or retransplantation when adjusted for potential confounders. Understandably this was a biased population in that those transplanted had acute kidney injury as the major manifestation of ACLF.

There are enormous data gaps on the role of LT in ACLF. While it remains a lifesaving intervention, the appropriate candidate is not well defined. This condition is associated with high morbidity and mortality and not uncommonly these patients end up in the ICU. While intuitively it would appear that LT is the intervention needed, it would behoove us to carefully select our patients to optimize patient outcomes while we ensure proper use of the scarce resource of donor organs. While post LT survival is the index bench mark of outcomes, thus far unmeasured variables should include quality of life, length of hospital stay, resource utilization such as dialysis and these factors should be instrumental in our decision on LT. If survival is the only measure, LT is reasonable but if other factors are important, careful candidate selection is necessary.

References
Transplant and ACLF: European Experience

In Europe, Acute-on-Chronic Liver Failure (ACLF) is a newly defined syndrome, characterized by organ/system failures defined by the chronic liver failure (CLIF)- sequential organ failure assessment (SOFA) score, and a 28-day mortality rate of at least 15% in a patient with an acute decompensation of cirrhosis [1]. An absence of improvement or resolution of these organ/system failures despite maximal supportive management, particularly by day 3 to day 7, is associated with a drastic outcome leading to futility of care, or consideration applied to the options of salvage liver transplantation (LT) [2,3]. This last option remains controversial. Indeed, transplantation in the sicker recipients, in particular cirrhotic patients requiring multi-organ support, is unquestionably associated with an improved survival benefit but could result in less acceptable longer term survival rates after LT. Moreover, the probability to access to LT is low for ACLF patients. In a large prospective European observational study (the CANONIC study), a minority (6%) of ACLF patients were transplanted. Mortality rate of more than 50% for ACLF patients was reported on the transplant waiting list, compared to about 15% of patients listed for other indications [4].

Experiences of LT in ACLF patients coming from European centers are progressively published. In CANONIC study, LT of ACLF patients (38% had ACLF grade 3 [ACLF-3]) was associated with an acceptable 1 year-post-LT survival of 75% [2]. Similarly, an excellent 1- and 5-year survival rate of 87% and 82% respectively was reported in a study from Austria of LT in 32 out of 144 ACLF patients [4]. A recent retrospective study from three French liver centers reported that 73 patients with ACLF-3 received LT with an outstanding 1-year-post-LT survival of 84%, suggesting that ACLF-3 per se should not be viewed as a contraindication for LT [5]. Moreover, the classical scores to predict post-LT outcomes as pre-allocation survival outcomes (P-SOFT), balance of risk (BAR) and UCLA futility risk score were inaccurate to predict post-LT mortality of transplanted ACLF-3 patients. In contrast however, a small single center study reported that 13 ACLF-3 patients (all supported by mechanical ventilation and vasopressors, and 77% by renal replacement therapy), were transplanted and a 1-year post-LT survival rate of 46% was observed [6]. Another recent small French retrospective study seemed to confirm these bad results for ACLF-3 (1-year post-LT survival rate of 43%) [7]. Moreover, post-LT complications of ACLF patients (observed in the majority of cases) were associated with longer intensive care unit and hospital stays after LT compared to patients without ACLF. Infectious, renal, pulmonary and neurological complications were the main events after LT.

Several unanswered queries remain in this challenging topic; which are the objective criteria for listing/de-listing of ACLF patients? What is the ideal timing of LT? Is MELD-driven allocation of organs adequate for these patients to reduce the high waiting-list mortality rate? The limits of this strategy need to be urgently addressed in a prospective way to maintain a system of fair
allocation of organs among different recipients yet not deny those who are at high risk of death without transplantation.

References
The population of patients with cirrhosis is aging. This is a result of general population trends in aging that are exacerbated by two additional phenomena specific to patients with liver disease.

- The first is the emergence of widely-available treatments for chronic hepatitis C (HCV) in the form of all oral direct-acting antiviral (DAA) regimens. While DAAs have offered individuals a realistic option for cure for chronic HCV, nearly half of these individuals are estimated to have cirrhosis by 2020,(1) meaning that their cure may come too late. Despite eradication of virus, these individuals remain at risk for hepatic decompensation and hepatocellular carcinoma, although these terminal events are developing at older and older ages (2).

- The second is the epidemic of non-alcoholic fatty liver disease (NAFLD), which is emerging as a leading indication for liver transplantation (3). NAFLD typically leads to cirrhosis after decades and decades of ongoing hepatic injury, so patients with NAFLD are frequently diagnosed with cirrhosis at older ages than patients with other chronic liver diseases such a HCV, alcohol, or autoimmune disease (4).

Why does the aging of patients with cirrhosis matter? Because if and when they experience acute hepatic decompensation and develop acute-on-chronic liver failure (ACLF), the combination of aging and aging-related comorbidities (e.g., diabetes, sarcopenia, coronary artery disease) may synergize with the effects of ACLF to adversely impact their outcomes disproportionately to the severity of ACLF itself. In Figure 1, I offer a schematic of how aging and aging-related comorbidities may adversely impact a cirrhotic patient’s ability to recover from ACLF.

Figure 1. Schematic of how aging and aging-related comorbidities (manifesting as low physiologic reserve) may alter the trajectory of recovery in a patient with cirrhosis after an acute decompensating event.
A patient with high physiologic reserve can withstand an episode of ACLF and recover to the point that he or she may be considered for liver transplantation and, once listed, withstand the wait for a suitable liver offer. A patient with low physiologic reserve, however, has lost the ability to adapt to physiologic stressors. An episode of ACLF will propel him or her into the “zone of adverse outcomes”, where one complication leads to another, resulting in prolonged hospitalization, loss of function, disability, and ultimately death.

Intuitively, it is easy to understand how advanced age and aging-related comorbidities reduce physiologic reserve in all patients, including those with cirrhosis. Indeed, there are data to support that factors such as advancing age, sarcopenia, coronary artery disease, and diabetes individually contribute to adverse outcomes in decompensated cirrhotic patients, independent of liver disease severity. But how does one quantify the impact of each individual factor – and the sum of all the factors – on a patient’s physiologic reserve for clinical decision-making?

For this answer, we can turn to the field of geriatrics. Geriatricians have long been assessing their patients’ physiologic reserve to inform their day-to-day decisions such as: should this patient undergo elective surgery? Would this patient benefit from cancer screening? What is the risk-benefit ratio of starting warfarin in this patient? Over the last decades, researchers in the field of aging have operationalized older adults’ physiologic reserve with a number of tools to measure the concept of “frailty” – the term referring to a state of decreased physiologic reserve and increased vulnerability to health stressors. “Classic” geriatric tools to measure frailty such as the Fried Frailty Index and the Clinical Frailty Scale have been applied to (non-geriatric) patients with cirrhosis and demonstrated strong associations between frailty and clinically relevant outcomes include hospitalizations and mortality. Similarly, geriatric tools to measure physical function (e.g., Short Physical Performance Battery, gait speed) or disability (e.g., Activities of Daily Living Scale) – both of which are concepts that are integrally related to physical frailty – also predict outcomes in decompensated cirrhotic patient. More recently, we have developed the Liver Frailty Index, consisting of 3 performance-based measures – grip strength, chair stands, and balance testing – that significantly improves the ability of MELDNa to predict mortality in cirrhotic patients awaiting liver transplantation. The Liver Frailty Index calculator is available at: http://www.liverfrailtyindex.ucsf.edu/.

Applying this concept of frailty in clinical hepatology practice, we can now begin to assess a patient’s likelihood that he or she will recover from an episode of ACLF. Let’s take as examples two 68 year old women with cirrhosis, diabetes, and coronary artery disease who differ only in their frailty status – one is “robust” and one is “frail” by the Liver Frailty Index that was assessed during their most recent outpatient clinic visits. Both develop ACLF and are now in the intensive care unit. Their trajectories in response to this episode of ACLF would be predicted to differ (Figure 1). A clinician could conclude that if the robust patient were to undergo liver transplantation, she would experience favorable outcomes, because the reasons that she is currently sick and in the intensive care unit are related to the acute insult and the underlying liver failure, and therefore reversible with liver transplantation. On the other hand, the patient who was frail even before her ACLF presentation is at high risk for remaining frail despite a new liver. With the acute severe stressor of ACLF on top of her frailty, she will not be able to regain enough reserve with a new liver – and quickly enough after receiving it. It is this circumstance in which liver transplantation should be considered futile (Figure 2).
As you can see from this example, what matters is not the patients’ advanced age or comorbidities, but how those factors impact their physiologic reserve as manifest clinically by their phenotype of frailty.

References


17. Dunn MA, Josbeno DA, Tevar AD, et al. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. *Am J Gastroenterol*.


ACLF is associated with substantial morbidity and mortality (1), the mortality rate increasing with an increasing number of organ failures. The potential for curative liver transplantation is available to <10% of patients with cirrhosis each year. Of those who are listed for transplant, up to 30% either die while waiting or are delisted due to severity of illness. The symptom burden of patients with cirrhosis is akin to patients with advanced malignancy. Cirrhosis is considered a palliative state (2, 3).

Although often misinterpreted as being isolated to end-of-life-care (last few months of life), palliative care has potential relevance at all stages of an incurable illness. As defined by the WHO, palliative care focuses on “the prevention and relief of suffering by early identification and treatment of pain and other symptoms”. It includes advance care planning (ACP) and goals of care designation (GCD) discussions, symptom control, psychosocial support, assessment of functional status and transitions to higher levels of care including hospice (4). In a range of other chronic conditions, the early integration of care with palliative principles has been associated with reductions in emergency department visits and hospitalizations by up to 50%, improved quality of life, improved symptom management, reductions in inpatient costs, and improved bereavement outcomes (5, 6).

Despite the well-known palliative nature of cirrhosis and the benefits of integrated palliative care, advance care planning (ACP) discussions and palliative care referral are rare occurrences. In a recent series of patients removed from the liver transplant waiting list due to disease severity, only 28% had documented goals of care designations (GCDs) while only 11% were referred to palliative care even though they had only a few months to live (7).

Several cirrhosis studies have reported promising results with strategies for integrating palliative care into routine clinical practice, including within the ICU setting (8), by outpatient referral to a multidisciplinary palliative care team (9) and by referral to hospice (10). Notably, the latter study even included patients who were transplant listed.

In the ideal setting, palliative care principles including ACP and GCD discussions would first be integrated alongside continued disease-modifying therapy, with the patient in a stable outpatient setting. Given the shortage of formally trained Palliative Care specialists, the growing prevalence of cirrhosis, the aging population and the vision to provide palliative care across the spectrum of cirrhosis, in most countries, practitioners without palliative care certification will need to provide for most patients’ palliative and symptom management needs (11). In addition to system-level changes, this will require the development of cirrhosis specific toolkits and educational opportunities for primary care and specialty providers. A focus on transitions of care will also be essential, including facilitation of communication and standardized care between...
non-physician allied health professionals, the ER, ICU and community practitioners. This approach will help to ensure that the care provided to our cirrhosis and ACLF patients is not only integrated and comprehensive, but also congruent with their life goals, values and wishes.

References

POSTER ABSTRACT SUMMARIES
Background: The data on ACLF - as defined by baseline advanced chronic liver disease (ACLD), precipitating insult, acute decompensation (AD, decompensating event presenting <2-4 weeks before admission), and high short-term mortality - from the region of authors are scarce. The aim of the study was to describe characteristics of ACLF in the cohort of patients (its) admitted with decompensated (d)ACLD.

Methods: Retrospective analysis (DJ) of prospectively gathered data from consecutive inpatients during the period of 7/2014 – 5/2017. Inclusion criteria: admission with dACLD. Exclusion criteria: malignancy; insufficient data. Recorded variables: age; gender; etiology of dACLD; type of dACLD (AD [with ACLF calculated according to CANONIC/CLIF on admission /D0/, and on D7], chronic decompensation [CD]); trigger, especially association with infection (i-ACLF); decompensating event; early course (ACLF grade evolution between D0-D7); in-hospital mortality.

Results: In study period of almost 3 years, 432 patients with dACLD were hospitalized; 18(4%) were excluded from analysis by predefined criteria; CD: 277(64%), AD: 137(32%). Median age: 57 years; female: 55(40%); etiology of ACLD: alcoholic liver disease (ALD) 116(85%), autoimmune syndromes 13(9%), others 8(6%). Decompensating events: ascites 66(48%), variceal bleeding 36(27%), hepatic encephalopathy 18(13%), infections 17(12%). Triggers: acute alcoholic hepatitis (AH) 52(38%), infections 41(30%), GI bleeding 31(23%), unknown 10(7%), TIPS, dehydration 3(2%). ACLF was present in 48(36%) of AD pts (11% of all dACLD pts); ACLF1-26(19% of AD/54% of ACLF), ACLF2-18(13%/37% ), ACLF3-6(4%/13%). In-hospital mortality in AD group (without ACLF) at D0, and D7 was 11%, and 8%, respectively. Mortality in ACLF group at D0/D7 was as follows: ACLF1-23%/42% (ns), ACLF2-44%/47%(ns), and ACLF3-67%/80%(ns), respectively.

Conclusion: In this cohort of pts with dACLD from tertiary referral centre, one-in-three was hospitalized with AD; of AD pts, one-in-three fulfilled diagnostic criteria for ACLF. The main etiology of ACLD was ALD, the main triggers were AH, infection, and bleeding. Mortality according to ACLF grades correlated with the data from the literature. Additional prognostic value of the first week dynamics of ACLF grade (final ACLF, severe early course) remains to be seen.
References:

Disclosure: Nothing to disclose.
THE LACE SCORE CANNOT PREDICT READMISSIONS IN CIRRHOTIC PATIENTS REGARDLESS OF ACUTE ON CHRONIC LIVER FAILURE

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Institution(s): VCU Medical Center and McGuire VA Medical Center1; McGuire VA Medical Center2; VCU School of Nursing3

Background: Acute on Chronic Liver Failure (ACLF) is associated with a poor prognosis. The LACE score is an inpatient score that has been validated to predict readmissions. It comprises the (L)ength of hospitalization, (A)cuity, (C)harlsons comorbidity index, (E)R admissions in the last 6 months. The modified LACE score incorporates Diabetes Mellitus, Renal disease and peptic ulcer disease to the Charlson score (henceforth referred to as LACE score). It is most predictive with a score ≥11 in multiple disease processes, but has not been studied to predict readmissions in ACLF patients. We aimed to determine if the modified-LACE score can predict readmissions in cirrhotics with ACLF compared to cirrhotics without ACLF.

Methods: Cirrhotic patients who were admitted non-electively from 2015 through 2016 were included. Demographics, etiology of cirrhosis, MELD score and LACE score on discharge were collected. ACLF was diagnosed using NACSELD criteria. Readmissions and their reason within 1 month and 3 months from discharge were evaluated. We excluded those who died during the index admission and who were lost to follow-up.

Results: 153 cirrhotic patients met eligibility criteria from 225 consented cirrhotic patients. Mean age was 56.4±9.1. Median MELD score was 20(15,29). Median LACE score for all patients at discharge was 13 (10.5,15). Out of 153 cirrhotics 38 patients (25%) had ACLF. Cirrhotics with ACLF had a high LACE score (≥11) on discharge compared to non-ACLF cirrhotics (14(12,16) vs 12(10,15), p<0.0009, OR 8.2 CI(1.9-36)). Readmissions in patients with ACLF was statistically similar to non-ACLF cirrhotics at 1 month (42% vs 29.5%, p=0.15) and 3 months (23.7% vs 22.6%, p=0.89). Using a LACE score of ≥11 as a cut off all cause readmissions between ACLF cirrhotics and non-ACLF cirrhotics at 1 month (44.4% vs 32.9,p=0.23) and 3months (25% vs 24%, p=0.91) were statistically similar. Similarly, liver-related readmissions at 1 month (30.5% vs 18.9%, p=0.7) and 3 months (16.6% vs 16.4%, p=0.93) were similar.
Table 1: Demographical and study variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non ACLF(115)</th>
<th>ACLF(38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>56±10</td>
<td>57.5±6.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Male sex(%)</td>
<td>56.5</td>
<td>60.5</td>
<td>0.66</td>
</tr>
<tr>
<td>MELD (median,IQR)</td>
<td>20(14,28)</td>
<td>24(16,29.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Etiology HCV (%)</td>
<td>19%(22)</td>
<td>34%(13)</td>
<td>0.07</td>
</tr>
<tr>
<td>Etiology Alcohol(%)</td>
<td>35.7%(41)</td>
<td>34%(13)</td>
<td>1</td>
</tr>
<tr>
<td>LACE score(median,IQR)</td>
<td>12(10,15)</td>
<td>14(12,16)</td>
<td>&lt;0.0009</td>
</tr>
</tbody>
</table>

Conclusion: Although ACLF patients had a high LACE score on discharge, neither a diagnosis of ACLF nor a high LACE score were associated with the risk for all cause and liver-related readmission at 1 month and 3 months in cirrhotic patients. Therefore, the LACE score with and without an ACLF diagnosis are not useful to predict readmissions in cirrhosis.

Disclosure: Nothing to disclose.
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**Background:** Acute on Chronic Liver Failure (ACLF) is distinct syndrome with high short term mortality due to an acute hepatic insult leading to liver failure and subsequent extra-hepatic organ failure in a patient with chronic liver disease. The type of insult, severity of liver disease is crucial for defining the outcome, hence the therapy. The present study aims to identify the etiologies for various acute and chronic insult and their impact on 90 days survival and complications.

**Methods:** 2714 ACLF (APASL definition) patients were enrolled from 30 centers across Asia into AARC database from October 2012 to June 2017 were analyzed for the various acute and chronic insult. The impact of etiology on disease severity, complications, organ failures and 90 days survival were analysed.

**Results:** In 2714 patients, mean age was 44.5±12.6 and male predominance was seen (85.1%) with respect to female (14.6%). Predominant acute insults was severe alcoholic hepatitis (SAH) (1251, 45.7%) followed by Drug induced (251, 9.2%), acute viral hepatitis (251, 9.2%), Autoimmune flare (57, 2.1%, 0.52) and (349, 12.8%) of unknown etiology. The various causes for chronic liver disease were Alcohol (1332, 48.7%), HBV (687, 25.1%), HCV (52, 1.9%), Autoimmune hepatitis (81, 3%), (540, 19.7%) cryptogenic or NASH. Drug induced liver injury (DILI) as an acute insult (HR=1.89, 95 CI 1.29-2.74, p<0.001) and presence of Hepatic encephalopathy (HR=2.19, 95CI 1.63-2.95, p<0.001) and Acute Kidney Injury (HR=2.68, 95CI 2.01-3.57, p<0.001) independently increases the 90 days mortality. Among the complications of ACLF at presentation, HE (HR=2.09, 95CI 1.54-2.82, p<0.001) and presence of extra hepatic organ failure were strongly associated with mortality (HR=2.79, 95CI 2.01-3.90, p<0.001). The mortality was significantly lower in patients who survived 90 days (HR=0.74, 95CI 0.66-0.83, p<0.001) and hence a higher disease severity was observed.
1.31-3.36, p<0.01) and variceal bleed (HR=2.24, 95CI 0.99-5.02, p<0.05) were frequently observed with drug as acute insult and AIH related CLD showed a significant association with HE (HR=1.34, 95 CI 0.12-0.92, p<0.03). Organ failure at presentation was very often seen in severe alcoholic hepatitis (3.3, 2.32-4.69, <0.001) followed by HBV (3.19, 1.89-5.39, <0.001) and DILI (2.29, 1.17-4.50, p<0.02). Similarly alcohol (3.39, 2.37-4.84, <0.001) and HBV (3.00, 1.86-4.84, <0.001) related CLD were associated with higher incidence of organ failure. The 90 days mortality with acute insult was highest with AIH flare (23/57, 57%) followed by drug induced (139/251, 55.5%) and was lowest for acute viral hepatitis (86/251, 34.3%). Similarly the mortality was highest among the cryptogenic CLD (254/540, 47.04%) followed by HCV (24/52, 46.15%).

**Conclusion:** Our results show that alcohol is the commonest acute insult as well as chronic liver disease in the Asian cohort and is associated with higher risk of organ failure. The AARC data shows that etiology predicts organ failure; drug induced liver injury and autoimmune flare are associated with AKI and HE and predict 90-day mortality.

**Disclosure:** Nothing to disclose.
ACUTE-ON-CHRONIC LIVER FAILURE IN WILSON’S DISEASE - A SERIES OF 38 CASES FROM APASL-ACLF RESEARCH CONSORTIUM (AARC)

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Institution(s): Yong Loo Lin School of Medicine1; Beijing You’an Hospital2; Asian Institute of Gastroenterology Hyderabad3; St. John Medical College4; ILBS5; PGIMER6; Hospital Selayang7; Ziauddin University Hospital8; KEM Hospital and Seth GS Medical College9; Christian Medical College10

Background: Acute on Chronic Liver Failure (ACLF) is a distinct syndrome with high short-term mortality due to an acute hepatic insult leading to liver failure and subsequent extra-hepatic organ failure in a patient with chronic liver disease. Wilson’s disease flare in the background of the chronic disease may result in the syndrome of ACLF, but the data is sparse on this aspect. We analyzed Wilson’s disease presenting as ACLF from the AARC data base.

Methods: 38 cases with Wilson’s disease, presented with ACLF (APASL definition) were recruited from March 2012 to July 2017. Data was obtained from multiple centres and aggregated on a common platform of AARC. Baseline parameters and further in-hospital course were followed til 90 days for death or liver transplant.

Results: Wilson disease constitute 1.3% (36 of 2732) of ACLF. 14 ACLF cases with underlying Wilson’s disease had defined acute etiological insult (Group-A) and were aged 34.9±22.1 with 11 males. in group-B. In rest of the 24 cases the etiology of the acute insult could not be defined (Group-B). They were aged 29.5±14.6 years with 14 males. All cases had index presentation as ACLF and were diagnosed as having Wilson’s disease subsequently. The etiology of acute insult was acute viral hepatitis in 7 cases (Hepatitis E in 3, Hepatitis A in 3, Epstein Barr Virus in 1 case), drug induced liver injury in 5 cases (3 were on anti-tuberculosis therapy), sepsis and ethanol in 1 case each. 20 cases (8 in Group-A) had hepatic encephalopathy (HE) at base line and 2 developed HE on day 4 (both from Group-A). The duration of jaundice was 63.9±31 days with all patients having ascites at baseline. Median hospital stay was 24 (range 9-64) and 9 (range 1-36) days p<0.001. The ALP to-bilirubin ratio of < 4 was observed in 9 cases (24%) whereas AST-to-ALT ratio was > 2 in 17 cases (45%). The in-hospital mortality was (7/14) 50% for Group-A cases which was better than (16/22) 73% for Group-B cases, while 2 in Group B underwent liver transplant. The mortality with diagnosis of ACLF is higher (63.9%) against the overall mortality (43.8%) in AARC cohort due to ACLF [HR: 1.83, 95Cl%, 1.22-2.74, p =0.003]. The mortality was (8/14) 57% for Group-A cases which was better than (16/22) 73% for Group-B cases (p<0.01), while 2 in Group B underwent liver transplant.
Conclusion: This prospective dataset is the largest series of Wilson’s disease presenting as ACLF. Wilson’s disease patients have a higher mortality with diagnosis of ACLF and is much higher in absence of an identifiable precipitant for the same. This distinct syndrome needs new and early interventional strategies.

Disclosure: Nothing to disclose.
ACUTE ON CHRONIC LIVER FAILURE (ACLF) HAS A BETTER LONG-TERM SURVIVAL THAN ACUTE DECOMPENSATION- A STUDY OF 4897 PATIENTS FROM APASL ACLF RESEARCH CONSORTIUM (AARC) WITH A FOLLOW-UP OF 5 YEARS.

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Institution(s): Ziauddin University Hospital1; Asian Institute of Gastroenterology2; Bangabandhu Sheikh Mujib Medical University3; Beijing You’an Hospital4; Tongji Hospital, Tongji Medical College5; Sir Salimullah Medical College, Mitford Hospital6; ILBS7; Medistra Hospital8; IMS & SUM Hospital9; Nork Clinical Hospital of Infectious Disease10; Hallym University College of Medicine11; St John Medical College12; Aga Khan University13; VGM Hospital14; PGIMER15; Humanity and Health Medical Group16; University of Santo Tomas17; Global Hospital18; Chulalongkorn University19; Cardinal Santos Medical Center20; CMC Vellore21; Yong Loo Lin School of Medicine22; Ankara University School of Medicine23; Queen Mary Hospital24; Bombay Hospital & Medical Research Centre25; Hospital Selayang26

Background: ACLF is a distinct entity with high short-term mortality due to severity of acute insult and rapid worsening of liver failure. It is not known whether patients surviving acute insult have a better long-term survival than those with decompensated cirrhosis. We studied the survival of ACLF patients beyond 90 days and compared with acute decompensation of previously decompensated cirrhosis.

Methods: Patients of cirrhosis with acute decompensation (within last 3 months) in presence of prior decompensation were compared with patients of ACLF for the survival outcome beyond 90 days. Patient from 40 centres across Asia from AARC cohort, since october 2012 to october 2016 were analyzed.

Results: ACLF (n=2743) and AD (2154) at enrolment were followed for 90 days, 1833 ACLF, and 1868 AD, were followed up to 5 years, with a median follow up of 14737 and 12904 person months respectively. At presentation, ACLF patients were younger (49.69±10.86 vs. 47.23±11.67 yr, p<0.001) with higher alcoholic hepatitis (29.5% vs. 8.7% , p<0.001), HBV reactivation (7.9% vs.2.3%, p<0.001), DILI (8.3% vs. 4.3%, p<0.001) as an acute insult and less of chronic insult like NASH (14.1% vs. 10.2%, p<0.001), HCV (10% vs. 6.1%, p<0.001) but of a higher HBV related CLD (13.9% vs. 7.3%). The ACLF patients had significantly higher total bilirubin, INR, serum creatinine and severity scores and lower Hb, platelet, serum albumin and sodium (p<0.001) in addition to raised AST and ALT (p<0.001)at baseline (table-1) as well as high disease severity score (MELD 33.2±13.7 Vs. 23.9±11.3, p<0.001). The 90 day survival [HR: 0.73(0.66-0.82), p<0.01] as well as follow up for 5 years [HR: 0.79(0.72-0.87), p<0.001] had lower cumulative survival with diagnosis of ACLF in comparison to AD (fig-2).
short-term (90 days) mortality in ACLF 33.2% (910/2743) and 23% (496/2154) (p<0.001) than AD and also at 6 months (35.2% vs. 24.9%), 12 months (37% vs. 26.8%) and 24 months (38.9% vs. 29.3%) but not beyond 24 months till 5 year follow up. But upon subgroup analysis with respect to time i.e. after 24 months of index presentation with ACLF the survival is worse in AD cohort [HR: 1.94 (1.17

Conclusion: ACLF as per APASL in absence of prior decompensation with cirrhosis or non-cirrhotic chronic injury and on subject to an acute hepatic insult had higher 90 days mortality due to severity of acute insult. Among the survivors at 90 days the hepatic reserve showed an improvement and beyond 2 years from index insult the survival is much better.

Disclosure: Nothing to disclose.
THE ROLE OF CLIF CONSORTIUM ACUTE-ON-CHRONIC LIVER FAILURE SCORE 
SCORE IN PREDICTING MORTALITY IN CIRRHOTIC PATIENTS WITH AND WITHOUT 
ACUTE-ON-CHRONIC LIVER FAILURE IN A NORTHEASTERN ROMANIAN TERTIARY 
CARE CENTER

Authors: S. Chiriac¹; A. Trifan¹; A. Singeap¹; I. Girleanu¹; T. Cuciureanu¹; O. Stoica¹; C. 
Stanciu¹

Institution(s): "Grigore T. Popa" University of Medicine and Pharmacy Iasi¹

Background: The CLIF Consortium acute-on-chronic liver failure score (CLIF-C ACLF Score) 
is a recently validated prognostic score for patients with liver cirrhosis, developed for assessing 
short-term mortality in cirrhotics with acute-on-chronic liver failure (ACLF).

Methods: We validated the CLIF-C ACLF Score in a cohort of consecutive patients with liver 
cirrhosis hospitalized between January 2015 and February 2016 for acute decompensation in 
the Institute of Gastroenterology and Hepatology Iasi, Romania, a tertiary care center. Patients 
were followed for 90 days and the traditional prognosis scores Child-Pugh and Model for 
End-Stage Liver Disease (MELD) were compared with the CLIF-C ACLF Score.

Results: One hundred forty one patients were included, mean age 63.3 ± 7.7 years, mostly 
men, 86 (61%). ACLF was diagnosed in 97 (68.8%) of the participants. The median 
Child-Pugh score was 12 (10-14) and the mean MELD score was 29 ± 6.9. Both Child-Pugh 
and MELD scores were good mortality predictors in patients with ACLF, receiver operating 
characteristic (ROC) analysis showing good specificity and sensitivity in predicting 28-day, 
[area under the ROC curve (AUROC) of 0.762 and 0.743, respectively] and 90-day mortality 
(AUROC 0.716 and 0.708, respectively). However, ROC analysis showed a better sensitivity 
and specificity for CLIF-C ACLF score in predicting 28-day and 90-day mortality (AUROC 
0.884 and 0.732, respectively). Interestingly, in the case of the patients with “simple” 
decompensation the CLIF-C ACLF score did not present good sensitivity for predicting neither 
28-day or 90-day mortality (AUROC 0.51 and 0.57, respectively).

Conclusion: ACLF is frequently diagnosed in patients hospitalized for acute decompensation 
of liver cirrhosis. The CLIF-C ACLF score is more accurate in predicting 28-days and 90-days 
mortality than the Child-Pugh or MELD scores in patients with ACLF but not in those with 
“simple” decompensation of liver cirrhosis.

Disclosure: Nothing to disclose.
THE PREVALENCE AND CLINICAL RELEVANCE OF ACUTE-ON-CHRONIC LIVER FAILURE IN CIRRHOTIC PATIENTS WITH LIVER DECOMPENSATION IN A NORTHEASTERN ROMANIAN TERTIARY CARE CENTER

Authors: S. Chiriac²; A. Trifan²; C. Cojocariu²; C. Sfarti²; I. Girleanu²; O. Stoica²; T. Cuciureanu²; C. Stanciu¹

Institution(s): Institute of Gastroenterology and Hepatology Iasi¹; "Grigore T. Popa" University of Medicine and Pharmacy Iasi²

Background: Acute-on-chronic liver failure (ACLF) is a newly characterized syndrome developed in order to better assess the prognosis of liver cirrhosis patients with acute decompensation. ACLF is diagnosed in the presence of acute decompensation with organ failure according to the CLIF Consortium Organ Failure Score.

Methods: We prospectively assessed the prevalence of ACLF in consecutive patients with liver cirrhosis hospitalized for decompensation in the Institute of Gastroenterology and Hepatology Iasi, Romania between January 2015 and February 2016. Patients were followed for 90 days. We analyzed the relation between ACLF and mortality both at 28 and at 90 days as well as the death rate according to ACLF stage.

Results: One hundred forty-one patients were included, mean age 63.3 ± 7.7 years, mostly men, 86 (61%). ACLF was diagnosed in 97 (68.8%) of the participants, 25 (18%) ACLF 1 stage, 24 (17%) ACLF 2 stage, and 48 (34%) ACLF 3 stage. In the ACLF group the mean MELD score was 32.4 ± 6.1, the median Child-Pugh score was 13 (12-14), total bilirubin 12.6 (5.2-17.3 mg/dl), creatinine 2.3 (1.68-3.10 mg/dl), sodium 129 (124-132 nmol/l), and INR 1.9 (1.7-2.4). There were significant differences between the patients with and without ACLF concerning, the incidence of ascites (87.6% vs 47.7%, P<0.001), hepatic encephalopathy (97% vs 70%, P<0.001), acute kidney injury (85.6% vs 31.8%, P<0.001), spontaneous bacterial peritonitis (37.1% vs 4.5%, P<0.001), and sepsis (53.1% vs 6.8%, P<0.001). 28-day mortality was 24% in ACLF 1 stage, 60.9% in ACLF 2 stage, and 91.7% in ACLF 3 stage, P<0.001. 90-day mortality was 56% in ACLF 1 stage, 95.5% in ACLF 2 stage, and 98% in ACLF 3 stage, P<0.001.

Conclusion: ACLF is frequently diagnosed in patients hospitalized for acute decompensation of liver cirrhosis. The patients diagnosed with ACLF are more likely to present complications and have worse 28-day and 90-day prognosis.

Disclosure: Nothing to disclose.
BOTH MELD SCORE AND NUMBER OF ORGAN FAILURES DEFINED BY THE LATEST CHRONIC LIVER FAILURE-ORGAN FAILURE SCORING SYSTEM EFFECTIVELY SELECT SUBJECTS WITH SEVERE ALCOHOLIC HEPATITIS WITH GOOD OUTCOMES WHEN TREATED WITH THE ELAD SYSTEM

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Institution(s): Drexel University1; University of Pittsburgh Medical Center2; Northwell Health3; University of Minnesota Medical Center4; Southern California Research Center5; St Vincent’s University Hospital6; VitalTherapies, Inc.7; Emory University School of Medicine8

Background: Mortality due to severe alcoholic hepatitis (sAH) is related to organ failures (OF), MELD score, presence of Systemic Inflammatory Response Syndrome (SIRS), and concurrent infections at presentation that impact the prognosis and response to medical treatment.

Methods: Vital Therapies’ VTI-208 study was conducted in subjects ≥18yrs old with a clinical or histologic diagnosis of sAH, bilirubin ≥8mg/dL, Maddrey discriminant function (DF) score ≥32, MELD score of 18-35, platelets ≥40,000/mm3, and without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized 1:1 to receive protocol-specified standard of care (SOC) based on AASLD and EASL guidelines alone (Control group) or SOC with a 3-5 days continuous treatment with the ELAD System consisting of human C3A hepatoblastoma cells contained in a cartridge (ELAD group).

Results: Analyses are based on an intent-to-treat population comprising 203 subjects (ELAD 96, Control 107). 76/203 subjects (ELAD 32/96, 33%; Control 44/107, 41%) had two or more OF (liver, kidney, brain, coagulation, circulatory and/or respiratory) at baseline, based on criteria defined in the Chronic Liver Failure-OF (CLIF-OF) scoring system for acute-on-chronic liver failure (ACLF). 191/203 (94%) had at least one OF, of which one OF was due to liver failure. Six subjects had only one OF in other body systems (1 Brain, 4 Coagulation and 1 Circulatory) and six other subjects (ELAD 2, Control 4) did not have any OFs. Of subjects with 2 or more OFs, more ELAD than Control subjects died by d91 (20/32, 63% vs 19/44, 43%, respectively; p=N.S.). In subjects with only one OF (ELAD 62/96, 65% vs Control 59/107, 55%), fewer ELAD (14/62, 31%) than Control subjects (21/59, 36%) died by d91 (p=N.S.). Only one (Control) of six subjects with no OFs died by d91. 135/203 subjects (61 ELAD, 74 Control) had baseline MELD ≤28. In subjects with baseline MELD≤28, fewer ELAD (14/61, 23%) than Control subjects (27/74, 36%) died by d91 (p=0.09). 68/203 subjects (35 ELAD, 33 Control) had MELD ≥28 at baseline and in this group, more ELAD (25/35, 71%) than Control subjects (14/33, 42%) died by d91 (p<0.05).

Conclusion: Both MELD ≤28 and restricting subjects to only liver failure are effective at predicting subjects who are likely to have a favorable response to treatment with ELAD. A new study is now enrolling that excludes subjects with evidence of secondary organ failures to exclude subjects likely to have an unfavorable response to treatment with ELAD.
Disclosure: Nothing to disclose.
IMPACT OF THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME ON 3-MONTH MORTALITY RATES IN SUBJECTS WITH SEVERE ALCOHOLIC HEPATITIS TREATED WITH THE ELAD SYSTEM

Authors: A. Al-khafaji6; R. Subramanian3; J. Thompson2; D. Reich5; R. MacNicholas1; S. Malik6; Z. Li4; J. Stange4; W. Frank4

Institution(s): St Vincent’s University Hospital1; University of Minnesota Medical Center2; Emory University School of Medicine3; Vital Therapies, Inc.4; Drexel University5; University of Pittsburgh Medical Center6

Background: Systemic Inflammatory Response Syndrome (SIRS) is a major predictor of multi-organ failure (MOF) and mortality in subjects with severe alcoholic hepatitis (sAH).

Methods: A randomized, open-label, multicenter, controlled study was conducted in subjects ≥18yrs old with a clinical or histologic diagnosis of sAH, bilirubin ≥8mg/dL, Maddrey discriminant function (DF) score ≥32, MELD score of 18-35 and platelets ≥40,000/mm3, without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized to either protocol-specified standard of care (SOC, Control group) or SOC plus 3-5 days continuous treatment with an investigational extracorporeal human allogeneic cellular liver system (ELAD) consisting of human C3A hepatoblastoma cells contained in a cartridge (ELAD group). SOC protocol was implemented based on AASLD and EASL guidelines.

Results: 203 subjects were enrolled in the study. Of the 203 subjects, 122 had a white blood cell count >12 or <4 x 103/mL, 93 had a pulse >90 beats/min, 13 had a temperature >38°C or <36°C, and 22 had a respiratory rate >20 breaths/min. In the ELAD group, 36 subjects compared with 31 subjects in the Control group had 2 or more of these criteria and had SIRS at randomization (14 and 13 subjects were receiving steroids in the ELAD and Control groups, respectively). In subjects with SIRS and MELD <28, the 3-month mortality rate in the ELAD group was 3/20, 15% compared with 7/17, 41% in the Control group (p=0.07). However, in subjects with SIRS and MELD ≥28, the 3-month mortality rate in the ELAD group was 12/16, 75% compared with 5/14, 36% in the Control group (p=0.03).

Conclusion: In sAH subjects with SIRS and MELD <28, lower 3-month mortality rates were observed when treated with ELAD plus SOC compared to SOC alone. However, in subjects with SIRS and MELD ≥28, 3-month mortality rates were higher in the ELAD group when compared to SOC. A current prospective randomized controlled clinical study in subjects with sAH and MELD <30, including subjects with SIRS, is underway.

Disclosure: Nothing to disclose.
HEPATITIS E AND ACUTE ON CHRONIC LIVER FAILURE: OUTCOME AND PREDICTORS OF MORTALITY IN ASIA PACIFIC REGION

Authors: A. Butt13; S. Hamid13; A. Choudhury10; W. Jafri13; Y. Chawla5; S. Taneja5; Z. Abbas4; A. Shukla16; M. Mahtab11; D. Amarapurkar9; M. Karim17; C. Eapen1; A. Goel1; H. Ghaziniyan19; P. Rao6; M. Sahu8; S. Shah14; C. Kalal14; H. Devarbhavi12; Z. Duan7; C. Yu7; S. Tan15; D. Payawa21; O. Yokosuka3; P. Jain10; I. Paulson10; S. Sarin10; A. AARC18

Institution(s): Christian Medical College1; Cardinal Santos Medical Center2; Chiba University3; Ziauddin University Hospital4; PGIMER5; Asian Institute of Gastroenterology6; Beijing You’an Hospital, Capital Medical University7; Bombay Hospital & Medical Research Centre8; Institute of Liver and Biliary Sciences10; Bangabandhu Sheikh Mujib Medical University11; St John Medical College12; Aga Khan University Hospital13; Global Hospital14; Hospital Selayang15; KEM Hospital and Seth GSMC16; Sir Salimullah Medical College, Mitford Hospital17; AARC APASL Working Party18; Nork Clinical Hospital of Infectious Disease19

Background: One of the distinctive factors that could lead to acute on chronic liver failure is acute hepatitis E (HEV). However, most of available data carries the limitation of smaller sample size or center based experiences. Here, the current study aims to analyze the APASL-ACLF research consortium (AARC) database to evaluate the clinical and biochemical profile, predicting factors of 90 days mortality and to compare the various existing prognostic models for predicting 90 days mortality in patients with ACLF triggered by acute hepatitis E infection.

Methods: APASL-ACLF research consortium (AARC), consisting of 24 tertiary centers across Asia-Pacific regions, maintains an online database for patients diagnosed to have ACLF according to APASL criteria. All patients who had ACLF with acute hepatitis E were reviewed for the current study.

Results: Out of 2897 patients with ACLF 230 (7.9%) had acute deterioration due to HEV. Mean age was 48.29±13.50 years and 83.9% were male. The most common cause of chronic liver disease was alcohol (26.5%) followed by cryptogenic cirrhosis (25.7%) and NASH (25.7%). Overall 64.8% patients survived at day 90. Liver transplantation was done in 4.3% cases. On univariate analysis presence of PSE, AKI on presentation, serum urea, creatinine, total bilirubin, INR, lactate, CTP, MELD, MELD Na, SOFA, CLIF-SOFA, AARC score were the factors associated with mortality. However, on multivariate analysis presence of PSE, SOFA, AARC score at base line were the factors associated with mortality. When we compared various prognostic models MELD and AARC scores were found to have higher accuracy.
Conclusion: Acute hepatitis E is one of the leading causes of ACLF in Asia pacific region and associated with high mortality without liver transplantation. Presence of PSE, SOFA, AARC score at base line were the factors associated with 90 days mortality. Among prognostic models MELD and AARC scores were found to have higher accuracy.

Reference(s):

Disclosure: Nothing to disclose.
VALIDATION OF AARC SCORES TO PREDICT SHORT TERM MORTALITY IN PATIENTS OF ACUTE ON CHRONIC LIVER FAILURE

Authors: P. Jain; A. Choudhury; M. Al Mahtab; H. Devarbhavi; Z. Duan; C. Yu; Q. Ning; K. Ma; C. Eappen; A. Goel; Y. Chawla; S. Taneja; S. Hamid; A. Butt; W. Jafri; S. Tan; D. Kim; H. Ghazian; D. Amarapurkar; S. Treeprasertsuk; J. Hu; L. Lesmana; R. Lesmana; G. Lee; S. Lim; A. Shukla; S. Shah; C. Kalai; M. Sahu; Z. Abbas; J. Sollano; G. Carpio; G. Lau; M. Karim; P. Rao; D. Payawal; A. Dokmeci; V. Saraswat; M. Yuen; V. Prasad; O. Yokosuka; I. Paulson; G. Kumar; S. Sarin; A. group

Institution(s): Ziauddin University Hospital; Queen Mary Hospital; Chiba University; Hallym University College of Medicine; St John Medical College; Hospital Selayang; Cardinal Santos Medical Center; Bangabandhu Sheikh Mujib Medical University; Humanity and Health Medical Group; Medistra Hospital; Sir Salimullah Medical College, Mitford Hospital; Christian Medical College; Tongji Hospital; SGPGI; Bombay Hospital & Medical Research Center; ILBS; Yong Loo Lin School of Medicine; PGIMER; VGM Hospital; Aga Khan University; Asian Institute of Gastroenterology Hyderabad; KEM Hospital and Seth GS Medical College; Chulalongkorn University; Beijing You'an Hospital; Ankara University School of Medicine; Nork Clinical Hospital of Infectious Disease; IMS &SUM Hospital; Global Hospital; University of Santo Tomas; 302 Military Hospital Beijing

Background: Acute on chronic liver failure is a rapidly progressive liver failure and is associated with a significant rate of mortality within 28 days. A simple and dynamic prognostic model is needed for early prognostication and listing for liver transplantation. This study was undertaken to validate a previously derived AARC score based on a prospective cohort of 1402 ACLF patients and to compare the AARC score with existing models in the new cohort.

Methods: 1494 ACLF patients were enrolled across 30 centers from Oct 2012 to Jan 2017 in Asia Pacific into APASL ACLF research consortium (AARC) for analysis. The AARC score [range 5-15] is based on five independent predictors of 28 days mortality; total bilirubin, creatinine, serum lactate, INR and hepatic encephalopathy [table1]. We validated AARC score on this cohort and compared it with existing prognostic models using AUROC.

Results: Of the 1494 enrolled patients, the 28-day survival was 71%. The AUROC of AARC score in this validation cohort was 0.77 with 75% sensitivity, 65% specificity, 45.4% PPV and 88.4% NPV respectively. The validated AARC score was comparable (p=0.086) with previous cohort (N=1402) of derived AARC score. It was found that AUROC of the validated AARC score (0.77) was significantly (p<0.001) higher than other CTP, MELD, SOFA, CLIF SOFA, APACHEE score with AUROC 0.64,0.71, 0.72, 0.72, 0.74 in predicting 28-day mortality. The new validated AARC score was categorized into grade [I:5-7, II: 8-10, III:11-15 points] having a cumulative mortality of 7.2%, 22.3% and 60.9% respectively [Fig 2]. A score of 9 was seen consistently same in the first week among survivors, where as a score of >10 was observed same in one week and increased exponentially at day15 among non survivors (p=0.001, GEE model) [fig1]
Table 1: Predictors of mortality at 28 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
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<tr>
<td></td>
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<td>HR</td>
<td>95CI</td>
<td>P</td>
<td>HR</td>
<td>95CI</td>
</tr>
<tr>
<td>Hb (gm/dl)</td>
<td></td>
<td>1.02</td>
<td>1.00-1.21</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WBCs Count</td>
<td></td>
<td>1.94</td>
<td>1.74-2.16</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT-INR</td>
<td></td>
<td>3.92</td>
<td>3.37-4.55</td>
<td>&lt;0.001</td>
<td>1.90</td>
<td>1.60-2.25</td>
</tr>
<tr>
<td>Urea (mg/ml)</td>
<td></td>
<td>1.70</td>
<td>1.58-1.84</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S Creatinine (mg/ml)</td>
<td></td>
<td>2.37</td>
<td>2.16-2.60</td>
<td>&lt;0.001</td>
<td>1.88</td>
<td>1.69-2.09</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl)</td>
<td></td>
<td>1.78</td>
<td>1.58-2.00</td>
<td>&lt;0.001</td>
<td>1.65</td>
<td>1.45-1.88</td>
</tr>
<tr>
<td>Lactate (mmol/ml)</td>
<td></td>
<td>2.52</td>
<td>2.28-2.78</td>
<td>&lt;0.001</td>
<td>2.09</td>
<td>1.85-2.35</td>
</tr>
<tr>
<td>Hepatic Encephalopathy (present/absent)</td>
<td>3.35</td>
<td>2.91-3.87</td>
<td>&lt;0.001</td>
<td>2.27</td>
<td>1.95-2.65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Validated AARC score vs
CLIF SOFA
0.77 (0.71-0.80) vs
0.72 (0.67-0.77),
p < 0.001

Validated AARC score vs
SOFA
0.76 (0.71-0.80) vs
0.70 (0.65-0.75),
p < 0.001
Estimated Marginal Means of MEASURE_1 Outcome 28

Survivor
Non Survivor

Day 0 Day 4 Day 7 Day 15

Baseline Grade
Baseline and day 4 grade

Grade I Grade II Grade III

Flg1 D 'tlamldt' orvalida'te1JAARCscor e au11Gr1le
**Conclusion:** AARC score is useful scoring systems to provide information on short term mortality in ACLF patients according to APASL definition. Moreover, it is superior to the existing prediction models and also predicts the need for intervention.

**Disclosure:** Nothing to disclose.
THE CASE FOR EARLY ADVANCED CARE PLANNING IN CIRRHOSIS: A QUALITY IMPROVEMENT PROJECT

Authors: P. Tandon¹; A. Brisebois¹; A. Sprange¹; E. Hjartarson¹

Institution(s): University of Alberta¹

Background: Cirrhosis is a chronic progressive disease. As the disease advances, its course is marked by frequent and often unpredictable acute events and organ failures (acute on chronic liver failure) that substantially increase morbidity and mortality. Liver transplantation, the only definitive treatment option, is available to less than 10% of patients, of which an estimated 20-30% will die prior to transplant. Despite this poor prognosis, Advance Care Planning (ACP) discussions (a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals and preferences regarding future medical care) are a rare occurrence. ACP rates in cirrhosis in Canada and the US have been reported in the range of 18-26%, even in the sickest patients. In other chronic disease populations, the early integration of ACP has been beneficial - leading to reduced hospitalizations, reduced use of life-sustaining treatments and improved quality of life. A barrier to having these discussions is a lack of clarity as to whether patients are interested in engaging in ACP in a stable outpatient setting, prior to the cycle of acute deterioration and repeated hospitalizations. In a stable outpatient cirrhosis population, the objectives of this study were to assess rates of ACP and patient preferences for engaging in ACP discussions.

Methods: We conducted a prospective analysis of consecutive consenting patients attending two urban tertiary cirrhosis clinics. The definition of ACP was provided, and patients completed a survey regarding demographics, understanding of their disease, and experience, knowledge, and preferences regarding ACP discussions. Descriptive statistics were utilized.

Results: The survey response rate was 71.6% (101/141). The average age was 61.8 years and 56.4% were male. The mean MELD score was 11.5 ± 5.3 and the mean CP score was 6.2 ± 1.5 with 71.3% of patients categorized as CP Class A. Only 53% percent of patients felt that cirrhosis would affect their quality of life at some point in the illness. Only 17.8% had participated in an ACP discussion. Eighty-five percent preferred having an ACP discussion in a stable outpatient clinic setting as opposed to during hospitalization. Ninety-seven percent stated it was important to know the truth about their health status and prognosis. Almost universally, patients expressed that it was important the practitioner carrying out the ACP was someone they trusted, took the time to understand who they were as a person and understood their medical issues.

Conclusion: The surveys were completed in an outpatient cirrhosis population with relatively low disease severity scores. Despite this, similar to research among other non-malignant,
chronic diseases, the majority of cirrhosis patients had not heard of ACP, but almost uniformly indicated that they would like to know the truth about their clinical condition and how it would affect their quality of life in the future. Importantly, 85% wanted to have these discussions in a stable outpatient setting. Recognizing the path of acute and often unpredictable deteriorations that our patients with cirrhosis face, this research emphasizes the importance of developing cirrhosis specific decision aids to assist clinicians and patients in engaging in early ACP discussions.

**Disclosure:** Nothing to disclose.
IMPACT OF BACTERIAL INFECTIONS AND ACUTE KIDNEY INJURY ON THE INCIDENCE AND OUTCOME OF ACLF

Authors: C. Yaghi¹; N. Chalhoub¹; A. Aidibi¹; R. Sayegh¹; J. Bou Jaoude¹; R. Slim¹; K. Honein¹

Institution(s): Hotel-Dieu de France University Hospital¹

Background: The CANONIC study in 2013 defined acute-on-chronic Liver Failure (ACLF) as a different entity from the acute decompensation of cirrhosis taking into account extrahepatic failures. It was present in 22.3% of people hospitalized for complications of cirrhosis and altered their prognosis. Subsequently, a scoring system for grading patients according to their severity was proposed. Previous reports stated that the bacterial resistance profile could be a risk factor for ACLF occurrence. Our aim was to assess the impact of bacterial infections and acute kidney injury on the incidence and outcome of ACLF.

Methods: Patients admitted for decompensation of cirrhosis from June 2014 to March 2017 were included. We excluded patients with impending severe prognosis comorbidities, and pediatric patients. The variables studied were patient characteristics (presence of infection and culture, different CLIF-OF scores, grade and ACLF score, CLIF-AD at admission, presence of acute kidney injury (AKI) and follow-up time Patients and intra-hospital survival status at 1 month and 6 months. Statistical analysis of the results was carried out by the SPSS Statistics 23.0 program.

Results: 112 admissions were included. Mean MELD-Na score was 19.3±9.1. The Mean follow-up was 264±283 days. At admission, 45 (38.8%) were considered having a bacterial infection, 24 (20.7%) had positive cultures. Identified infections were in urinary tract in 26, hemoculture 4, ascites 20, respiratory tract 7, and skin and connective tissue in 5. Twelve resistances to antibiotics were identified in 11 patients, with ESBL, VRE, and MDR in respectively 8, 2, and 2. Other decompensations included esophageal or gastric varices bleeding in 40 (23.3%), ascitis in 24 (20.7%), and AKI in 29 patients (25%). CLIF-AD score was 51.5±6.9, and admission ACLF Score was 50.2±7.3, and day 3 ACLF Score was 57.3±13.1. The number of patients who developed ACLF were respectively 27 (24.1%), 5 (4.5%), and 3 (2%) grade1, 2, and 3. ACLF grade 2 and 3 were associated with an in-hospital, 1-month, and 6-months mortality in respectively 62.5%, 85.7%, and 100% as compared to 3.8%, 5.7%, and 16.7% in the absence of ACLF (P<0.001).In the latter, the presence of AKI was found to be the main factor associated with mortality with a respective risk of in-hospital, 1-month, and 6-months mortalities of 12.5% vs 1.6% (P=0.041), 18.8% vs 1.9% (P=0.011), and 40% vs 9.8% (P=0.006). Infection per se was not associated with an increased ACLF score. The presence of ESBL (P=0.19) or VRE (P=0.094) were not significantly associated with an increased risk of developing ACLF and the grade of ACLF was grade 1 in those who developed ACLF (P=0.037). VRE but not ESBL was associated with an increased risk of in-hospital mortality and 6-months mortality.
**Conclusion:** The prevalence of ACLF in hospitalized population was 35% and is a determining prognostic factor during hospitalization and at 6 months. Excepted for VRE that was shown to increase mortality, the presence of multidrug resistance strains or BLSE neither affected the ACLF grade nor the mortality. Acute kidney injury with or without ACLF was also a determining factor for prognosis.

**Disclosure:** Nothing to disclose.
OUTCOME OF LIVING DONOR LIVER TRANSPLANTATION FOR ACUTE ON CHRONIC LIVER FAILURE: A SINGLE-CENTER EXPERIENCE FROM INDIA

Authors: R. Mohanka¹; P. Shenoy¹; C. Kalal¹; V. Solao¹; A. Shukla¹; M. Vora¹; R. Kohli¹; P. Rao¹; S. Shah¹

Institution(s): Global Hospital Mumbai¹

Background: Acute on chronic liver failure (ACLF) is characterized by acute decompensation of chronic liver disease and is associated with organ failures and high short-term mortality risk. Liver transplant is offered for definitive treatment of ACLF patients not improving with supportive measures. Data on outcomes of living donor liver transplant (LDLT) in ACLF is scarce.

Methods: ACLF patients were classified per EASL-CLIF criteria and outcomes were compared between LDLT vs. non-transplant patients. We prospectively evaluated 20 patients with ACLF undergoing LDLT at our center from June 2015 to July 2017 and compared them to ACLF patients who did not undergo a transplant. In non-transplant group, there were 43 patients requiring 46 hospitalizations. Primary end point was survival at 3 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDLT (n = 20)</th>
<th>No Transplant (n = 43)</th>
<th>p value</th>
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<tbody>
<tr>
<td>ACLF grade</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7</td>
<td>7</td>
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</tr>
<tr>
<td>II</td>
<td>10</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: Female</td>
<td>16: 4</td>
<td>33: 10</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>47.55 ± 12.51</td>
<td>52 ± 11.1</td>
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</tr>
<tr>
<td>Etiology</td>
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</tr>
<tr>
<td>Alcoholic</td>
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<td>20</td>
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<tr>
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<td>4</td>
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</tr>
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<td>HCV</td>
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</tr>
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<td>NASH</td>
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<td>9</td>
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<tr>
<td>AIH</td>
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<td>3</td>
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</tr>
<tr>
<td>Wilsons</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>0</td>
<td>3</td>
<td></td>
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<tr>
<td>MELD score</td>
<td>35.15 ± 4.6</td>
<td>32.7 ± 6.8</td>
<td>0.14</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17.8 ± 4.9</td>
<td>21.1 ± 8.1</td>
<td>0.11</td>
</tr>
<tr>
<td>CLIF-SOFA</td>
<td>11.5 ± 2.6</td>
<td>11.9 ± 3.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Time to LDLT</td>
<td>15 (3-64) d</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ICU stay</td>
<td>16 (4-38) d</td>
<td>7 (2-20)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>25 (10-67) d</td>
<td>10 (3-54)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>3 month survival</td>
<td>14 (70%)</td>
<td>5 (11.6%)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Conclusion: Timely LDLT for ACLF patients offers favorable outcomes. Large multi-centre studies are needed to determine optimal timing and suitability for transplant.
The two groups were comparable with demographics, disease severity scores and etiology. The ICU and hospital stay were significantly higher in the transplanted patients. The 3 month survival was significantly better in the transplant group.

**Disclosure:** Nothing to disclose.
DOES SERUM CREATININE AND EGFR AT LISTING PREDICT ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) ON THE LIVER TRANSPLANT WAITING LIST?

Authors: E. Neong2; Z. Galvin2; N. Selzner2; F. Wong1

Institution(s): University Health Network, Department of Hepatology1, Toronto; University Health Network, Multi-organ Transplant2

Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of underlying chronic liver disease associated with organ failures and high-mortality rates. NACSELD-ACLF (North American Consortium for Study of End-Stage Liver Diseasess acute-on-chronic liver failure) is defined by > 2 extra-hepatic organ failures.

Methods: Aim To establish whether serum creatinine (sCr) and estimated glomerular filtration rate (eGFR) at listing predict the development of ACLF in patients on the liver transplant waiting list.

Methods
Single-centre retrospective study of consecutive adults receiving single organ liver transplant between 1 January 2011 and 31 December 2014. Patients who were transplanted for fulminant liver failure, hepatocellular carcinoma, hepatopulmonary syndrome, metabolic diseases, polycystic disease, re-transplants and all patients who had evidence of intrinsic kidney disease were excluded. Data was retrieved from a prospectively collected liver transplant (LT) database, which included demographics, laboratory tests, co-morbidities, medications, hospital admissions and pre-and post-transplant course. Organ failures were defined as: cerebral failure=West Haven Grade III or IV hepatic encephalopathy, respiratory failure=intubation, renal failure=renal replacement therapy and circulatory failure=inotropic support. Patients were assessed for development of ACLF during their last hospital admission prior to their transplant. Any variables found to be significant on univariate analysis were included in a multivariate logistic regression model.

Results: 316 (ACLF+ 37, ACLF- 279) patients out of 642 (48.9%) who had liver transplantation during the study period were included. Of these, 37 (11.7%) patients had evidence of ACLF on their last admission in the 18 months prior to liver transplantation. Median number of organ involvement in the ACLF group was 2 (2-3). Patients who had ACLF had significantly higher listing and transplant MELD scores with shorter waiting time to their transplant (Table 1). Serum creatinine and eGFR on date of listing were significantly different in the ACLF versus non-ACLF group (Table 1). Using logistic regression, sCr and bilirubin on date of listing remained significant for predicting development of ACLF (p=0.005 and p=0.005).
Table 1. Demographic and biochemical characteristics of ACLF and non-ACLF liver transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>*ACLF+ (n=37)</th>
<th>*ACLF- (n=279)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 (43-65)</td>
<td>56 (47-63)</td>
<td>0.872</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>26 (70.3%)</td>
<td>187 (67%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
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<td>0.151</td>
</tr>
<tr>
<td>Age at listing</td>
<td>57 (46-63)</td>
<td>54 (46-60)</td>
<td>0.142</td>
</tr>
<tr>
<td>Age at transplant</td>
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<td>0.207</td>
</tr>
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<td>27 (19-39)</td>
<td>18 (15-23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Transplant MELD</td>
<td>31 (24-37)</td>
<td>20 (15-26)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Days from listing to transplant</td>
<td>12 (5-74)</td>
<td>87 (26-234)</td>
<td>0.0001</td>
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<tr>
<td><strong>Aetiology [n (%)]</strong></td>
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<tr>
<td>Other</td>
<td>2 (5.4)</td>
<td>21 (7.6)</td>
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<tr>
<td><strong>Laboratory parameters at time of listing</strong></td>
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</tr>
<tr>
<td>Creatinine</td>
<td>141 (76-408)</td>
<td>78(64-110)</td>
<td>0.00006</td>
</tr>
<tr>
<td>eGFR</td>
<td>40(15-87)</td>
<td>85(56-105)</td>
<td>0.00001</td>
</tr>
<tr>
<td>INR</td>
<td>1.7(1.4-2.7)</td>
<td>1.6(1.3-1.9)</td>
<td>0.132</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>148(51-533)</td>
<td>64(38-132)</td>
<td>0.00038</td>
</tr>
<tr>
<td>Albumin</td>
<td>28(24-37)</td>
<td>28(24-32)</td>
<td>0.259</td>
</tr>
<tr>
<td>Sodium</td>
<td>135(131-139)</td>
<td>135(131-137)</td>
<td>0.538</td>
</tr>
<tr>
<td>White cell count</td>
<td>5.9(3.2-7.7)</td>
<td>5.1(3.2-7.0)</td>
<td>0.220</td>
</tr>
<tr>
<td>Platelet</td>
<td>65(39-88)</td>
<td>82(50-126)</td>
<td>0.025</td>
</tr>
<tr>
<td>AST</td>
<td>74(36-111)</td>
<td>56(37-94)</td>
<td>0.387</td>
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<tr>
<td>ALT</td>
<td>34(17-70)</td>
<td>35(20-60)</td>
<td>0.957</td>
</tr>
<tr>
<td>ALP</td>
<td>176(126-251)</td>
<td>216(141-387)</td>
<td>0.148</td>
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</table>
Conclusion: Almost 12% of patients on the LT waiting list developed ACLF in the 18 months prior to transplant. sCr, eGFR and bilirubin at time of listing were significantly different in the ACLF group compared with those who did not develop ACLF. Clinically this is useful because it enables us to identify high risk patients on the LT waiting list.

Disclosure: Nothing to disclose.
FRACTIONAL EXCRETION OF UREA PREDICTS THE DEVELOPMENT OF ACUTE ON CHRONIC LIVER FAILURE IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ACUTE KIDNEY INJURY

Authors: K. Patidar¹; L. Kang¹; A. Sanyal¹; D. Carl¹; J. Bajaj¹

Institution(s): Virginia Commonwealth University¹

Background: Acute kidney injury (AKI) is the most frequent organ failure in acute on chronic liver failure (ACLF). In this setting, factors such as infection/marked systemic inflammation precipitate renal hypoperfusion which is a central mechanism for AKI development and its phenotypes [prerenal (PR), hepatorenal syndrome (HRS), and acute tubular necrosis (ATN)]. Thus, detecting substantial decreases in renal perfusion could translate to identifying those at risk for developing ACLF. Fractional excretion of urea \( \text{FeUrea} = \frac{\text{Serum Creatinine x Urine Urea}}{\text{Serum Urea x Urine Creatinine}} \) % is dependent on renal perfusion and therefore could be applied to predict those at risk for developing ACLF and its related outcomes.

AIM
Evaluate the diagnostic ability of FeUrea in predicting ACLF, the need for hemodialysis (HD), and 30-day mortality in decompensated cirrhotic patients who were admitted for AKI.

Methods: FeUrea was calculated using admission values. AKI phenotypes were clinically determined by an expert nephrologist/hepatologist. AKI and HRS was defined per ICA criteria. PR/ATN was defined per KDIGO guidelines. ACLF was defined using NACSELD criteria. A multi-variable analysis including variables that were significant on univariate analysis was created for prediction of the aforementioned outcomes.

Results: 100 patients [57yrs, 65% male, 34% HCV and 31% ETOH in etiology, MELD-Na 28, CTP 11] were included.

AKI details: AKI phenotypes were determined as follows: 42 PR, 33 HRS, and 25 ATN. Identifiable causes for AKI were infection (40%) and diuretic use (30%); 20% were unidentified. Median FeUrea was statistically different across all phenotypes of AKI (30.1 PR vs. 20.2 HRS vs. 43.6 ATN, \( p<0.001 \)).

ACLF details: 40 patients developed ACLF. Median FeUrea was statistically lower in those with ACLF (20.9 vs. 30.8, \( p=0.004 \)). HRS was the most common phenotype of AKI associated with ACLF (HRS=30, ATN=9, PR=1, \( p<=0.001 \)). Thirty seven patients had a need for HD (\( p<=0.001 \)) and 25 were dead at 30-days (\( p<=0.001 \)).

Outcomes prediction: FeUrea, white blood cell count, stage of AKI, age, and CTP score were found to be independent predictors on univariate analysis for each outcome. After adjusting for independent variables on multivariate analysis, FeUrea was found to be an excellent predictor.
for all outcomes: ACLF [AUC 0.86 (95% CI 0.79, 0.95)], need of HD [AUC 0.87 (95% CI 0.79, 0.94)], and 30-day mortality [AUC 0.82 (95% CI 0.73, 0.91)].

**Conclusion:** FeUrea, a marker of renal perfusion, can differentiate between phenotypes of AKI, and independently predict ACLF, need for HD, and 30-day mortality in decompensated cirrhotic patients admitted with AKI.

**Disclosure:** Nothing to disclose.
ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) ON THE LIVER TRANSPLANT WAITING LIST: EFFECT ON PATIENT AND RENAL OUTCOME

Authors: S. Neong¹; Z. Galvin¹; F. Wong¹

Institution(s): Toronto General Hospital¹

Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterised by acute decompensation in cirrhotics, associated with organ failures and high short-term mortality rates. NACSELD-ACLF (North American Consortium for Study of End-Stage Liver Diseases acute-on-chronic liver failure) is defined by ≥2 extra-hepatic organ failures.

Methods: Single-centre retrospective study of consecutive adults receiving single organ liver transplant between 1 January 2011 and 31 December 2014. Patients who were transplanted for fulminant liver failure, hepatocellular carcinoma, hepatopulmonary syndrome, metabolic diseases, polycystic disease, re-transplants and all patients who had evidence of intrinsic kidney disease were excluded. Data was retrieved from a prospectively collected liver transplant (LT) database, which included demographics, laboratory tests, co-morbidities, medications, hospital admissions and pre-and post-transplant course. Organ failures were defined as: cerebral failure=West Haven Grade III or IV hepatic encephalopathy, respiratory failure=intubation, renal failure=renal replacement therapy and circulatory failure=inotropic support. Patients were assessed for development of ACLF during their last hospital admission prior to their transplant. Patients were followed-up for 24-month post-transplantation.

Results: 316 (ACLF+ 37, ACLF- 279) patients out of 642 (48.9%) who had liver transplantation during the study period were included. Of these, 37 (11.7%) patients had evidence of ACLF on their last admission in the 18 months prior to liver transplantation. Median number of organ involvement in the ACLF group was 2 (2-3). Both groups have similar baseline demographics. Patients who had ACLF had significantly higher listing serum creatinine (sCr), bilirubin and MELD scores and lower eGFRs (Table 1). Almost one third of the ACLF group required RRT post-transplant and this was significantly different to the non-ACLF group (p=0.002). The 3 and 12 month post-LT sCr and eGFRs were significantly different between the two groups. The 3,6,12 and 24 month survival was better in the non-ACLF group.
Table 1. Demographic and biochemical characteristics of ACLF and non-ACLF liver transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>ACLF+ (n=37)</th>
<th>ACLF- (n=279)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56 (43-65)</td>
<td>56 (47-63)</td>
<td>0.872</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>26 (70.3%)</td>
<td>187 (67%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>28.3 (25.5-31.2)</td>
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<td>0.132</td>
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<td>Bilirubin</td>
<td>148 (51-533)</td>
<td>64 (38-132)</td>
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</tr>
</tbody>
</table>

ACLF=acute-on-chronic liver failure; BMI=body mass index; MELD=model for end-stage liver disease; NASH=non-alcoholic steatohepatitis; PBC=primary biliary cholangitis; PSC=primary sclerosing cholangitis; AIH=autoimmune hepatitis; eGFR=estimated glomerular filtration rate; INR=international normalised ratio; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase

Table 2. Patient and renal outcomes on the liver transplant waiting list

<table>
<thead>
<tr>
<th></th>
<th>ACLF+ (n=37)</th>
<th>ACLF- (n=279)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant RRT [n(%)]</td>
<td>10 (27%)</td>
<td>7 (3%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Post-transplant sCr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month</td>
<td>101 (79-138)</td>
<td>90 (71-110)</td>
<td>0.050</td>
</tr>
<tr>
<td>6-month</td>
<td>102 (88-136)</td>
<td>94 (78-117)</td>
<td>0.066</td>
</tr>
<tr>
<td>12-month</td>
<td>111 (88-136)</td>
<td>95 (81-115)</td>
<td>0.043</td>
</tr>
<tr>
<td>Post-transplant eGFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month</td>
<td>64 (41-75)</td>
<td>71 (54-87)</td>
<td>0.055</td>
</tr>
<tr>
<td>6-month</td>
<td>64 (46-74)</td>
<td>66 (51-84)</td>
<td>0.112</td>
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<tr>
<td>12-month</td>
<td>43 (15-61)</td>
<td>60 (40-79)</td>
<td>0.002</td>
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<tr>
<td>Survival</td>
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<td></td>
<td>Log Rank</td>
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<td>3-month</td>
<td>84%</td>
<td>95%</td>
<td>0.0001</td>
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<tr>
<td>6-month</td>
<td>76%</td>
<td>94%</td>
<td>0.0001</td>
</tr>
<tr>
<td>12-month</td>
<td>73%</td>
<td>92%</td>
<td>0.0001</td>
</tr>
<tr>
<td>24-month</td>
<td>73%</td>
<td>91%</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

*Median (Interquartile range); ACLF=acute-on-chronic liver failure; RRT=renal replacement therapy; sCr=serum creatinine; eGFR=estimated glomerular filtration rate
**Conclusion:** Almost 12% of patients on the LT waiting list developed ACLF in the 18 months prior to transplant. Patients with ACLF had significantly worse renal outcomes and overall survival when compared with those with no ACLF.

**Disclosure:** Nothing to disclose.
INDOCYANINE GREEN DYE ELIMINATION TEST: EARLY DIAGNOSTIC MARKER TO IDENTIFY THE SUBSET “ACUTE ON CHRONIC LIVER FAILURE”

Authors: N. Gupta²; S. Sarin¹

Institution(s): Institute of Liver and Biliary Sciences¹; Saint Peters University Hospital/Rutgers University²

Background: Acute on Chronic liver failure (ACLF) as defined by a working group on behalf of the World Gastroenterology Organization is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterised by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of INR) and one or more extra hepatic organ failures that is associated with increase mortality within a period of 28 days and up to 3 months from outset.

Pathophysiology of ACLF using PIRO system included predisposition (underlying liver disease), insult (precipitating event), response to injury, and organ failure. At present, there is dearth of a marker that identifies the final common pathway from response to injury to organ failure, which defines the subset ACLF in population of chronic liver disease, compensated cirrhosis and decompensated cirrhosis, as 28- day mortality rate of this subset is greater than 15%.

We hereby exploited the database from a tertiary care hospital to evaluate a diagnostic marker indocyanine green dye elimination test to identify this subset of population (ACLF) prior to extra hepatic organ failure

Methods: 40 patients over age of 18 years were taken. 20 patients diagnosed with cirrhosis on liver biopsy (grade 4) with jaundice, 20 patients with cirrhosis with ascites were included in the study and 40 healthy control with BMI of 21-26 and indocyanine green elimination test was conducted in these patients. Indocyanine green dye (aurogreen) at 0.5mg/kg was injected IV in the left cubital fossa in 80 of the subjects and sample of blood were drawn from right cubital fossa at 0min, 2 min, 4 min, 6 min and 8 min and indocyanine measurement was done in beckman spectrophotometer at 824 nm and percentage of dye left in the blood was calculated. All the patients were followed for one month for signs of liver failure (bilirubin more than 5mg% and INR >1.5) and/or encephalopathy (grade 3 or 4) by West haven criteria and/or acute kidney injury.

Results: In all healthy controls dye concentration in blood at 4 min was 0%. 28 patients out of 40 had less than 10% dye concentration at 8 min and on follow upon 1 patient developed signs of liver failure and/or encephalopathy and/or acute kidney injury within 30 days. 12 patients out of 40 had more than 80% dye concentration at 8 min and on follow up 10 patients of 12 developed signs of liver failure and/or encephalopathy and/or acute kidney injury.

Conclusion: Indocyanine green elimination test can identify the onset of liver failure and thus can be used as a surrogate to identify subset of cases which are prone to develop Acute on
chronic liver failure or as a marker for early onset Acute on chronic liver failure, thereby can be subjected to adequate support and a higher level of care in the hospital setting decreasing the mortality of this subset of patients.

**Disclosure:** Nothing to disclose.
PLASMA S100A8/A9 IS A NOVEL MECHANISTIC BIOMARKER IN INNATE IMMUNE ACTIVATION AND ORGAN DYSFUNCTION IN ACUTE-ON-CHRONIC LIVER FAILURE

Authors: A. Singanayagam¹; R. Nathwani¹; E. Triantafyllou¹; V. Patel²; F. Lebosse¹; A. Dhar¹; W. Khamri¹; G. Auzinger²; C. Bernsmeier²; M. McPhail²; J. Wendon²; C. Antoniades¹

Institution(s): Imperial College London¹; King's College London²

Background: Acute-on-chronic liver failure (ACLF) is driven by systemic inflammation but lacks a reliable diagnostic or prognostic biomarker. Circulating S100A8/A9 heterodimer (calprotectin) is secreted by activated neutrophils and monocytes under proinflammatory conditions, though its effect on immune cells remains incompletely understood. This study aims to determine the performance of plasma S100A8/A9 as a biomarker in ACLF and its effect on monocyte immunophenotype.

Methods: Plasma S100A8/A9 concentrations of 84 patients at admission to King's College Hospital from 2013-17 were analysed using an S100A8/A9 ELISA in ACLF (n=58), cirrhosis without organ failure (n=25) and healthy control (n=30) groups. A multiarray cytokine immunoassay was also performed across both patient groups (n=38). Clinical and laboratory data were collected (table 1). The phenotype (CD16, HLA-DR, Mer tyrosine kinase [MerTK], CD163 and CD206) of healthy monocytes exposed to recombinant S100A8/A9 in vitro for 24 hours at 0, 1000 and 2500 ng/ml was assessed using flow cytometry (n=6).

Results: Plasma S100A8/A9 concentration at admission was significantly higher in ACLF (median: 2049 ng/ml, range 272-8914) compared with cirrhotics without organ failure (median: 914.6 ng/ml [155-3621]) and healthy control (median: 963 ng/ml [113-2812], p=0.0003 Kruskal Wallis) (figure 1). In patients, S100A8/A9 levels were higher in those with systemic inflammatory response syndrome (SIRS) and non-survivors (figure 1) and positively correlated with clinical, laboratory or cytokine parameters, including interleukin-1 beta and transforming growth factor-beta (figure 2). The area under the receiver operator curve (AUROC) for S100A8/A9 to detect the presence of ACLF was 0.719 (95% CI 0.607-0.832, p=0.01). In ACLF, for 90-day mortality, AUROC for S100A8/A9 was 0.695 (0.552-0.839, p=0.017) but highest for the CLIF-ACLF score at 0.787 (0.660-0.914, p<0.001) (figure 3). S100A8/A9 >1633 ng/ml (sensitivity 0.70 specificity 0.64) was associated with increased risk of death on Kaplan-Meier transplant-free survival analysis (p=0.004, figure 4). In flow cytometric analysis, DRhigh MerTKlow monocytes (%) significantly increased (p=0.01, Friedman’s ANOVA & Dunn’s test) as S100A8/A9 concentration increased from 1000 to 2500 ng/ml (figure 5) with a trend to reduction in CD206 (p=0.13).
Figure 1: (A) Plasma S100A8/A9 (calprotectin) concentration (ng/ml) in healthy control, cirrhosis without organ failure and acute-on-chronic liver failure (ACLF); p<0.003, Kruskal-Wallis (n=84); p<0.01 after Dunn’s Correction. (B) S100A8/A9 plasma concentrations are higher in non-survivors vs. transplant-free survivors at 90 days (p<0.01, Mann-Whitney U). (C) S100A8/A9 plasma concentrations are higher in patients with systemic inflammatory response syndrome (SIRS, n=27) vs. those without (n=49, p<0.05, Mann-Whitney U).

Figure 2: Correlation matrix (Spearman’s correlation) with hierarchical clustering for physiological, laboratory and plasma proteins and cytokines in the patient population. Of note, plasma S100A8/A9 (calprotectin) positively correlates with WCC (r=0.538, p<0.01), neutrophils (r=0.578, p<0.01), IL-1β (r=0.572, p<0.01), IL-10 (r=0.32, p=0.05) and TGF-β (r=0.596, p<0.01) and negatively correlates with MAP (r=-0.432, p<0.01).

Figure 3: ROC Analysis for 90-day transplant-free mortality in ACLF. AUC Calprotectin 0.695 (95% CI 0.552-0.839, p=0.017), AUC CLIF-ACLF 0.787 (0.656-0.914, p=0.01), AUC CLIF SOFA 0.725 (0.581-0.869, p=0.006) AUC MELD score 0.777 (0.641-0.912, p=0.001).

Figure 4: Kaplan-Meier survival curve for 90-day transplant-free survival in all patients where plasma S100A8/A9 concentration was below and above optimal cutoff of 1633 ng/ml (p=0.004).
Figure 5: Changes to immunophenotype (DR/MerTK/CD163/CD206) on CD14+ selected healthy monocytes (n=6) over 24 hours of exposure to 0, 1000 ng/ml (median concentration for healthy control) and 2500 ng/ml (median for ACLF) of recombinant S100A8/A9 (calprotectin) in vitro. The higher concentration invokes an activated pro-inflammatory phenotype with significant increase in DR+/MerTK+ % (p=0.01; Friedman's ANOVA and after Dunn's correction), and non-significant reduction in CD206 (p=0.13) and CD163 (p=0.93). No significant changes were seen with CX3CR1 or CCR7 (data not shown).

Table 1: Admission Data for All Included Patients and Transplant-free Survivors Versus Non-Survivors at 90 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=76)</th>
<th>Survivors (n=44)</th>
<th>Non-survivors (n=32)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>51 (16)</td>
<td>51 (20)</td>
<td>52 (13)</td>
<td>0.819f</td>
</tr>
<tr>
<td>Gender, male: female</td>
<td>45:31</td>
<td>27:17</td>
<td>18:14</td>
<td>0.654f</td>
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<tr>
<td>Etiology</td>
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<td>Alcohol</td>
<td>49</td>
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<td>NAFLD</td>
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<td>Reason for Admission</td>
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<td>Septis</td>
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<tr>
<td>Gastrointestinal bleeding</td>
<td>16</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Other / Unknown</td>
<td>16</td>
<td>9</td>
<td>7</td>
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<tr>
<td>Day 1 Variables</td>
<td></td>
<td></td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>75 (62-113)</td>
<td>78 (63-113)</td>
<td>72 (62-109)</td>
<td>0.051</td>
</tr>
<tr>
<td>Vasoressin, yes/no</td>
<td>34.41</td>
<td>13.30</td>
<td>21.11</td>
<td>0.007f</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84 (18)</td>
<td>80 (17)</td>
<td>85 (19)</td>
<td>0.139f</td>
</tr>
<tr>
<td>CVVHDF, yes/no</td>
<td>35.41</td>
<td>12.32</td>
<td>23.3</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>Mechanical ventilation, yes/no</td>
<td>34.42</td>
<td>14.30</td>
<td>20.12</td>
<td>0.008f</td>
</tr>
<tr>
<td>Pco2 %</td>
<td>30 (21-46)</td>
<td>21 (21-46)</td>
<td>38 (21-50)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>PaO2, kPa</td>
<td>11.9 (7.42-22.0)</td>
<td>11.9 (7.42-18.1)</td>
<td>11.3 (7.62-22.0)</td>
<td>0.279f</td>
</tr>
<tr>
<td>PaO2/Fio2, kPa</td>
<td>35.1 (10-86)</td>
<td>41 (14-86)</td>
<td>32 (13-63)</td>
<td>0.021f</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.5 (9.9)</td>
<td>36.7 (8.8)</td>
<td>36.3 (13.3)</td>
<td></td>
</tr>
<tr>
<td>White cell count, x10⁹/L</td>
<td>9.7 (1.3-31.63)</td>
<td>7.43 (1.3-31.6)</td>
<td>12.6 (1.6-29.7)</td>
<td>0.004f</td>
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<tr>
<td>Neutrophil/Lymphocyte ratio</td>
<td>7.39 (1.4-47.3)</td>
<td>4.79 (1.4-41.8)</td>
<td>13.11 (3.5-67.3)</td>
<td>&lt;0.001f</td>
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<tr>
<td>Platelet count, x10⁹/L</td>
<td>86 (7-298)</td>
<td>84 (7-298)</td>
<td>86 (18-263)</td>
<td>0.893f</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>115 (11-699)</td>
<td>69 (11-489)</td>
<td>222 (23-609)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>2.2 (0.70-11.6)</td>
<td>1.45 (0.74-7.7)</td>
<td>2.55 (0.7-11.8)</td>
<td>0.001f</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 (7.19-7.56)</td>
<td>7.44 (7.19-7.56)</td>
<td>7.39 (7.19-7.51)</td>
<td>0.022f</td>
</tr>
<tr>
<td>INR</td>
<td>1.92 (1.01-7.34)</td>
<td>1.69 (1.01-3.10)</td>
<td>2.20 (1.25-7.34)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>113 (20-427)</td>
<td>75 (20-426)</td>
<td>165 (57-427)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>137 (5)</td>
<td>137 (4)</td>
<td>137 (8)</td>
<td>0.761f</td>
</tr>
<tr>
<td>Albunum, g/dL</td>
<td>27 (10)</td>
<td>27 (11)</td>
<td>28 (9)</td>
<td>0.181f</td>
</tr>
<tr>
<td>C-Reactive Protein, CRP</td>
<td>46.6 (2.0-247.7)</td>
<td>35.8 (2.0-247.7)</td>
<td>50.1 (2.1-191.7)</td>
<td>0.195f</td>
</tr>
<tr>
<td>MELD</td>
<td>29 (7-52)</td>
<td>20 (7-44)</td>
<td>39 (12-52)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>CLIF-SOFA</td>
<td>12 (6-18)</td>
<td>10 (6-18)</td>
<td>16 (9-18)</td>
<td>&lt;0.001f</td>
</tr>
<tr>
<td>S100A8/A9, ng/ml</td>
<td>1502 (192-8721)</td>
<td>1170 (192-4696)</td>
<td>2465 (361-8914)</td>
<td>0.003f</td>
</tr>
</tbody>
</table>

NOTE: Values listed as median (range or interquartile range)
Patients transplanted within 90 days (n=8) excluded from analysis
* Student t-test
** Chi-square test
*** Mann-Whitney U test
Conclusion: Plasma S100A8/A9 is significantly elevated in ACLF and is associated with SIRS and increased 90-day mortality, showing promise as a diagnostic and prognostic biomarker. Our novel findings of a significant increase in a pro-inflammatory DRhigh MerTKlow monocyte phenotype with pathological S100A8/A9 concentrations in vitro, reflecting innate immune activation, in addition to correlation with both pro- (e.g. IL-1β) and anti-inflammatory (e.g. TGFβ and IL-10) cytokines, provides the basis for further work focusing on its mechanism of action on myeloid cells in ACLF.

References

Disclosure: Nothing to disclose.
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<td>Oscar Santos</td>
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<td>Christopher Siegel, MD, PhD</td>
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<tr>
<td>Kelly Siegel</td>
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