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Acute-on-Chronic Liver Failure

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Abstract

For years, the natural history of patients with cirrhosis has been described as a period of stable compensated liver disease followed by a tumultuous progression in decompensated liver disease towards eventual liver transplantation or death. During this progression, the Model for End-Stage Liver Disease (MELD) has been the single best predictor of outcome. However over the last two decades, the concept of acute-on-chronic liver failure (ACLF) has been proposed as an alternate path in the natural history of cirrhosis. Unlike acute liver failure (ALF) that occurs in patients without underlying liver disease, ACLF occurs in patients with chronic liver disease and is characterized by a precipitating event (identified or surreptitious) often resulting in acute deterioration in liver function, multi-organ system failure, and high short-term mortality. The purpose of this review is to demonstrate the differing ways ACLF is characterized and define the natural course of patients with ACLF especially as it relates to management of cirrhotic patients on the transplant waiting list and its impact on liver transplantation outcomes.

Keywords

Acute-on-Chronic Liver Failure; Acute Liver Failure; Organ Failure; Liver Transplantation

Introduction

According to the Centers for Disease Control, chronic liver disease and cirrhosis is the 12th leading cause of death in the United States, and liver disease related mortality remains unchanged over the last 3 decades despite dramatic improvements in general medical care, hepatology care, and post-liver transplant outcomes achieved during that time.[1] Chronic liver disease is not only a significant cause of morbidity and mortality, but it accounts for a substantial portion of healthcare expenditure in the United States and worldwide.[3] Therefore, to improve outcomes in patients with chronic liver disease, we must first more accurately quantite all aspects of liver dysfunction during the natural history of liver disease. Although often discussed as compensated vs. decompensated cirrhosis, quantitation of liver dysfunction was first reasonably accurately accomplished by the Child-Turcott-Pugh (CTP) score and is now accomplished in a more granular manner by the Model for End-Stage Liver Disease (MELD) score.[7, 8] However, when a cirrhotic patient experiences an acute event,

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such as an infection, their pre-event MELD does not accurately predict their mortality risk. The concept of acute-on-chronic liver disease was born because cirrhotics often experience a non-linear progression in their liver disease (Figure 1).[4–6] However, this notion has struggled to achieve universal acceptance as a uniform entity. In an effort to understand the concept, define the physiology, report the prevalence, and describe its implication peri-transplant, an understanding of its necessity is important.

Acute-on Chronic Liver Failure is Not Decompensated Cirrhosis

ACLF is a distinct entity from compensated and decompensated liver disease (presence of ascites, hepatorenal syndrome, variceal hemorrhage, hepatic encephalopathy, and/or synthetic dysfunction). In a population based study, persons with compensated cirrhosis had a 5-fold and persons with decompensated cirrhosis had a 10-fold increased risk of death compared to the general population.[12] Of note, most of the deaths among subjects with compensated cirrhosis occurred due to a transition to decompensation and resultant complications. However, unlike the simple features of ascites, encephalopathy, hepatorenal syndrome, variceal hemorrhage, and hepatic synthetic dysfunction that characterize hepatic decompensation, ACLF focuses on the acute events that transition patients from low-risk to high-risk of organ failure and death.

Physiology of Acute-on-Chronic Liver Failure

Borrowing from the sepsis literature, Jalan and colleagues parsed the pathophysiological basis of ACLF into a 4-part model: 1) predisposition, 2) injury due to precipitating event, 3) response to injury, and 4) organ failure.[4–6, 13, 14] In their model, **predisposition** refers to underlying cirrhosis and concomitant illnesses. Patients with worse liver function measured by either MELD or CTP are at greater risk to experience a precipitating event. In high MELD patients this is coupled with an impaired hepatic reserve.

Injury may be due to one of many insults (Table 1). All etiologies can cause ACLF, however there are geographic differences in prevalence: reactivation of hepatitis B and development of acute hepatitis A, D and E are important causes ACLF in Asian centers whereas acute alcoholic hepatitis and infections are more common precipitants of ACLF in western centers. Despite continent wide differences, an identifiable precipitating injury remains unknown in the majority of cases.

Since the vast majority of events that precipitate ACLF, regardless of the continent, are ischemic or infectious in nature, the **inflammatory response** plays a critical role in the outcome of ACLF. Given that about half of subjects with cirrhosis admitted have evidence of infection and a further 25% develop nosocomial infections with high inpatient mortality, infection plays an overwhelming factor in the natural history of ACLF (jalan moreau jhep). Overt bacterial infection and possibly covert bacterial translocation with subsequent systemic inflammatory response may be responsible for transition from a compensated to decompensated state.[5] The inflammatory response is important: a robust response is measured by an elevated C reactive protein (CRP) or an elevated leukocyte count and is associated with worse outcomes. It is unclear whether the inflammation is a response to the inciting event or a part of the inciting event. On the other hand, failure of the initial or more

likely subsequent response (often seen as immunologic paralysis caused by an initial infection) is also important given the association between nosocomial or second infections and a higher risk of mortality.[15]

Organ failure is the last component of ACLF; increasing numbers of organ failures (i.e. renal, cerebral, circulatory, and pulmonary) portend progressively worse outcomes in patients with underlying cirrhosis. It should be noted that the definition of ACLF, like the definition of ALF, requires liver disease and dysfunction, but is prognostically based on extrahepatic organ failures, which will now be discussed separately.

Renal

Acute renal failure in patients with cirrhosis is associated with an almost 8 fold increase risk of death.[16] This known association resulted in serum creatinine's incorporation into the MELD score.[17] The cause of renal dysfunction, in addition to the absolute serum creatinine, determines prognosis; hepatorenal syndrome and infection related renal dysfunction portend a worse prognosis than chronic renal failure.[18] However, the MELD score does not differentiate between causes of renal failure nor incorporate differences in baseline creatinine.[19] Recent data has shown that much smaller increases (≥0.3 mg/dL) in creatinine, some of which occur below the 1.0 mg/dL creatinine cutoff for MELD point allocation, have significant prognostic implications.[20, 21] The chance for recovery is partially related to the absolute change in creatinine, and unfortunately the risk for death does not completely abate even if patients experience resolution of their acute renal failure (Figure 2).[20] This has resulted in novel categorizations of renal dysfunction in patients with cirrhosis being proposed and validated beyond just hepatorenal syndrome.[20, 21, 23] These scores (Table 2) acknowledge the importance of earlier diagnosis for acute kidney injury and do not require the absence of chronic renal disease. Unlike hepatorenal syndrome, the adoption of these new scoring systems in clinical trials of novel therapeutics will facilitate earlier implementation of therapy and hopefully improve clinical outcomes.

Brain

Akin to ALF but in contrast to chronic decompensation, patients with ACLF can develop cerebral edema. The resultant increase in intracranial pressure can be reversed with liver transplantation. Brain edema may be due to the synergy between elevated ammonia and the inflammatory response that is often superimposed on an additional hepatic injury.[5] The role of rifaximin as a potential reducer of bacterial translocation with subsequent diminution of inflammation, is hypothesized to be of benefit but remains untested in persons with ACLF.[5]

Circulatory

ACLF is characterized by a “paralysis of immune response” similar to changes seen in severe sepsis.[24] Patients with ACLF usually first experience the systemic inflammatory response system (SIRS) and second the compensatory anti-inflammatory response system (CARS). Unlike SIRS, CARS down-regulates antigen presentation, causes macrophage deactivation, results in anti-inflammatory cytokine production and can result in anergy.[28–30] Therefore, once ACLF occurs, patients are at risk for second infections.[31] In fact, there is a

strong correlation between ACLF, prior history of acute decompensation, leukocyte count and risk of death (Figure 3).

The increased infectious risk is often coupled to cardiac dysfunction; there may be failure to appropriately increase the cardiac output in response to the insult. This is in contrast to chronic decompensated cirrhosis where cardiac output is appropriately increased. Inotrope support is often needed, similar to persons with acute liver failure. The appropriate inotrope is unknown; however, norepinephrine has been shown in small studies to improve renal function in patients with hepatorenal syndrome and therefore may be beneficial.[32, 33]

Pulmonary

The impact of pulmonary compromise on mortality in ACLF is highlighted by its incorporation into the CLIF-SOFA and the S-ACLF scores. Although some patients are intubated for airway protection for severe encephalopathy, several other pulmonary complications can occur. Hepatic hydrothorax can result in pulmonary compromise and, like ascites, can become infected. Transfusion-related acute lung injury (TRALI) likely occurs more often than it is diagnosed,[34] and may ignite or increase the systemic inflammation present during ACLF.

However, the vast majority of pulmonary complications that result in ACLF are related to pneumonia. Numerous factors increase this risk of aspiration including diminished airway protection from encephalopathy, increased intra-abdominal pressure from ascites, and endoscopy in the setting of gastrointestinal bleeding. In addition, bacterial colonization more commonly occurs with microaspiration or translocation because of over utilization of proton pump inhibitors.[35, 36] As a result, respiratory tract infections represent 14–48% of infections in cirrhotic patients[37]; however, they disproportionately increase a cirrhotic patient's risk of death.[31, 37] Therefore, it is appropriate that respiratory function be incorporated into models used to predict mortality.

Definitions of Acute-on Chronic Liver Failure

The most widely accepted definition of ACLF created by an American Association for the study of Liver Diseases (AASLD)/European Association for the Study of the Liver (EASL) consortium is the presence of a precipitating event (identified or surreptitious) in subjects with underlying chronic liver disease leading to acute deterioration of liver function and often ending in multi-organ dysfunction characterized by a high short-term mortality (Table 3).[4–6] However, three separate definitions are described below that are derived from multicenter efforts from the Asia-Pacific Region [Asia Pacific Association for the Study of the Liver (APASL)], Europe [European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF)] as well as North American [North American Consortium for the Study of End-Stage Liver Disease (NACSELD)] groups.

APASL

APASL, comprised of experts within the Asia Pacific region, defined ACLF as an “acute hepatic insult manifesting as jaundice (bilirubin >5mg/dL) and coagulopathy (INR >1.5)

complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease." (SArin SK, Kumar A, almeida JA Hep Int 2009) Reactivation of hepatitis B as well as super infection with hepatitis E virus were the predominant causes, and the presence of cirrhosis was not required. The authors questioned whether sepsis acted as an initial precipitating event or played a role in the progression of ACLF, and debate occurred over whether surgery and variceal bleeding should be included as potential precipitants.

EASL-CLIF

Moreau and colleagues, on behalf of EASL-CLIF, recently reported a novel scoring system for ACLF (Figure 4).[25] In their study population, 31% of patients had ACLF, the majority of whom had ACLF in the setting of alcoholic liver disease. Bacterial infections were the number one precipitating event, although no precipitant was found in 44% of cases.

The most common cause of death was multi-organ system failure. Cirrhotics with ACLF had a mortality rate of 34% versus 1.9% for patients with decompensation without ACLF. The type of organ failure (renal failure carried the highest risk) was a risk factor for mortality, and mortality rates increased as the number of organs with dysfunction increased. . ACLF was defined on the basis of occurrence of acute decompensation, organ failure, and mortality within 28 days of >15% and characterized into 3 grades (Figure 4). The 28-day mortality was 5%, 22%, 32%, and 77% for grades 0, 1, 2, and 3 respectively. Subjects with elevated leukocytes and plasma C-reactive protein did worse; infection or inflammatory response was one of the most important risk factors for poor outcomes after ACLF.[25, 38]

NACSELD

NACSELD recently examined survival in sepsis-related ACLF (S-ACLS). Overall organ failures were purposefully simply defined: circulatory failure was shock, cerebral failure was West Haven grade 3 or 4 hepatic encephalopathy, renal failure was need for dialysis, and pulmonary failure was need for mechanical ventilation. S-ACLF was defined as ≥2 organ failures, and 30-day mortality increased with the number of extra-hepatic organ failures present: 8%, 27%, 49%, 64%, and 77% for 0, 1, 2, 3 and 4 respectively (Figure 5). Independent predictors of ACLF were nosocomial infections, non-spontaneous bacterial peritonitis as the first infection, low admission bloodmean arterial pressure, and admission MELD score. In addition to the S-ACLF score, second infections, MELD, and admission WBC count were independent predictors of 30-day mortality while a higher admission serum albumin was protective.

Regional Differences in defining ACLF

Several differences exist in the definition of ACLF partly contingent on regional variation in putative etiologies of ACLF. First, a majority of subjects had reactivation of hepatitis B in the APASL group, alcohol related cirrhosis in the EASL-CLIF group and HCV in the NACSELD group. Second, definitions proposed by APASL suggest a duration of the inciting event to be <4 weeks with manifestations of ACLF being characterized by ascites and encephalopathy. However, Western centers place less emphasis on deterioration of liver

function and more emphasis on development of extra hepatic organ failure. Third, whereas APASL and NACSELD definitions rely on presenting factors (e.g. multiorgan system failure), the EASL-CLIF definition includes the outcome (mortality >15%) in the definition. Fourth, the definition of underlying liver disease also varies across the groups. Chronic liver disease is enough to qualify for the APASL definition whereas EASL-CLIF and NACSELD require the presence of cirrhosis. Fifth, renal failure and infection play a more paramount role in EASL-CLIF and NACSELD as compared to viral hepatitis in APASL definitions.

Predictive models

Several models may help predict outcomes in patients with ACLF. Certain models were developed to be etiology-specific. Patients with acute alcoholic hepatitis are at a higher risk for ACLF compared to other admitted cirrhotic patients.[25] For such persons, MELD predicts early mortality, but has not been validated in patients with ACLF.[39, 40] The Lille model assesses short-term prognosis in subjects with alcoholic hepatitis treated with steroids.[41] For cirrhotics undergoing surgery, who are at risk for an ischemic or infectious insult that can result in ACLF, a combination of the MELD score, age and American Society of Anesthesiologists (ASA) classification are predictive of short-term mortality.[42]

Other models are not disease specific, and capture risk of mortality based on liver function such as the CTP or MELD score. Given that multiorgan failure is common, models that address end organ dysfunction such as the Sequential Organ Failure Assessment (SOFA) as well as the Acute Physiology Age and Chronic Health Evaluation (APACHE) have been utilized. Moreau et al. examined the sequential SOFA score modified to include factors associated with liver disease (SOFA-CLIF) as discussed earlier (Figure 4). In contrast to elaborate models, Bajaj et al. using data from the NACSELD data set showed that increasing number of organ failures was sufficient to predict short-term mortality in patients with S-ACLF (Figure 5).

Although laboratory and clinical models may predict outcome, stool analysis may as well. Analysis of the gut microbiome, using the cirrhosis dysbiosis ratio (CDR), demonstrates a progressive decrease in the CDR with worsening liver dysfunction that is predictive of short-term organ failure and death (Bajaj J HEP 2013).

ACLF in Pre-Transplant Patients

Data on ACLF and outcomes among cirrhotics awaiting LT are sparse. Given the high short-term mortality, persons who may be candidates for transplant with ACLF need to be evaluated with rapidity. Finkenstedtet al. examined ACLF on the waiting list in a single center European cohort between 2002 and 2010 using the APASL definition (n=144).[44] Although no precipitant was found in 40%, infection and bleeding were the most common precipitants identified. The mean MELD was 28, hepatorenal syndrome developed in 53%, waitlist mortality was 54% (median survival was 54 days), and only 10 persons survived without LT over a median follow up of 1.5 years. Subjects with better renal function and lower CRP were more likely to receive a LT as compared to those with sepsis or those needing mechanical ventilation. The majority of patients who underwent LT had this occur during their ACLF event. Though not explicitly stated there appeared to be increased short-

term mortality; however, there was no difference in long-term (1-, 3-, and 5-year) post-transplant mortality between those transplanted with and without ACLF.

Bahirwani et al. examined subjects at a large American transplant center with ACLF (defined as a rise in MELD score of >5 points within 4 weeks of LT) between 2002 and 2006.[45] There was no significant difference in 3-year renal function, risk of recurrent cirrhosis, graft loss and death between those transplanted with and without ACLF. However, both studies lacked a comparison with a MELD matched cohort without ACLF.

Medical Therapy

There is no ACLF specific treatment. Appropriate intensive care management of subjects with ACLF is the mainstay of treatment as recently reviewed.[4] Management of ACLF is contingent on first diagnosing and addressing the precipitating event. For example, in the setting of acute alcoholic hepatitis, administration of prednisolone early in the course may play a critical role if warranted by the disease severity and absence of contraindications. Administration of tenofovir for ACLF due to reactivation of hepatitis B may lead to improved survival.[46] However, a major impact in ACLF risk reduction will only be achieved though novel infection prevention strategies. Although antibiotic based gastrointestinal bleeding prophylaxis and SBP prophylaxis remain essential, ideally the future of ACLF prevention would be with non-antibiotic related preventative interventions.

Liver Assist Devices

The role of liver assist devices in ACLF management remains unclear.[47] MARS, a non-biologic molecular adsorbent recirculating system was examined in a multicenter study of 180 ACLF patients complicated with either hepatorenal syndrome, hepatic encephalopathy, or worsening hyperbilirubinemia who were randomized to receive standard medical therapy with or without MARS. Subjects assigned to MARS showed significant improvement in bilirubin, creatinine, and hepatic encephalopathy, but no 28 days survival benefit was observed.[48] Similarly, in a study of the non-biological device Prometheus (that uses fractional plasma separation absorption and dialysis) an overall survival benefit was not observed in ACLF patients, but was seen in subgroup analysis of persons with type I hepatorenal syndrome and MELD scores >30.[47]

ACLF and Outcomes After Liver Transplant

The decision to proceed with liver transplant in an individual recipient is based on organ availability, recipient disease severity, and the absence of contraindication. It is unclear whether criteria that are applicable to ALF should be applied for ACLF. Currently, there is no specific priority assigned to persons with ACLF above and beyond the inevitable increase in MELD that occurs with ACLF. Recent data suggest that candidates with the highest MELD scores (above 36) should be assigned either similar or higher priority than status 1 patients given their significant wait list mortality.[49] However, the presence of cerebral edema, active infection, and hemodynamic instability often present in persons with ACLF remain obvious contraindications to transplantation. Therefore, timing of transplant is

critical. Currently we lack accurate laboratory parameters or biomarkers that signal the earliest “safe” window of transplant opportunity.

Living donor LT has been utilized in patients with ACLF due to hepatitis B reactivation.[50, 51] In a single Hong Kong center analysis of 32 subjects with ACLF between 1996 and 2002, living donor LT was utilized for patients with ACLF in the intensive care unit with a mean MELD score of 36.[52] Overall operative morbidity was significant (59%) resulting in a 38 day mean length of stay. Fortunately, patient and graft survival were both 88% at a medium follow-up of almost 2-years, and was similar to a reference group who underwent elective living donor with lower MELD scores.

The role of SLKT in patients with ACLF and renal dysfunction was recently examined among persons undergoing deceased donor transplantation at a single Chinese center between 2001 and 2009 in 133 patients with a mean MELD of 32.[53] Subjects were divided into 3 groups: 1) those with ACLF without renal dysfunction who underwent LT (5-year survival = 72%), 2) those with ACLF with renal dysfunction who underwent LT (5-year survival = 56%), and 3) those with ACLF with renal dysfunction who underwent SLKT (5-year survival = 82%). Many key factors about these patients remain unclear such as how many patients had acute vs. chronic kidney disease and how long the renal dysfunction was present before transplant.[54] Therefore validation is essential.

Unresolved questions

Despite the progress in defining ACLF, several questions remain. First, an element of reversibility is proposed amongst persons with ACLF who are successfully navigated through the acute decompensation. Theoretically once the acute insult is managed, the long-term prognosis should be similar between MELD matched patients with and without ACLF. However, this has not been well studied, and there is likely a point of no return that is yet to be defined. Second, definitions from the various groups need to be aligned with the establishment of a common understanding of the underlying substrate (chronic liver disease versus compensated cirrhosis versus decompensated cirrhosis). Third, It is unclear whether all renal dysfunction in persons with ACLF is reversible.[5] Recent investigations have highlighted the importance of the cause, severity, and duration of renal dysfunction as critical determinants of outcome; even persons with “normal renal function” can develop irreversible renal dysfunction after LT.[55–57] Whether this is more pronounced in persons with ACLF is unknown. Lastly, the best way to improve ACLF outcomes would be through prevention. Since the most common precipitant of ACLF is infection, development of accurate risk stratification schemes followed by implementation of novel (preferably non-antibiotic) prevention strategies is desperately needed.

REFERENCES

1. Asrani SK, Larson JJ, Yawn B, et al. Underestimation of liver-related mortality in the United States. Gastroenterology. 2013; 145:375–82. e1–2. [PubMed: 23583430]
2. Manos MM, Leyden WA, Murphy RC, et al. Limitations of conventionally derived chronic liver disease mortality rates: Results of a comprehensive assessment. Hepatology. 2008; 47:1150–7. [PubMed: 18264998]

3. Kim WR, Brown RS Jr, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. Hepatology. 2002; 36:227–42. [PubMed: 12085369]
4. Olson JC, Wendon JA, Kramer DJ, et al. Intensive care of the patient with cirrhosis. Hepatology. 2011; 54:1864–1872. [PubMed: 21898477]
5. Jalan R, Gines P, Olson JC, et al. Acute-on Chronic Liver Failure. J Hepatol. 2012
6. Rosselli M, MacNaughtan J, Jalan R, et al. Beyond scoring: A modern interpretation of disease progression in chronic liver disease. Gut. 2013; 62:1234–1241. [PubMed: 23645629]
7. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60:646–9. [PubMed: 4541913]
8. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000; 31:864–71. [PubMed: 10733541]
9. O'Leary JG, Landaverde C, Jennings L, et al. Patients with NASH and cryptogenic cirrhosis are less likely than those with hepatitis C to receive liver transplants. Clin Gastroenterol Hepatol. 2011; 9:700–704. e1. [PubMed: 21570483]
10. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Journal of Hepatology. 2006; 44:217–231. [PubMed: 16298014]
11. Jepsen P, Vilstrup H, Andersen PK, et al. Comorbidity and survival of Danish cirrhosis patients: A nationwide population-based cohort study. Hepatology. 2008; 48:214–220. [PubMed: 18537190]
12. Fleming KM, Aithal GP, Card TR, et al. All-cause mortality in people with cirrhosis compared with the general population: A population-based cohort study. Liver International. 2012; 32:79–84. [PubMed: 21745279]
13. Olson JC, Kamath PS. Acute-on-chronic liver failure: what are the implications? Curr Gastroenterol Rep. 2012; 14:63–6. [PubMed: 22086408]
14. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care. 2011; 17:165–9. [PubMed: 21326095]
15. Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extra-hepatic organ failures. Hepatology. 2014:n/a–n/a.
16. Fede G, D'Amico G, Arvaniti V, et al. Renal failure and cirrhosis: A systematic review of mortality and prognosis. Journal of hepatology. 2011
17. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001; 33:464–70. [PubMed: 11172350]
18. Martin-Llahi M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology. 2011; 140:488–496. e4. [PubMed: 20682324]
19. Francoz C, Prie D, Abdelrazek W, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl. 2010; 16:1169–77. [PubMed: 20879015]
20. Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology. 2013; 145:1280–8. e1. [PubMed: 23999172]
21. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011; 60:702–9. [PubMed: 21325171]
22. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010; 139:1246–56. 1256, e1–5. [PubMed: 20558165]
23. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol. 2013; 59:482–9. [PubMed: 23665185]
24. Wasmuth HE, Kunz D, Yagmur E, et al. Patients with acute on chronic liver failure display 'sepsis-like' immune paralysis. Journal of Hepatology. 2005; 42:195–201. [PubMed: 15664244]
25. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013; 144:1426–37. 1437, e1–9. [PubMed: 23474284]

26. Mookerjee RP, Stadlbauer V, Lidder S, et al. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. Hepatology. 2007; 46:831–40. [PubMed: 17680644]
27. Garg V, Garg H, Khan A, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. Gastroenterology. 2012; 142:505–512. e1. [PubMed: 22119930]
28. Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock. 2001; 16:83–96. [PubMed: 11508871]
29. Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. Crit Care Med. 1996; 24:163–72. [PubMed: 8565523]
30. Ward NS, Casserly B, Ayala A. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. Clin Chest Med. 2008; 29:617–25. viii. [PubMed: 18954697]
31. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology. 2012; 56:2328–35. [PubMed: 22806618]
32. Singh V, Ghosh S, Singh B, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. J Hepatol. 2012; 56:1293–8. [PubMed: 22322237]
33. Duvoux C, Zanditenas D, Hezode C, et al. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology. 2002; 36:374–80. [PubMed: 12143045]
34. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet. 2013; 382:984–94. [PubMed: 23642914]
35. Bajaj JS, Ratliff SM, Heuman DM, et al. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. Aliment Pharmacol Ther. 2012; 36:866–874. [PubMed: 22966967]
36. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology. 1995; 108:1828–34. [PubMed: 7768389]
37. Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol. 2007; 102:1510–7. [PubMed: 17509025]
38. Wang FS, Zhang Z. Liver: How can acute-on-chronic liver failure be accurately identified? Nat Rev Gastroenterol Hepatol. 2013; 10:390–1. [PubMed: 23609466]
39. Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology. 2005; 41:353–8. [PubMed: 15660383]
40. Dunn W, Angulo P, Sanderson S, et al. Utility of a new model to diagnose an alcohol basis for steatohepatitis. Gastroenterology. 2006; 131:1057–63. [PubMed: 17030176]
41. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. 2007; 45:1348–54. [PubMed: 17518367]
42. Teh SH, Nagorney DM, Stevens SR, et al. Risk Factors for Mortality after Surgery in Patients with Cirrhosis. Gastroenterology. 2007 in press.
43. Katoonizadeh A, Laleman W, Verslype C, et al. Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. Gut. 2010; 59:1561–9. [PubMed: 20675694]
44. Finkenstedt A, Nachbaur K, Zoller H, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. Liver Transpl. 2013; 19:879–86. [PubMed: 23696006]
45. Bahirwani R, Shaked O, Bewtra M, et al. Acute-on-chronic liver failure before liver transplantation: impact on posttransplant outcomes. Transplantation. 2011; 92:952–7. [PubMed: 21869735]
46. Garg H, Sarin SK, Kumar M, et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. Hepatology. 2011; 53:774–780. [PubMed: 21294143]
47. Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. Curr Opin Crit Care. 2011; 17:195–203. [PubMed: 21346566]

48. Banares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology. 2013; 57:1153–62. [PubMed: 23213075]

49. Sharma P, Schaubel DE, Gong Q, et al. End-stage liver disease candidates at the highest model for end-stage liver disease scores have higher wait-list mortality than status-1A candidates. Hepatology. 2012; 55:192–8. [PubMed: 21898487]

50. Chok KS, Fung JY, Chan SC, et al. Outcomes of living donor liver transplantation for patients with preoperative type 1 hepatorenal syndrome and acute hepatic decompensation. Liver Transpl. 2012; 18:779–85. [PubMed: 22290625]

51. Chan AC, Fan ST, Lo CM, et al. Liver transplantation for acute-on-chronic liver failure. Hepatol Int. 2009; 3:571–81. [PubMed: 19680733]

52. Liu CL, Fan ST, Lo CM, et al. Live-donor liver transplantation for acute-on-chronic hepatitis B liver failure. Transplantation. 2003; 76:1174–1179. [PubMed: 14578749]

53. Xing T, Zhong L, Chen D, et al. Experience of combined liver-kidney transplantation for acute-on-chronic liver failure patients with renal dysfunction. Transplant Proc. 2013; 45:2307–13. [PubMed: 23871182]

54. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant. 2012; 12:2901–8. [PubMed: 22822723]

55. Nadim MK, Genyk YS, Tokin C, et al. Impact of the etiology of acute kidney injury on outcomes following liver transplantation: acute tubular necrosis versus hepatorenal syndrome. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2012; 18:539–48.

56. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology. 2003; 37:233–43. [PubMed: 12540770]

57. Asrani SK, Kim WR, Heimbach JH, et al. Acute Tubular Necrosis in present in the majority of patients undergoing liver transplantation. Hepatology. 2011; 54:159A.

Key Points

- ACLF is characterized by the presence of a precipitating event in subjects with underlying chronic liver disease leading to acute deterioration of liver function and often ending in multi-organ system failure.
- The physiology of ACLF can be divided into a 4-part model: 1) predisposition, 2) injury due to precipitating event, 3) response to injury, and 4) organ failure.
- Most precipitants of ACLF are ischemic or infectious in nature, and therefore the inflammatory response plays a critical role in the outcome of ACLF.
- The definition of ACLF, like the definition of ALF, requires liver disease and dysfunction, but is prognostically based on extrahepatic organ failures.
- Increasing numbers of organ failures (i.e. renal, cerebral, circulatory, and pulmonary) portend progressively worse outcomes in patients with underlying cirrhosis.
- Acute renal failure in patients with cirrhosis is associated with an almost 8 fold increased risk of death; smaller increases (≥0.3 mg/dL) in creatinine, some of which occur below the 1.0 mg/dL creatinine cutoff for MELD point allocation, have significant prognostic implications.
- Regional variation in underlying liver diseases, ACLF definitions, and agreed upon precipitants continues.
- ACLF carries a high mortality in wait-listed patients and in those that survive, they are often transplanted during their ACLF event.
- Development of accurate risk stratification schemes followed by implementation of novel ACLF prevention strategies is needed.

Table 1

Events known to precipitate acute-on-chronic liver failure.

-Acute alcoholic hepatitis
-Acute hepatotrophic viral infection
-Acute hepatitis A
-Reactivation hepatitis B
-Acute hepatitis D in the presence of hepatitis B
-Acute hepatitis E
-Drug-induced liver injury
-Gastrointestinal bleeding
-Infection
-Ischemia
-Hypotension
-Surgery
-Trauma
-Portal Vein Thrombosis

Table 2

Definitions of renal dysfunction in patients with cirrhosis.

	Hepatorenal Syndrome	Acute Kidney Injury Network	IAC & ADQI
Cirrhosis required	Yes	Yes	Yes
Absence of underlying renal disease	Required	Not required	Not required, Acute on chronic kidney disease defined
Minimum serum Creatinine	≥1.5	Stage 2 & 3 yes, serum creatinine ≥1.5	No
Stages/Types	Yes	Yes	No
Criteria	1) ascites, 2) no improvement after 2 days of diruetic w/drawal & volume expansion, 3) no shock, 4) no nephrotoxic drugs; Type 1: Doubleing in serum creatinine to ≥2.5 in <14 days	Stage 1= ≥0.3 mg/dL in <48 hrs or increase 1.5-2 × baseline	AKI: ≥0.3 mg/dL in <48 hrs or >50% over baseline
		Stage 2 = increase 2-3 × baseline	
		Stage 3 = increase >3 × baseline or >4.0 mg/dL with an acute ≥0.5mg/dL increase	CRD: estimated GFR < 60 mL/min for > 3 months by MDRD6

IAC, International Ascites Club; ADQI, Adult Dialysis Quality Initiative, AKI, acute kindney injury; CRD, chronic renal disease; MDRD6, Modification of Diet in Renal Disease 6 formula

Table 3

Differences in definitions of acute-on-chronic liver failure (ACLF). (Adapted from JS Bajaj. Gastroenterology 144:1337-9)

	APASL Definition	AASLD/EASL Consensus
Duration	<4 weeks	Not defined
Chronic Liver Disease	Any fibrosis stage	Cirrhosis only
Most Common Precipitant	Hepatotrophic viruses	Infections
Other Agreed Upon Precipitants	Alcohol, drug-induced liver injury, ischemia	
Variceal bleeding	No consensus	Yes
Infection	No	Yes

APASL, Asia-Pacific Association for the Study of Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the study of the Liver