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Acute-on-chronic liver failure

Sumeet K Asrani, MD, MSc¹, Douglas A Simonetto, MD², and Patrick S Kamath, MD^{2,*}

¹Division of Hepatology, Baylor University Medical Center, Dallas, Texas

²Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota

Abstract

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 decompensated cirrhosis. ACLF is thus characterized by the presence of a precipitating event (identified or unidentified) in subjects with underlying chronic liver disease leading to rapid progression of liver injury and ending in multi-organ dysfunction characterized by high short term mortality. Multiple organ failure and increased risk for mortality are key to diagnosis of ACLF. The prevalence of ACLF ranges from 24–40% in hospitalized patients. The pathophysiological basis of ACLF can be explained using a 4 part model of predisposing event, injury due to precipitating event, response to injury and organ failure. Though several mathematical scores have been proposed for identifying outcomes with ACLF, it is yet unclear whether these organ failure scores are truly prognostic or are only reflective of the dying process. Treatment paradigms continue to evolve but consist of early recognition, supportive intensive care, and consideration of liver transplantation prior to onset of irreversible multiple organ failure.

INTRODUCTION

For years, a dichotomous fate had been assigned to persons with chronic liver disease or cirrhosis: period of stable compensated liver disease followed by progression to decompensated liver disease towards eventual death in the absence of liver transplantation (LT). Decompensation was heralded by the onset of ascites, jaundice, variceal bleeding, or hepatic encephalopathy with a median survival of two years. There was no term to describe the events between decompensated cirrhosis and multiple organ failure that these patients eventually died of. 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 decompensated cirrhosis. Multiple organ failure and increased risk for mortality are key to diagnosis of

Corresponding Author: Patrick S Kamath, 200 First Street SW, Rochester, Minnesota 55905, Fax: 507-284-0538, Telephone: 507-284-1649, Kamath.patrick@mayo.edu.

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ACLF. It is now recognized that patients with compensated cirrhosis and patients with chronic liver disease without cirrhosis may also develop multiple organ failure and are included among ACLF. The purpose of the review is to update our current understanding of ACLF (definitions and pathophysiology), characterize associated extra-hepatic organ dysfunction, identify current prognostic markers and predictive models, and describe potential therapies.

DEFINITION

As compared to the general population, persons with compensated cirrhosis have a five-fold (hazard ratio, HR=4.7, 95% confidence interval, CI 4.4–5.0) and persons with decompensated cirrhosis have a 10-fold (HR=9.7, 95% CI 8.9–10.6) increased risk of death.¹ In a recent population based study of Danish alcoholic cirrhotics, the median 1 year survival was 83% in persons with compensated cirrhosis and between 36–80% for persons with decompensated cirrhosis.² The underlying premise of defining ACLF is to identify a subset of patients with either chronic liver disease or cirrhosis that have an unexpected rapid and abrupt decompensation of hepatic function with extrahepatic organ failure. There is an elevated risk of short term mortality similar to persons with acute liver failure (ALF) and substantially higher than expected with the natural progression of cirrhosis with chronic decompensation.³ In a recent study, cirrhotics with ACLF had 90 day mortality rates of 34% versus 1.9% for chronic decompensation. ACLF is characterized by a “paralysis of immune response” akin to changes seen amongst persons with severe sepsis.⁴ This is in contradistinction to ALF which is characterized by onset of coagulopathy and encephalopathy within 8 weeks in subjects *without* underlying chronic liver disease.⁵ Cerebral edema may be encountered in ACLF, but is rarely seen in decompensated cirrhosis without ACLF.

Three separate definitions have been derived from multicenter efforts from the Asia-Pacific Region, European as well as North American groups.^{3, 6–9} (Table 1) It must be recognized that the characterization of each organ failure was different between the separate consortium definitions. In addition, the timing of precipitating injury, importance placed on extra hepatic organ failure, especially infection, and definition of chronic liver disease and cirrhosis were different across the three iterations. In order to consolidate the complementary definitions, a framework was proposed by a working group on behalf of the World Gastroenterology Organization.³ According to this consensus, ACLF is a “syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR [International Normalized Ratio]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from it.” Further ACLF is classified based on whether it occurs in patients without cirrhosis (type A, e.g. reactivation of hepatitis B), in persons with compensated cirrhosis (type B, e.g. acute alcoholic hepatitis in patient with cirrhosis) or in those with a history of prior hepatic decompensation (type C, e.g. infection in patient with history of ascites) (Figure 1).^{10–12} Since organ failure is required for defining ACLF, the diagnosis of ACLF may currently be made at a time point that the process is largely irreversible.

Therefore, a definition that takes into consideration prognostic factors other than organ failure is required to allow early diagnosis and treatment of ACLF.

PREVALENCE AND NATURAL HISTORY

The prevalence of ACLF is hard to assess given variation in definitions of ACLF. In the European multicenter study, the prevalence among hospitalized cirrhotics was 31%.⁶ In the North American experience, the prevalence of infection associated ACLF (>2 associated organ failures) was approximately 24.3%.⁹ Similarly, in a European population based cirrhotic cohort (2001–2010), the prevalence of infection-related ACLF was 24%.¹³ In a single center prospective nationwide inception cohort study in Italy, ACLF was observed in 12% of hospitalized cirrhotics.¹⁴ In another study, ACLF developed in 40% at 5 years for persons with cirrhosis.¹⁵

Limited data exists on the natural history of ACLF. Using follow up data from the CLIF consortium, of 388 patients, about 50% had resolution or improvement in their ACLF, 20% worsened and 30% had a steady or fluctuating course. The prognosis was best in patients with grade 1 ACLF (discussed later) with the highest resolution in grade 1 ACLF (resolution 54.5%) as compared to ACLF grade 3 (16%).¹⁰ The time course assessing improvement, resolution or worsening could be determined within 48 hours in 40%, 3–7 days in 15%, and 8–28 days in another 15% of the population. Long term outcomes may also be different based on the precipitating factor. In a single center study of 405 patients with ACLF from China, subjects with hepatic insults (e.g. viral hepatitis, hepatotoxic drugs) as compared to extra hepatic insults (e.g. bacterial infection or surgery) had similar short term mortality (48.3% vs. 50.7% 28 day transplant free mortality) but lower 1 year mortality (63.9% vs. 74.6%, $p<0.02$).⁸ There were also differences in predictors of poor prognosis such as presence of multi-organ failure being more predictive of deaths in subjects with extra-hepatic precipitants rather than hepatic related insults.

ETIOLOGY

There are also differences in etiologies of ACLF based on the region of the world. Reactivation of hepatitis B and superimposition of acute hepatitis A or hepatitis E on chronic liver disease are important causes of ALF as well as ACLF in Asia. Alcoholic hepatitis and infections are reportedly more common in western centers, but do contribute to a significant proportion of patients with ACLF in the East too. Given that about half of subjects with cirrhosis admitted have evidence of infection or sepsis and a further 25% develop nosocomial infections with high inpatient hospital mortality, infection plays an overwhelming role in the natural history of ACLF.

COSTS

Unfortunately, there are sparse data on the cost of ACLF as it is often hard to parse out hospital level data and accurately identify subjects with ACLF versus non ACLF related decompensated liver disease. In one estimate of the nationwide inpatient sample in the United States, the mean cost per ACLF hospitalization was twice as high as that for patients

with cirrhosis without ACLF (approximately \$32,000 for ACLF, compared to \$16,000 for cirrhosis without ACLF).¹⁶

PATHOPHYSIOLOGY

Borrowing from the sepsis literature, Jalan and colleagues described the pathophysiological basis of ACLF using a 4 part model of predisposing event, injury due to precipitating event, response to injury and organ failure.^{10–12, 17, 18} (Figure 2). In their model, **predisposition** refers to underlying cirrhosis and concomitant illnesses. **Injury** may be due to one of many insults such as alcoholic hepatitis, superimposed viral hepatitis, reactivation of hepatitis B, gastrointestinal bleeding (variceal or non variceal), drug induced liver injury, ischemia, and surgery. The prevalence of identified bacterial infection is higher among persons with ACLF as compared to those without ACLF.⁶ Precipitating injury may be unknown in about half of the cases. The inflammatory **response** is important with a robust response as judged by presence of elevated C reactive protein (CRP) or an elevated leukocyte count associated with worse outcomes. It is unclear whether the inflammation is a response to the inciting event or a part of the inciting event. It is also likely that the compensatory anti-inflammatory response is important in determining the risk for nosocomial infection and the higher risk of mortality.¹⁹ **Organ failure** is the last component with increasing numbers of organ failures (i.e. hemodynamic collapse, renal failure, pulmonary compromise, liver failure) portending poor outcomes especially in the setting of chronic liver disease.

In normal conditions, the liver exerts an important defensive role against pathogens and related antigens. The liver resident-macrophages, i.e. Kupffer cells, and sinusoidal endothelial cells act as first-line defense mechanisms against gut-derived toxins and bacteria. Kupffer cells are present within the lumen of the hepatic sinusoids and exert potent phagocytic activity.²⁰ Upon activation of Kupffer cells, there is significant release of proinflammatory cytokines (IL-1, IL-6, IL-17, IL-18, tumor necrosis factor- α) which induces leukocyte recruitment and oxidative stress, as well as complement activation. Both Kupffer cells and sinusoidal endothelial cells also have antigen presenting capabilities, through expression of MHC class I and II.

In cirrhosis, there is loss or damage of Kupffer cells, due to sinusoidal fibrosis and capillarization, portosystemic shunt formation and impaired hepatic synthesis of complement proteins and soluble pattern recognition receptors. In addition, compromise of circulating immune cell function has been demonstrated in cirrhosis.²¹ Patients with ACLF demonstrate significant cellular immune depression, as measured by reduced ex vivo TNF- α production and monocyte HLA-DR expression after lipopolysaccharide (LPS) stimulation. This effect is significantly more pronounced in ACLF patients compared to those with compensated cirrhosis.²² A large gene-expression profiling study of cirrhotic peripheral blood mononuclear cells (PBMC) demonstrated induction of “immune paralysis” after ex vivo exposure to LPS. In comparison to healthy controls, LPS-stimulated cirrhotic PBMCs showed higher expression of certain proinflammatory cytokines and chemokines.²³ Patients with HBV-related ACLF demonstrate an increase in the regulator T cells and a functional decrease of myeloid dendritic cells, which are associated with poor outcome^{24, 25}. ACLF patients also display increased numbers of monocytes and macrophages expressing MER

receptor tyrosine kinase (MERTK), which displays a potent suppressive effect on the innate immune response²⁶. Recent studies on the beneficial use of granulocyte-colony stimulation factor (G-CSF) for patients with ACLF, showed an increase in circulating and intrahepatic myeloid and plasmacytic dendritic and T cells.^{27, 28}

These findings demonstrate some similarities between the pathophysiology of ACLF and severe sepsis. Septic patients also exhibit both a proinflammatory phase, leading to multiorgan failure/dysfunction, and an antiinflammatory phase, characterized by suppression of the immune system.^{29, 30} Unfortunately, there are no current studies on the immune system response at the different stages of ACLF. These studies would be helpful in further understanding the sequence of events leading to organ failure and death.

In addition to bacterial translocation and infection contributed to by impaired immune response in cirrhosis, sterile mechanisms associated with hepatocellular damage may also elicit a prominent inflammatory response. Sterile inflammation, as induced by alcohol, surgery, acetaminophen or ischemic/reperfusion, is mostly driven by damage-associated molecular patterns (DAMPs) as opposed to pathogen-associated molecular patterns (PAMPs)^{31, 32}. DAMPs derive from necrotic hepatocytes and have been demonstrated to activate host pattern recognition receptors, such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs)³³. These in turn promote expression of adhesion proteins and release of proinflammatory cytokines (e.g. IL-1B, IL-18) and growth factors, which further attract and activate additional inflammatory cells³⁴. Several DAMPs have been described in the literature, but their role in ACLF needs to be further elucidated. Recently, a small study found increased serum levels of high mobility group box chromosomal protein 1 (HMGB1), an important hepatocyte-derived DAMP, in patients with ACLF³⁵ (Figure 2).

EXTRAHEPATIC ORGAN FAILURE

The presence of multi-system organ failure is a requirement for the diagnosis of ACLF and critical in differentiating this condition from decompensated cirrhosis. Also, the number of systems affected has important prognostic value⁶.

Renal System

Kidney dysfunction is common and associated with high mortality in cirrhotic patients. Overall, isolated renal failure carries a 28-day mortality rate up to 18.6% in patients with ACLF⁶. The diagnosis of renal failure has been defined as serum creatinine greater than 1.5 mg/dL or need for renal replacement therapy in patients with cirrhosis^{36, 37}. A newer definition of acute renal failure has been proposed by the Acute Kidney Injury Network (AKIN) which considers the absolute change in serum creatinine or change in urine output over a 48 hour period³⁸. The AKIN criteria have been recently validated as a prognostic tool in hospitalized cirrhotic patients on a stage dependent fashion^{39–42}. The AKIN criteria have yet to be incorporated, however, into a prognostic score for ACLF.

The most common causes of acute kidney injury in cirrhosis include: volume-responsive prerenal azotemia, acute tubular necrosis, and hepatorenal syndrome (HRS)⁴³. Hepatorenal

syndrome is a unique form of pre-renal azotemia that is not responsive to volume expansion alone but is usually reversible with liver transplantation. HRS results from a hyperdynamic circulatory state, leading to significant renal vasoconstriction⁴⁴. Management of HRS includes the use of splanchnic vasoconstrictors which promote an increase in the effective renal arterial blood volume. Vasoconstrictor drugs such as terlipressin significantly improve renal function and overall short-term survival.⁴⁵ Patients with severe ACLF and sepsis-associated HRS are less likely to respond to terlipressin, suggesting alternative mechanisms of renal impairment in this population.⁴⁶ In addition, response to terlipressin in ACLF may not simply be related to degree of renal impairment and other factors may play a role.⁴⁷

In addition to circulatory changes, AKI in ACLF is also likely modulated by systemic inflammation. This is supported by the beneficial role of pentoxifylline in decreasing the risk of renal failure in patients with severe alcoholic hepatitis⁴⁸ and the renal protective effect of intravenous albumin in spontaneous bacterial peritonitis³⁶. Bacterial infection is the precipitating event of AKI in about 30–40% of patients with cirrhosis⁴⁹ and is an important driver of inflammation in this group. Renal failure associated with infections carries a poor prognosis, with a 3-month survival rate of 31% in one study⁴⁹. Intestinal decontamination with daily oral norfloxacin in prevention of spontaneous bacterial peritonitis leads to a significant decrease in the incidence of AKI and improves survival⁵⁰.

In addition to renal failure, hyponatremia is known to have an important prognostic value in cirrhosis⁵¹. Indeed, the presence of hyponatremia in patients with ACLF was associated with lower 3-month survival compared to patients with ACLF and without hyponatremia (35.8% vs. 58.7%, respectively)⁵².

Hepatic Encephalopathy

Hepatic encephalopathy is a common complication of cirrhosis and is associated with higher in-hospital mortality^{53–55}. Hepatic encephalopathy can present in three different settings: acute liver failure, decompensated cirrhosis, and ACLF. Isolated hepatic encephalopathy seems to occur in older cirrhotics, without evidence of extrahepatic organ dysfunction. The prognosis is typically good in this older group of patients with HE, even in those requiring ICU admission and mechanical ventilation⁵⁶. HE associated with ACLF, on the other hand, occurs in the setting of extrahepatic organ failure(s) and carries a poor prognosis⁵⁷. This prognostic gap is likely related to superimposed systemic inflammation, characteristic of ACLF, in addition to circulating neurotoxins such as hyperammonemia which is observed in both groups⁵⁸.

Another important difference between isolated HE and HE associated with ACLF is that the latter may lead to cerebral edema and elevated intracranial pressure, whereas the former will typically not^{11, 59–61}. Animal studies suggest the development of acute brain edema to be a result of hyperammonemia plus systemic/neuroinflammation⁶². Hyponatremia has also been identified as an important risk factor for cerebral edema, likely due to differences in osmolality between the intra and extracellular spaces^{63, 64}.

Cardiovascular system

Similar to decompensated cirrhosis, ACLF patients also demonstrate important hemodynamic changes, including a decrease in mean arterial pressure, systemic vascular resistance and cardiac index and a significant increase in hepatic venous pressure gradient (HVPG). These portal and systemic circulatory changes improve significantly after resolution of the acute episode and correlate well with clinical recovery⁶⁵.

Systemic inflammation likely accounts for the acute vascular changes observed in ACLF, similar to septic shock. Increase in circulating proinflammatory cytokines, such as tumor necrosis factor, promotes peripheral vasodilation^{66, 67} and aggravates intrahepatic resistance⁶⁸. Also, patients with ACLF may demonstrate relative adrenal insufficiency and, consequently, low serum cortisol levels⁶⁹. This in turn, results in decreased peripheral response to vasoconstrictors^{69, 70}.

Respiratory System

Respiratory failure in patients with ACLF is usually related to pulmonary infections, although patients may require mechanical ventilation for other indications, including airway protection during variceal bleeding and/or advanced grades of hepatic encephalopathy. Pulmonary infections account for 14% to 48% of all infections in cirrhotic patients⁷¹. Both acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) occur. The need for mechanical ventilation is a poor prognostic indicator in ACLF, with 1-year mortality at 89%. Ventilation longer than 9 days, and elevated total bilirubin at ICU discharge were identified as independent risk factors associated with high mortality⁷².

Coagulation System

Prolonged prothrombin time and low platelet count are common features of cirrhosis and are used as surrogate markers of coagulation dysfunction in this population. Unfortunately, the abnormalities in the coagulation and fibrinolytic systems are extensive and not recognized by routine testing⁷³. In stable cirrhosis, both the pro- and anti-coagulant factors are equally decreased, resulting in either normal thrombin generation, or a tendency to hypercoagulability⁷⁴. Bacterial infections in cirrhotic patients are thought to impair coagulation by increasing endogenous heparinoids. This seems to be a temporary effect which resolves after the infection has cleared⁷⁵. Platelet dysfunction has also been observed in infected patients, especially those with renal failure, and likely contributes to the hemostatic impairment⁷⁶. These detrimental vascular effects are further countered by the protective role of antibiotics in reducing early variceal rebleeding rates⁷⁷.

POTENTIAL BIOMARKERS

As our understanding and recognition of ACLF increases, so does our need to accurately diagnose and risk stratify patients for better outcome prediction and therapy guidance. Currently, only a few studies have investigated potential biomarkers for the diagnosis of ACLF. A recent study evaluating the metabolomic profile of patients with alcoholic cirrhosis admitted to the hospital with ACLF identified signals related to ACLF, compared to compensated or decompensated cirrhosis, including lactate, pyruvate, ketone bodies,

glutamine, phenylalanine, tyrosine, and creatinine⁷⁸. Metabolic profiling has been applied in patients with HBV-related ACLF and 38 characteristic serum metabolites were identified, 17 of which also demonstrated a potential prognostic role⁷⁹. Systemic inflammatory response is an important pathophysiologic feature of ACLF, and therefore, inflammatory or immune markers have also been investigated in this condition. A significant up-regulation of tumor necrosis factor-alpha and interferon gamma was observed in HBV-related ACLF, compared to chronic hepatitis and normal controls⁸⁰.

However, more data are required before these biomarkers can be widely applied as diagnostic or prognostic tools.

PREDICTIVE MODELS

Multiple scoring systems have been employed or developed to help predict outcomes in patients with ACLF. The Model for End-Stage Liver Disease score (MELD score), the Maddrey discriminant function and the Lille model have been shown to predict early mortality in acute alcoholic hepatitis^{81–84}. A recent study in patients with alcoholic hepatitis has shown that the combination of MELD score at admission and Lille score after one week of steroids has the best discriminant as well as calibration value of all models or combination of models.⁸⁵ This combined model may help in making treatment decisions including selecting patients for specific treatments as well as determining futility of care.⁸⁶ A combination of the MELD score, age and American Society of Anesthesiologists classification has been validated for predicting survival in cirrhotic patients undergoing surgery, another common precipitant of ACLF⁸⁷.

The commonly used scoring systems in cirrhosis, i.e. Child-Turcotte-Pugh score and MELD score, only assess, in addition to the liver, the kidney, brain and coagulation systems⁸⁸. Therefore, an improved scoring system for ACLF is required which takes into consideration inflammation and other organ dysfunction. Recently, the EASL-CLIF Consortium proposed a modified Sequential Organ Failure Assessment score (SOFA) to include factors associated with chronic liver disease (CLIF-SOFA scale)⁶.

The CLIF-SOFA scale assessed the function of 6 organ systems (liver, kidneys, brain, coagulation, circulation and lungs) (Table 2). A recent retrospective study, including 971 patients, validated the use of CLIF-SOFA score in cirrhosis. The SOFA and CLIF-SOFA had similar abilities to predict patient survival, with greater area under the receiver operating curve (AUROC) values than those obtained from MELD and Acute Physiology and Chronic Health Evaluation (APACHE) II scores.⁸⁹

A simplification of the CLIF-SOFA score has been proposed. Two new cut-points for each organ system have been added to distinguish three severity categories that were correlated with 28-day mortality (CLIF-C OFs). The “CLIF-C OFs” had a similar performance to the original CLIF-SOFA score in predicting 28-day mortality. The authors then developed a mathematical model, including age and white blood cell count, to improve the CLIF-C OFs performance. This new score, CLIF-C ACLFs, was proven to be superior to MELD and MELD-Na in predicting mortality in ACLF in the study population and in an externally validated cohort.⁹⁰

In contrast to these elaborate models, Bajaj et al. using data from the NASCELD group proposed the mere presence of increasing number of organ failures may be sufficient to accurately predict short term mortality at least among persons with ACLF that develop an infection. Hence, the overarching theme is that regardless of the underlying liver disease, it is the presence of multiorgan failure that predominantly drives the outcomes.

Gustot and colleagues assessed ACLF grades at different time points to evaluate the clinical course in this group of patients. Interestingly, they found that ACLF grade at 3–7 days was a better predictor of severity independent of initial assessment. Patients with non-severe early course had a 28-day transplant-free mortality of 6–18%, compared to 42–92% mortality in patients with severe early course.⁹¹ It is yet unclear whether these organ failure scores are truly prognostic (that is, allow early recognition and can improve the outcome) or are only reflective (that is, they are describing the dying process).

THERAPIES

There is no ACLF specific treatment; rather treatment follows the paradigm of addressing the predisposing event, preventing injury, attenuating the inflammatory response and providing supporting care for ensuing organ failures (Table 3). Appropriate intensive care management of subjects with ACLF is the mainstay of treatment.¹⁰ Early recognition of subjects at highest propensity to either present with or develop ACLF is important so that urgent evaluation for liver transplantation can take place. The role of alcohol as a common precipitant is a confounding factor given the variability of center specific criteria for abstinence.

Management of any decompensation is contingent on first addressing the precipitating event. For example, in the setting of acute alcoholic hepatitis, administration of prednisolone early in the course may play a role if warranted by the severity of disease. However, the interplay between the high prevalence of infection amongst persons with ACLF and administration of prednisolone is unknown. Further, the absolute reduction in mortality with steroid based therapy is apparent only at 28 days; long-term reduction in mortality is related to abstaining from alcohol. Reduction of risk of infection with early use of antibiotics in persons with gastrointestinal bleeding may improve outcomes. Administration of antiviral therapy for ACLF due to reactivation of hepatitis B may lead to improved survival.⁹² In a single center study from India, subjects with spontaneous reactivation of chronic hepatitis B with ACLF and no access to LT were randomized to receive of either tenofovir or placebo. Three-month survival was higher amongst persons receiving tenofovir as compared to the placebo group (57% vs. 15%). In a recent meta-analysis, subjects with ACLF who received nucleos(t)ide analogues had significantly lower 3-month mortality (45% vs. 73%, $p < 0.01$) as well as incidence of reactivation (1.8% vs. 18%, $p < 0.01$) compared to those who did not.⁹³

The role of granulocyte colony-stimulating factor as a promoter of hepatic regeneration has been reported in small group of patients with ACLF and a larger group of subjects with decompensated cirrhosis.²⁸ In this latter single center placebo controlled randomized trial, receipt of a combination of G-CSF and darbopoietin α was associated with improved

survival at 1 year (68.6% vs 26.9%; $p<0.01$) with a lower rate of septic shock in follow up (6.9% vs. 38.5%, $p<0.01$).²⁷

The role of liver assist devices remain unclear.⁹⁴ MARS (Gambro), a non-biologic molecular adsorbent recirculating system was examined among persons with ACLF. In the RELIEF multicenter study which included 180 patients with ACLF, there was no survival difference between patients randomized to MARS or standard therapy (28-day mortality was 41% vs. 40% and subjects with MARS vs. standard of care alone).⁹⁵ In a study of another nonbiological device, Prometheus ®, using fractional plasma separation absorption and dialysis, survival benefit was not observed in persons with ACLF (mortality was 34% vs. 37% in subjects assigned to the device vs. standard of care). There was survival benefit seen only amongst persons with type I hepatorenal syndrome and MELD scores greater than 30.⁹⁴ Bio-artificial liver assist devices are also being studied. (<http://clinicaltrials.gov/show/NCT01471028>)

LIVER TRANSPLANTATION

Currently, there is no urgent status assigned to persons with ACLF and it is unclear whether ALF criteria should be applied to subjects with ACLF. Given that timing of LT is important, it is also unclear whether King's college hospital ALF criteria should also be applied for ACLF or whether MELD based organ allocation is appropriately applicable. Driven by the presence of multi-organ failure, subjects with ACLF often have high MELD scores. Candidates with MELD scores above 35 have higher wait list mortality than status 1 patients and receive priority for liver transplantation second only to patients with ALF.⁹⁶ However, the presence of severe cerebral edema, intracranial bleeding, active infection in a majority, need for ventilator support and hemodynamic instability that may be present in persons with ACLF are obvious contraindications to transplantation.⁷ Further, recent data suggests that certain diagnoses previously not considered for LT globally such as acute alcoholic hepatitis may have acceptable outcomes after liver transplantation. In a single center European cohort inclusive of ACLF with acute alcoholic hepatitis (2002–2010, mean MELD 28, 144 subjects) ⁹⁷, only 10 persons survived without LT over a median follow up of 1.5 years. Among the highly selected 33 patients who underwent liver transplantation, the 1- and 5-year survival rates of 87% and 82% were comparable to the rates for non-ACLF patients. Subjects with better renal function and lower CRP were more likely to receive a LT as compared to those patients with sepsis or needing mechanical ventilation. Bahirwani et al. examined subjects with ACLF between 2002 and 2006 (50% hepatitis C) at a large American transplant center. ACLF was defined as a rise in MELD score of 5 points within 4 weeks before LT. There was no significant difference in deaths post-transplant or renal failure after LT. ACLF was not a predictor of death after LT but was a significant predictor when simultaneous liver-kidney transplant (SLKT) was included. In another recent single center study from China (100 patients, 2004–2012, mean MELD 32), the 1 and 5-year cumulative survival rates were 76.8% and 74.1%, respectively post-transplant. In all studies, no comparison was performed between patients with ACLF and those with chronic decompensation matched for disease severity by the MELD score.

The role of living donor LT has also been evaluated for subjects with ACLF due to reactivation of hepatitis B virus infection^{98–100} In a single center study the 5 year survival rate was 93% for persons with ACLF due to chronic hepatitis B, 90% for other causes of ACLF, 79% for persons with other causes of cirrhosis, and 91% for persons with acute liver failure. Overall hepatitis B was disproportionately represented across all the etiologies..⁹⁹

The role of SLKT for ACLF patients with renal dysfunction was recently examined among persons undergoing deceased donor transplantation (China, 133 subjects, 2001–2009).¹⁰¹ The survival rate for those without renal dysfunction was 72% at 5 years which was comparable to 82% for those that underwent simultaneous liver and kidney transplantation. Subjects with ACLF due to hepatitis B and hepatorenal syndrome that only underwent LT alone had a 5 year survival rate of 56%.

Conclusion

ACLF is an increasingly recognized entity associated with high mortality. The pathogenesis of inflammation and organ failure, and optimal management are the subject of intensive investigation across continents. More data are required before ACLF can be accurately defined and treated. Future strategies include defining the group of patients who need urgent liver transplantation; those who would benefit from intensive care alone; those who will benefit from liver supportive devices or hepatic regenerative therapies; and those patients in whom all intervention is futile.

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List of Abbreviations

LT	liver transplantation
MELD	Model for end stage liver disease
INR	international normalized ratio
SLK	simultaneous liver–kidney transplantation
HCC	Hepatocellular carcinoma
ALF	acute liver failure
ACLF	acute-on-chronic liver failure

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Figure 1.

Proposed types of ACLF (from Jalan et al. Ref 3)

Proposed unifying pathogenesis for different types of acute-on-chronic liver failure (ACLF).

Figure 2.
Pathophysiology of ACLF (see attached figure)

Table 1

Definitions of acute on chronic liver failure

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

Table 2

CLIF SOFA score system

Organ	Measurement	Score
Liver		
Bilirubin, mg/dL	<1.2	0
	1.2 to <2.0	1
	2.0 to <6.0	2
	6.0 to <12.0	3
	12.0	4
Kidney		
Creatinine, mg/dL	<1.2	0
	1.2 to <2.0	1
	2.0 to <3.5	2
	3.5 to <5.0	3
	5.0 or RRT	4
Coagulation		
INR	<1.1	0
	1.1 to <1.25	1
	1.25 to <1.5	2
	1.5 to <2.5	3
	2.5 or platelet count < 20,000	4
Circulation		
Mean arterial pressure, mmHg	≥ 70	0
	<70	1
	Dopamine ≤ 5 or dobutamine or terlipressin	2
	Dopamine >5 or E < 0.1 or NE < 0.1	3
	Dopamine >15 or E >0.1 or NE >0.1	4
Respiratory		
PaO ₂ /FiO ₂	>400	0
	>300 to < 400	1
	<200 to < 300	2
	>100 to < 200	3
	< 100	4
SpO ₂ /FiO ₂	>512	0
	>357 to < 512	1
	>214 to < 357	2
	>89 to < 214	3
	< 89	4
Cerebral		
	No HE	0

Organ	Measurement	Score
	I	1
	II	2
	III	3
	IV	4

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Table 3

Management of ACLF based on the PIRO model for assessment and intervention in ACLF (adapted from Jalan et al. Gastroenterology 2014)

	Assessment		Intervention
Predisposition	Severity, Etiology	MELD score, CTP score	
Injury	Precipitating Event	Viral Hepatitis	Early antivirals for hepatitis B Prednisone?
		Alcohol	
		Drugs	
		Infection	Early Antibiotics
			Nosocomial Infection coverage
Response	Inflammation		GCSF?
	Immune Failure		Role of albumin?
Organ failure	Number of organs	Renal Failure	Early RRT
	Cardiopulmonary	Intensive Care	?goal Directed Therapy
	Prognostic Score	SOFA, APACHE, CLIF	Artificial/Bio- artificial liver in selected patients? Liver transplantation