

Review

Acute-on-chronic liver failure

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Acute-on-chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease. Although there are no widely accepted diagnostic criteria for ACLF, the Asia–Pacific Association for the Study of the Liver (APASL) and the American Association for the Study of Liver Disease and the European Association for the Study of the Liver (AASLD/EASL) consensus definitions are commonly used. It is obvious that the APASL and the AASLD/EASL definitions are based on fundamentally different features. Two different definitions in two different parts of the world hamper the comparability of studies. Recently, the EASL-Chronic Liver Failure Consortium proposed new diagnostic criteria for ACLF based on analyses of patients with organ failure. There are areas of uncertainty in defining ACLF, such as heterogeneity of ACLF, ambiguity in qualifying underlying liver disease, argument for infection or sepsis as a precipitating event, etc. Although the exact pathogenesis of ACLF remains to be elucidated, alteration of host response to injury, infection, and unregulated inflammation play important roles. The predisposition, infection/inflammation, response, organ failure (PIRO) concept used for sepsis might be useful in describing the pathophysiology and clinical categories for ACLF. Treatment strategies are limited to organ support but better understanding of the pathophysiology is likely to lead to discovery of novel biomarkers and therapeutic strategies in the future. (*Clin Mol Hepatol* 2013;19:349-359)

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease.¹

Scrutiny of the existing data indicates several important conclusions regarding ACLF. First, it results in significantly higher short-term mortality than expected with decompensated liver cirrhosis. Second, the occurrence of organ failure(s) in patients with cirrhosis

indicates a poor prognosis with high mortality. It is not the severity of underlying liver disease that is important, but the severity of end-organ failure that determines prognosis. Third, it is usually associated with a precipitating event. And it has a reversible component to the acute deterioration, although the underlying cirrhosis is not reversible.

The in-hospital mortality of cirrhosis patients who need intensive care is greater than 50% in the United States. More concerning is the finding that intensive care unit (ICU) mortality rates as-

Abbreviations:

AASLD, The American Association for the Study of Liver Disease; ACLF, acute-on-chronic liver failure; AD, acute decompensation; ALF, acute liver failure; APACHE II, Acute Physiology and Chronic Health Evaluation II; APASL, The Asia–Pacific Association for the Study of the Liver; CANONIC, chronic liver failure (CLIF) Acute-on-Chronic Liver Failure in Cirrhosis; CLIF, Chronic Liver Failure; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; EASL, The European Association for the Study of the Liver; HE, hepatic encephalopathy; ICU, intensive care unit; IL, interleukin; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; PIRO, predisposition, infection/inflammation, response, organ failure; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; TNF, tumor necrosis factor

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sociated with cirrhosis have remained essentially unchanged over 20 years.² This review summarizes the current understanding of ACLF from clinical and pathophysiologic perspectives and provides an overview for current areas of uncertainty.

DEFINITIONS OF ACLF

Liver failure can develop as acute liver failure (ALF) in the absence of pre-existing liver disease, ACLF of known or unknown underlying chronic liver disease, or a chronic decompensation of an end-stage liver disease. ACLF should be clinically distinguished from ALF and decompensated liver disease that are clearly understood and defined (Fig. 1).³

ALF is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in individuals without known preexisting liver disease. The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually an International Normalized Ratio (INR) ≥ 1.5 , and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks' duration.⁴ ALF manifests itself in a much different fashion than does ACLF.

Cerebral edema is a prominent feature of the pathophysiology and management of ALF.⁵ However, the term ALF is often incorrectly applied to patients with ACLF.⁶

Conceptually, multiorgan failure can occur as a result of either a gradual but progressive decompensation or a precipitating illness on the background of previously stable cirrhosis. While both entities can lead to various features of multiorgan failure, the underlying mechanisms of liver failure, and therefore the clinical outcomes, are likely to be quite different. This latter condition has been referred to as having ACLF.⁷

The term of ACLF was first used in 1995 to describe a condition in which two insults to the liver are operating simultaneously, one of them being ongoing and chronic while the other being acute.^{3,8} In 2002, the London group proposed a working definition of ACLF: Acute deterioration in liver function over a period of 2-4 weeks, usually associated with a precipitating event, leading to severe deterioration in clinical status with jaundice and hepatic encephalopathy and/or hepatorenal syndrome with a high Sequential Organ Failure Assessment/Acute Physiology and Chronic Health Evaluation II (SOFA/APACHE II) score.⁹⁻¹¹ There have been over 13 different definitions of ACLF to date.¹²

Although there are no widely accepted diagnostic criteria for

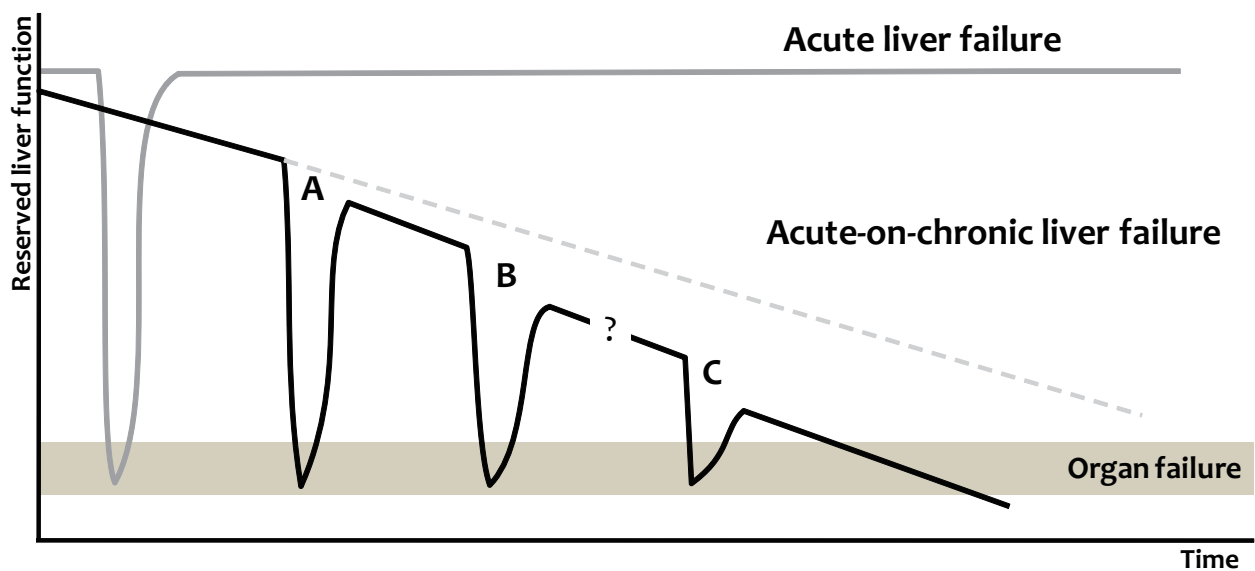


Figure 1. A conceptual schema of acute liver failure, acute-on-chronic liver failure, and decompensated liver cirrhosis. The gray line describes the course of a patient with acute liver failure. Acute-on-chronic liver failure (ACLF) is depicted by the black line. The dotted line indicates the expected course of chronic liver disease without precipitating insults. The patient with ACLF who may often have good liver function reserve can deteriorate acutely, usually in association with a precipitating event which results in organ failure and high risk of death. This patient has a potential for reversibility and recovery to the state the patient was in, although not complete. The ACLF encompasses 'severely acute on moderate chronic liver disease' entity (A) and 'moderately acute on severe chronic liver disease' entity (B) of ACLF. The clinical concept of ACLF is different from that of life-threatening decompensation of liver cirrhosis. During the course of a patient with decompensated cirrhosis, life threatening exacerbation will at some point develop organ dysfunction where the chance of reversibility is very limited (C).

ACLF, two representative consensus definitions are commonly used. The first was put forward by the Asia-Pacific Association for the Study of the Liver (APASL) in 2009³; 'Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease'. The second was a working definition as proposed by a research consortium from the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL)⁶; 'Acute deterioration of preexisting, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure' (Table 1). However, these two definitions are not evidence-based, moreover, they are incongruent.

It is obvious that the APASL and the AASLD/EASL definitions

are based on fundamentally different features. The APASL definition stresses the occurrence of ascites and/or encephalopathy within a time frame of 4 weeks in chronic liver disease, whereas the AASLD/EASL definition underlines the occurrence of multiorgan failure in patients with chronic liver disease, resulting in 3 months mortality. Two different definitions in two different parts of the world hamper the comparability of studies.¹² And this difference has led to the misconception between ACLF and acute decompensation of liver cirrhosis.¹³

Recently, the EASL-Chronic Liver Failure (EASL-CLIF) Consortium performed the EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study which was designed to develop a definition of ACLF that is able to identify cirrhotic patients with a high risk of short-term mortality (Table 1).¹⁴ And the EASL-CLIF Consortium proposed diagnostic criteria for ACLF based on analyses of 1343

Table 1. Definitions of acute-on-chronic liver failure^{3,6,14}

Proposed by	Definitions and descriptions
APASL (2009)	Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. [Note: Jaundice (serum bilirubin ≥ 5 mg/dL [85 μ mol/L]) and coagulopathy (INR >1.5 or prothrombin activity $<40\%$) are mandatory in defining ACLF]
AASLD-EASL (2011)	Acute deterioration of preexisting, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure.
EASL-CLIF Consortium (2013)	<p>Definitions of Organ Failures (using a modified SOFA score, called the CLIF-SOFA score):</p> <p>Liver failure was defined by a serum bilirubin level of ≥ 12.0 mg/dL; Kidney failure was defined by a serum creatinine level of ≥ 2.0 mg/dL or the use of renal replacement therapy; Cerebral failure was defined by grade III or IV hepatic encephalopathy, according to the West Haven classification; Coagulation failure was defined by an international normalized ratio >2.5 and/or a platelet count of $20 \times 10^9/L$; Circulatory failure was defined by the use of dopamine, dobutamine, or terlipressin; Respiratory failure was defined by a $PaO_2/FiO_2 \leq 200$ or an $SpO_2/FiO_2 \leq 200$.</p> <p>Diagnostic Criteria and Grade of ACLF:</p> <p>No ACLF This group comprises 3 subgroups: (1) patients with no organ failure, (2) patients with a single "non-kidney" organ failure (ie, single failure of the liver, coagulation, circulation, or respiration) who had a serum creatinine level <1.5 mg/dL and no hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level <1.5 mg/dL. [Note: The 28-day and 90-day mortality rates were 4.7% and 14%, respectively.]</p> <p>ACLF grade 1 This group includes 3 subgroups: (1) patients with single kidney failure, (2) patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate hepatic encephalopathy, and (3) patients with single cerebral failure who had a serum creatinine level ranging from 1.5 and 1.9 mg/dL. [Note: The 28-day and 90-day mortality rates were 22.1% and 40.7%, respectively.]</p> <p>ACLF grade 2 This group includes patients with 2 organ failures. [Note: The 28-day and 90-day mortality rates were 32.0% and 52.3%, respectively.]</p> <p>ACLF grade 3 This group includes patients with 3 organ failures or more. [Note: The 28-day and 90-day mortality rates were 76.7% and 79.1%, respectively.]</p>

APASL, Asia-Pacific Association for the Study of the Liver; AASLD-EASL, American Association for the Study of Liver Disease-European Association for the Study of the Liver; INR, International Normalized Ratio; ACLF, acute-on-chronic liver failure; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment.

patients with cirrhosis and acute decompensation (AD, defined by development of ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) who were revealed to have organ failure (defined by the chronic liver failure-sequential organ failure assessment [CLIF-SOFA] score) and high 28-day mortality rate (> 15%). This CANONIC study showed that ACLF is very frequent (overall prevalence of 30.9%) and an extremely relevant syndrome which is distinct from "mere" AD, based not only on the presence of organ failure(s) and high mortality rate (15 times higher short-term mortality than that in patients with AD alone) but also on age, precipitating events, and systemic inflammation.¹⁴

PATHOPHYSIOLOGY OF ACLF

Although the exact pathogenesis of the development of ACLF remains to be elucidated, alteration of host response to injury, infection, and unregulated inflammation play important roles. In these complex patients, a concept similar to the predisposition, infection/inflammation, response, organ failure (PIRO) concept in sepsis¹⁵ might be useful in describing the pathophysiology and clinical categories.¹

Underlying liver disease (predisposition, P)

Predisposition corresponds to the severity and etiology of underlying liver disease. Compensated cirrhosis of any etiology is the majority of disease qualified as underlying chronic liver disease of ACLF. Cholestatic and metabolic liver diseases are also qualified as underlying disease. In addition, chronic hepatitis and nonalcoholic steatohepatitis are possible underlying disease. However, steatosis is not included as an underlying disease.³

Alcoholic cirrhosis constitutes 50-70% of all underlying liver diseases of ACLF in the Western countries, whereas hepatitis-related cirrhosis constitutes about 10-30% of all cases. However, in most of the Asian countries, hepatitis B constitutes about 70% and alcohol only about 15% of all the etiologies of ACLF.^{1,3,6}

Patients with cirrhosis are more likely to develop infection and sepsis than the general population. The reasons for this are multifactorial and include dysfunction of the reticuloendothelial and cellular immune system and defects in the barriers to bacterial translocation. Because infection has such an intimate relationship with ACLF, infection may in fact be the central feature of this entity, although this is yet to be proven. The powerful association between infection and deleterious outcomes in cirrhosis mandates

aggressive surveillance and early treatment of suspected infection.⁶

The severity of underlying disease can be assessed by the Child-Turcotte-Pugh (CTP) or Model for End-Stage Liver Disease (MELD) scores.

Precipitating events (infection/inflammation, I)

The precipitating events (Table 2) vary depending on the geographic region and the population under study. In the East, reactivation of hepatitis B or superimposed viral hepatitis is common, whereas alcohol and drugs predominate in the West.

Injury is indicated by both hepatic and nonhepatic precipitating events by Western experts.^{1,6} On the other hand, in the APASL consensus recommendations,³ "the experts also felt that the primary precipitating event, the acute hepatic insult, should be hepatic in origin. However, this may not always be easy to discern." This difference between the East and the West is particularly distinct for cases of sepsis or variceal bleeding.

Bacterial translocation may play a pivotal role in the progression from compensated to decompensated liver cirrhosis (as marked by the development of ascites, variceal bleeding, encephalopathy) via the systemic inflammatory response syndrome (SIRS).

However, a considerable proportion of patients with ACLF have no precipitating events. The lack of a specific precipitating factor in about 40% of patients with ACLF is intriguing. This finding places an impetus into the discovery of novel biomarkers that could predict ACLF development that occurs without 'classic' precipitating factors.¹³ In the CANONIC study, the proportion of cases without previous episodes of acute decompensation (development of ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) was 23.2% of patients with ACLF at enrollment, indicating a relatively frequent development of acute decompensation of cirrhosis in the form of ACLF.¹⁴

Table 2. Precipitating events of ACLF

Infection (bacterial, fungal, or viral)
Reactivation of hepatitis B (or C) or superimposed viral hepatitis (e.g., hepatitis E in India)
Alcohol
Drug-induced liver injury (e.g., herbal medicines)
Gastrointestinal bleeding
Portal vein thrombosis
Surgery
Ischemia
Flare of autoimmune hepatitis or Wilson disease

Host response to injury (response, R)

Host response determines the severity of injury. Inflammation and neutrophil dysfunction are of major importance in the pathogenesis of ACLF. There is increasing evidence that SIRS (the presence of 2 or more of the following SIRS components: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; heart rate $>90/\text{min}$; respiratory rate $>20/\text{min}$ or $\text{PaCO}_2 <32 \text{ mmHg}$; $\text{WBC} >12,000/\text{mm}^3$, $<4,000/\text{mm}^3$, or $>10\%$ 'bands'), characterized by a prominent pro-inflammatory cytokine profile, causes the transition from stable cirrhosis to ACLF.^{7,9,16}

The relationship between SIRS and infection leads one to hypothesize that an inflammatory response may lead to immune dysregulation, which may predispose to infection that would then further aggravate a pro-inflammatory response resulting in a vicious cycle.^{1,17} Wasmuth et al¹⁸ demonstrated that patients with ACLF have immunologic 'defects' that are comparable to those in patients with sepsis. The clinical pictures of ACLF and septic shock are strikingly similar, characterized by progressive vasodilatory shock and multiple organ failure.^{3,18}

Cytokines are believed to play an important role in ACLF. Elevated serum levels of several cytokines, including tumor necrosis factor (TNF)- α , sTNF- α R1, sTNF- α R2, interleukin (IL)-2, IL-2R, IL-4, IL-6, IL-8, IL-10, and interferon- α , have been described in patients with ACLF.¹⁹ TNF- α and IL-6 probably have dual actions of inducing hepatocyte death and promoting hepatocyte proliferation. The transition from a stable cirrhotic condition to acute decompensation leading to liver failure is based on acute SIRS, mainly mediated by cytokines.^{3,20}

Inflammation, as measured by C-reactive protein (CRP), was unable to predict clinical outcome at the onset of organ failure. However, change in CRP levels over time was able to discriminate survivors from nonsurvivors. Poorer outcome in the patients whose CRP levels failed to improve leads to the hypothesis that inability to resolve inflammation may be pathophysiologically important in this syndrome.⁷

Clinical outcomes (organ failure, O)

Patients with ACLF have a statistically higher mortality rate at the same MELD score than patients without ACLF.⁶

Regardless of the precipitating event, the final common pathway leading to acute deterioration of liver function and multiorgan failure appears to be a deranged and exaggerated activation of systemic inflammation, which is then followed by a period of immune system paralysis.^{18,21} The initial cytokine storm is responsible

for profound alterations in macrocirculation, microcirculation, and disruption of normal organ function, resulting in multiorgan failure.²² After the initial 'storm' subsides, a resultant compensatory antiinflammatory response system sets the patient up for subsequent nosocomial infection, sepsis, and further deterioration; a pattern not uncommon in critically ill cirrhotic patients.⁶

A 'multiple hit' or 'critical mass' hypotheses have been suggested. The finding that patients with recent hospitalization (within 6 months) have markedly worse mortality (78% vs. 34% in those without recent hospitalization) suggests that multiple 'hits' predispose patients to poor outcomes. The mechanism is suspected to be related to the lack of full recovery to previous baseline (reduction in functional cell mass) and/or derangements in the function of immune and inflammatory response systems.⁶

The occurrence of organ failure alters the natural history of cirrhosis. Recent data clearly show that the patients who recover from organ failure and are discharged from the hospital have almost universal mortality over the next three years, suggesting that the natural history of cirrhosis is altered by the occurrence of organ failure.⁷

Liver dysfunction

Hyperbilirubinemia is almost invariably present and jaundice is considered an essential criterion of ACLF.⁹ Ongoing liver injury begets an intensified inflammatory response with further liver injury, which culminates in an inexorable downward spiral and death.²

ACLF due to nonspecific insults such as a variceal hemorrhage or bacterial infection is likely to be different from those due to liver-specific insults such as alcohol, drug-induced liver injury, or superimposed viral hepatitis. There are no differences in portal hemodynamics between decompensated cirrhosis and ACLF when defined according to the APASL criteria. However, portal pressure was markedly higher in those with ACLF than in decompensated cirrhosis when ACLF was defined according to the AASLD/EASL definition. These results demonstrate the need for careful definition of the population under study.^{1,23,24}

Besides jaundice, another hallmark of liver dysfunction is coagulopathy. Coagulation tests are usually abnormal in cirrhotic patients due to impaired synthesis and increased consumption of coagulation factors. Prolongation of the prothrombin time is common but spontaneous bleeding is rare. A relative decrease in anticoagulant factors serves to offset the decrease in procoagulant factors.² Bleeding abnormalities and hypercoagulability may coexist.

Kidney dysfunction

The most common organ to fail besides liver is the kidney. Renal failure may be categorized into four types: hepatorenal syndrome, parenchymal disease, hypovolemia-induced and drug-induced renal failure.² Epidemiologic data suggest that prerenal acute kidney injury develops in 68% of patients, and intrinsic kidney injury including acute tubular necrosis in 32%.²⁵

Bacterial infection (such as spontaneous bacterial peritonitis) is the most common precipitating cause of renal failure in cirrhosis, followed by hypovolemia (secondary to gastrointestinal bleeding, excessive diuretic treatment).^{2,26,27} The role of inflammation in modulating renal dysfunction associated with ACLF is highlighted by the benefit of anti-inflammatory agents such as albumin, pentoxifylline and N-acetylcysteine, which decrease the risk of renal dysfunction in patients with alcoholic hepatitis.¹

Biomarkers of interest are markers of tubular injury such as kidney injury molecule-1, pi and alpha glutathione S-transferase; as well as markers of inflammation such as NAG, NGAL, FABP, and IL-18.^{1,28}

In the CANONIC study, kidney failure was the most prevalent organ failure for ACLF grade 1. For ACLF grade 2, liver failure was the most prevalent organ failure, followed by kidney, cerebral, and coagulation failures. For ACLF grade 3, the prevalence of all organ failures was high or moderately high.¹⁴

Brain dysfunction

In ACLF, hepatic encephalopathy (HE) is a common manifestation. HE may either be a precipitating factor or a consequence of ACLF.⁹

Local and systemic changes have been implicated in the pathophysiology of development of HE. From a pathophysiological perspective, brain swelling is an important feature of ACLF, similar to the situation in ALF. As this syndrome occurs in the background of existing cirrhosis and chronic portocaval shunting, brain atrophy may be protective against brain swelling, resulting in a moderate increase in intracranial pressure.¹

Reduction in bacterial translocation using a nonabsorbable antibiotic, rifaximin, was shown to prevent the occurrence of HE, suggesting that reducing inflammation may be protective as well.²⁹

Cardiac and circulatory dysfunction

The hallmark of ACLF is cardiovascular collapse akin to that in patients with ALF and severe sepsis, often requiring large doses of inotropes. Unlike in decompensated cirrhosis, where cardiac output remains elevated, in ACLF, cardiac output can be reduced

where both systolic and diastolic function are affected. This cardiovascular abnormality is associated with an increased risk of death, particularly in those patients who present with renal dysfunction.¹

Lung dysfunction

Respiratory complications in ACLF can be broadly categorized as acute respiratory failure (e.g., pneumonia) and those that arise as a consequence of cirrhosis (e.g., portopulmonary hypertension and hepatopulmonary syndrome). Patients with cirrhosis are at increased risk of pneumonia. The risk of aspiration pneumonia is also high because of altered consciousness, gastric stasis, increased intra-abdominal pressure due to ascites, and ileus resulting from infection and electrolyte abnormalities.²

PROGNOSTIC EVALUATION

In a prospective study from India, the 30- and 90-day mortality was 50% and 63%, respectively, which are similar to those found in Western literature.^{30,31}

Two categories of prognostic models have been used: first, those evaluating the severity of liver disease and, second, those evaluating the dysfunction of several organ systems. It has been shown that liver function is not the main determinant of clinical outcome for patients with decompensated cirrhosis; thus liver-specific scoring systems, such as the CTP or the MELD score, have limitations in accurately predicting the outcome of patients with ACLF. Organ failure scores, such as the APACHE II and III and SOFA score, are more helpful in predicting survival.^{6,9,17}

Although the SOFA score has been shown to accurately assess early short-term mortality in ACLF, a key problem of using the SOFA score is that it is reflective and not predictive of organ failure, thereby limiting its usefulness as an early intervention tool. The perfect system for early identification of patients with cirrhosis who are likely to suffer from ACLF has not been defined.^{6,9,17}

AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Differences in definition of ACLF between the East and the West

The differences in definition largely reflect the differences in un-

Table 3. Differences in current definitions of acute-on-chronic liver failure¹³

	APASL	AASLD/EASL
Qualification for chronic liver disease	Mainly compensated cirrhosis but including other chronic liver diseases	Only cirrhosis, including prior decompensation
Qualification for precipitating events	Not include sepsis & No consensus on variceal bleeding	Sepsis and variceal bleeding qualifies as precipitants
Duration between insult and ACLF	4 weeks	Not defined
Duration showing high mortality	Not defined	3 months

derlying etiologies of acute deterioration of liver disease between the East and the West. In the Asia-Pacific region, the majority of ACLF is precipitated by hepatitis B flares and acute hepatitis A or E superimposed on chronic liver disease which is not necessarily cirrhosis. In sharp contrast, in Western societies, these viral etiologies are largely supplanted by nonviral insults, especially bacterial infections, in patients who are either known or are discovered to have cirrhosis upon admission (Table 3).¹³ There is an urgent need for a worldwide consensus definition for ACLF.

Heterogeneity of ACLF and its prognostic significance

ACLF constitutes an illness in which two simultaneous insults are operating: acute and chronic. Different combinations of each insult may result in the same level of decompensation. There are two scenarios. One case with moderate chronic liver disease but severely acute liver insult leading to ACLF (Fig. 1A) and another case with severe chronic liver disease and moderately acute insult leading to ACLF (Fig. 1B). The resulting severity of ACLF is the same in these two situations.³ The prediction of the outcome of ACLF patients is difficult because of the complexity of ACLF that depends on two simultaneous insults, acute and chronic. It is unclear whether the prognosis of the patient depends on the degree of severity of the acute event or on the preexisting chronic liver disease or on the combination of both.¹²

Ambiguity in qualifying underlying liver disease: decompensation

Development of jaundice, ascites, hepatic encephalopathy, or variceal bleeding is known to constitute hepatic decompensation.³ Acute deterioration of life-threatening decompensated cirrhosis is not regarded as ACLF. But the differentiation between ACLF and decompensated liver cirrhosis may remain difficult (Fig. 1C). It is likely that the most important difference between both entities is

the potentially reversible nature of ACLF, by controlling the precipitating factor.⁹

Patients presenting with decompensated cirrhosis without an acute precipitating event may also suffer from multiorgan dysfunction. In clinical practice, such patients, although not considered as ACLF, are treated in the same way as ACLF patients and have a similar bad prognosis. This is because both patient groups, decompensated cirrhosis and ACLF, start with a comparable bad clinical condition that deteriorates in a subacute or acute way, respectively. There is a 'gray zone' between these two groups and a clear distinction remains problematic.¹² Olson et al⁶ distinguished the natural progression of cirrhosis that leads to life threatening decompensation from the acute insult that results in the ACLF syndrome. When the decompensation of cirrhosis is prior to the onset of an acute event, patients should not be referred to as ACLF patients. This is also in agreement with Garg et al.³⁰ Nevertheless, no simple diagnostic tool exists for differentiating decompensated cirrhosis from ACLF.

Controversy in defining liver failure

The characteristics of the APASL definition are as follows: first, both jaundice and coagulopathy are mandatory in defining liver failure; second, laboratory abnormalities are relatively mild compared to other studies. The APASL recommendations explain these characteristics as follows: "Jaundice is considered an essential criterion for the diagnosis of ACLF. Various authors have used different cutoff levels of jaundice, varying from a serum bilirubin of 6-20 mg/dL. All the experts unanimously agreed to take a lower cutoff level of serum bilirubin (i.e., 5 mg/dL) to enroll a larger group of patients for the evaluation of the natural history of these patients. All agreed on the concept of coagulopathy as mandatory for defining liver failure. As in acute liver failure, INR >1.5 was considered an essential criterion for the diagnosis of coagulopathy."³

Interestingly, in the CANONIC study, cirrhotic patients with acute decompensation (i.e., with ascites, encephalopathy, gastro-

intestinal hemorrhage, or bacterial infection) and single liver failure (or any other single 'nonkidney' organ failure) had a low risk of death unless they also had kidney dysfunction and/or mild to moderate hepatic encephalopathy. These findings indicate that, when isolated, liver failure (as defined by the CLIF-SOFA score; bilirubin ≥ 12 mg/dL) is not necessary for the diagnosis of ACLF.¹⁴

Argument for infection or sepsis as a precipitating event

Of the precipitating events identified, infection is regarded as the most common cause and associated with the worst prognosis in the West.^{1,2} However, in the APASL consensus recommendations, sepsis is not regarded as an acute event in ACLF; "Sepsis plays an important role in the progression and management decisions of ACLF, but whether it acts as an initial precipitating event or not is debatable. The existing literature from the United Kingdom and the United States have included sepsis as an integral cause for the development of ACLF. However, it was argued that sepsis alone might not directly cause an acute hepatic insult but could result in worsening of the condition of the patient. Furthermore, sepsis per se can cause organ failure in cirrhotic patients without direct hepatic derangements. It was therefore not considered as a cause of acute insult. To bring homogeneity to the population under consideration for ACLF, it was proposed that any infectious agent directly afflicting the liver leading to acute derangement in its function should be included."³

In the CANONIC study, bacterial infection was seen more frequently in those with worse ACLF grade (Fig. 2).¹⁴ Higher CLIF-SOFA score and increased leukocyte count were independently and significantly associated with mortality. Moreover, the prevalence of bacterial infections could have been higher if more sensitive diagnostic techniques had been used. Alternatively, the release of pathogen-associated molecular patterns (resulting from 'aseptic' intestinal bacterial translocation) or danger-associated molecular

patterns (resulting from tissue injury) might be unrecognized precipitating events.^{14,17} In the multicenter North American Consortium for the Study of End-Stage Liver Disease (NACSELD) study, infections in patients with cirrhosis were associated with a significantly high risk of mortality that was independent of their liver disease severity.³¹

Debate on variceal bleeding as a precipitating event

Gastrointestinal bleeding is regarded as a common precipitant of acute deterioration of chronic liver disease in the West.^{1,2} Although 'variceal bleed' is defined as an acute event in the APASL consensus recommendations, the level of evidence is low and the grade of recommendation is weak; "Variceal bleeding has also been taken as an acute insult of ACLF in some western trials. It was extensively debated whether to consider variceal bleed as an acute event of ACLF... Most experts considered variceal bleed as an expression of elevated portal pressure and a form of decompensation of underlying chronic liver disease but not as an acute event leading to ACLF. However, no unanimous consensus could be reached to label acute variceal bleeding as an acute event for ACLF."³

In the CANONIC study, gastrointestinal hemorrhage was not more frequent across worsening ACLF grade (Fig. 2).¹⁴

MANAGEMENT

Early interventions to reduce or correct injury are crucial. The goals of treatment are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs.² Intensive care management is frequently required in the management of patients with ACLF. Care of these critically ill patients with impending multiple organ failure requires a team approach with expertise in both hepatology and critical care.¹

Echocardiography provides a robust assessment of ventricular function and response to volume infusion. The optimal mean arterial pressure goal is unknown. Norepinephrine is titrated to achieve a mean arterial pressure of 65-70 mmHg. Terlipressin is norepinephrine-sparing in sepsis and appears to have a similar effect in patients with cirrhosis.²

Endotracheal intubation for airway control is mandatory in patients with severe encephalopathy and/or in the presence of active upper gastrointestinal bleeding. Routine administration of seda-

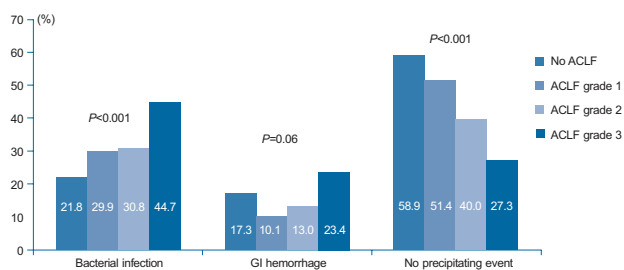


Figure 2. Patient characteristics at CANONIC study enrollment.¹⁴ ACLF, acute-on-chronic liver failure; GI, gastrointestinal.

tives is rarely necessary. In fact, sedatives delay extubation and prolong altered consciousness.²

Renal replacement therapy is recommended to treat fluid, electrolyte, and acid-base abnormalities, but is not associated with improved outcomes in hepatorenal syndrome.²

Elevated intraabdominal pressure due to tense ascites may also result in abdominal compartment syndrome, which can lead to renal, cardiovascular, and respiratory dysfunction.^{2,32} Maintenance of appropriate intraabdominal pressure by large volume paracentesis with concomitant albumin replacement is required.

Because overt signs of infection may be absent, a high index of suspicion is necessary for diagnosis. In patients in whom infection is suspected, early use of broad spectrum antibiotics, preferably within 1 hour of admission, is highly recommended. Testing for *Clostridium difficile* infection should be routinely performed and repeated in critically ill patients with diarrhea. This serious infection may be overlooked in patients receiving lactulose therapy.^{2,33}

Interventions to normalize abnormal coagulation parameters are hard to achieve and volume overload can limit the use of fresh frozen plasma. Vitamin K, given at 2 mg intravenously daily for 3-5 days, should be administered to eliminate vitamin K deficiency. Contrary to widely held beliefs, even patients with a prolonged INR can develop deep vein thrombosis and resultant complications. In the absence of contraindications, patients with cirrhosis should have mechanical deep vein thrombosis prophylaxis, but routine pharmacologic deep vein thrombosis prophylaxis is not recommended.^{2,34}

Massive acute hemorrhage should be managed with transfusion of red blood cells and fresh frozen plasma given in a 1:1 or 2:1 ratio with transfusion of platelets and cryoprecipitate to address consumption. Fibrinolysis is common. Treatment of fibrinolysis with epsilon-aminocaproic acid or tranexamic acid is indicated when bleeding persists. When the partial thromboplastin time is excessively prolonged, use of protamine, even in the absence of heparin therapy, may be beneficial to counteract endogenous heparin-like compounds.²

Thiamine deficiency should be considered in all patients with chronic liver disease. Trace mineral deficiencies such as zinc and selenium are well documented in cirrhosis. Zinc replacement at a dose of 25-50 mg elemental zinc three times daily is required.²

'Tight' glucose control is not desirable. Thus, in patients with cirrhosis, maintaining blood sugars in the range of 140-180 mg/dL is recommended.³⁵ Patients with relative adrenal insufficiency may benefit from steroid therapy with hemodynamic improvement and decreased mortality. However, routine use of steroids was not

beneficial in a recent controlled trial.³⁷ Therefore, in the absence of adrenal insufficiency, steroid therapy in critically ill patients with cirrhosis is not recommended.^{2,36,37}

In a recent randomized clinical trial, granulocyte-colony stimulating factor therapy, which restores neutrophil function, was associated with improved survival of patients with ACLF.³⁸ More studies are needed to provide firm evidence.

Liver transplantation is required in selected patients to improve survival and quality of life. Treatment is futile in some patients, but it is difficult to identify these patients *a priori*.²

Liver support devices including acellular artificial livers such as albumin dialysis and plasma exchange/diafiltration and cellular bioartificial livers which incorporate animal, transformed or human cells did not show any survival benefit so far and failed to gain U.S. Food and Drug Administration approval at this time.

CONCLUSIONS

ACLF is a devastating syndrome which defines a subgroup of patients with chronic liver disease who develop organ failure with high mortality. ACLF is a clinically, pathophysiologically, and prognostically distinct entity. In ACLF, deranged host response to precipitating injury plays a pivotal pathophysiological role, such as SIRS. The degree of background immune paralysis and severity of organ failure determine the outcome of this syndrome. However, there are areas of uncertainty in defining ACLF, such as heterogeneity of ACLF, ambiguity in qualifying underlying liver disease, argument for infection or sepsis as a precipitating event, etc. Treatment strategies are limited to organ support but better understanding of the pathophysiology of ACLF is likely to lead to discovery of novel biomarkers and therapeutic strategies in the future.

Conflicts of Interest

The authors have no conflicts to disclose.

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