Curr Hepatology Rep (2015) 14:40–45
DOI 10.1007/s11901-015-0254-x

MANAGEMENT OF THE CIRRHOTIC PATIENT (NS REAU AND A CARDENAS, SECTION EDITORS)

Acute-on-Chronic Liver Failure: Can We Agree on a Definition?

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Published online: 27 February 2015

Abstract Acute-on-chronic liver failure (ACLF) has recently received more recognition. It is a condition characterized by acute clinical deterioration in patients with chronic liver disease and is often associated with a precipitant event. It is a form of decompensated cirrhosis characterized by the presence of extrahepatic organ failure and high short-term mortality. Several definitions have been recently proposed for ACLF; however, larger prospective studies are still needed to refine our understanding of this new entity. This article explores the most recently proposed definitions, classification, and prognostic models of ACLF.

Keywords Liver failure · Cirrhosis · Hepatic decompensation · Multiorgan failure

Introduction

Chronic liver disease and cirrhosis remain the 12th leading cause of death in the USA, despite major improvements in the care of this population in the last several decades [1].

Cirrhosis progression often follows a nonlinear pattern, and this observation leads to the concept of a potentially reversible condition termed acute-on-chronic liver disease (ACLF) (Fig. 1). Over the recent years, multiple definitions have been proposed for ACLF, some with significant differences, which has led to confusion in the field. Therefore, a clear and universal definition of ACLF is urgently needed, so this entity can be easier recognized and we can provide better care and counseling to our patients.

This article is part of the Topical Collection on *Management of the Cirrhotic Patient*

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Definition

Until the recent years, our knowledge of the natural history of cirrhosis was limited to two clinical stages: compensated and decompensated. A large systemic review including 118 studies and a total of 23,797 patients then divided each of these stages into two subgroups according to the presence or absence of esophageal varices and ascites, the latter considered a landmark sign of decompensated cirrhosis [2]. These studies, however, did not evaluate the prognostic value of single- or multiple-organ failures in the course of chronic liver diseases. Patients with cirrhosis and acute organ failure(s) have high short-term mortality rates and have generally been considered as having acute-on-chronic liver failure (ACLF). This concept was, until 2013, based mostly on expert opinion given the lack of evidence-based definitions.

Both the Asia Pacific Association for the Study of the Liver (APASL) and a joint conference of European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) proposed definitions for acute-on-chronic liver failure. Unfortunately, there were significant differences in the definitions, and a unifying concept for ACLF was still lacking.

The APASL defined ACLF as "acute hepatic insult manifesting as jaundice (bilirubin level >5 mg/dL) and coagulopathy (international normalized ratio >1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease" [3•]. Both cirrhotic and noncirrhotic chronic liver disease are

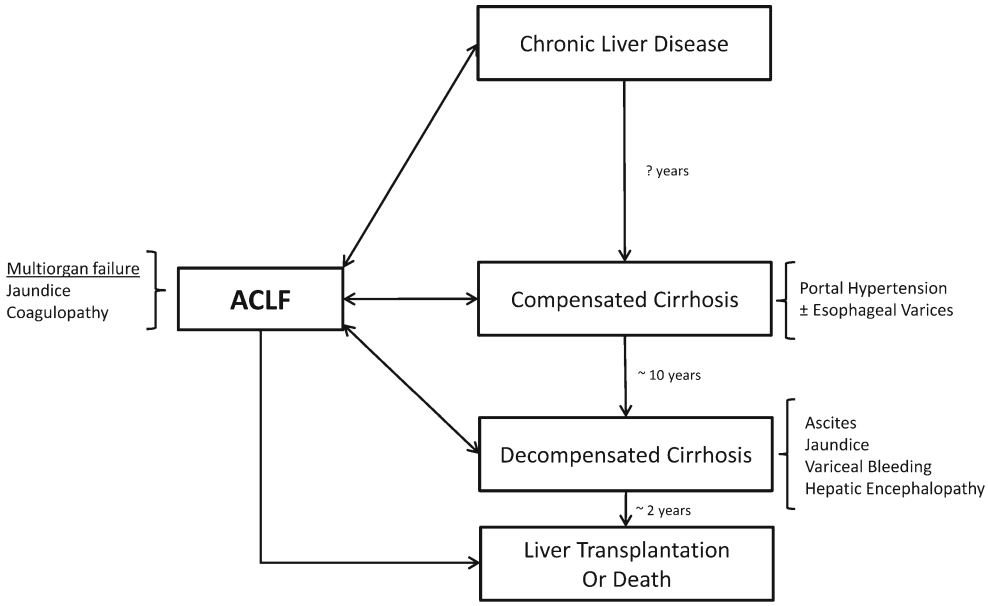

Fig 1 Natural history of chronic liver disease and acute-on-chronic liver failure (ACLF)

included in the APASL definition, but only primarily hepatic-related insults are considered as precipitating events. EASL/AASLD defined ACLF as "an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure" [4•]. Only cirrhotic disease is included in their definition, and extrahepatic insults such as sepsis are also considered as precipitating events.

In 2013, the European Chronic Liver Failure (CLIF) Consortium, endorsed by the EASL, published the first multicenter, prospective, observational study in patients with acute-on-chronic liver failure [5••]. The study enrolled 1343 cirrhotic patients from eight European countries between February and September 2011. Acute decompensation was defined by the development of large ascites, gastrointestinal hemorrhage, bacterial infections, or any combination of these events. The investigators then used a modified Sequential Organ Failure Assessment (SOFA) score (CLIF-SOFA scale) to define organ failure(s). This scale was designed prior to the onset of the study, and it assessed the function of six systems (liver, kidneys, brain, coagulation, circulation, and lungs). ACLF was then diagnosed based on a predefined 28-day mortality rate of 15 %. Acute kidney injury as defined was associated with a higher mortality compared to any other single-organ failure. Also the importance of extrahepatic organ failure for the diagnosis of ALCF was demonstrated by a lower mortality rate (4 %), for example, in patients with significantly elevated serum bilirubin without any extrahepatic damage.

The North America Consortium for the Study of End-Stage Liver Disease (NACSELD) study also attempted to define a group of cirrhotic patients at risk for multiorgan failure and consequently higher mortality rates [6•]. This study also demonstrated the importance of organ failure with the presence of two or more extrahepatic organ failures being associated with poor survival in cirrhotic patients. This study, however, only included cirrhotic patients with acute bacterial infections.

Because of limited prospective data, a unifying interim concept for ACLF has been recently proposed on behalf of the World Gastroenterology Organization (WGO) [7••]. The WGO working party on "Definition of Acute on Chronic Liver Failure" defined ACLF as "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 International Normalized Ratio [INR]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset" (Table 1). This is a working definition and serves as a guideline as to which patients are to be studied and data collected.

Precipitating Events

One important feature of ACLF is the presence of one or more precipitating events leading to acute hepatic decompensation (Table 2). These factors, however, do differ based on geographic location: reactivation of hepatitis B and superimposed hepatitis A, D, or E are important causes of ACLF in the East [8], whereas in the Western centers, acute alcoholic hepatitis and bacterial infections are far more common. It has been estimated that infections are present at admission or develop during hospitalization in about 25–35 % of cirrhotic patients, and they increase 3.75-fold the mortality risk in this

Table 1 Precipitant events

Precipitant events of acute-on-chronic liver failure
1. Viral hepatitis
Acute hepatitis A
Acute hepatitis E
Superimposed acute hepatitis D on chronic hepatitis B
Hepatitis B reactivation
2. Bacterial infections
3. Acute alcoholic hepatitis
4. Gastrointestinal bleeding
5. Major surgery
6. Drug-induced liver injury
7. Insertion of transjugular intrahepatic portosystemic shunt
8. Large-volume paracentesis without intravenous albumin administration
9. Hypotension
10. Major surgery
11. Portal vein thrombosis
12. Idiopathic

population [9–12]. Of note, the CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) Study identified bacterial infection as a precipitating event in only about 33 % of patients with ACLF. Alcoholic hepatitis is another frequent cause of ACLF, present in about 24.5 % of patients. This involves a younger population more likely to receive corticosteroids for severe alcoholic hepatitis.

Other identified insults include drug-induced liver injury, insertion of a transjugular intrahepatic portosystemic shunt, large-volume paracentesis without intravenous albumin administration, gastrointestinal bleeding, hypotension, and major surgery. Of note, however, a precipitating factor cannot be identified in about 45 % of patients with ACLF admitted to the hospital.

Most events are either ischemic or infectious in nature, and the inflammatory response seems to play an important role in the outcomes of ACLF. The CANONIC Study demonstrated that elevated serum C-reactive protein (CRP) and/or an increased leukocyte count are associated with worse outcomes.

Extrahepatic Organ Failure

An extremely important component of ACLF is the presence of organ failure. As mentioned earlier, the definition of ACLF is based on the presence of one or more extrahepatic organ failures in the setting of acute hepatic dysfunction. This concept is critical in differentiating ACLF from decompensated cirrhosis.

Renal Dysfunction

Acute kidney injury has been associated with high mortality in patients with underlying cirrhosis, which is reflected by the weight of serum creatinine level in the Model for End-Stage Liver Disease (MELD) score [13]. Renal failure as defined by the CLIF-SOFA score carries the most prognostic value in ACLF as, even in the absence of other organ failures, it is associated a 28-day mortality of 18.6 %, compared to the defined single-liver, coagulation, circulation, respiration, or cerebral failure which are associated with a 28-day mortality of 5–8 % [5••].

The pathophysiology of renal dysfunction, in addition to its severity, also has prognostic implications. Hepatorenal syndrome (HRS), a well-known complication of cirrhosis, is thought to be secondary to severe circulatory dysfunction leading to splanchnic vasodilatation and significant renal vasoconstriction [14]. A different mechanism, associated with systemic bacterial infection, seems to be mediated by increased proinflammatory cytokines in addition to circulatory changes. Indeed, in about 30–40 % of patients with cirrhosis who develop acute kidney injury, a bacterial infection is the precipitating event [15]. Whereas HRS is felt to be a reversible condition after liver transplantation, evidence of renal tubular injury increases the likelihood of renal replacement therapy posttransplant [16]. Another evidence of the role of inflammation in ACLF-related kidney dysfunction is the observed benefit of the anti-inflammatory agent, pentoxifylline, in decreasing the risk of kidney injury in patients with alcoholic hepatitis [17]. Finally, long-term intestinal decontamination with daily oral norfloxacin for primary prophylaxis of spontaneous

Table 2 Proposed definitions of ACLF

Comparison of proposed definitions of ACLF			
	AASLD/EASL consensus	APASL definition	WGO definition
Duration	3 months	Less than 4 weeks	Less than 3 months
Manifestations	Not specified	Jaundice Coagulopathy Ascites and/or HE	Jaundice Coagulopathy
Organ failure	Multisystem organ failure	Not specified	One or more extrahepatic organ failure
Chronic liver disease	Only cirrhosis stage	Any stage	Any stage

bacterial peritonitis leads to a significant reduction of acute renal failure and improved survival [18].

Cerebral Dysfunction

Similar to acute liver failure, and as opposed to those with chronic hepatic decompensation, patients with ACLF may develop cerebral edema [4••]. The cerebral edema in this population is thought to result from a combination of hyperammonemia and the systemic inflammatory response. The synergy between hyperammonemia and inflammation in the development of acute brain swelling has been demonstrated in animal studies [19]. Rifaximin, a non-absorbable antibiotic, has been shown to decrease gut bacterial translocation and consequently systemic inflammation [20]. The role of non-absorbable antibiotics in the prevention of ACLF needs further study.

Circulatory Dysfunction

Similar to severe sepsis, the cardiovascular changes in ACLF are driven by systemic inflammatory response syndrome (SIRS) and a consequent increase in proinflammatory cytokines, such as tumor necrosis factor and nitric oxide, which promote peripheral vasodilation. Also the appropriate response to vasoconstrictors is impaired in ACLF as a consequence of low cortisol levels [21]. This exaggerated peripheral vasodilation in ACLF further decreases the cardiac afterload. Inotrope support is often required, but the preferred agent in this condition is unclear [22].

Respiratory Dysfunction

Most patients admitted to medical ICU require mechanical ventilation for various reasons, including airway protection on hepatic encephalopathy and/or variceal bleed and respiratory failure, often related to pulmonary infections. Respiratory tract infections represent 14 to 48 % of all infections in cirrhotic patients [23]. Unfortunately, the 1-year mortality in patients with ACLF who require mechanical ventilation is extremely high at 89 %. Elevated serum bilirubin at discharge from ICU and length of ventilation greater than 9 days are independent risk factors for poor survival [24].

Coagulation Dysfunction

Multiple abnormalities in the coagulation and fibrinolytic systems are present in patients with cirrhosis [25]; however, the pro- and anticoagulant factors are thought to be in equilibrium in stable cirrhosis with normal levels of thrombin generation [26]. In cirrhotic patients with bacterial infection, endogenous low-molecular-weight heparinoids have been identified in the serum, but not in noninfected patients. These disappeared after the resolution of infection [27].

Sepsis is known to cause defects in platelet aggregation [28], and this may contribute to the hemostatic impairment observed in infected cirrhotics. Finally, the well-known protective effect of antibiotics in reducing early variceal rebleeding rates also illustrates the detrimental effect of bacterial infections in the coagulation system in cirrhosis [29].

Prognostic Models

Multiple generic scoring systems may be used to help predict outcomes in patients with ACLF. Few models may be applied based on the potential cause of ACLF. The MELD score and the Maddrey discriminant function have been shown to predict early mortality in acute alcoholic hepatitis, a common precipitant of ACLF [30–32]. The Lille model is also used in this group of patients for the assessment of short-term prognosis in response to glucocorticoid therapy [33]. For cirrhotic patients undergoing surgery, another important precipitant for ACLF, a combination of the MELD score, age, and American Society of Anesthesiologists classification is predictive of short-term mortality [34].

Commonly used scoring systems, including the Child-Turcotte-Pugh score and the MELD score, are fairly liver specific. The MELD score also assess the kidney function and coagulation [13]. Given that ACLF is characterized by the presence of extrahepatic (multi)organ failure, a generic organ failure score, such as the SOFA score, has been used. Recently, the EASL-CLIF Consortium proposed a modified SOFA score to include factors associated with chronic liver disease (CLIF-SOFA scale) [5••].

The CLIF-SOFA scale assessed the function of six organ systems (liver, kidneys, brain, coagulation, circulation, and lungs). Each organ system received a subscore from 0 (normal) to 4 (most abnormal), with a total range of 0 to 24. Liver failure was defined by serum bilirubin greater than 12.0 mg/dL. Kidney failure was defined by serum creatinine greater than 2.0 mg/dL or need for renal replacement therapy. This degree of serum creatinine elevation represents significant dysfunction, but is highly specific in the prediction of mortality. Perhaps, the use of the AKIN definition would be more sensitive as a predictor of mortality. Cerebral failure was defined by grade III or IV hepatic encephalopathy based on the West-Haven Classification. Coagulation failure was defined by an INR greater than 2.5 and/or platelet count of 20×10^9/L or less. Circulatory failure was defined by the use of catecholamines or terlipressin for systolic arterial pressure of less than 90 mmHg. Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (FiO2) of 200 or less or a pulse oximetric saturation of FiO2 ratio of 200 or less.

Classification

The recently published CANONIC study divided cirrhotic patients admitted to the hospital for an acute complication into four groups, based on the association of organ failure(s) with short-term (28 days) mortality: no ACLD and ACLF grades 1, 2, and 3. Patients with no organ failure or with a single-organ failure but no evidence of kidney dysfunction (creatinine less than 1.5 mg/dL) and/or mild to moderate encephalopathy are not considered as having ACLF. Grade 1 ACLF includes patients with single-organ failure (liver, coagulation, circulation, or respiration) plus kidney dysfunction (creatinine greater than 1.5 mg/dL) and/or hepatic encephalopathy as well as patients with a single-kidney failure. This group has a 28-day mortality rate of 18–30 %. Grade 2 ACLF includes patients with two organ failures, with a 28-mortality rate of 32 %, and grade 3 ALCF includes those with three or more organ failures, with a very high 28-day mortality above 75 % [5••].

The WGO working party on "Definition of Acute on Chronic Liver Failure" recently proposed dividing ACLF into three categories based on whether or not there is underlying cirrhosis and whether or not there is a history of prior hepatic decompensation. Extrahepatic organ failure is a present feature in all types and differentiates decompensated cirrhosis from ACLF. Type A ACLF is seen in noncirrhotic patients with underlying chronic liver disease. This group includes patients with reactivation of hepatitis B, hepatitis A, or hepatitis E superimposed upon chronic hepatitis B, autoimmune hepatitis, and hepatitis E infection or drug-induced liver injury in patients at risk for nonalcoholic steatohepatitis [35–39]. Type B ACLF results from an acute deterioration in patients with well-compensated cirrhosis. Major precipitant factor in this group includes acute viral, drug, or alcoholic hepatitis, infection, or surgery. Extrahepatic organ failure usually develops within 4 weeks of the precipitating event. Finally, type C ACLF occurs in cirrhotic patients with a history of prior hepatic decompensation including variceal bleeding, ascites, or hepatic encephalopathy. Interestingly, the short-term mortality seems to be higher in patients without a history of hepatic decompensation who develop ACLF (type B ACLF), based on the CANONIC study results, compared to patients without prior decompensation (type C ACLF) [5••].

Management

The current medical management of ACLF is nonspecific and involves mostly intensive care support. Management of precipitant events is also extremely important. In the setting of severe alcoholic hepatitis, for instance, administration of prednisone or pentoxyphylline may have a significant impact in survival. Similarly, initiation of tenofovir in patients with reactivation of hepatitis B may improve outcomes [40].

Liver Transplantation

Patients with ACLF have been shown to benefit from liver transplantation without increased risk for posttransplant complications compared to non-ACLF patients. The MELD score also seems to be the appropriate scoring system to prioritize organ allocation in this group [41]. Unfortunately, cerebral edema, active infection, and hemodynamic instability, commonly present in a patient with ACLF, are major contraindications for liver transplant. Therefore, further studies are needed to determine timing of transplant and whether prioritizing criteria for ALF is also applicable for ACLF.

Conclusion

Our understanding of ACLF has quickly expanded in the recent years although still several questions remain. The definition of ACLF is only a proposal at this time, and future prospective studies should aim at refining our current knowledge of this condition. Development of comprehensive prognostic scores is another important step in the management of patients of ACLF. These scoring systems would help determine which patients might benefit from intensive care, which patients may require early liver transplantation, or those in whom treatment may be futile.

Compliance with Ethics Guidelines

Conflict of Interest Douglas A. Simonetto and Patrick S. Kamath declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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