Acute on Chronic Liver Failure: A New Clinical Entity

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Patients hospitalized for an acute complication of cirrhosis who also have organ failure(s) are at high risk of short-term death. The term *acute-on-chronic liver failure* (ACLF) is used to characterize these patients. Until recently, there was no evidence-based definition of ACLF. The results of a large prospective observational European study called Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure in Cirrhosis study were published in 2013 establishing diagnostic criteria for ACLF in a large series of hospitalized patients who had an acute complication of cirrhosis. In addition, this study described the natural history of ACLF. According to the Acute-on-Chronic Liver Failure in Cirrhosis study, ACLF is now considered a new clinical entity because it is distinct from traditional decompensated cirrhosis, based not only on the presence of organ failure(s) and high mortality rate but also on younger age, alcoholic etiology of cirrhosis, higher prevalence of some precipitating events (bacterial infections, active alcoholism), and higher level of systemic inflammation. ACLF is a new entity also because it cannot be explained entirely by severe sepsis or severe alcoholic hepatitis; a large proportion of cases are of unknown origin. ACLF should be considered as a whole that includes subcategories such as severe sepsis, severe alcoholic hepatitis, and others, which have yet to be defined. ACLF is a relatively common syndrome because it occurs in 31% of hospitalized patients with cirrhosis who have an acute complication of their liver disease. In these patients, ACLF is the most common cause of death.

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Patients with cirrhosis may rapidly (within <2 weeks) develop complications such as ascites, hepatic encephalopathy, gastrointestinal hemorrhage, or bacterial infection.[1] The development of one of these acute complications is a very common cause of hospitalization. On admission, a proportion of patients with acute complications have newly developed liver and/or extrahepatic organ failure(s), while others do not have failing organs.[2] Patients with cirrhosis and acute organ failure(s) have high short-term mortality rates[3,4] and generally are considered as having acute-on-chronic liver failure (ACLF).[3–5] However, important studies investigating the natural history and prognostic predictors in cirrhosis have focused on compensated and decompensated states but paid little attention to the prognostic value of the development of organ failures.[6] In addition, until 2013 (see later), there was no established evidence-based definition of ACLF; the only published definitions of ACLF were based on expert opinion.[5] Moreover, the definitions of ACLF used differed between Eastern and Western countries. In Asia, the following liver-centered definition has been suggested: acute hepatic insult manifesting as jaundice (serum bilirubin level, ≥5 mg/dL) and coagulopathy (international normalized ratio [INR], ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[7] This definition has been used to conduct randomized clinical trials in patients with ACLF caused by direct liver injury (reactivation of hepatitis B[8,9] or severe alcoholic hepatitis[9]). In Europe and the United States, experts have proposed defining ACLF as an acute deterioration of liver function in patients with cirrhosis, which usually is associated with a precipitating event and results in the failure of one or more organs and high short-term mortality rates.[3,4] The Sequential Organ Failure Assessment (SOFA) score, which is widely used to diagnose organ failures in general intensive care units,[10] also has been used for this purpose in patients with cirrhosis admitted to the intensive care unit.[11–13] In these patients, the SOFA score was a better predictor of short-term prognosis than liver-specific scores (ie, Child–Pugh score and model for end-stage liver disease score).[11–13]

In 2009, a group of European investigators decided to create the Chronic Liver Failure (CLIF) Consortium with the objective of stimulating research on complications of cirrhosis. The Consortium was endorsed by the European Association for the Study of the Liver (EASL) and as a

Abbreviations used in this paper: ACLF, acute on chronic liver failure; CANONIC, CLIF Acute-on-Chronic Liver Failure in Cirrhosis; CLIF, Chronic Liver Failure; EASL, European Association for the Study of the Liver; Fio_2, fraction of inspired oxygen; INR, international normalized ratio; SOFA, Sequential Organ Failure Assessment.

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result has been named the EASL-CLIF Consortium. One of the first decisions made by the Steering Committee of the EASL-CLIF Consortium was to perform a multicenter, prospective, observational study in patients with an acute decompensation of cirrhosis. This study was called the CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study. Its goals were to define ACLF and to describe the phenotype of patients with ACLF.

This article comments on the main results of the CANONIC study and specifies areas of future research identified by this study.

Diagnostic Criteria of Organ Failure in Cirrhosis

The CANONIC study prospectively enrolled 1343 patients with cirrhosis hospitalized in 29 Liver Units from 8 European countries between February and September 2011. Enrolled patients were hospitalized for at least 1 day and had an acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infections, or any combination of these. For the diagnosis of organ failures, investigators used a modified SOFA scale, called the CLIF-SOFA scale, which had been designed specifically by the Writing Committee of the CANONIC study before the onset of this study. Similar to the original scale,[10] the CLIF-SOFA scale assessed the function of 6 organ systems (liver, kidneys, brain, coagulation, circulation, and lungs) but also took into account some specificities of cirrhosis.[14] Each organ system received a subscore ranging from zero (normal) to 4 (most abnormal). A total CLIF-SOFA score ranging from 0 to 24 was calculated. All variables included in the CLIF-SOFA scale were variables that are easy to obtain in every hospital. The definitions of organ failures based on the CLIF-SOFA scale were the following. Liver failure was defined by serum bilirubin levels of 12.0 mg/dL or more. Kidney failure was defined by serum creatinine levels of 2.0 mg/dL or more, or the use of renal-replacement therapy. Cerebral failure was defined by grade III or IV hepatic encephalopathy; unlike the original SOFA scale which used the coma Glasgow score, the CLIF-SOFA scale used the West Haven classification.[14] Coagulation failure was defined by an INR of more than 2.5 and/or a platelet count of 20×10^9/L or less. Platelet count was present in the original SOFA scale and was kept in the modified CLIF-SOFA scale because low platelet count is a surrogate marker for severity of cirrhosis in terms of portal hypertension and presence of disseminated intravascular coagulation. Of note, the original SOFA scale did not use the INR.[10] Circulatory failure was defined by the use of catecholamines or terlipressin to maintain arterial pressure; the study protocol recommended using catecholamines to maintain systolic arterial pressure of 90 mm Hg or greater. The use of terlipressin, which is very specific for patients with cirrhosis, was not taken into account by the original SOFA scale.[10] Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (Fio_2) of 200 or less or a pulse oximetric saturation to Fio_2 ratio of 200 or less. The pulse oximetric saturation to Fio_2 ratio was not used in the original SOFA scale.

Patients With Acute on Chronic Liver Failure Have Alterations in Organ Functions and a High Risk of Short-term Mortality

Once results of the CANONIC study were prospectively collected, investigators defined ACLF and its grades by examining the association of organ failure(s) at enrollment with short-term (28-day) mortality. It is important to note that it was prespecified in the study protocol that patients with ACLF should have a 28-day transplant-free mortality rate of at least 15%. The results of the CANONIC study are now published[14]; these results show that ACLF is a new clinical entity that is distinct from decompensated cirrhosis. A description of patients who have or do not have ACLF is provided later.

Patients with cirrhosis admitted to the hospital for an acute complication can be divided into 4 different groups: no ACLF (ie, decompensation), and ACLF grade 1, grade 2, and grade 3 (Table 1).[14] In some patients, the diagnosis of the absence or presence of ACLF directly relies on the number of organ failures when this number is 0, 2, or 3 or more. Indeed, patients with no organ failure (no ACLF) have a very low 28-day mortality rate (~5%), while patients with 2 organ failures (ACLF grade 2) or those with 3 organ failures or more (ACLF grade 3) have a high mortality rate (32% and ~80%, respectively) (Table 1).

Patients with a single organ failure are not mechanically included in the group of patients with ACLF grade 1 (Table 1). In fact, only patients with single kidney failure, who have a 28-day mortality rate of 18.6%, are considered to have ACLF grade 1. For patients with a single nonkidney organ failure, the border between the absence and the presence of ACLF grade 1 is determined by the presence or absence of kidney dysfunction (ie, serum creatinine levels ranging from 1.5 to 1.9 mg/dL) and/or mild-to-moderate hepatic encephalopathy (ie, encephalopathy grades 1–2). For example, patients with a single failure of the liver, coagulation, circulation, or respiration who have serum creatinine levels less than 1.5 mg/dL and no hepatic encephalopathy are not included in the ACLF group because their mortality ranges from 5% to 7%. Similarly, patients with a single cerebral failure who have serum creatinine levels less than 1.5 mg/dL are not included in the group without ACLF because of their low mortality rate (8%) (Table 1). On the other hand, patients with single failure of the liver, coagulation, circulation, or respiration, who have kidney dysfunction or mild-to-moderate hepatic encephalopathy or both, and those with single cerebral failure who have kidney dysfunction,