Acute-on-Chronic Liver Failure: Recent Concepts

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A proportion of patients hospitalized for an acute complication of cirrhosis 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. In 2013 a definition has been proposed based on results of a large prospective observational European study, called "European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study. Results of this study led to elaborate new concepts about ACLF. First, it was found that ACLF is a syndrome that is distinct from mere decompensated cirrhosis. It was also shown that ACLF is a dynamic syndrome which can improve or conversely worsen. Patients who worsen die rapidly from multiorgan failures. The CANONIC study also found that identifiable precipitating events (e.g., bacterial infection, active alcoholism) are found in only 50% of cases of ACLF indicating that these events are dispensable for defining ACLF. In addition precipitating events may be initiators of ACLF but do not drive the outcome. An important concept derived from the CANONIC study is that ACLF is associated with systemic inflammation even in patients who do not have identifiable precipitating events. Finally it was found that ACLF may develop in patients without prior episodes of decompensation or in those with recent decompensation (<3 months). Moreover these patients with "early" ACLF were more severe than patients who developed ACLF after a long of history of decompensated cirrhosis. (J Clin Exp Hepatol 2014;5:81–85)

A proportion of patients admitted to the hospital for an acute complication of cirrhosis may rapidly die within one month. The term Acute-on-Chronic Liver Failure (ACLF) is universally used to characterize these patients.[1–3] However, until recently (see below) there were only definitions of ACLF based on expert opinions and remarkably definitions differed according of the origin of experts (Eastern vs. Western countries). In Asia, the following definition has been suggested: acute hepatic insult manifesting as jaundice (serum 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.[4] This definition is based on the dogma that liver failure is the primary and driving event of severity in patients with ACLF. The Asian definition has been already operative as it was used to enroll patients with direct liver injury (reactivation of hepatitis B[5,6] or severe alcoholic hepatitis[6]) in randomized interventional trials. In Europe and the United States of America experts proposed to define ACLF as an acute deterioration of liver function in patients with cirrhosis which is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality.[1,2] There is now an evidence-based definition of ACLF; indeed results of a large prospective observational European study called "European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC)" study have been published in 2013 establishing diagnostic criteria for ACLF in 1343 hospitalized patients who had an acute decompensation (AD) of cirrhosis.[7] AD was defined as an acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage or bacterial infections, or any combination of these.[7] The study was performed under the umbrella of the EASL–CLIF Consortium and involved 29 Liver Units from 8 European countries which enrolled patients between February and

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Abbreviations: ACLF: acute-on-chronic liver failure; AD: acute decompensation; CANONIC: Consortium Acute-on-Chronic Liver Failure in Cirrhosis; CLIF: chronic liver failure; CRP: C-reactive protein; EASL: European Association for the Study of the Liver; INR: international normalized ratio; SOFA: sequential organ failure assessment; SBP: spontaneous bacterial peritonitis
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September 2011. Here we will review the new concepts regarding ACLF that have been generated by the design and the results of the CANONIC study.

ASSESSMENT OF ORGAN FAILURES IN CIRRHOSIS REQUIRES SPECIFIC TOOLS

The Sequential Organ Failure Assessment (SOFA) scale which is widely used to diagnose organ failures in general intensive care units[8] has also been used for this purpose in patients with cirrhosis admitted to the ICU.[8–11] In these patients, the SOFA score was a better predictor of short-term prognosis than liver-specific scores (i.e., Child-Pugh score and MELD score).[9–11] However, components of the SOFA scale do not take into account some specific pathophysiological and clinical features of cirrhosis. This gave rise to the concept that the diagnosis of organ failures should be assessed by using tools specifically designed for patients with cirrhosis irrespective of their site of admission (ICU, ward). Thus the Committee in charge of the design of the CANONIC study decided to modify the SOFA scale and established a new scale called CLIF–SOFA that was subsequently used by all investigators of the study. Like the original scale,[8] the CLIF–SOFA scale assessed the function of six organ-systems (liver, kidneys, brain, coagulation, circulation, and lungs) but also took into account some specificities of cirrhosis.[7] Each organ-system received a subscore ranging from zero (normal) to four (most abnormal). A total CLIF–SOFA score ranging from zero to twenty-four was calculated; the total score assesses the overall severity. All variables included in the CLIF–SOFA scale were variables easy to obtain in every hospital. The definitions for 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.[7] Coagulation failure was defined by an International Normalized Ratio (INR) of more than 2.5 and/or 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. The original SOFA scale did not include the INR.[8] 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 ≥90 mm Hg. The use of terlipressin, which is very specific for patients with cirrhosis, was not taken into account by the original SOFA scale.[8] Respiratory failure was defined by a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (FiO_2) of 200 or less or a pulse oximetric saturation (SpO_2) to FiO_2 ratio of 200 or less. The SpO_2 to FiO_2 ratio was not used in the original SOFA scale.

ACUTE-ON-CHRONIC LIVER FAILURE IS DISTINCT FROM MERE DECOMPENSATED CIRRHOSIS

Once results of the CANONIC study were prospectively collected, a first analysis was performed to obtain a definition of ACLF and ACLF grades. This analysis was done by examining the relationship between phenotypes measured at enrollment and short-term (28-day) transplant-free mortality. Of note it was prespecified in the study protocol that patients with ACLF should have a 28-day transplant-free mortality of at least 15%. The results of the CANONIC showed that ACLF is a new syndrome which is distinct from mere decompensated cirrhosis.[7]

The first group was composed of the majority of patients (77.5%); these did not have ACLF but had "mere" decompensated cirrhosis and were divided into three subgroups: 1) patients with no organ failure; 2) patients with a single "non-kidney" organ failure (i.e., single failure of the liver, coagulation, circulation or respiration) who had serum creatinine <1.5 mg/dL and no hepatic encephalopathy; and 3) patients with single cerebral failure who had serum creatinine <1.5 mg/dL. The 28-day mortality rate in this group was far below the threshold of 15% (i.e., 4.7%).

The second group included 11% of enrolled patients and was called ACLF grade 1. This group was divided into three subgroups: 1) patients with single kidney failure; 2) patients with single failure of the liver, coagulation, circulation or respiration, who had serum creatinine ranging from 1.5 to 1.9 mg/dL or mild-to-moderate hepatic encephalopathy or both; and 3) patients with single cerebral failure who had serum creatinine ranging from 1.5 to 1.9 mg/dL. The 28-day mortality rate in this group was very significant (22.1%).

The third group included 8% of enrolled patients and was called ACLF grade 2. This group included patients with two organ failures and was associated with high 28-day mortality (32%).

The last group included 3.5% of enrolled patients and was called ACLF grade 3. This group included patients with three organ failures or more and was associated with very high 28-day mortality (76.7%).

ACUTE-ON-CHRONIC LIVER FAILURE IS A DYNAMIC SYNDROME

In the CANONIC study, ACLF was present in 23% of patients on admission or developed in 11% of patients who did not have ACLF on admission.[7] Another lesson from this study was that multiorgan failure (i.e., ACLF grade