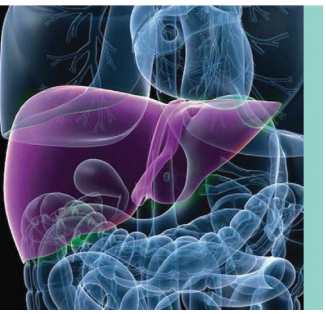

Acute-on-Chronic Liver Failure: Which Definition Is Appropriate in Latin America?

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Acute-on-chronic liver failure (ACLF), an increasingly recognized syndrome that develops in patients with advanced chronic liver disease, is associated with decreased short-term survival.[1] ACLF has been reported to occur in any liver disease leading to liver failure, including chronic viral hepatitis and alcoholic liver disease, the most common causes of cirrhosis in Latin America.[2]

Since the term ACLF was initially used in 1995,[3] more than 13 operational definitions with different criteria and ability to predict prognosis have been proposed.[1] This is confusing because virtually every study uses its own definition, most of which are based on personal experience or consensus agreement. A large number of those studies assessed hospitalized patients with decompensated cirrhosis who likely required renal replacement therapy, intensive care support, and/or liver transplantation. Therefore, there was a concern about the likelihood of selection bias toward the inclusion of patients in worse condition. Furthermore, there is no unanimity among the definitions in terms of criteria for liver failure, the nature of the acute precipitating event, the time frame for the development of liver or other organ failure (4-12 weeks), and the stage of underlying chronic liver disease (cirrhotic versus noncirrhotic).

To be validated and gain widespread use, it is crucial that any diagnostic criteria are capable of capturing early changes in the natural course of ACLF, allowing appropriate patient management and prediction of high risk for mortality. In the absence of such a definition and until a worldwide definition is available, the three most commonly used definitions are: (1) the Chronic Liver Failure Consortium (CLIF-C), which is affiliated with the European Association for the Study of the Liver; (2) the Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium (AARC); and (3) the North American Consortium for the Study of End-Stage Liver Disease (NACSELD).

The CLIF-C definition was based on the CANONIC study,[4] a prospective European study of 1343 patients

Abbreviations: AARC, Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; INR, international normalized ratio; NACSELD, North American Consortium for the Study of End-Stage Liver Disease.

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with acute decompensation of cirrhosis recruited from 29 hospitals in 12 countries. Thus, all patients with ACLF were acutely decompensated by default, defined as new-onset development of ascites, encephalopathy, gastrointestinal bleeding, or bacterial infection followed by one or more organ dysfunctions, including liver, kidney, brain, coagulation, circulatory, and respiratory failures (assessed by an adapted version of the Sequential Organ Failure Assessment score). The definition was calibrated to identify patients with a predicted 28-day mortality rate higher than 15%. The CLIF-C definition was based on the following criteria: (1) patients with single kidney failure (serum creatinine ≥2 mg/dL); (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; (3) patients with single cerebral failure who had serum creatinine concentration between 1.5 and 1.9 mg/dL; and (4) patients with two or more organ failures.

The 2009 AARC definition,[5] based on a consensus conference, considered ACLF acute hepatic injury manifesting as jaundice (bilirubin >5 mg/dL) and coagulopathy (international normalized ratio [INR] ≥1.5), complicated by ascites and/or encephalopathy within 4 weeks in a patient with previously diagnosed or undiagnosed chronic liver disease (cirrhotic or noncirrhotic). Only liver and coagulation failure with different cutoff values for bilirubin and INR leading to short-term decompensation were considered by AARC as ACLF. The definition was updated in 2014 and 2019 using prospectively/retrospectively collected data from 5200 cases from major hepatology centers across Asia to include assessment of 28-day mortality.[6,7] The AARC definition does not take prior history of acute decompensation of cirrhosis into account on the assumption that this would represent underlying end-stage liver disease. Extrahepatic precipitating events such as bacterial infection are also not taken into account. The AARC definition of ACLF is very different from the one proposed by CLIF-C, but it is important to highlight that it may be more reliable in Asia compared with Europe because the exacerbation of chronic hepatitis B, superimposed hepatitis A and E, and herb-induced liver injury are known precipitating events that lead to increased morbidity and mortality in Asian subjects with liver disease.

NACSELD,[8] a consortium of 14 tertiary care hepatology centers in North America initially formed to study the role of infections in hospitalized adult patients, developed a definition based on the following parameters: two or more organ failures as defined by grade 3 or 4 hepatic encephalopathy using the West Haven Criteria, circulatory shock (mean arterial pressure <60 mm Hg or the need for vasopressor drugs for treating hypotension despite adequate fluid resuscitation and cardiac output), need for mechanical ventilation, and need for renal replacement therapy. Organ failures defined by the NACSELD are more severe compared with the CLIF-C definition.

Comparison of the CLIF-C and AARC definitions reveals a small percentage of cases diagnosed as ACLF by both classifications, showing that different populations with different trigger factors have been selected.[9] It is not surprising given the differences in ACLF definition and the heterogeneity seen in underlying liver disease and precipitating events. This is illustrated by the predominance of alcoholic cirrhosis in the CLIF-C cohort[4] versus hepatitis B virus infection in the AARC cohort.[6,7] Furthermore, the CLIF-C had the primary objective of characterizing ACLF as a syndrome, in particular, multiorgan failure and short-term mortality. The NACSELD[8] criteria mainly used extrahepatic organ failures to define ACLF, whereas the AARC was focused on the identification of liver-specific injuries that could predict the development of extrahepatic organ failure and mortality.

The nature of the precipitating factor can also impact the ACLF phenotype. For example, direct hepatic injury is more likely to result in coagulopathy, whereas bacterial infections are more apt to cause acute kidney injury. The global differences in patterns of alcohol consumption, obesity, and prevalence of the most common ACLF precipitating factors (i.e., hepatitis A, B, or E virus; infection with multidrug-resistant bacteria, use of hepatotoxic herbal medicines) raise the question of which definitions are most suitable for ACLF in other parts of the world, such as Latin America and Africa. In this regard, it should be mentioned that Latin America is a high-prevalence region for hepatitis A virus infection, and this could influence the expression of ACLF syndrome.

Until now, only one prospective study from Porto Alegre, Brazil, has directly compared the ability of the three classifications to predict mortality head-to-head.[10] In the 146 hospitalized adult patients in the cohort, 29% met the CLIF-C, 4% the NACSELD, and approximately 10% the AARD definition. The global accuracy for predicting 28-day mortality was 0.710 for CLIF-C, 0.560 for AARC, and 0.561 for NACSELD (P = 0.002). Regarding 90-day mortality,

the accuracy was 0.760, 0.554, and 0.555, respectively ($P < 0.001$). At 28- and 90-day mortality, the CLIF-C had higher sensitivity and positive and negative predictive values, whereas the AARC had the highest specificity.

In conclusion, although few data are available, published evidence suggests that the CLIF-C ACLF definition allows an increasing number of patients to be diagnosed with ACLF and has a better prognostic performance for predicting mortality in Brazil and probably throughout Latin America. Future studies are warranted to better characterize ACLF and its triggering factors in this region of the world.

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