Acute-on-Chronic Liver Failure: An Old Entity in Search of Clarity

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The first appearance of the term "acute-on-chronic liver failure" (ACLF) in the literature was in 1995 in a Japanese brief review describing cases of acute liver injury superimposed on cirrhosis, mainly alcoholic hepatitis, and distinguishing it from acute liver failure (ALF),[(1)] a distinction that still challenges many practitioners. It is common to receive transfers of patients labeled as having "acute liver failure," and most of the time these are patients with alcoholic hepatitis superimposed on cirrhosis.

One of the confusing aspects is that liver failure in these two contexts may appear similar but is defined and managed differently. Classically, ALF is defined by encephalopathy and coagulopathy in a patient with acute hepatocellular damage without preexisting liver disease; workup for liver transplant for these patients is initiated immediately. While the development of encephalopathy and coagulopathy in a patient with underlying chronic liver disease/cirrhosis also forms a principal part of the definition of ACLF, it is also defined by the presence of extrahepatic organ failures, with kidney failure being the most common.[(2,3)] Although one should still consider liver transplantation in these patients, transplant candidacy is not assessed immediately but efforts are directed at identifying and treating the precipitant and improving organ failures.

The entity is not new. All physicians who have followed hospitalized patients with cirrhosis have been seeing this type of patient over their entire career. We used to call them very sick patients with cirrhosis or patients with terminal cirrhosis. The need to define this entity arose with the advent of liver support strategies, namely albumin dialysis,[(4)] that would theoretically support the liver until it could return to its baseline state or as a bridge to liver transplantation.[(5)] Defining this entity as ACLF had the goals of distinguishing these patients from those with mere decompensated cirrhosis and stratifying them into different prognostic groups so that the effect of such therapies could be better assessed (Fig. 1). Although these promising liver support strategies have not had the expected beneficial effect, ACLF has taken on a life of its own and has led to a vast body of literature that has provided insight into these goals.[(6)] However, it has also led to confusion because ACLF is considered by many as a new diagnostic entity rather than, what it really is, an old entity of prognostic significance that is still in search of a unifying definition. The need for such definition becomes more relevant in the context of research into innovative treatment strategies.

To consider ACLF a diagnostic entity constitutes a step back in determining the diagnostic and therefore therapeutic options for a specific patient. I will exemplify this with two cases that were recently presented to me. One was a case of a patient with acute alcoholic hepatitis superimposed on cirrhosis that met criteria for ACLF; the differential diagnosis

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure.

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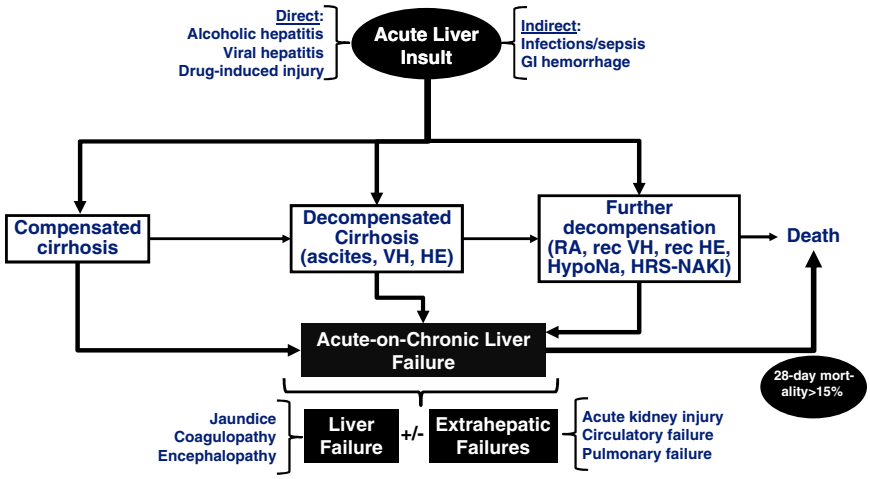

FIG. 1. Three stages of cirrhosis: compensated, decompensated (early decompensation), and further decompensated (late decompensation) and how at each of these stages an acute precipitant liver injury (direct or indirect) can lead to ACLF, which is characterized by typical features of liver failure with or without extrahepatic organ failures. The overall 28-day mortality of ACLF is >15%, but the number of organ failures clearly correlates with a higher mortality, with failure of >60% in patients with more than two organ failures. Abbreviations: GI, gastrointestinal; HE, hepatic encephalopathy; HRS-NAKI, hepatorenal syndrome not acute kidney injury (previously referred to as HRS-2); hypoNa, hyponatremia; RA, refractory ascites; rec, recurrent; VH, variceal hemorrhage.

presented to me for this case was either acute alcoholic hepatitis or ACLF. The other case was that of a patient with cirrhosis presenting with variceal hemorrhage that led to aspiration pneumonia and subsequently to jaundice and kidney failure; the diagnosis proposed was ACLF. To diagnose these two entirely different cases solely as ACLF while describing a very sick patient with a high mortality does not describe the probable precipitants or the possible pathogenic mechanisms that led to this poor prognostic state and therefore does not allow for the formulation of a diagnostic/therapeutic management strategy. Further evidence of the confusion generated is illustrated in an autopsy report for which the final diagnosis is ACLF. In an autopsy, we would like to know whether there were pathologic findings that would clarify the causes that led to the demise of this patient who, by definition, had terminal cirrhosis.

Currently, the definition of ACLF is heterogeneous and varies the most between Western and Eastern countries, perhaps because of marked differences in the precipitating injury (alcohol and infections in the West, viruses in the East)[6-8] with Eastern countries considering noncirrhotic chronic liver disease as the underlying entity.[7] In fact, the World Gastroenterology Organization has proposed the following unifying definition still requiring validation of

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> 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 the 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.[9]

A predicted mortality that is measured in weeks rather than months or years (typically a 28-day mortality >15%) is more comparable to that of ALF, establishes ACLF as the most severe stage of chronic liver disease, and should distinguish it from decompensated cirrhosis.

However, the distinction between "decompensated" cirrhosis and ACLF is still a source of confusion. Cirrhosis is categorized into two main prognostic stages, compensated and decompensated, defined by the presence (or absence) of decompensating events, specifically, ascites, variceal hemorrhage, and hepatic encephalopathy. Decompensation is the main determinant of survival in cirrhosis with a median survival of ~2 years (compared to >12 years in compensated cirrhosis).[10] A patient with decompensated cirrhosis may develop further (late decompensation) by developing two or more decompensating events and/or by developing complications of the complications (e.g., refractory ascites, hyponatremia) but would not be considered as having ACLF. While jaundice was originally considered an event defining decompensation, it is not only a rare initial cause of decompensation but, being the only variable indicative of liver insufficiency (as opposed to the other events that are predominantly caused by portal hypertension), compensated patients that decompensate with jaundice may well be patients with ACLF. The presence of indicators of liver failure (jaundice, encephalopathy, coagulopathy) makes sense in the definition of ACLF, but extrahepatic organ failures in the absence of liver failure can also meet criteria for ACLF,[2,3] and this is more difficult to reconcile. Acute kidney injury and hypotension could be the consequence of cardiocirculatory abnormalities that result from advanced cirrhosis and portal hypertension[11] and could justify their inclusion in the definition of ACLF. However, they could also result from the precipitant itself, e.g., renal failure may be due to acute tubular necrosis from hypovolemic or septic shock. Clarifying these aspects may be of mechanistic and therapeutic relevance. For example, a cytoprotective therapy may be more relevant in the presence of liver failure while an anti-inflammatory therapy would be more relevant in the presence of extrahepatic organ failure.

In this sense, the term ACLF has also led to confusion. Going back to the cases, one can clearly understand how a precipitant causing direct liver injury (such as alcoholic hepatitis or acute viral hepatitis) superimposed on a cirrhotic liver could be defined as ACLF, while in the second case, the liver injury is more indirect, either hypovolemia (with consequent ischemic hepatitis) and/or sepsis (which can lead to ischemia and hepatocyte apoptosis). In fact, the nature of the precipitant has been shown to be associated with differences in mortality, being lower in ACLF precipitated by direct liver injury rather than by infection,[12] raising the possibility of a different response to cytoprotective therapies.

The definition of ACLF has nevertheless led to greater prognostic granularity through the development of different scoring systems, with the number of organ failures (not surprisingly) being predictive of an increasingly poorer prognosis.[2,3] Perhaps more importantly, we now know that ACLF is a dynamic entity that may improve, stabilize, or deteriorate, and short-term mortality may be more accurately predicted by its clinical course in the first 3-7 days rather than at the time of ACLF development .[13]

At the end of the day, ACLF should be described as the stage of chronic liver diseases/cirrhosis associated with the highest mortality, so that when the cases above are being presented, the diagnoses would be that of a patient with (previously compensated or decompensated) cirrhosis with superimposed alcoholic hepatitis that has led to ACLF with a predicted 28-day mortality of an X percentage or that of a patient with variceal hemorrhage complicated by pneumonia and sepsis leading to ACLF with a 28-day predicted mortality of an X percentage. This would allow for a management strategy that at this point in our knowledge would consist of 1) identification and elimination/treatment of the precipitant, 2) support of extra-organ failures, and/or 3) strategies targeted at inflammatory pathways that are key in the development of ACLF and/or targeted at restoring/replacing the failing liver. In the future, one would hope that identification of the very early stage of ACLF and identification of the type of

injury (e.g., cytoprotective versus anti-inflammatory) would lead to specific therapies that would prevent its progression and that very late-stage ACLF could also be defined where any therapy would be considered futile.

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