Pro: Acute-on-Chronic Liver Failure

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Physicians taking care of patients with cirrhosis have identified for many years patients with standard acute decompensation of cirrhosis, and other patients in whom acute decompensation is associated with a rapid progression to further hepatic or extrahepatic organ failure and high short-term mortality. This latter situation has been traditionally called acute-on-chronic liver failure (ACLF), and therefore, this concept has been widely used for many years in the daily clinical practice in the hepatology wards and, in particular, in intensive care units. However, although acute decompensation of cirrhosis and ACLF have been recognized as separate clinical entities in daily clinical practice, should ACLF be really considered a distinct syndrome rather than a progression of decompensated cirrhosis?

Until recently, there was no accepted definition or diagnostic criteria available for ACLF. The concept of ACLF was first defined by the Asian Pacific Association for the Study of the Liver (APASL) in 2009 and some Western studies, but these definitions were based on consensus or single-center studies and were heterogeneous.[1,2] Recently, 2 large prospective studies, 1 from Europe and the other from Canada and the United States, have proposed definitions that for the first time are based on data from prospective cohorts.[3,4] The study from the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) included only patients with cirrhosis and bacterial infections,[3] whereas the Canonic study performed by the Chronic Liver Failure Consortium (CLIF) included all patients with cirrhosis admitted to the hospital for any acute decompensation of the disease.[4] Overall, definitions from Europe and North America define ACLF as an acute decompensation of a preexisting cirrhosis, which is associated with hepatic and extrahepatic organ failures and high short-term mortality.[3,4] Therefore, the development of multiple organ failures is the main feature that differentiates ACLF from decompensated cirrhosis without ACLF. To assess the existence of organ failures, the Canonic study developed a specific score which is a modified version of the Sequential Organ Failure Assessment (SOFA) score adapted to patients with cirrhosis, called Chronic Liver Failure (CLIF)–SOFA score or its simplified version, CLIF-C Organ Failure (OF) score (Table 1).[4]

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; AUROC, area under the receiver operating curve; CI, confidence interval; CLIF consortium, chronic liver failure; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; FiO_2, fraction of inspired oxygen; HBV, hepatitis B virus; HE, hepatic encephalopathy; IL, interleukin; INR, international normalized ratio; LPS, lipopolysaccharide; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; OF, organ failure; PAMP, pathogen-associated molecular pattern; PaO_2, partial pressure of arterial oxygen; PRR, pattern recognition receptor; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; SpO_2, pulse oximetric saturation; WGO, World Gastroenterology Organization.

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TABLE 1. CLIF-C Organ Failure (CLIF-C OF) Score System

Organ/System	Subscore = 1	Subscore = 2	Subscore = 3*
Liver: bilirubin, mg/dL	<6	≥6 to < 12	≥12*
Kidney: creatinine, mg/dL	<2	≥2 to < 3.5*	≥3.5 or RRT*
Brain: HE (West-Haven grade)	0	1-2	3-4*
Coagulation: INR	<2.0	≥2.0 to < 2.5	≥2.5*
Circulation: MAP, mm Hg	≥70	<70	Vasopressors*
Respiratory: PaO_2/FiO_2 or SpO_2/FiO_2	>300 or > 357	≤300 and >200 or > 214 and ≤357	≤200 or ≤ 214*

*The criteria for the diagnosis of organ failures.

TABLE 2. Current Available Definitions for ACLF

	APASL Definition	CLIF-C Definition	NACSELD Definition	WGO Proposal
Geographic area	Asia	Europe	United States and Canada	Unified proposal from Eastern and Western countries
Definition	Liver failure defined as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%), complicated within 4 weeks by clinical ascites and/or HE in patients with previously diagnosed or undiagnosed chronic liver disease	Acute decompensation of cirrhosis associated with organ failures ACLF grade 1: Single kidney failure. Single nonrenal OF plus renal dysfunction (creatinine ranging from 1.5-1.9 mg/dL) and/or grade 1-2 HE ACLF grade 2: 2 OF ACLF grade 3: ≥ 3 OF	Bacterial infection-related acute decompensation of cirrhosis associated with 2 or more OFs	ACLF is a syndrome characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and 1 or more extrahepatic OF that is associated with increased mortality within a period of 28 days and up to 3 months from onset.
Organ failure assessment	Only liver failure, defined by bilirubin and INR levels, is included in the definition.	CLIF-OF score (see Table 1)	Kidney: need for RRT Brain: HE grade 3-4 according to West-Haven criteria Circulation: shock defined by MAP <60 mm Hg or a reduction of 40 mm Hg in systolic blood pressure from baseline, despite adequate fluid resuscitation Respiratory: need for mechanical ventilation	No specific definition

Considering the differences between Eastern and Western definitions, recently the World Gastroenterology Organization (WGO) performed a consensus meeting where it was suggested to define ACLF as a syndrome that occurs 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 international normalized ratio [INR]) and 1 or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset.[5] Table 2 summarizes the current available definitions for ACLF.

Since the publication of these prospective studies proposing evidence-based definitions for ACLF, there has been a large amount of emerging data supporting the rationale that ACLF should be considered as a distinct clinical syndrome. In this review, we will summarize the most recent data showing that rather than a terminal event in patients with decompensation of cirrhosis, ACLF should be considered a new syndrome.

Identifying a New Syndrome: Epidemiology

Since the publication of the recent prospective studies proposing the diagnostic criteria to define ACLF, there have been different publications reporting the prevalence of ACLF based on the definition from Western countries. According to these data, ACLF is a frequent complication in patients with cirrhosis and a common cause of admission in these patients. Overall, the prevalence of ACLF is approximately 30%, with

studies performed in different geographic areas showing similar results.[3,4,6-8] Data from the Canonic study reported a prevalence of ACLF of 30%, with 20% of patients presenting ACLF at admission and 10% developing it during hospitalization.[3] Data from North America, including only patients with cirrhosis and bacterial infections, showed a prevalence of 24%.[4] Finally, data from Asia including patients with hepatitis B virus (HBV)–related cirrhosis and with ACLF defined according to the Canonic criteria, showed a prevalence of 34%.[6] Data from a recent interesting study show that ACLF represents a marked and increasing health and economic burden in the United States. Results from this study, reviewing a large amount of data from the National Inpatient Sample from 2001 to 2011, showed that the prevalence of ACLF among hospitalizations for cirrhosis has increased from 1.5% (5400) to 5% (32,300) and that the inpatient costs in ACLF have increased 5-fold ($320 million to $1.7 billion).[9]

Clinical Characteristics

There are clinical data to support the fact that ACLF should not only be considered as a terminal event of decompensated cirrhosis, but a different entity. Results from recent studies show that ACLF may also appear in patients with previously compensated cirrhosis and represent the first clinical manifestation of the disease.[4] In fact, previous decompensations of cirrhosis were absent in 23% of patients with ACLF from the European cohort. Moreover, patients with previous compensated cirrhosis developed more severe forms of ACLF, showed higher levels of C-reactive protein (CRP) and leukocyte count, and had higher mortality compared with patients with ACLF with previous decompensated cirrhosis (28-day mortality of 42% versus 29%, respectively).[4] Finally, other clinical differences that were found in the Canonic study show that patients with ACLF were younger than those patients with decompensated cirrhosis without ACLF.[4]

Distinct Pathophysiological Features

Currently, the pathophysiology of ACLF is still not completely understood. However, in recent years, there is growing evidence suggesting that ACLF has distinct pathophysiological features compared with decompensated cirrhosis without ACLF, which may explain the development of organ failures that are associated with poor outcomes.[7-12] The existence of key distinct pathophysiological mechanisms further supports the definition of ACLF as a different syndrome.

Although the Canonic study was not designed to investigate the pathophysiology of ACLF, interestingly, results from this study showed that leukocyte count and CRP, 2 well-known markers of systemic inflammation, were markedly increased in patients with ACLF compared with patients with decompensated cirrhosis without ACLF. Moreover, leukocyte count and CRP levels were associated with the number of organ failures and mortality.[4] In addition, in most cases, ACLF is associated with precipitating factors typically known to cause systemic inflammation (ie, bacterial infections, alcoholic hepatitis, or reactivation of viral hepatitis). However, even in those patients without an identifiable precipitating event, leukocyte count and CRP were markedly increased and associated with prognosis.[4] These results led investigators to raise the hypothesis of an excessive systemic inflammatory reaction as the key mechanism leading to ACLF.

It has already been known for many years that patients with decompensated cirrhosis show features of systemic inflammation. Circulating immune cells of patients with decompensated cirrhosis present an increased production of proinflammatory cytokines, which is further increased in response to bacterial infections or lipopolysaccharide (LPS) stimuli.[13] Therefore, one could argue that findings from patients with ACLF are only the progression of those existing in decompensated cirrhosis. However, we now know that ACLF may suddenly develop even in patients with compensated cirrhosis. Moreover, recent published studies provide evidence of the characteristics of this excessive inflammatory reaction occurring in ACLF, which may also be associated with concomitant anti-inflammatory and immunosuppressive features.

EXCESSIVE SYSTEMIC INFLAMMATION AND IMMUNOSUPPRESSION IN ACUTE-ON-CHRONIC LIVER FAILURE

In recent years, there is evidence suggesting that ACLF is associated with a remarkable "inflammatory storm" which may be a consequence of an acute and

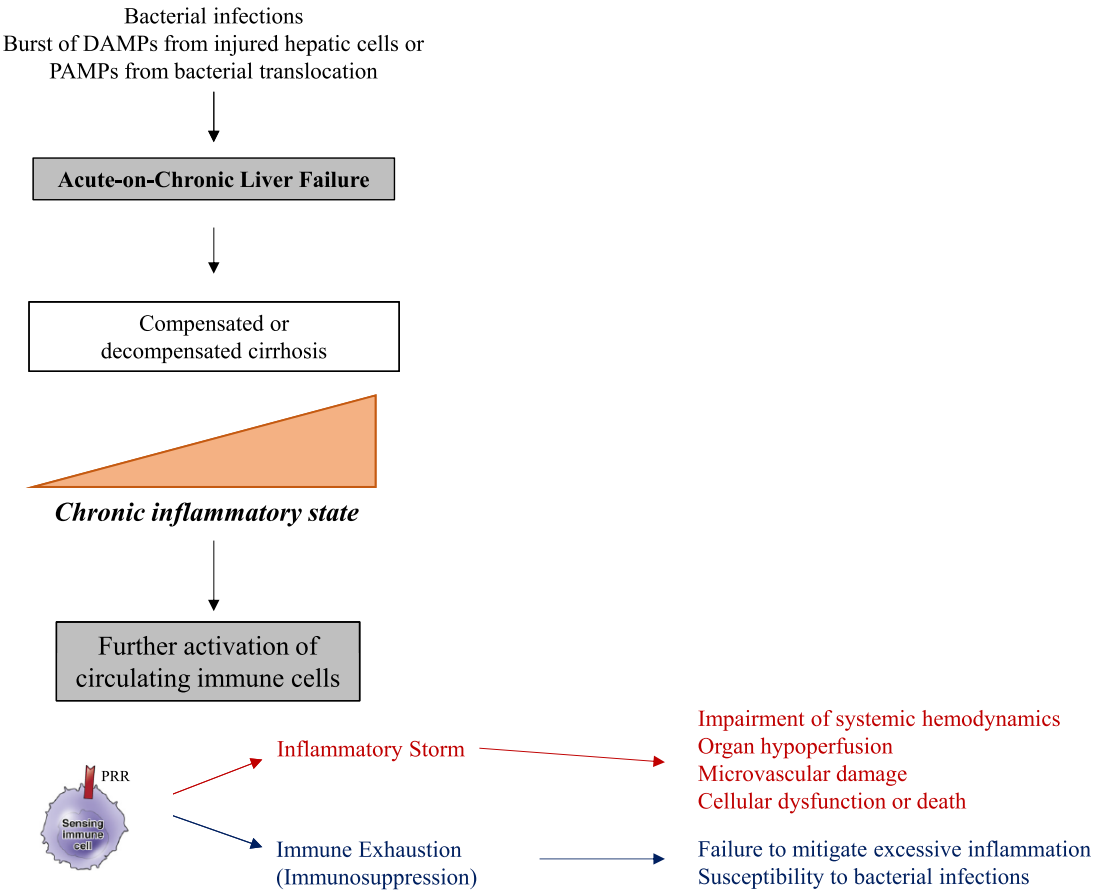

FIG. 1. Hypothesis of the pathophysiology of ACLF. The current hypothesis is based on the existence of an excessive inflammatory reaction in patients with a preexisting chronic systemic inflammation. The excessive inflammatory reaction may be likely a consequence of an acute and severe inflammatory response to bacterial infections, DAMPs from hepatic injured cells or a burst of PAMPs translocation. In parallel with the excessive inflammation, there is probably an excessive immunosuppressive state which would not be sufficient to mitigate immunopathology and would explain the high susceptibility to bacterial infections.

severe inflammatory response to bacterial infections, damage-associated molecular patterns (DAMPs) from injured hepatic cells or a burst of pathogen-associated molecular patterns (PAMPs) translocation, occurring in patients with a preexisting chronic inflammatory state and leading to rapid and severe multiorgan failure (Fig. 1).[7-12] Earlier studies showed increased serum levels of interleukin (IL) 6 and IL10 in patients with ACLF compared with patients with stable cirrhosis, in a manner similar to that of patients with sepsis.[14] Two recently published studies investigated the circulating cytokine profile in patients with decompensated cirrhosis with and without ACLF and showed similar findings. Results from both studies show that patients with ACLF have markedly increased levels of circulating proinflammatory cytokines and chemokines (ie, IL6, IL8, tumor necrosis factor α, monocyte chemoattractant protein 1, vascular cell adhesion molecule 1, vascular endothelial growth factor A) compared with patients with acute decompensation without ACLF.[15,16] Interestingly, these cytokines impaired in ACLF syndrome are mainly related to chemotaxis and migration of leukocytes, particularly monocytes, and macrophages.[15] Results of these studies show that although patients with decompensated cirrhosis already present increased circulating cytokines, plasma cytokine levels are markedly enhanced in patients with ACLF. Moreover, levels of some proinflammatory cytokines (ie, IL6, IL8, and intercellular cell adhesion molecule 1) were associated with the clinical course of ACLF, the number of organ failures, and mortality.[15,16]

Although data on patients with cirrhosis are limited, the current hypothesis suggests that because it occurs with severe sepsis, the excessive inflammatory reaction

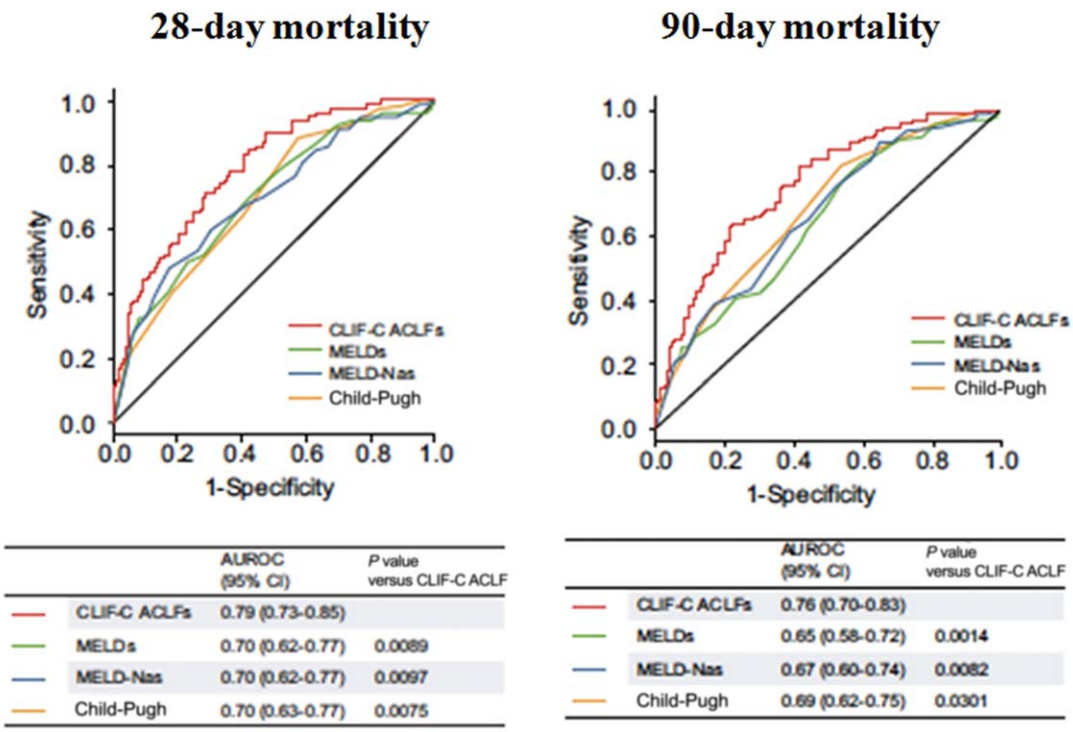

FIG. 2. AUROC to predict (left) 28-day mortality and (right) 90-day mortality of the CLIF-C ACLF score compared with Child-Pugh, MELD, and MELD-Na scores. Adapted with permission from Jalan et al.[20] (2014).

would explain the development of organ failure characteristic of ACLF as a consequence of organ hypoperfusion and/or by the direct effect of inflammatory mediators on cell function by a mechanism known as immunopathology.[10,17,18]

Besides an excessive systemic inflammation, patients with ACLF also show a marked increase of anti-inflammatory cytokines, such as IL10 and IL1Ra.[15,16] These findings suggest the existence of a compensatory immune response that would not be enough to mitigate the excessive inflammation. Moreover, earlier studies showed that ex vivo monocytes from patients with ACLF present significantly lower production of cytokines in response to LPS and show decreased activation markers (ie, human leukocyte antigen DR), findings that are similar to those described in sepsis.[14] Finally, a recent study showed that patients with ACLF present an increase in the number of monocytes expressing MERTK, a transmembrane receptor that acts as an important negative regulator of innate immune response, compared with patients with decompensated cirrhosis without ACLF.[19] Similar to what has been described in patients with sepsis, these findings suggest the existence of a marked immunosuppression as a consequence of the excessive inflammatory reaction and this could explain the high susceptibility to secondary bacterial infections typical of patients with ACLF, and which represent 1 of the main causes of death.

Prognosis: The Role of New Specific Prognostic Scores

ACLF is associated with very poor prognosis, with mortality rates significantly higher than those of patients with decompensated cirrhosis without ACLF. Overall mortality of ACLF defined according to the Canonic definition ranges approximately 30%-50% at 3 months and correlates with the severity of the syndrome and the number of organ failures.[3,4,6-11] These high mortality rates are consistent along different geographic areas, etiologies, and different definitions. In Europe, results from the Canonic study showed a 28-day transplant-free mortality of 2% in patients with acute decompensation without ACLF, compared with

33% in patients with ACLF (23% in ACLF grade 1, 31% in ACLF grade 2, and 74% in ACLF grade 3).[4] In the North American population, a study using the NACSELD definition showed a 30-day mortality of 8% in patients with infection-related decompensated cirrhosis, compared with 27% in patients with ACLF with 1 organ failure and 49%, 66%, and 74% in patients with 2, 3, and 4 organ failures, respectively.[3] Finally, data from the Chinese population using the definition from the Canonic study showed similar features, with 28-day transplant-free mortality of 3% in patients with HBV-related decompensated cirrhosis compared with 44% in patients with ACLF.[6]

Traditional scores used to assess prognosis in patients with decompensated cirrhosis, such as Child-Pugh and Model for End-Stage Liver Disease (MELD) scores, do not include variables assessing all organ failures that may be involved in ACLF. Therefore, it appears that accurate methods to predict prognosis in ACLF should not only include variables to evaluate liver function and liver-related complications but variables for a multiorgan evaluation. Interestingly, studies analyzing the Canonic cohort have developed new scores to specifically assess prognosis in patients with ACLF that have shown to be more accurate than Child-Pugh and MELD score.

The CLIF-C OF score described above, which is useful for the diagnosis of ACLF, has also been shown to be useful to predict outcomes.[4] The prognostic accuracy of the CLIF-C OF score is slightly superior to that of Child-Pugh and MELD scores. However, a later study defined the CLIF-C ACLF score, with higher prognostic accuracy compared with CLIF-C OF score. The CLIF-C ACLF score includes the CLIF-C OF score together with age and leukocyte count, 2 baseline variables which were independently associated with short-term mortality. CLIF-C ACLF score showed higher prognostic accuracy to predict 28-day and 90-day mortality than MELD, MELD-Na, and Child-Pugh scores (Fig. 2).[20] Score ranges from 0 to 100, with higher scores indicating worse prognosis. The score can be easily calculated at the European Foundation CLIF.[21]

ACLF is a dynamic syndrome and potentially reversible; therefore, the assessment of prognosis needs to be sequential to evaluate its clinical course and response to treatment. Data from the Canonic study showed that most patients achieve the final ACLF grade on a short time period, within days 3-7 after diagnosis, and this has been shown to be the most accurate time point to assess prognosis.[22] Indeed, the accuracy of CLIF-C ACLF score on days 3-7 was higher than at diagnosis.[20]

In conclusion, overall there are emerging data showing the existence of distinct clinical and pathophysiological features, and the usefulness of new and more accurate prognostic scores, to support the idea that ACLF should be considered a distinct syndrome among the complications of patients with chronic liver disease. However, there are still some differences among new definitions, and there are pathophysiological mechanisms that are not completely understood. Unfortunately, there is also no specific or effective treatment for patients with ACLF. Therefore, more efforts are needed in the near future to completely understand this syndrome and improve its poor outcome.

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