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New perspectives in the definition and classification of acute-on-chronic liver failure

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The term "acute-on-chronic liver failure" (ACLF) was initially proposed nearly 30 years ago.[1] ACLF is distinct from decompensated cirrhosis and acute liver failure, representing an independent clinical syndrome resulting from an acute insult on the background of chronic liver disease.[2,3]

With the ongoing research on ACLF, hepatologists have gained a clearer understanding of its pathogenesis, precipitating factors, and clinical course.[4–11] However, significant progress in ACLF treatment remains elusive. Current management still primarily involves addressing the underlying cause, combined with organ support therapy, and liver transplantation remains the only definitively effective, life-saving intervention.[4,12,13]

Progress in research on specific ACLF treatments is limited by the lack of a unified definition.[14] The efficacy of the same therapeutic approaches (such as stem cell therapy,[15,16] artificial liver support,[17,18] granulocyte-colony stimulating factor,[19,20] and non-selective beta-blockers[21–23]) varies among patients defined by different criteria. These treatments are effective in patients diagnosed according to the criteria of the Asia-Pacific Association for the Study of the Liver (APASL), but do not improve the prognosis of patients diagnosed according to the criteria of the European Association for the Study of the Liver (EASL).

Additionally, prognostic scores have different predictive values under different diagnostic standards, leading to discrepancies in treatment strategies, such as the choice between liver transplantation and palliative care.[24–26] Furthermore, no global epidemiological observational studies have been done on ACLF; the only available data are a meta-analysis of the prevalence of ACLF based on EASL diagnostic criteria.[27] Inconsistencies in ACLF definitions have significantly hindered disease diagnosis and treatment. Narrowing these differences or unifying the diagnostic criteria is a critical issue that needs to be addressed.

Prevailing Definition of Acute-on-Chronic Liver Failure

Various ACLF definitions [Table 1] consistently emphasize the high mortality rate and the manifestation as acute liver dysfunction against the backdrop of chronic liver disease. The definitions proposed by the Chinese Medical Association (CMA) and APASL[28] were based on expert consensus. According to APASL, ACLF is characterized by the onset of jaundice (bilirubin ≥5 mg/dL) and prolonged international normalised ratio (INR) (INR ≥1.5), within a 4-week period, in patients with previously uncompensated cirrhosis or chronic liver disease. The CMA's definition aligns closely with that of APASL, but includes individuals with a history of decompensated cirrhosis. The EASL[29] and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD)[30] definitions of ACLF were derived from prospective cohort studies. The EASL defines ACLF as the most severe form of acute decompensation in cirrhosis, characterized by organ failure in one or more of the following six organ systems: liver, kidney, brain, coagulation, circulation, and respiration, and high mortality, with severity stratified based on the number of organ failures. The NACSELD defines ACLF as occurring in patients with cirrhosis and infection during the decompensated phase, with at least two or more organ failures.

Moreover, Chinese researchers established the COSSH criteria,[31] also known as the hepatitis B virus (HBV)-ACLF criteria, for HBV-infected populations. This definition addresses the lack of HBV infection data according to the EASL-ACLF criteria. The organ failure standards within the

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Table 1: Definition of ACLF by different organizations.

Item	CMA	APASL	EASL	NACSELD	ACG	AASLD
Definition	Acute liver failure, developing on the basis of chronic liver disease, is indicated by serum TBil = 10 times the ULN or increasing by 17.1 μmol·L^{-1}·day^{-1}, with PTA ≤40% or an INR ≥1.5	Acute hepatic insult, manifesting as jaundice (Bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated within 4 weeks by clinical ascites and/or encephalopathy	An acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multi-organ failure	Presence of at least two severe extrahepatic organ failures, including shock, grade III/IV HE, RRT, or mechanical ventilation	A potentially reversible condition in patients with chronic liver disease that is associated with the potential for multiple organ failure and mortality within three months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation	Acute onset with rapid deterioration in clinical condition, the presence of liver failure defined by elevated bilirubin and elevated INR, and the presence of at least one extrahepatic (neurologic, circulatory, respiratory, or renal) organ failure
Underlying liver diseases	Non-cirrhotic, compensated cirrhosis, decompensated cirrhosis	Non-cirrhotic, compensated cirrhosis	Compensated cirrhosis, decompensated cirrhosis	Compensated cirrhosis, decompensated cirrhosis	Non-cirrhotic, compensated cirrhosis, decompensated cirrhosis	Non-cirrhotic, compensated cirrhosis, decompensated cirrhosis
Organ failures	Intrahepatic	Intrahepatic	Intrahepatic and/or extrahepatic	Extrahepatic	Intrahepatic and/or extrahepatic	Intrahepatic and extrahepatic

AASLD: American Association for the Study of Liver Diseases; ACG: American College of Gastroenterology; ACLF: Acute-on-chronic liver failure; APASL: Asia-Pacific Association for the Study of the Liver; CMA: Chinese Medical Association; EASL: European Association for the Study of the Liver; HE: Hepatic encephalopathy; RRT: Renal replacement therapy; INR: International normalised ratio; NACSELD: North American Consortium for the Study of End-Stage Liver Disease; RRT: Renal replacement therapy; TBil: Total bilirubin; ULN: Upper limit of normal.

HBV-ACLF definition are similar to those of the EASL-ACLF criteria; however, the HBV-ACLF criteria recognize that HBV- ACLF can occur in both cirrhotic and non-cirrhotic patients.

As evidenced in the aforementioned studies, the definition of ACLF varies significantly. A recent systematic analysis reviewed ACLF-related research reports published between 1990 and 2022 from database searches. The study[32] observed the utilization of various ACLF definitions and found that the majority of studies (53.2%) employed the EASL definition, followed by the APASL definition (33.3%), with the NACSELD definition being the least used. The definitions overlap considerably. The overlap between the EASL and APASL definitions ranged from 14% to 80%, that between the EASL and NACSELD definitions ranged from 13% to 25%, and that between the APASL and NACSELD definitions was the lowest at 7.7%. Liver failure was the predominant feature in the studies based on the APASL definition, whereas kidney failure was the predominant feature in the studies based on the EASL definition. The 30-day mortality rates also varied among the definitions: APASL reported a mortality rate of 38.9% (95% confidence interval [CI]: 31.2%–46.9%), EASL reported a mortality rate of 47.9% (95% CI: 42.2%–53.5%), and NACSELD reported a mortality rate of 52.2% (95% CI: 51.9%–52.5%). Patients who meet multiple criteria generally have poor prognoses.

Efforts to Reduce Discrepancies among Different ACLF Definitions

There is an ongoing effort to create standardized diagnostic criteria that integrate the key elements from various definitions. To reduce discrepancies among definitions and better promote research outcomes related to ACLF, in 2014, the World Gastroenterology Organization (WGO)[33] proposed categorizing chronic liver disease in ACLF into three types: Type A (non-cirrhotic), Type B (compensated cirrhosis), and Type C (decompensated cirrhosis). The CMA subsequently endorsed this classification in its updated liver failure guidelines.[34]

In 2022, the American College of Gastroenterology (ACG)[35] released its first guidelines on the diagnosis and treatment of ACLF. These guidelines summarize the clinical characteristics of the three ACLF definitions (APASL, EASL, and NACSELD) and define ACLF as a potentially reversible condition occurring in patients with chronic liver disease, with or without cirrhosis, that can lead to multi-organ failure and death within three months in the absence of appropriate treatment, liver support, or liver transplantation. ACLF can be identified by the presence of chronic liver disease, elevated serum total bilirubin levels, and prolonged INR, with the diagnosis supported by the presence of renal, respiratory, circulatory, or brain failure. This definition emphasizes the importance of liver injury markers in the initial presentation of ACLF and its potential reversibility.

In 2024, the American Association for the Study of Liver Diseases (AASLD) released guidelines on ACLF,[36] recognizing three types of chronic liver disease. They also defined ACLF as the presence of elevated bilirubin and prolonged INR as initial signs, but additionally required at least one extrahepatic organ failure (neurological, circulatory, respiratory, or renal).

The aforementioned guidelines and consensus acknowledge the reversibility of ACLF that can occur in patients with

or without cirrhosis. Recently, Professor Shiv Kumar Sarin proposed recommendations for bridging these different definitions.[37] The first recommendation is to redefine ACLF while still emphasizing that liver dysfunction is the core of ACLF, which may or may not be accompanied by renal dysfunction (serum creatinine >1.5 mg/dL), and is associated with a higher 28-day mortality rate. Another suggestion is to reclassify ACLF into two types: the previous definitions by APASL and EASL-chronic liver failure (CLIF) can be reclassified as types A and B, respectively. Type A includes the APASL and Japanese definitions, and can be graded based on the AARC scoring. Type B includes the EASL-CLIF definition, which encompasses the COSSH and NACSELD definitions, and can be graded based on the CLIF-sequential organ failure assessment (SOFA) score for organ failure.

This opinion reiterates that liver injury in patients with ACLF should be identified by hyperbilirubinemia and prolonged INR at onset. A consensus has been reached among most countries and regions regarding the clinical presentation and reversibility of ACLF in relation to chronic liver disease. However, in 2023, the ACLF guidelines issued by the EASL still emphasize the inclusion of patients with or without decompensation in the definition of ACLF, highlighting its short-term mortality, without specifying its reversibility.[38] Thus, despite the trend toward uniformity in the definition of ACLF, discrepancies remain.

Reclassifying ACLF Based on Onset Clinical Presentation

Regardless of the etiology of the underlying chronic liver disease, our research team classified ACLF clinical presentations into two types based on hepatic and extrahepatic organ failure characteristics at onset.[39] Type I ACLF represents acute liver injury with a background of chronic liver disease, primarily affecting the liver, with jaundice and coagulation dysfunction as the main features, with or without hepatic encephalopathy (Haven 1–2), and exhibiting a certain degree of reversibility. Type II ACLF occurs similarly in chronic liver disease with acute hepatic decompensation. In addition to hepatic dysfunction at onset, it is accompanied by at least one extrahepatic organ failure within one week, including the kidney, brain, respiratory and circulatory systems (diagnosed based on the EASL-CLIF criteria) [Figure 1].

A retrospective cohort study[40] included 582 patients meeting the criteria of elevated bilirubin (≥5 mg/dL) and prolonged INR (≥1.5). The results revealed 535 cases (91.9%) of Type I ACLF and 47 cases (8.1%) of Type II ACLF. Type I predominantly arises from chronic, non-cirrhotic liver disease (28.2%) and compensated cirrhosis (56.8%), with 28-day and 90-day mortality rates of 15.5% and 27.5%, respectively. Predictive scores, including the MELD, MELD-Na, and CLIF-C ACLF scores, can effectively predict the prognosis of patients with Type I ACLF. Type II mainly occurs in patients with cirrhosis (95.7%) and multi-organ failure, whereas only a minority have chronic non-cirrhotic liver disease as an underlying condition (4.3%). Patients with Type II ACLF exhibit critical conditions, with 28-day and 90-day

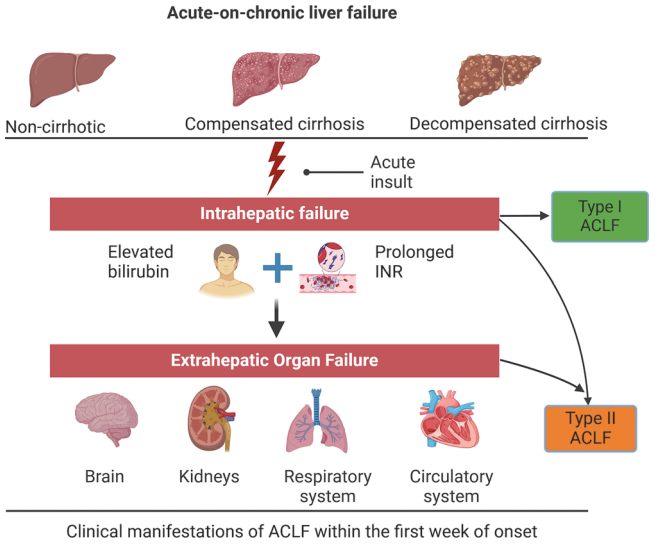

Figure 1: Reclassifying ACLF based on clinical presentation at onset. Created with BioRender.com (https://app.biorender.com/illustrations). ACLF: Acute-on-chronic liver failure; INR: International normalised ratio.

mortality rates of 38.3% and 53.2%, respectively, indicating a poorer prognosis than those with Type I ACLF. The CLIF-C ACLF score shows good predictive value for Type II ACLF, but MELD and MELD-Na scores may underestimate the severity of the illness.

From the perspectives of liver disease background, type of organ failure, and clinical indicators, Type I ACLF aligns more closely with the diagnostic criteria of APASL and the "Guidelines for Diagnosis and Treatment of Liver Failure in China (2018)," while Type II resembles the diagnostic criteria of EASL-CLIF. The results indicate differences in liver disease background, clinical features, and prognosis between Type I and Type II ACLF, emphasizing the importance of different prognostic scoring systems for each type. This classification system provides evidence-based guidance for ACLF diagnosis and treatment. However, as this was a single-center retrospective study with a limited sample size of Type II ACLF patients, further validation is warranted through multicenter, large-sample, prospective cohort studies to explore the characteristics of this novel ACLF classification system.

In summary, recent guidelines and consensus statements from various regions worldwide indicate that scientists are striving to establish a unified global definition of ACLF. However, this goal is yet to be achieved. The new clinical classification of ACLF based on organ failure characteristics at onset incorporates disease features from both Eastern and Western perspectives. This approach aligns with clinical practice, aiding clinicians in formulating individualized treatment strategies, assessing disease prognosis, and determining the urgency of liver transplantation. This allows for a more scientific management and intervention in patients, leading to more efficient and rational use of medical resources.

Future efforts should focus on large-scale multinational epidemiological studies to collect comprehensive data on

ACLF using standardized criteria. This can provide robust evidence to support a unified definition and promote compatible diagnostic and treatment strategies across different populations and healthcare settings.

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Conflicts of interest

None.

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