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EDITORIAL

Defining acute-on-chronic liver failure: East, West or Middle ground?

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Abstract

Acute-on-chronic liver failure (ACLF), a newly recognized clinical entity seen in hospitalized patients with chronic liver disease including cirrhosis, is associated with high short- and medium term morbidity and mortality. None of the definitions of ACLF proposed so far have been universally accepted, the two most commonly used being those proposed by the Asia-Pacific Association for the Study of Liver (APASL) and the European Association for the Study of Liver - Chronic Liver Failure (EASL-CLIF) consortium. On paper both definitions and diagnostic criteria appear to be different from each other, reflecting the differences in cut-off values for individual parameters used in diagnosis, the acute insult or precipitating event and the underlying chronic liver disease. Data directly comparing these two criteria are limited, and available studies reveal different outcomes when the two are applied to the same set of patients. However a review of the literature suggests that both definitions do not seem to identify the same set of patients. The definition given by the APASL consortium is easier to apply in day-to-day practice but the EASL-CLIF criteria appear to better predict mortality in ACLF. The World Gastroenterology Organization working party have proposed a working definition of ACLF which will identify patients from whom relevant data can be collected so that the similarities and the differences between the two regions, if any, can be clearly defined.

Key words: Acute-on-chronic liver failure; Chronic liver disease; Cirrhosis; Ascites; Hepatic encephalopathy

Core tip: Acute-on-chronic liver failure, a relatively new clinical entity seen in patients with chronic liver disease including cirrhosis, is associated with high morbidity and mortality. The two most commonly used definitions given by the Asia-Pacific Association for the Study of Liver and the European Association for the Study of Liver - Chronic Liver Failure consortium, are different and appear to identify different set of patients. Because of limited data on these definitions, the World Gastroenterology Organization working party has proposed a new definition to identify patients from

whom data can be collected to ultimately arrive at a uniform definition.

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INTRODUCTION

Patients with cirrhosis who develop superadded insults like infections or organ failure from any other cause, have a poorer prognosis as compared to those who do not[1,2]. Though transient and potentially reversible, such events, either directly affecting the liver or involving another part of the body, can dramatically worsen the liver reserve in patients with pre-exiting stable liver disease. This worsening differs from the progression of the primary chronic liver disease (CLD) which leads to chronic decompensation, being largely irreversible in the majority of cases because of the accompanying parenchymal extinction. Patients in the former group tend to be younger, more commonly alcoholic, show higher levels of white blood cell counts and C-reactive protein and have a higher prevalence of infections as compared to decompensated cirrhotics[3].

Increasing realization of the differences between the two scenarios lead to the recognition of acute-on-chronic liver failure (ACLF), a term used for the first time in 1995 to describe a condition in which two liver insults are present concurrently, *i.e.,* one ongoing and chronic, and the other, recent and acute[4]. A typical feature of ACLF is its rapid progression and the association with high short and medium term mortality (30%-60%)[3,5]. ACLF is frequently encountered in day-to-day practice and has been reported to occur in up to 30% of cirrhotics[3]. Intensive medical care is necessary for most patients with ACLF thus increasing the per-patient costs significantly.

DEFINITIONS FOR ACLF

Since the term ACLF was used for the first time, up to thirteen different definitions have been suggested, contributing to a great deal of confusion regarding what constitutes the condition[6]. The two most commonly used definitions have been provided by the Asia-Pacific Association for the study of Liver (APASL) and the European Association for the study of Liver - Chronic Liver Failure (EASL-CLIF) consortium (Table 1).

The definition provided by the APASL in 2009 characterizes ACLF as an "acute hepatic insult manifesting as jaundice [serum bilirubin $\geqslant$ 5 mg/dL (85 micromoles/L) and coagulopathy international normalized ratio (INR) $\geqslant$ 1.5, or prothrombin activity < 40%] complicated within 4 wk by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD/cirrhosis"[7]. This was based on data collected from 200 patients. A subsequent consensus meeting evaluated the as yet unpublished data on approximately 1300 patients from 14 countries from the APASL ACLF research consortium (AARC) database along with newer evidence and altered the definition only to the extent of additionally mentioning the associated high 28-d mortality[8].

Experts in Europe and United States, on the other hand, have characterized ACLF as "a syndrome that defines a subgroup of cirrhotic patients who develop organ failure following hospital admission with or without an identifiable precipitating event and have increased mortality rates"[9]. In view of paucity of any established evidence-based definition of ACLF, investigators of the EASL-CLIF consortium performed the multicenter, prospective observational CANONIC (CLIF Acute-on-Chronic Liver Failure in Cirrhosis) study which defined acute decompensation as an acute development of hepatic encephalopathy, large ascites, bacterial infections or gastrointestinal hemorrhage, or any combination of these. It also defined cut-off levels for diagnosing extra-hepatic organ failure and stratified patients with ACLF into 4 subgroups characterized by increasing mortality (Table 1)[3]. There are many differences between the two definitions including the underlying CLD, the type of acute worsening and its time frame, and prior decompensation raising the question as to which of these might be appropriate for clinical use.

The APASL definition is liver centered. Simply put, the condition basically reflects acute liver failure with two additional requirements - the serum bilirubin should be 5 mg/dL or above and ascites should be present in case encephalopathy is not. On the other hand, the EASL-CLIF consortium defines ACLF based on the failure of one or more organs of which liver is only one.

DIFFERENCES IN THE APASL AND EASL-CLIF DIAGNOSTIC CRITERIA

The individual parameters that make up the diagnostic criteria differ considerably between the two definitions (Table 2). For example, the cut off for serum bilirubin level to define liver failure was found to be 12 mg/dL in the CANONIC study as levels above this were associated with a 28-d mortality above 15%. However, the bilirubin level by itself was not important, since the mortality was only 4% even among patients with elevated serum bilirubin levels if they did not have extra-hepatic organ failure[10]. The cut-off level for serum bilirubin was kept at 5 mg/dL in the APASL criteria ACLF because patients with bilirubin between 5 and 10 mg/dL included in the AARC data, had a mortality of about 38%[8].

Similarly, coagulation failure was defined as INR $\geqslant$ 2.5 as per the CANONIC study, and $\geqslant$ 1.5 as per the APASL criteria[3,8]. INR reportedly reflects the acute liver failure as per APASL; however, in the CANONIC study, all patients had acute decompensation of cirrhosis and

Table 1 Diagnostic criteria of acute-on-chronic liver failure as per the chronic liver failure acute-on-chronic liver failure in cirrhosis study

No ACLF - This group consists of 3 subgroups
Patients with no organ failure
Patients with a single "non-kidney" organ failure (*i.e.*, single failure of the liver, coagulation, circulation, or respiration) who had a serum creatinine level < 1.5 mg/dL and no hepatic encephalopathy
Patients with single cerebral failure who had a serum creatinine level < 1.5 mg/dL
ACLF grade 1 - This group consists of 3 subgroups
Patients with single kidney failure
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
Patients with single cerebral failure who had a serum creatinine level ranging from 1.5 and 1.9 mg/dL
ACLF grade 2 - This group consists of patients with 2 organ failures
ACLF grade 3 - This group consists of patients with 3 organ failures or more
Definitions of organ failures - CANONIC study
Liver failure - serum bilirubin level of 12.0 mg/dL or more
Kidney failure - serum creatinine level of 2.0 mg/dL or more, or the use of renal replacement therapy
Cerebral failure - grade Ⅲ or Ⅳ hepatic encephalopathy
Coagulation failure - an international normalized ratio of more than 2.5 and/or a platelet count of 20×10^9/L or less
Circulatory failure - use of dopamine, dobutamine, or terlipressin
Respiratory failure - ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (FiO_2) of 200 or less or a pulse oximetric saturation to FiO_2 ratio of 200 or less

Adapted from Moreau *et al*[3]. ACLF: Acute-on-chronic liver failure; CANONIC: Chronic liver failure acute-on-chronic liver failure in cirrhosis.

Table 2 Principle differences in the definition and diagnostic criteria of acute-on-chronic liver failure between Asia-Pacific and West

	APASL definition	EASL-CLIF definition
Total bilirubin	5 mg/dL or more	12 mg/dL or more
INR	1.5 or more	2.5 or more
Hepatic encephalopathy	Any grade	Only grade Ⅲ and Ⅳ
Ascites	May be present	Not included
Duration between insult and ACLF	4 wk	Not defined
Acute event - sepsis	No	Yes
Acute event - variceal bleeding	No unless producing jaundice and coagulopathy defining ACLF	Yes
Extra-hepatic organ involvement	No	Yes
What is chronic disease	Chronic liver disease with/without only compensated cirrhosis	Only cirrhosis, including those with prior decompensation

APASL: Asia-Pacific Association for the Study of Liver; EASL-CLIF: European Association for the Study of Liver-chronic Liver Failure; INR: International normalized ratio; ACLF: Acute-on-chronic liver failure.

causes other than liver failure including sepsis may have contributed equally to coagulopathy. Additionally, platelet count ($\leqslant 20 \times 10^9$/L) was also used to define coagulation failure in the CANONIC study and not as per the APASL consensus.

Hepatic encephalopathy, irrespective of its grade, is an important criterion for diagnosis as per the APASL criteria, whereas, as per the CANONIC study, mild to moderate encephalopathy (Grade 1 or 2) would be important only if associated with another organ failure (liver, coagulation, circulation or respiration)[3,8].

Clinically detectable ascites was present in 91% of patients with ACLF in the AARC database and it was included as a diagnostic criterion as per the APASL consensus[8]. In the CANONIC study, ascites was significantly more common in those with, compared to those without ACLF (78.7% and 63.4%; $P \leqslant 0.001$); however, it did not differ among the three grades of the former suggesting thereby that its presence per se may not have influenced the outcome[3].

Renal failure was observed in 55.8% of the patients included in CANONIC study[3]. On the contrary, studies based on the APASL definition reported renal failure in only 30%-35% of patients with ACLF[5,11]. Associated renal dysfunction has been well recognized to worsen the outcome in decompensated cirrhosis. The high mortality in ACLF was irrespective of the creatinine level as per the AARC data as mentioned in the APASL consensus statement. Hence the APASL criteria do not include serum creatinine level to define ACLF.

ACUTE INSULT

The term precipitating event is generally used in the West to refer to the acute insult, and the major events recorded are primarily non-hepatic, most often being

Table 3 Acute insult/precipitating event in patients with acute-on-chronic liver failure

As per APASL criteria	As per EASL-CLIF criteria
Hepatotropic viral infections	Bacterial infection
Reactivation of HBV	Gastrointestinal hemorrhage
HEV super-infection	Active alcoholism within the past 3 mo
Active alcohol consumption (within last 28 d)	Other precipitating events
Drug induced liver injury	Transjugular intrahepatic portosystemic shunting
Complimentary and alternative medicines	Major surgery
Severe autoimmune hepatitis	Therapeutic paracentesis without use of intravenous albumin
Flare of Wilson's disease	Hepatitis
Non-hepatotropic insults (if producing direct hepatic insult)	Alcoholic hepatitis (liver biopsy required for diagnosis)
Surgery	No precipitating event identified
Trauma	
Viral infections	
No acute insult identifiable	

Adapted from Sarin *et al*[8] and Moreau *et al*[3]. ACLF: Acute-on-chronic liver failure; APASL: Asia-Pacific Association for the Study of Liver; EASL-CLIF: European Association for the Study of Liver-chronic Liver Failure; HEV: Hepatitis E virus; HBV: Hepatitis B virus.

bacterial infections and sepsis. Spontaneous bacterial peritonitis (SBP) and bacterial pneumonia were the most common precipitating events, seen in 32.6% of patients in the CANONIC study[3]. Superadded Hepatitis A or E or reactivation of hepatitis B infections is seldom, if ever encountered in the West. On the other hand, APASL consensus contends that the acute insults should be hepatic, since liver failure is the core part of ACLF. Among these, super-added hepatitis E virus infection and reactivation of hepatitis B virus (HBV) are the leading causes of acute insult in ACLF (Table 3)[12-15]. Among the non-infectious etiologies, alcohol-related liver injury is the major cause of acute worsening of CLD and this is equally reported in studies from the two regions[3,5]. Events outside the liver, whether related to the underlying liver disease *per se* (*e.g.,* SBP and variceal bleeding), or not (*e.g.,* pneumonia or urinary infections), do not qualify as acute insults leading to ACLF as per the APASL definition unless the liver is secondarily affected so as to cause jaundice, coagulopathy and ascites or hepatic encephalopathy.

Both documents recognize that an acute insult may not be identifiable in a significant proportion of patients with ACLF as was seen in 43.6% in the CANONIC study[3]. Interestingly, the identification or otherwise of a precipitating event was unrelated to the severity of ACLF as well as short term mortality.

UNDERLYING CLD

The diagnosis of CLD in the context of ACLF is primarily made by history, physical examination and laboratory, radiologic or endoscopic investigations[16]. However, most of the ACLF patients in the Asia-Pacific region present with liver failure without having been previously evaluated for liver disease. Unlike the EASL-CLIF definition, the APASL includes non-cirrhotic, CLD s such as chronic hepatitis and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) also as underlying CLD. This is because even such patients carry a poor prognosis with mortality rates being as high as 33% at 4 wk once they meet the other threshold criteria for ACLF[8]. On the other hand, both the CANONIC and North American Consortium for End-Stage Liver Disease studies included only patients with cirrhosis[3,17].

DOES PRIOR DECOMPENSATION MATTER?

In the CANONIC study, up to 50% of the patients with ACLF had prior history of decompensation or developed ACLF in 3 mo or less after the first episode of decompensation. Previous studies from the West have concluded that hepatic decompensation in the past was an independent predictor of mortality in patients with ACLF[18]. Contrarily, in the CANONIC study, patients with ACLF and no prior acute decompensation had a higher prevalence of organ failure and a more severe grade of ACLF as compared to those with acute decompensation in the past. As expected, the former group also showed a significantly higher mortality at 28 d (42.2% *vs* 29.6%; $P = 0.03$). Despite this difference however, patients with previous decompensation are not excluded since they too have a mortality above the 15% cut off considered relevant in the study. Also, for any given value of leucocyte count, the probability of mortality was significantly higher in those without prior decompensation compared to in those with[3]. This could imply that those without previous decompensation have an inappropriately exaggerated inflammatory response and immune dysfunction leading to worse outcome than those with previous decompensation. However, as per the APASL criteria, patients with known previous decompensation with jaundice, ascites and hepatic encephalopathy are excluded from being defined as ACLF based on the AARC data. In a retrospective study, patients who met the APASL criteria for ACLF but also

had prior decompensation in addition were older, more often had non-hepatic insults as a cause for acute worsening and generally had less severe hepatic damage compared to ACLF patients without any decompensation in the past[19]. The 28-d survival was however similarly high (58.9% *vs* 61.4%) in the two groups. A study from India with a smaller number of patients showed similar results[11]. Further research is needed to explore this issue.

Liver biopsy continues to be an important tool to differentiate between the underlying cirrhotic and non-cirrhotic liver disease and to establish the etiology of CLD in certain situations. Excluding patients with prior decompensation and including those with chronic hepatitis and NAFLD as it does, the APASL definition would necessitate a more frequent need for doing a liver biopsy for diagnosing the underlying CLD. Coagulopathy being a necessary part of the definition, the trans-jugular approach, needing expertise and adding to the cost of care, would be necessary for obtaining the liver biopsy in almost all who need the same. In the absence of liver biopsy, there is a possibility that conditions such as acute Budd-Chiari syndrome or abdominal tuberculosis with hepatic and peritoneal involvement might be mistaken for ACLF, though these conditions are rather uncommon.

DO THE TWO DEFINITIONS IDENTIFY THE SAME PATIENTS?

The differences in the two definitions would not matter if they identified mostly the same patients. Data from the literature however suggests they do not. Two studies from Asia in patients with acute worsening of CLD looked at how the two definitions fared in these patients. Zhang *et al*[20] found that 118 (29.9%) of their 394 patients met both the criteria for ACLF by EASL and APASL, while 276 (70.1%) met only the APASL criteria. On the other hand Dhiman *et al*[11] found that 38 (76%) of their 50 patients met the EASL criteria, whereas only 19 (38%) met the APASL criteria. The relative proportion of patients with ACLF by one or the other definition may vary from study to study depending on the background liver disease population from which they are drawn. But the proportions differing in the same study when the two definitions are applied clearly shows that they identify different patients with some overlap.

Because underlying chronic hepatitis and NASH are considered for inclusion but previous decompensation is not as per the APASL definition, patients meeting these criteria clearly are in an earlier stage of CLD compared to those meeting the EASL-CLIF criteria. This would mean that the former would have a higher inflammatory response from the acute event compared to the latter, other factors being equal. This could also be the reason why the higher thresholds for serum bilirubin and INR come into play in the EASL-CLIF definition. Shi *et al*[21] have shown recently that ACLF precipitated by acute hepatic injury and by extra-hepatic insults are distinct but overlapping conditions which have similarly high transplant-free, 28-d mortality (48.3% *vs* 50.7%; P = 0.22). The former group had compensated cirrhosis, liver and coagulation failure being frequent in them, while the latter had advanced underlying cirrhosis and a high frequency of extra-hepatic organ failure. Thus, conceptually, the acute precipitating events as per EASL-CLIF not directly involving the liver by and large, would need to raise the indicators of liver damage such as bilirubin and INR to a higher level to cause a mortality equivalent to Asian patients with ACLF. As would be expected from these, infections are less frequent in Asian patients with ACLF compared to their Western counterparts[8]. It thus becomes clear that the patients defined by the two definitions actually differ considerably. Further studies using the World Gastroenterology Organization (WGO) consensus definition (see below) would help confirm this.

PREDICTING OUTCOMES IN ACLF

The APASL consensus document stated that in the absence of studies on prognostic parameters to further stratify the outcome in patients with ACLF, the SOFA score may be used[8]. In a study from China, out of the 276 patients who met the APASL criteria, 83 (30.1%) progressed to ACLF as per the EASL-CLIF criteria post-enrollment and the mortality in them was over 50% compared to less than 5% in the rest[20]. When the patients who met the APASL criteria were compared with those who met EASL-CLIF criteria from among cirrhotics with acute worsening, the 90-d mortality between the two groups differed significantly (59.3% *vs* 13.1% respectively)[20]. Dhiman *et al*[11] from India found that the short-term mortality was significantly higher in those with ACLF than those without, if EASL-CLIF criteria were used (47.4% *vs* 8.3%, respectively) but not if the APASL definition was used (36.8% *vs* 38.7%, respectively). They concluded that the former criteria were better than the latter for defining ACLF and that the CLIF-SOFA score, and not the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ), Child-Pugh (CP) scores and Model for end-stage liver disease (MELD) scores was a significant independent predictor of mortality. The first study was retrospective, and the second one included a small number of patients. Agrawal *et al*[22] showed that simple organ failure count is better than the CANONIC system of severity grading for predicting the in-hospital mortality in Asian patients with ACLF. Jalan *et al*[23] added two other individual predictors of mortality, *i.e.,* age and white blood cell count to the simplified organ function scoring system (CLIF Consortium Organ Failure score, CLIF-C OFs) to develop the CLIF Consortium ACLF score (CLIF-C ACLFs) which was compared and was found to have higher predictive accuracy than MELD, MELD-Sodium (MELD-Na), and CP score. It was subsequently validated in an external cohort and found to perform better than the other prognostic scores for sequential use in stratifying the mortality risk in patients

Table 4 Subtypes of acute-on-chronic liver failure as per World Gastroenterology Organization working party

Type A ACLF - non-cirrhotic chronic liver disease with an acute flare; often indistinguishable from acute or sub-acute liver failure
Reactivation of hepatitis B
Hepatitis A or E superimposed on chronic hepatitis B
Autoimmune hepatitis
Hepatitis E infection in patients at risk for NASH
Type B ACLF - well compensated cirrhosis with an acute insult
Type C ACLF - cirrhosis with previous hepatic decompensation

Adapted from Jalan *et al*[10]. ACLF: Acute-on-chronic liver failure; NASH: Non-alcoholic steatohepatitis.

with ACLF. Further comparative studies and extensive research would be needed to determine the predictors of mortality that can be applied to patients with ACLF as defined by APASL criteria.

ARE THE DIFFERENCES REGION-SPECIFIC?

The possibility exists that the two definitions may be region-specific because of the differences in the pattern of the underling liver diseases and the prevalence of acute events.

This would mean that one is best served by using the definition applicable to one's own region. However, some concerns surface. One of the problems in comparing different studies from the same region would be that the background CLD and the acute insults may differ between them. For example, Zhang *et al*[20] found that CLD from chronic HBV infection constituted 52.5% of the patients while alcohol abuse was the acute insult in only 23.4%. Even within studies from India, the cause of underlying CLD differed, hepatitis B infection being the most common cause in a study from Mumbai (29.6%) and alcohol, in the study from Chandigarh (66%)[22,24]. Similarly the etiology of acute insult was also different, acute viral hepatitis A or E being seen in 33.3% patients in the former, while acute hepatitis E noted in 7% in the latter study[22,24].

EASE OF USE

With its simple clinical parameters, the definition given by the APASL consortium is easier to apply in day-to-day practice. The consensus document also states that it has a high degree of predictive ability[8]. However Dhiman *et al*[11] concluded that the APASL criteria did not predict mortality as well as the CLIF-SOFA criteria and that the latter is better to stratify patients with ACLF so as to predict the outcomes. Thus, lack of validated criteria to stratify the risk of mortality and the possible increased need for liver biopsy are the limitations of the APASL criteria. The practical application of the CLIF-SOFA criteria could, on the other hand, be difficult in the hands of internists, gastroenterologists, or hepatologists[25].

NEW DEFINITION - THE WORLD GASTROENTEROLOGY ORGANIZATION CONSENSUS

Because of the limited prospective data and of the differing definitions offered by APASL consensus and EASL-CLIF consortium, the WGO working party have proposed a definition of ACLF which is primarily only to identify patients from whom relevant data can be collected so as to arrive at a uniform definition which could bridge the gap between the Asia-Pacific region and the West[10].

The working definition characterizes ACLF as "a syndrome in patients with CLD 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 extra-hepatic organ failures that is associated with increased mortality within a period of 28 d and up to 3 mo from onset". Thus, this definition includes patients with chronic hepatitis, compensated cirrhosis as well as cirrhosis with previous decompensation (Table 4). As per the CANONIC study, the 28-d mortality was significantly lower in patients with type C ACLF. It is hoped that future studies will enroll patients as per this definition so that patients falling into the different sub-categories with possible different outcomes can be compared and more useful data would emerge thereby.

CONCLUSION

Despite the diversity of early data on ACLF, two consensus definitions have emerged in recent years which appear to represent two different but overlapping conditions. Several questions still remain to be answered regarding which definition to use and whether there are differences within a region based on the pattern of patients seen in each. Now that a third important definition has emerged, that proposed by the WGO, it is likely that relevant data collected will help clarify many of these issues so as to further improve the management of patients with ACLF ultimately contributing to improved outcomes in these patients.

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