Toward a Better Definition of Acute-on-Chronic Liver Failure

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Acute-on-chronic liver failure (ACLF) has been defined differently in the East and West. The definitions given by Asian Pacific association for the study of liver (APASL) and American association for the study of liver (AASLD) and European association for the study of liver (EASL) working group have fundamental deficiencies and contradictions and do not encompass all patients with ACLF seen in the East and West. Although the World Gastroenterology Organisation (WGO) working party attempted to provide an improved definition but this too is not appropriate. In this article, we have compared the various definitions of ACLF given by APASL, EASL-AASLD and WGO and suggest a comprehensive definition for prospective collection of data on ACLF. (J CLIN EXP HEPATOL 2017;7:262–265)

Acute-on-chronic liver failure (ACLF) is a syndrome which is distinct from chronic liver failure or decompensated cirrhosis in view of the presence of a precipitating factor, rapid deterioration leading to liver and/or extra hepatic multi-organ failure with a high short term (28 days and 90 days) mortality.^{1–3} In spite of this catastrophic presentation, there is a component of potential reversibility and reversion back to the original state if these patients are supported well and the precipitating factor is taken care of.^{4–6} For others liver transplantation with or without liver support by liver assist devices may be the only hope of survival.^{7–10} Even though the clinical syndrome is not new and was seen and managed all across the globe for many years, this has been defined only recently both in the East and West.^{11,12} Both the definitions given by Asian Pacific association for the study of liver (APASL) and American association for the study of liver (AASLD) and European association for the study of liver (EASL) working group have deficiencies and do not encompass all patients with ACLF seen in the East and West. To improve upon the existing definition World Gastroenterology Organisation (WGO) working party recently came out as a third umpire and gave an improved definition but is also not a complete by itself.¹³

In this article, we have reviewed and compared the definitions of ACLF given by APASL, EASL-AASLD and WGO and suggest a comprehensive definition for prospective collection of data on ACLF.

EXISTING DEFINITIONS OF ACLF AND THEIR DEFICIENCIES

Even though many definitions of ACLF exist, three important definitions in clinical practice are from APASL, AASLD-EASL and WGO.^{11–13} APASL defined ACLF first in 2009 as ‘Acute hepatic insult manifesting as jaundice, and coagulopathy complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease’.¹¹ In its revised definition in 2014, APASL has added the occurrence of high short-term mortality at 28 days in the definition of ACLF.¹⁴ The original definition of APASL was based on the expert opinion, however the revised definition of APASL given in 2014 is based on the prospectively/retrospectively collected data.¹⁴

AASLD and EASL working group defined ACLF as “Acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure.”¹² AASLD-EASL working party definition was based on the consensus emerging out of a single topic symposium on ACLF whereas the EASL chronic liver failure consortium (CLIF-C) CANONIC study definition was based on the prospectively collected multi-center data in large number of patients.^{12,15}

WGO working party recently gave an improved definition of ACLF as “ACLF is 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 + prolonged international normalized ratio (INR)) and one or more extrahepatic organ failure that is associated with increased

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Abbreviations: AASLD: American association for the study of liver diseases; ACLF: Acute-on-chronic liver failure; APASL: The Asian Pacific association for the study of the liver; CLD: chronic liver disease; CLIF-C: chronic liver failure consortium; EASL: European Association for the Study of the Liver; WGO: World Gastroenterology Organisation

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Table 1 showing the Comparison Between the APASL, AASLD-EASL and WGO Definitions of ACLF.

Parameters	APASL definition	AASLD/EASL working party definition	WGO definition
Duration between acute insult and ACLF	Four weeks	Not defined	Not defined
What qualifies as the underlying chronic liver disease	Non-cirrhotic chronic liver disease and only compensated cirrhosis	Only cirrhosis (non-cirrhotic chronic liver disease not included). Including patients with cirrhosis with prior decompensation	Non-cirrhotic chronic liver disease Compensated cirrhosis Decompensated cirrhosis
What qualifies as acute precipitating event	Alcohol, drugs, hepatotropic viruses, surgery, trauma	Alcohol, drugs, hepatotropic viruses, surgery, trauma Infection/sepsis Variceal bleed	Alcohol, drugs, hepatotropic viruses, surgery, trauma Infection/sepsis Variceal bleed
Organ Failure in the definition	Hepatic failure	Extra-hepatic organ failure	Hepatic failure Extra-hepatic organ failure
Increased mortality at 28 and/or 90 days in the definition	Yes	Yes	Yes

mortality within a period of 28 days and up to 3 months from onset.”¹³

Table 1 summarizes the salient points of the three definitions.

Duration Between Acute Insult and ACLF

Even though APASL definition is clear about the duration between the acute insult and the development of liver failure as 4 weeks, both AASLD-EASL and WGO definitions are silent about this time interval.¹⁶ Even though most patients with ACLF present with hepatic or extra-hepatic organ failure within 4 weeks of acute insult, cirrhotic patients can deteriorate and can present as ACLF as early as 1–2 weeks following surgery or hepatic resection. On the other hand some patients with alcoholic hepatitis superimposed on alcoholic cirrhosis or those with HBV flare on underlying chronic hepatitis B (CHB) can present as ACLF as late as 12 weeks and will still be called as ACLF even though they have not presented within 4 weeks. Prospective studies would be required to analyze as to how many patients present before and after 4 weeks of acute insult, and to study the duration between the acute insult and the occurrence of hepatic or extra-hepatic organ failure but any person presenting with liver failure due to an acute precipitating event with underlying chronic liver disease can be defined as ACLF even if the duration between acute insult and development of ACLF is more than 4 weeks.

What Qualifies as the Underlying Chronic Liver Disease?

As per the APASL definition, both groups of patients with underlying non-cirrhotic chronic liver disease (CLD) and those with cirrhosis can be included in the definition of ACLF.¹¹ Non-cirrhotic liver disease as the underlying CLD

in patients with ACLF refers to underlying CLD (pre-cirrhotic) related to any etiology without imaging or histological evidence of cirrhosis but where the patient presents as ACLF after an acute precipitating event. This would be applicable to many patients with Nonalcoholic Steatohepatitis (NASH), CHB, etc. without cirrhosis which can decompensate as ACLF with superadded acute precipitating event. This has been defined and accepted by the APASL and WGO definitions but not by the EASL-AASLD group.

APASL definition does not include patients with previous and current hepatic decompensation in the definition. Whereas as per the AASLD-EASL definition both compensated and decompensated group of patients with cirrhosis can be included in the definition of ACLF but does not include non-cirrhotic patients with CLD.¹² On the other hand WGO working party definition is broader including patients with non-cirrhotic CLD and both compensated and decompensated cirrhosis.¹³ Since ACLF can develop in many patients with hepatitis B, NASH and alcohol related CLD without cirrhosis and similarly patients with decompensated cirrhosis can also have acute deterioration amounting to ACLF; as suggested by WGO working party, all patients with CLD [non-cirrhotic and cirrhosis (compensated and decompensated)] should be included in the definition of CLD and they should be divided into type A (non-cirrhotic CLD), B (compensated cirrhosis) and C (decompensated cirrhosis) as per the WGO working party definition.¹³

What Qualifies as Acute Precipitating Event?

Though both APASL definition and AASLD-EASL definition agree to include hepatotropic viruses, alcohol, drugs and surgery as the acute precipitating events, in contrast to AASLD-EASL definition, APASL definition does not include infection/sepsis as the acute precipitating event and has no consensus on variceal bleed as the acute

precipitating event.^{11,12} On the other hand, WGO working party definition suggests that infection/sepsis can qualify as acute precipitating event in ACLF.¹³ Enough literature exists from East and West which supports infection/sepsis as one of the precipitating events in patients with ACLF.¹⁷⁻²² Since in many patients it becomes difficult to ascertain as to whether infection/sepsis triggered the ACLF or developed as a complication, it should be included as the acute precipitating event in situations where all other possible acute precipitating events have been excluded and a temporal relation could be established between the occurrence of infection/sepsis and development of ACLF. Similarly if ACLF clinical syndrome follows an episode of variceal bleed it can be included as the acute precipitating event.

Organ Failure in the Definition of ACLF

A major difference between the APASL definition and AASLD-EASL definition is about the focus on liver failure by the former and extra-hepatic organ failure by the later.¹⁶ APASL definition includes jaundice, coagulopathy, ascites and/or encephalopathy in the definition of ACLF whereas AASLD-EASL definition includes multi-system organ failure in the definition.^{11,12} Though a bilirubin level >5 mg/dl and INR >1.5 is required by the APASL definition; as per the CANONIC study patients with acute decompensation can have ACLF as defined by extra-hepatic organ failures even when the bilirubin is <5 mg/dl and INR <1.5 . WGO working party includes liver failure and one or more extra-hepatic organ failure in the definition of ACLF.¹³ Within the extra-hepatic organ failure the focus by the AASLD-EASL group is predominantly on renal failure. As per the EASL CLIF-C CANONIC study, patients of cirrhosis with acute decompensation and renal failure would qualify to be called as ACLF even if the liver functions are normal and there is no hepatic decompensation.¹⁵ Since ACLF syndrome pertains to liver failure, hepatic decompensation with jaundice, coagulopathy, ascites and or encephalopathy must be present at the diagnosis of ACLF and it may or may not be accompanied by extra-hepatic organ failure. The presence of extra-hepatic organ failure though help in prognosticating these patients, it may not be included in the definition of ACLF.²⁰⁻²⁷ In addition to the standard of care, baseline and delta model for end-stage liver disease, Acute Physiology and Chronic Health Evaluation (APACHE), CLIF-C ACLF and other prognostic scores and number of organ failures can help in deciding the inclusion of patients in various therapeutic trials or subjecting them to liver transplantation.

Should Mortality be Included in the Definition of ACLF?

The purpose of any definition would be to define patients at risk and their outcome. However, a patient need not die

so as to fit in to the definition of a particular disease. All the three existing definitions by APASL, AASLD-EASL and WGO working party includes high mortality in patients with ACLF in the definition.¹¹⁻¹³ The original definition by APASL though did not include increased mortality in the definition of ACLF; its recent revision has included high 28 days mortality in the definition of ACLF.¹⁴ AASLD and EASL working group includes increased mortality at 3 months in the definition which was revised to 28 days mortality in the CANONIC study; the WGO working party includes high mortality at 28 days and up to 3 months in the definition of ACLF.¹³⁻¹⁵ However, inclusion of mortality creates a false impression that ACLF diagnosis is probably post-mortem. Moreover, in spite of having ACLF, more than 50% of patients with ACLF do survive for 28 or 90 days.^{6,19-22,26-28} Though the prognostic evaluation based on various scoring systems and number of organ failures at admission and subsequently so as to decide on various modalities of treatment including liver transplantation are very important in patients with ACLF, increased mortality in ACLF may not be included in the definition of ACLF.

WHAT SHOULD BE THE DEFINITION OF ACLF?

Based on the discussion over the various elements which form part of the ACLF definition, the ACLF can be defined as follows:

“ACLF is a syndrome in patients with CLD [with or without cirrhosis, previously diagnosed or undiagnosed, compensated or decompensated, which is characterized by acute hepatic decompensation within 12 weeks of an acute precipitating event, (both hepatic and/or non-hepatic) in the form of ascites and/or hepatic encephalopathy, associated with jaundice (serum bilirubin >5 mg/dl) and prolonged INR (>1.5)”.

Inclusion criteria

1. Unequivocal evidence of CLD [with or without cirrhosis (compensated or decompensated)] based on clinical parameters, biochemical and hematological investigations, imaging, previous transient elastography, gastroscopy with or without liver biopsy.
2. Presence of hepatic or extrahepatic acute precipitating events as detailed below.
3. Presence of jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR >1.5).
4. Hepatic decompensation in the form of ascites and/or hepatic encephalopathy.
5. Presence or absence of extra-hepatic organ failure.

Acute precipitating events in ACLF

1. Acute viral hepatitis
2. Alcoholic hepatitis
3. Drug induced liver injury
4. Variceal bleed
5. Ischemic hepatitis
6. Surgery
7. Infection/sepsis
8. Idiopathic

CONCLUSIONS

In this commentary, we have tried to simplify and homogenize the definition of ACLF taking into account the lacunae inherent in the existing three important definitions. The definition of ACLF should include all patients with CLD including those with and without cirrhosis which could be compensated or may have decompensated and are prone for acute deterioration. Similarly, both hepatic and extra-hepatic acute insults can incite ACLF and should be included as acute precipitating events. Liver failure can occur up to 12 weeks after acute insult and should be the hall mark of this syndrome. Liver failure may be accompanied by one or more extra-hepatic organ failure and the number of organ failures though is an important determinant of severity of ACLF, it may not be included in the definition. Even though patients with ACLF have high short term mortality, the diagnosis of ACLF should not be based on the mortality and high mortality may not be included in the definition of this syndrome.

CONFLICTS OF INTEREST

The authors have none to declare.

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