

# 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)**

**A**cute-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.<sup>1–3</sup> 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.<sup>4–6</sup> For others liver transplantation with or without liver support by liver assist devices may be the only hope of survival.<sup>7–10</sup> 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.<sup>11,12</sup> 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.<sup>13</sup>

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.<sup>11–13</sup> 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’.<sup>11</sup> In its revised definition in 2014, APASL has added the occurrence of high short-term mortality at 28 days in the definition of ACLF.<sup>14</sup> 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.<sup>14</sup>

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.”<sup>12</sup> 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.<sup>12,15</sup>

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.”<sup>13</sup>

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.<sup>16</sup> 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.<sup>11</sup> 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.<sup>12</sup> On the other hand WGO working party definition is broader including patients with non-cirrhotic CLD and both compensated and decompensated cirrhosis.<sup>13</sup> 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.<sup>13</sup>

**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



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