Acute on Chronic Liver Failure—What is in a 'Definition'?

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Acute on chronic liver failure (ACLF) is a recently recognized syndrome and its definition has been evolving over last two decades. Currently, there is no universal consensus about the definition as kind of cases being seen in the Western world appear to be somewhat different from those that are seen in Asia Pacific region. But every one agrees that definition of ACLF should include following components. (a) The status of pre-existing liver disease, (b) defining the acute insult that leads to rapid deterioration of liver status, (c) time frame during which the acute insult can lead to rapid deterioration, (d) the quantification and definition of liver failure status after deterioration, which will determine the severity of ACLF, and (e) prediction of prognosis after analyzing first four components in the short and long terms. There is some consensus that number of organ failures may be the main determinant of prognosis. Whatever the definition is being used, the central role that superadded infections play in ACLF cannot be denied and need to be tackled aggressively. Apart from that, recovery may be possible if the acute insult or the baseline disease is curable, i.e. with the use of nucleoside analogs for hepatitis B, and corticosteroids for severe autoimmune hepatitis. Development of dynamic criteria with observations in Hospital may improve our understanding of prognosis as well as our approach to the management of ACLF. (J Clin Exp Hepatol 2016;6:233–240)

Arriving at a universal consensus on definition of liver failure has always been difficult. Earlier, East and West could never agree on a common definition for acute and subacute hepatic failure.[1–5] The new kid on the block, acute on chronic liver failure (ACLF) seems to have inherited all of that and more.[6] The term ACLF was possibly first used way back in early 1990s and denoted two components of same disease—a preexisting chronic liver disease with superadded acute deterioration brought on by a precipitating event.[7] Since then, there have been several attempts to define it and a consensus is still eluding as is evident from Table 1.[7–31] Earlier controversies about acute and subacute liver failure were primarily related to the timing of various manifestations of liver failure (Figure 1). Experts, from Indian subcontinent at that time, were seeing a lot of patients with ascites as the main manifestation of liver failure in the course of viral hepatitis and wanted to reserve the term of sub acute hepatic failure for it, while the Western World hardly ever saw a similar case. Over time, even in India, the frequency of such presentation has gradually declined and many presume that this entity was nothing but a presentation of ACLF. Whether all cases of subacute hepatic failure were caused by acute hepatitis super-added on chronic liver disease without cirrhosis (Type-A, ACLF as per WGO classification[29] or recently described compensated advanced chronic liver disease or cACLD[32]) remains to be determined. In those days, it was not possible to diagnose cACLD, as there was no transient elastography available and trans-jugular liver biopsies were not routinely done in Indian subcontinent.

As the term implies, the definition should define a disease with high specificity and sensitivity. Diagnostic criteria should be objective and cover the whole range of liver failure cases. It should be possible to select cases prospectively using the diagnostic criteria. At the same time, the criteria should be validated in different cohorts of patients. Ideally, when diagnostic criteria are met, the disease should be ACLF and nothing else. Not only that, as classified by definition, it should be possible to predict the outcome. In relation to ACLF, definition will need to have several components, for example:

(a) First component is pre-existing chronic liver disease and its severity should be specified if possible as it is likely to impact the ultimate outcome. There has been an attempt to classify first component by WGO group into subtypes A, B and C[29] depending on severity of pre-existing liver disease.

(b) Second component is acute insult and they can differ in severity as well as type. There have been various ways to sub-classify this event but it is important to spell out not only the severity of this component but also the potential of

Keywords: Acute on chronic liver failure, Acute liver failure, Cirrhosis of liver, Decompensated cirrhosis, Organ failure, Sepsis

Received: 22.08.2016; *Accepted:* 26.08.2016; *Available online:* 1 September 2016

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Abbreviations: ACLF: acute on chronic liver failure; ASA: American Society of Anesthesiologists; INASL: Indian Association for study of the liver; MELD: Model for End-Stage Liver Disease; NACSELD: North American Consortium for Study of End Stage Liver Disease; SBP: spontaneous bacterial peritonitis; SOFA: Sequential Organ Failure Assessment

http://dx.doi.org/10.1016/j.jceh.2016.08.011

Table 1 Various Definitions of Acute on Chronic Liver Failure Used in Literature.

S. no.	Author	Acute insult	Chronic disease	Signs of failure	Appeared after how much time of acute insult	Increased mortality during how much time	Basis
1	Ohnishi et al.[7]	Precipitating events	Ongoing liver disease	Deterioration	Not defined	Not defined	Arbitrary
2	Yang et al.[8]	Acute hepatitis	CH B	ALT > 10× ULN, Bilirubin > 15 mg/dL, prolonged PT > 5 s and HE	Not defined	Not defined	Arbitrary
3	Jalan and Williams[9]	UGI Bleed	Well compensated CLD	Renal dysfunction of HE	Not defined	Not defined	Arbitrary
4	Sen et al.[10]	Inflammation-related precipitant (infection or alcoholic hepatitis) or UGIB	Cirrhosis	Increasing jaundice (Bilirubin 6 mg/dL or more) and either HE (Grade 2) or HRS	2–4 weeks	Not defined	Arbitrary
5	Wasmuth[11]	Not defined	Liver cirrhosis based on a histopathological diagnosis or compatible laboratory data and sonographic findings	Jaundice, ascites, hemodynamic instability and/or HEgrade III–IV compatible with the definition of hepatic decompensation necessitating further treatment in the ICU	Recent	Not defined	Arbitrary
6	Yu et al.[12]	Acute or subacute hepatitis	Hepatitis B or C carrier, chronic hepatitis or cirrhosis	Bilirubin > 10 mg/dL, Ascites, HE >Grade 2 and prolonged PT (PTI < 40%)	2 weeks to 6months	Not defined	Arbitrary
7	Laleman et al.[13]	Alcoholic hepatitis	Alcoholic cirrhosis	Persistent deterioration despite treatment with bilirubin > 12 mg/dL	Not defined	Not defined	Arbitrary
8	Wang et al.[14]	Acute decompensation	CLD	Severe liver dysfunction, HE grade 2 or higher	Not defined	Not defined	Arbitrary
9	Sarin et al. (APASL)[15]	Hepatotropic viruses, Other viruses, bacterial infection and sepsis, alcohol and other toxins, variceal bleed, HBV flares	NAFLD, NASH, Chronic hepatitis, Undiagnosed cirrhosis, known jaundice and coagulopathy, compensated cirrhosis, decompensated cirrhosis	Jaundice and coagulopathy followed by ascites and/or HE	4 weeks	Not defined	Arbitrary
10	Krishna et al.[16]	Acute Hepatitis A or E	Cirrhosis	A high SOFA/APACHE II score with jaundice and either HE or renal failure	2–4 weeks	Not defined	Arbitrary
11	Sun et al.[17]	Decompensation	CLD	Severe debilitation and dysfunction of the alimentary tract, with Bilirubin > 10 mg/dL or an increase of Bilirubin > 10 mg/dL/day; and PTI < 40%	Not defined	Not defined	Arbitrary
12	Shi[18]	Acute deterioration	CLD	Bilirubin > 10 mg/dL, PTI < 40%, ascites and or HE	Not defined	Not defined	Arbitrary
13	Novelli et al.[19]	Acute deterioration	CLD	Increasing jaundice	Not defined	Not defined	Arbitrary
14	Katoonizadeh et al.[20]	Acute hepatic insult	Compensated CLD with Bilirubin > 5 mg/dl (without extrahepatic obstruction)	Rise in bilirubin levels by >50% or up to 20 mg/dl, or HE more than grade 2, or fresh development of ascites and or HRS	4–8 weeks	Not defined	Arbitrary
15	Karvellas et al.[21]	Not defined	Cirrhosis	Decompensation such as variceal bleed, HE, HRS, MOF requiring organ support	Not defined	Not defined	Arbitrary
16	Zhai et al.[22]	Acute deterioration	Compensated CLD, chronic hepatitis B or hepatitis B virus carriers	HE, ascites, bleeding, or HRS	Not defined	Not defined	Arbitrary
17	Zhihui et al.[23]	Not defined	CLD	Recent development of bilirubin > 10 mg/dL and PTI < 40%, HE (grade 2 or more),	Not defined	Not defined	Arbitrary

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