Liver Transplantation for Acute on Chronic Liver Failure

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Acute-on chronic liver failure (ACLF) is defined as acute insult on previous liver disease that causes sudden worsening of liver functions. ACLF is characterized by high incidence of organ failure (OF) and prognosis is remarkably worse than patients with cirrhosis. Incidence of OFs is very high despite best medical care and timely liver transplant before development of multi-OF is associated with good survival rates. At present, there are no reliable score or ways to correctly identify patients who are going to recover from patients who will need transplantation. OFs are important part of prognosis and to define need or futility of early liver transplantation (LT). Asian Pacific Association for the Study of the Liver (APASL) published their recommendations regarding ACLF in 2014. Several important studies regarding course/nature of disease and transplantation for ACLF became available after 2014 APASL recommendations and still there are some unanswered areas. The current review discusses various issues regarding LT in patients with ACLF. (J Clin Exp Hepatol 2017;7:247–252)

The syndrome of acute-on chronic liver failure (ACLF) is different from decompensated cirrhosis as it is precipitated by some acute event that leads to rapid deterioration. ACLF is characterized by hepatic/extrahepatic organ failures (OFs) and is associated with high short-term mortality.[1–6] As name suggests there is a component of reversibility and these patients may recover to state before onset of ACLF; the prognosis is poor in absence of improvement. ACLF patients have a significant risk of development of OFs and mortality in absence of improvement and liver transplantation (LT) should be considered in such patients before development of multi-OF.[7–9] Thus, these patients have a small window of opportunity (LT) before development of OFs and it is important to identify prognosis of ACLF before it is too late.[10]

VARIOUS DEFINITIONS OF ACLF

Multiple definitions have been used in literature for ACLF.[11] The first systemic attempt to define ACLF was published by Asian Pacific Association for the Study of the Liver (APASL) in 2009 based on expert consensus. The ACLF was defined as 'acute hepatic insult manifesting as jaundice (bilirubin >5 mg/dl), and coagulopathy (INR > 1.5) complicated within 4 weeks by ascites and or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease'. The cut-offs of bilirubin and INR were arbitrary.[12] APASL revised this definition based on database collected from APASL ACLF Research Consortium. The revised definition included 'occurrence of high short-term mortality at 28 days'.[2] The definition given by European Association for the Study of the Liver (EASL) was based on prospective database from EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study. It was based on the presence of the 3 important characteristics of ACLF syndrome: acute decompensation (inclusion criterion), OF defined by the SOFA-CLIF score (modified SOFA score) and high 28-day mortality rate.[4] The EASL definition is applicable to patients with cirrhosis only as compared to APASL definition which also include noncirrhotic liver disease as underlying chronic liver disease. EASL definition include extrahepatic OFs also which APASL definition does not include.[1] The World Gastroenterology Organisation also proposed a definition for ACLF including noncirrhotic chronic liver disease as underlying chronic liver disease while the rest was kept as similar to EASL definition.[5]

COURSE AND PROGNOSIS IN PATIENTS WITH ACLF

It is important to look at course of ACLF as LT should not be done in patients who will recover with medical treatment and early LT should be considered in patients with worsening or no improvement to before development of multi-OF. The course of ACLF (improvement or

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Abbreviations: ACLF: acute-on chronic liver failure; APASL: Asian Pacific Association for the Study of the Liver; DDLT: deceased donor liver transplantation; EASL: European Association for the Study of the Liver; MELD: model for end stage liver disease; LDLT: living donor liver transplantation; LT: liver transplantation; OFs: organ failures; SIRS: systemic inflammatory response syndrome
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worsening) may be very rapid. Gustot et al. showed that grade of ACLF changed very rapidly (defined as within 48 h) in 40% of patients, it changed rapidly (defined as 3–7 days) in approximately 14.7% of patients and changed slowly (defined as change of ACLF grade in 8–28 days) in 14.7% of patients. The grade of ACLF at day 3–7 was better to predict prognosis than grade of ACLF at admission.[7] The final grade of ACLF remained same as ACLF grade at day 3–7 in 81% of patients. As course of ACLF patients may change rapidly, it is important to identify need of LT before patients develop multi-OF and do not remain candidates for transplant.[7] The authors found CLIF-C ACLF and liver failure as independent prognostic markers of early severe copurse.[7] ACLF resolved or improved in 49.5% patients, it remained steady or fluctuating in 30.4% and worsened in 20.1% (CANONIC database). The resolution rates were 54.5%, 34.6% and 16% for ACLF grade 1, 2 and 3 respectively. The ACLF worsened in 21.2% of ACLF-1, 25.7% of ACLF 2 and it remained steady/fluctuating in 68% of ACLF-3.[7]OFs are an important part of prognosis in patients with ACLF and prognosis worsens in patients with higher number of OFs (with higher ACLF grades). As discussed earlier, ACLF definition from EASL also include extrahepatic OFs and EASL CLIF score have been shown to be better than APASL ACLF definition.[13] The SOFA score consists of 6 variables (Table 1), each OF have various categories and a higher score is given for worse organ function. The SOFA score was modified and definition of OF are proposed as shown in Table 1 (shown in bold letters). The patients of ACLF are divided as no ACLF (no OF or single non-kidney OF with creatinine <1.5 mg/dl), grade 1 ACLF (single kidney failure or 1 OF with serum creatinine 1.5 to 1.9), grade 2 ACLF (2 OFs) and grade 3 ACLF (3 or more OFs) as per EASL definition.[4] While no ACLF had mortality of 1.9% and 10% at 28 days and 90 days, these mortality rates are 23% and 41% for ACLF grade 1, 31% and 55% for ACLF grade 2 and 74% and 78% for ACLF grade 3 respectively. Overall ACLF (total) had a mortality of 33% at 28 days and 51% at 90 days.[4] This CLIF-OF score was further modified to CLIF-C ACLF score by creating 3 subcategories (Table 1) of OF severity and including age and white blood cell count. The CLIF-C ACLF score can be calculated online. The CLIF-C ACLF score was better to predict mortality than other scores in CANONIC database.[3] Bajaj et al. analyzed data of 507 patients with inclusion of infection as acute event and overall mortality was 23%. The mortality was >50% in presence of ≥2 OFs.[6] Some of the Indian studies evaluating mortality of patients with ACLF are shown in Table 2.[8,14–21] These studies show a mortality rate ranging from 41.4% (median of 8 days) to 74.5% at 90 days.[18,19] It has also been shown that mortality at 28 days and 90 days remains almost similar in presence of hepatic or non-hepatic acute event.[19]

ACLF is very heterogeneous condition with different combinations of acute and chronic events. Acute event ranges acute viral hepatitic illness to non-hepatototropic infections, alcohol, drug induced liver injury, surgery, reactivation/flare up of basic disease (hepatitis B, Wilson's disease, autoimmune hepatitis).[2,4,14] Alcohol as acute event has been shown to be associated with worse outcomes.[9,17] Shalimar et al. analyzed data of 213 patients of ACLF prospectively from Delhi, India. Acute event was continuous alcohol consumption in 77 (33.3%) and acute hepatitis E in 39 patients. The mortality rates were higher for alcohol with hazard ratios of 4.08. The etiology was independent predictor of mortality. The mortality was 54% in alcoholic group versus 12.8% in hepatitis E group.[9] Pati et al. also showed more mortality in alcohol group (81.1%) versus nonalcoholics (55.8%).[17] Shalimar et al. showed that mortality was higher in patients with silent chronic liver disease (33.9%) as compared to patients with overt chronic liver disease (53.5%).[9] One study from Dr. Sarin's group (Delhi, India) showed that absence of systemic inflammatory response syndrome (SIRS) in patients with ACLF was associated with good prognosis.[20] New onset SIRS and sepsis developed in 75% and 8% at a median 7 days. The mortality was 42.8% in no SIRS group as compared to 65% in SIRS group.[20]

LT FOR ACLF

As course of ACLF changes rapidly and higher ACLF grades do not improve in majority and are associated with

Table 1 Organ Failures and CLIF-C ACLF Subscores.[3]

Organ/system	Subscore 1	Subscore 2	Subscore 3
Liver (bilirubin, mg/dl)	<6	≥6	**≥12**
Kidney (creatinine, mg/dl)	<2	**≥2 to <3.5**	≥3.5
Brain (West-Haven grade for hepatic encephalopathy)	0	Grade 1 or 2	**Grade 3 or 4**
Coagulation (INR)	<2.0	≥2.0 and <2.5	**INR ≥ 2.5**
Circulation (mean arterial pressure)	≥70 mm/Hg	<70 mm/Hg	**Vasopressors**
Respiratory (PaO_2/FiO_2) Or SpO_2/FiO_2	>300 >357	≤300 and >200 >214 and ≤357	**<200** **≤214**

Organ failure's cut-off is shown as bold characters.