Acute on Chronic Liver Failure: Lessons from a Decade of EASL-CLIF Definition and Scoring Systems

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Acute on chronic liver failure (ACLF) remained a poorly defined, and thereby poorly researched and understood, complex syndrome up until 2002 when Prof R Jalan ventured the first definition.[1] He defined it as an acute deterioration in liver function over a period of 2–4 weeks due to a precipitating event, leading to severe organ failure and high SOFA/APACHE II score. In 2009, APASL proposed a definition: ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis, and is associated with a high 28-day mortality.[2]

EASL-CLIF ACLF Definition and CLIF-SOFA Score

In 2013, Richard Morreau et al. published the landmark CANONIC study of the EASL-CLIF Consortium and defined it as an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure.[3]

The study proposed the CLIF-SOFA score (Table 1) that defined thresholds for various organ failures to grade the severity of ACLF. The score is a modification of the SOFA score routinely used in intensive care. The organs included are hepatic, coagulopathy, renal, encephalopathy, hemodynamic, and respiratory. Based on the number of organ failures, ACLF was graded into three grades with respect to the 28- and 90-day mortalities in these three grades (Table 2). The threshold to differentiate between dysfunction and failure were identified based on observed mortality subsets. The 3-month mortality is distinctly high in the ACLF group vs no ACLF group (Fig. 1).

The simplicity of this score has led to quick acceptance in clinical practice in liver units and intensive care units all over the world in the last decade. Research has also become uniform across the world due to CLIF-SOFA score, and our understanding of this complex syndrome has tremendously increased in the decade following the landmark CANONIC study. The uniqueness of CLIF-SOFA OF score lies in that it is used to identify (define), measure severity (grading) and even prognosticate outcomes based on score on day 3 and day 7 score. Acute on chronic liver failure is a dynamic condition and single day score may have limitations and hence the scores on day 3 and day 7 are more useful to predict outcomes.[4]

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Table 1: CLIF-SOFA organ failure score[5]

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dL)	<6	6– ≤512	>12
Kidney, creatinine (mg/dL)	<2	2–<3.5	≥3.5 or renal replacement
Brain, grade (West-Haven)	0	1–2	3–4
Coagulation, INR	<2.0	2.0–<2.5	≥2.5
Circulation, MAP (mm Hg)	≥70	<70	Vasopressors
Respiratory PaO$_2$/FiO$_2$	>300	≤300 and >200	≤200
or SpO$_2$/FiO$_2$	>357	>214 and ≤357	≤214

*Grey zone marks organ failure

Table 2: Grades of ACLF[5]

No ACLF	No organ failure or 1 single organ failure, not including kidney failure, with serum creatinine <1.5 mg/dL and no hepatic encephalopathy
ACLF-1	Single kidney failure or 1 single organ failure linked to kidney failure (creatinine between 1.5 and 1.9 mg/dL or level 1–2 hepatic encephalopathy
ACLF-2	2 organ failures
ACLF-3	≥3 organ failures

Role Inflammation: CLIF-C ACLF Score

The underlying pathophysiology is distinct from acute decompensation in terms of hyperinflammation and immune exhaustion, which are an integral part of ACLF but absent in AD. As a consequence of uncontrolled inflammation and high cytokines, circulating extrahepatic organs get dysfunctional or fail and underlying liver functions also deteriorate due to local inflammation. The phase of excess cytokines is followed by immune exhaustion which predisposes the patients to sepsis and multiorgan failure. The inflammation was measured using WBC count and CRP in the CANONIC study. R Jalan et al. in 2014 published a study in which they developed and validated the prognostic CLIF-C ACLF score which adds age and WBC to organ failure score and is calculated using a mathematical equation.[5]

Score Formula

$$CLIF\text{-}C\ ACLF = 10 \times [0.33 \times CLIF\text{-}OFs + 0.04 \times Age + 0.63 \times Ln (WBC)] - 2.$$

A CLIF-C ACLF of 40 or lower had a 90% negative predictive value and 97% sensitivity, while a score of 60 or higher allowed for an 82% positive predictive value and 94% specificity in predicting 30- and 90-day mortality.[5]

Incidence and Prevalence

Mezzano et al.,[6] measured the global burden of ACLF from the publications in the last decade.[6] They found that the global prevalence of ACLF among patients admitted for decompensated cirrhosis was 35% (95% CI, 33–38%). The region with the highest prevalence was South Asia at 65%. The global 90-day mortality was 58% (95% CI, 51–64%).

Why Do We Need New Score?

MELD and MELD Na, CTP all have been found to be inferior in prognosticating ACLF. A recent systematic review published in December 2022 looked at 50 studies from all over the world including India concluded the superiority of CLIF-SOFA OF score and CLIF-C ACLF score in predicting short-term outcomes.[7]

Why Do We Need to Identify and Grade Severity of ACLF?

The importance of recognizing and grading the severity of ACLF in routine clinical practice in intensive care cannot be emphasized more. Early recognition and timely transplantation has been able to reduce mortality as demonstrated in recent study by Luca Belli.[8] One-year post-transplant survival was 80% for ACLF 1 and 2, and 50% for ACLF 3. Without transplantation, the 3-month mortality of ACLF 2 is 45–50% and ACLF 3 is upwards of 80%. The CHANCE study is a multicenter observation study ongoing to assess the results of transplantation in ACLF 2 and 3 across 22 countries in Europe. This study will help identify right candidates and plan timing of transplantation better in ACLF. Indian studies have also shown a good survival post-transplant for ACLF. Transplantation in ACLF is the most challenging frontier for any center and has been made possible due to higher standards of critical care given to these sick patients. A multidisciplinary team effort involving surgeons, anesthesiologist intensivists, hepatologists, ID specialists, dietitian, physio and rehab specialists is crucial to the success of transplant in ACLF.

In this edition of IJCCM, Prof Ramadoss has undertaken external validation of the CLIF-SOFA and ACLF scores in a tertiary care
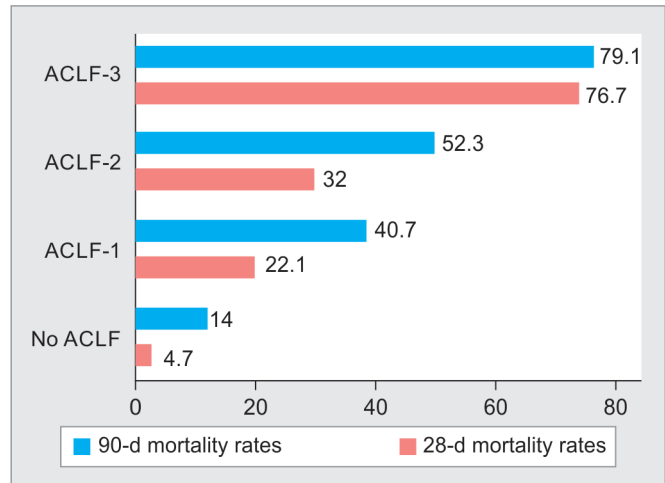

Fig. 1: Mortality in ACL[9,10]

non-transplant center. About 40 patients were identified to have ACLF out of a total 300 cirrhosis admissions in the year of the study. Number of ACLF three patients in the cohort were however only 10, majority being grade II and I. They have not only prospectively demonstrated the 28- and 90-day survival in the three grades but also demonstrated that the CLIF OF score on day 0, day 3, and day 7 is a great tool to prognosticate ACLF. Their study also demonstrates an excellent AUROC for CLIF-C ACLF score: AUROC of 0.86 and 0.84 for predicting 28- and 90-day mortality.

We can conclude that in the Indian population of ACLF also, both CLIF OF score and ACLF score are good tools to predict outcomes at 28 and 90 days.

Conclusion

Acute on chronic liver failure remains a distinct subset of patients who are at high risk of short-term mortality. Identifying these patients and transplanting them if they do not have any contraindications is the only curative option. Although this study comes from a non-transplant center, it helps understand the natural history of this devastating entity and reemphasizes the usefulness of the CLIF-SOFA and CLIF-C ACLF scores in grading and prognosticating ACLF in the Indian population. This will lead to early identification and interventions with timely transplant with the aim to cut down the high short-term mortality.

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