ORIGINAL ARTICLE

Clinical Profile, Short-term Prognostic Accuracies of CLIF-C ACLF Score and Serial CLIF-C OF Scores in Acute-on-chronic Liver Failure Patients: A Prospective Observational Study

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Abstract

Background: Acute-on-chronic liver failure (ACLF) is a recently defined entity that carries high short-term mortality. The European Association for Study of Liver (EASL) has given a different definition for ACLF and derived two scores called Chronic Liver Failure-Consortium Organ Failure (CLIF-C OF) and CLIF-C ACLF to diagnose and predict the short-term outcome, respectively.

Materials and methods: This was the prospective observational study, included 40 ACLF patients diagnosed as per the EASL definition and calculated CLIF-C ACLF as well as other scores (CTP, MELD, MELD-Na, CLIF-C OF) on admission. Serial CLIF-C OF scores were also calculated (Day 3 and Day 7). The 28-day and 90-day mortality was recorded.

Results: Alcohol was the predominant etiology of cirrhosis (32 patients—80%). Infection was the chief precipitating factor in 19 patients (47.5%). The 28-day and 90-day mortality was 45% and 52.5%. Mean (SD) of CLIF-C ACLF scores of survivors and non-survivors on Day-90 were 44.11(6.62) and 53.86 (7.83). The prognostic accuracy of the CLIF-C ACLF score (Area Under Receiver Operating Characteristic Curve—AUROC) to predict 28-day and 90-day mortality was 0.86 and 0.84, respectively. MELD-Na and CLIF-C ACLF scores had higher AUROC for predicting 28-day and 90-day mortality, respectively. The AUROC of the CLIF-C OF score on Day 3 was found to be higher than the values of Day 1 and Day 7, but it was not statistically significant.

Conclusion: CLIF-C ACLF has good short-term prognostic accuracy and it is as good as other available scores. Serial CLIF-C OF scores were equally good in predicting in short-term mortality.

Keywords: Cirrhosis, CTP score, EASL, MELD, MELD-Na, 28-day mortality, 90-day mortality.

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Highlights

- As per the EASL definition, ACLF is diagnosed when the acute decompensation of cirrhosis meets the specified criteria for organ failure.
- Chronic Liver Failure-Consortium Organ Failure (CLIF-C OF) score is used to diagnose ACLF. It is unique from other scores because it considers circulatory and respiratory functions.
- CLIF-C ACLF score has good predictive accuracy for short-term mortality.

Introduction

Acute-on-chronic liver failure (ACLF) is a newly defined condition lacking a universally accepted definition. As per The European Association for the Study of the Liver (EASL), ACLF is defined as a "syndrome characterized by acute decompensation of cirrhosis, organ failure(s) and high short-term mortality."[1] The global prevalence of ACLF (as per EASL definition) among decompensated cirrhotic patients was 35%, with the highest rate in South Asia at 65%, and it had a high 90-day mortality of 58%.[2]

The European Association for Study of Liver conducted a multicenter, prospective study called the CANONIC study, from which the ACLF definition was derived. Additionally, two scoring systems were developed based on the same study. The first, Chronic Liver Failure-Consortium Organ Failure (CLIF-C-OF), serves to diagnose and grade ACLF, while the second, CLIF-C ACLF, aids in predicting mortality. The CLIF-C OF score evaluates six organ systems: liver, kidney, respiration, circulation, brain, and coagulation.

Chronic Liver Failure-Consortium Acute-on-chronic failure (CLIF-C ACLF) is a composite score that integrates the CLIF-C OF score, age, and total leukocyte count as components in its calculation.[1,3] These two scoring systems are different from other available scores, such as Model for End-stage Liver Disease (MELD), MELD-Na, and Child-Turcotte-Pugh (CTP), because they have taken circulatory and respiratory functions into account.

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Table 1: CLIF-C OF scoring system and criteria for organ failures. The shaded area describes the criteria for diagnosing organ failures

		Score		
Organ system	*Variable*	*1 point*	*2 points*	*3 points*
Liver	Bilirubin (mg/dL)	<6.0	≥6.0–<12.0	≥12.0
Kidney	Creatinine (mg/dL)	<2.0	≥2.0–<3.5	≥3.5 or use of RRT
Cerebral	HE grades (West Haven criteria)	0	I–II	III–IV or intubation in view of HE
Coagulation	INR	<2.0	≥2.0–<2.5	≥2.5
Circulation	MAP (mm Hg)	≥70	<70	Use of vasopressors
Respiration	PaO_2/FiO_2	>300	<200–≤300	≤200
	SpO_2/FiO_2	>357	>214–≤357	≤214 Or use of mechanical ventilation

FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, International normalized ratio for prothrombin time; MAP, mean arterial pressure; PaO_2, partial pressure of arterial oxygen; RRT, renal replacement therapy; SpO_2, oxygen saturation measured in pulse oximeter

Table 2: Diagnosis and grading of severity of acute-on-chronic liver failure

ACLF grade	*Criteria*
No ACLF	(a) Patients with no organ failure (b) Patients with single hepatic, coagulation, circulatory, or respiratory failure with serum creatinine <1.5 mg/dL, and no HE (c) Patients with cerebral failure and serum creatinine <1.5 mg/dL
ACLF grade I	(a) Patients with renal failure (b) Patients with other single organ failure with serum creatinine between 1.5 and 1.9 mg/dL and HE grades I–II (c) Patients with single cerebral failure and serum creatinine levels between 1.5 and 1.9 mg/dL
ACLF grade II	Patients with two-organ failures
ACLF grade III	Patients with three or more organ failures

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy

Acute-on-chronic liver failure is considered a dynamic disease because the organ functions may improve or worsen in response to the intervention. So, the serial assessment of these scores can help to understand the clinical course of the disease. It will be useful to find out the ideal time to calculate these scores to predict mortality better.[3,4]

There is a limited number of Indian studies that have validated the CLIF-C OF and CLIF-C ACLF scores in ACLF patients.[5–7] If these scores predict the mortality of ACLF patients better than other existing scores (MELD, MELD-Na, CTP), it can guide us better in the management to reduce the mortality. Also, none of the studies have evaluated the serial CLIF–C OF scores and their predictive accuracy on mortality.

Our study was conducted with the following three objectives: (1) To estimate the prognostic accuracy of CLIF-C-ACLF score in predicting mortality at both 28-day and 90-day. (2) To compare the prognostic accuracy of CLIF-C ACLF with prognostic accuracies of other scores (3) To compare the prognostic accuracy of baseline CLIF-C OF score (Day 1) with subsequent CLIF-C OF scores (on 3rd day and 7th day) in predicting both 28-day and 90-day mortality.

Materials and Methods

Our study design was prospective and observational. It was carried out at the Department of Medicine in a tertiary care teaching institute in South India. It was conducted from April 2022 to June 2023. Institutional Ethics Committee (IEC) approved the study protocol and the approval number was JIP/IEC/2021/307, dated 30 March 2022. Written informed consent was obtained from all participants.

Study Participants

Cirrhosis of liver patients aged 18 years or older having acute decompensation and organ failure meeting the defined criteria for ACLF, were included (Table 1).[1,3] The diagnostic criteria and grading of ACLF are mentioned in Table 2.[1,3] Patients were excluded if they had acute liver failure, unresolved previous decompensation of cirrhosis, chronic kidney disease, underlying heart and lung diseases, HIV infection, taking immunosuppressive drugs, and pregnancy.

Study Procedure

After the enrollment, all patients were asked for a detailed medical history about the disease, previous decompensation, details of alcohol intake, and precipitating events (infection, variceal bleeding, encephalopathy, and ascites). Relevant physical examination and laboratory parameters were done to look up organ dysfunction and primary etiology of cirrhosis, if not already done. If clinically warranted, a sepsis workup, comprising a complete hemogram, chest radiography, urine examination, cultures and sensitivity of blood and urine was conducted. Ascitic fluid analysis was done if peritonitis was suspected. Admission time parameters of six different organ functions were collected and the CLIF-C OF score (Table 1) was computed. The diagnosis and grading of ACLF were determined using the CLIF-C OF score. Then, CLIF-C ACLF was computed using the formula: "CLIF-C ACLF = $10 \times [0.33 \times$ CLIF-C OF $+ 0.04 \times$ Age $+ 0.63 \times \ln$ (WBC count)–2]".[3] Additionally, we computed the CTP, MELD, and MELD-Na scores using their respective formulas upon admission. Patients received standard-of-care management for their acute decompensation of cirrhosis and

organ failures. None of our patients underwent liver transplantation due to constraints like the non-availability of donors. We followed them during the hospital stay and calculated CLIF-C OF scores again on day 3 and day 7. The outcome of hospital admission, either discharge or death, was noted. The survival status of discharged patients on day 28 and day 90 was collected telephonically.

Definitions

Cirrhosis:[6] Cirrhosis was diagnosed based on a "composite of clinical, imaging (heterogeneous echotexture of the liver with irregular outline, altered liver size, or portosystemic collaterals), laboratory (low serum albumin, aspartate aminotransferase/alanine aminotransferase ratio >1) and endoscopic findings (≥ grade II esophageal varices)."

Acute Decompensation:[1] "The acute development of one or more major complications of liver disease, that is, ascites, encephalopathy, gastrointestinal hemorrhage, or bacterial infection."

Statistical Analysis

Categorical variables were described as percentages, while continuous data were represented either as mean with standard deviation or as median with interquartile ranges. A comparison of categorical outcome variables was conducted using the Chi-square test. AUROCs of all scores [CLIF-C ACLF, CLIF-C OF, CTP, MELD, and MELD-Na] were calculated. The DeLong test was used to compare the AUROC of different scores. *p*-value was considered significant if it was less than 0.05. Data analysis was performed using Stata Statistical Software: Release 12, College Station, TX: StataCorp LP. Microsoft Excel was utilized to create selected charts and graphs.

Results

Throughout the study period, 306 cirrhotic patients having acute decompensation were admitted and screened for ACLF. Forty patients fulfilled the inclusion criteria and were enrolled, while the remaining 266 patients were excluded for reasons detailed in Figure 1.

Demographic and Clinical Details

Demographic details, clinical features of patients and the distinctions between survivors and non-survivors at Day 90 are given in Table 3. Among 40 patients recruited, 35 patients (88%) were men. The mean age was 43 years with a standard deviation of 12.2 years. Alcohol was the predominant etiology of cirrhosis (32 patients - 80%), followed by hepatitis B (7.5%) (Supplementary Fig. 1).

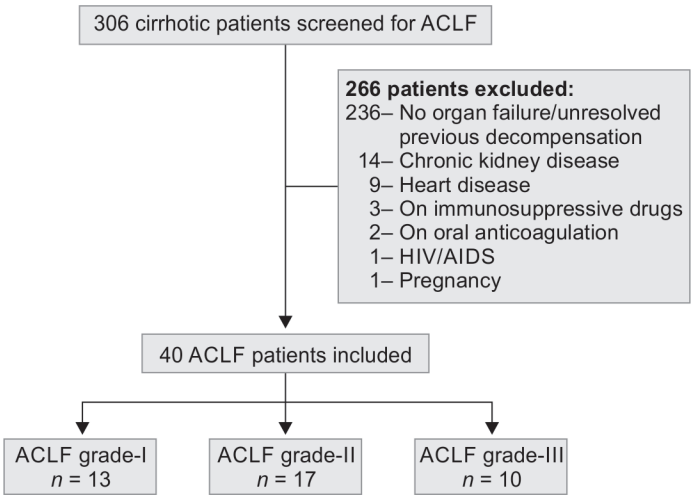


Fig. 1: Study flowchart. ACLF, acute-on-chronic liver failure; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome

Table 3: Comparison of demographic and clinical characteristics between survivors and non-survivors on day 90

Variables	*Total study population* (n = 40)*	*Survivors at day-90* (n = 19)*	*Non-survivors at day-90* (n = 21)*	*p-value*
Age, in years, mean ±SD	43.3 ± 12.2	41.5 ± 13.5	44.9 ± 10.9	0.38
Gender—male	35 (88)	16 (84.2)	19 (90.4)	0.64
Fever at presentation	27 (67.5)	9 (47.3)	18 (85.7)	**0.01**
Altered sensorium	21 (52.5)	6 (31.5)	15 (71.4)	**0.01**
Alcoholic cirrhosis	32 (80)	15 (78.9)	17 (80.9)	0.09
Previous decompensation	17 (42.5)	8 (42.1)	9 (42.9)	0.96
Infection as precipitant	19 (47.5)	6 (31.5)	13 (62)	0.05
Spider nevi	18 (45)	5 (26.3)	13 (62)	**0.02**
Bilirubin, mg/dL, Median (IQR)	16.1 (10.1,26.1)	14.1 (8.4, 23)	19.5 (10.9, 26.6)	0.64

(Contd...)

Table 3: *(Contd...)*

Variables	*Total study population* (n = 40)*	*Survivors at day-90* (n = 19)*	*Non-survivors at day-90* (n = 21)*	*p-value*
Creatinine, mg/dL, Median (IQR)	1.6 (0.8,2.4)	1.2 (0.8, 2.4)	1.8 (1.4, 3.2)	**0.02**
INR	2.2 (1.8,3.2)	1.9 (1.4, 2.3)	2.8 (2.2, 4.0)	**0.02**
MAP, mm Hg, mean ± SD	69.9 ± 8	71.1 ± 7.8	68.9 ± 8.2	0.40
Sodium, mEq/L, mean ± SD	130.7 ± 5.2	131.7 ± 3.5	129.8 ± 6.3	0.12
TLC (10^3counts/cu.mm), Median (IQR)	12.5 (7.9, 16.9)	10.2 (6.6,16.5)	13(11,19)	0.07
Liver failure	28 (70)	13 (68.4)	15 (71.4)	0.84
Coagulation failure	17 (42.5)	4 (21)	13 (62)	**0.009**
Cerebral failure	16 (40)	6 (31.5)	10 (47.6)	0.30
Renal failure	14 (35)	6 (31.5)	8 (38)	0.67
Circulatory failure	4 (10)	0 (0)	4 (19.5)	0.11
Respiratory failure	3 (7.5)	1 (5.3)	2 (9.8)	1.00
ACLF grade I	13 (32.5)	9 (47.3)	4 (19.5)	**0.01**
ACLF grade II	17 (42.5)	9 (47.3)	8 (38)	**0.01**
ACLF grade III	10 (25)	1 (5.3)	9 (42.9)	**0.01**
CLIF-C-ACLF score, mean ± SD	49.2 ± 8.7	44.11 ± 6.62	53.86 ± 7.83	<**0.001**
CLIF-C-OF score day 1, Median (IQR)	10 (10,12)	10 (10,11)	12 (11,13.5)	<**0.01**
CLIF-C -OF score day 3, Median (IQR)	10 (9.2,12.8)	10 (9, 10)	12 (10, 15)	**0.005**
CLIF-C-OF score day 7, Median (IQR)	10 (8,12.2)	9 (8, 10)	13 (10, 15)	**0.02**
MELD score, mean ± SD	32.3 ± 6.6	29 ± 5.4	35 ± 6.2	**0.002**
MELD – Na score, mean ± SD	33.5 ±6.2	30.1 ± 4.8	36.6 ± 5.9	<**0.001**
CTP score, mean ±SD	12.2 ± 1.5	11.4 ± 1.7	12.9 ± 0.8	**0.02**
ICU admission	14 (35)	2 (10.5)	12 (57.1)	<**0.001**
Length of hospital stay, days, median (IQR)	9 (7,13.75)	9 (7,16)	9 (4,12)	0.46

*all are numbers (percentages) unless specified in the variable column. ACLF, acute-on-chronic liver failure; CLIF-C, chronic liver failure-consortium; CTP, Child-Turcotte-Pugh score; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; MAP, mean arterial pressure; MELD, model for end-stage liver disease; Na, sodium; OF, organ failure; SD, standard deviation; TLC, total leukocyte count. Bold values are statistically significant ($p < 0.05$)

Twenty-three (57.5%) of them were newly diagnosed cirrhotic patients. The previous decompensation of cirrhosis (but resolved) was found in 17 patients (42.5%) and the numbers were almost equal in both groups. Spider naevi was the clinical finding noticed in high numbers in non-survivors (62 vs 26%). The chief precipitating factors for ACLF were infection and active alcoholism, seen in 16 (40%) and 9 (22.5%) patients, respectively (Supplementary Fig. 2). Among infections, the most common was peritonitis (13/19 patients—68.4%) followed by pneumonia (2/19 patients).

Organ Failure

The median (IQR) serum creatinine level and INR of the study population were 1.8 (0.8, 2.4) mg/dL and 2.2 (1.8, 3.2), respectively, and these parameters were found statistically significant between survivors and non-survivors at day 90 (1.2 vs 1.8 mg/dL, 1.9 vs 2.8). Among the six organ failures assessed in our study, liver failure ($n = 28$, 70%) was the leading one followed by coagulation failure ($n = 17$, 42.5%). Cerebral and renal failures were noted in 17 (42.5%) and 16 (40%) patients, respectively. Only a few patients had circulatory ($n = 4$, 10%) and respiratory failure ($n = 3$, 7.5%). Seven patients (17.5%) required mechanical ventilation and hemodialysis was done for 5 patients (12.5%). The details of the number of organ failures are depicted in Supplementary Figure 3. There was a statistically notable difference in the occurrence of coagulation failure between survivors and non-survivors at day 90 (62 vs 21%, $p = 0.009$).

ACLF Grades and Mortality among Different ACLF Grades

More number of patients in the study belonged to ACLF grade II (17 patients – 42.5%) followed by grade I (13 patients – 32.5%) and grade III (10 patients—25%). Mortality rates of various ACLF grades at day 28 and day 90 are shown in Figure 2. Overall mortality at day 28 and day 90 were 45% and 52.5%, respectively. For grade I ($n = 13$), grade II ($n = 17$), and grade III ($n = 10$) ACLF patients, the mortality rates at 28 days were 15, 41, and 90%, and at 90 days were 30, 47, and 90%, respectively. The dynamic course of different ACLF grades is mentioned in Supplementary Table 2.

Scores at Admission

The mean (±SD) CLIF-C ACLF score at admission was 49.2 (±8.7). The admission CLIF-C ACLF scores significantly differed between non-survivors and survivors at both 28-day (54.83 vs 44.64, $p < 0.001$) and 90-day (53.86 vs 44.11, $p < 0.001$) survival periods. Similar to the CLIF-C ACLF score, other scores computed at admission were also notably higher in non-survivors compared with survivors and statistical significance was found for all scores (Table 3).

Serial CLIF-C OF Scores

The median CLIF-C OF score among all patients on Day 1 was 10 (IQR: 10–12). The median of the same score was similar on Day 3 [10 (9.2, 12.8)] and Day 7[10 (8, 12.2)], but the IQR varies. Figure 3

depicts the trend of median CLIF-C OF scores on Days 1, 3, and 7 among both survivors and non-survivors on Day 90. By day 7, a significant difference in the median CLIF-C OF scores [9 (IQR: 8–10) for survivors, compared with 13 (IQR: 10–15) for non-survivors] was evident. We could see that scores were predominantly reducing trend among survivors and increasing trend among non-survivors (Supplementary Figure 4).

Prognostic Accuracy of CLIF-C ACLF and Other Scores

Table 4 illustrates the prognostic accuracy of CLIF-C ACLF assessed through AUROC analysis. The AUROC values of CLIF-C ACLF measured for mortality on day 28 and day 90 were 0.86 (0.7–0.94) and 0.84 (0.7–0.95), respectively. At a cut-off value of 48.5 for 28-day mortality, the sensitivity and specificity were 83.3% and 77.3%. For 90-day mortality, with a cut-off value of 45.5, the sensitivity and specificity were 81% and 73.7%. Additionally, all patients with scores exceeding 57 ($n = 5$) did not respond to treatment and succumbed within 28 days. A comparison of prognostic accuracies of all five scores is shown in Figure 4 and Table 5. MELD-Na demonstrated higher absolute AUROC values [0.88 (0.78–0.99)] for predicting 28-day mortality, whereas CLIF-C ACLF displayed higher absolute AUROC values [0.84 (0.71–0.96)] for predicting 90-day mortality. No statistical significance was observed when comparing the AUROC values of other scores with CLIF-C ACLF for mortality at day 28 and day 90.

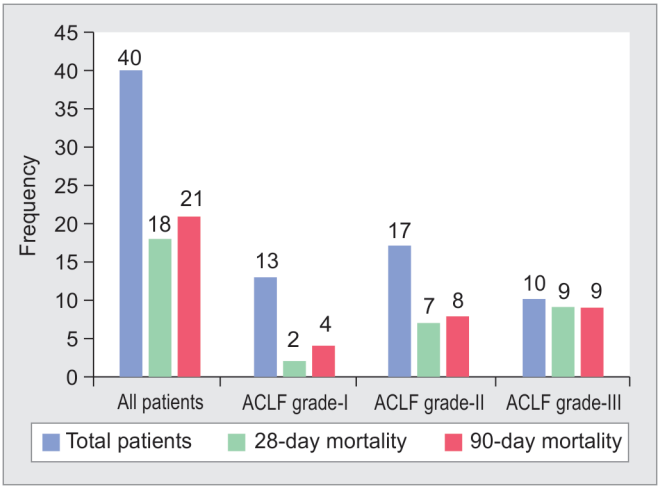


Fig. 2: Mortality among different ACLF grades

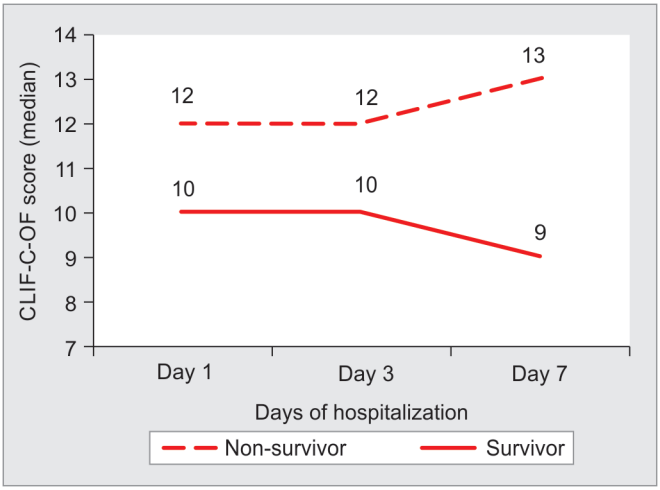


Fig. 3: The trend of serial CLIF-C OF score between survivors and non-survivors on day 90

CLIF-C OF, chronic liver failure-consortium organ failure

Prognostic Accuracy of Serial CLIF-C OF Scores

Figure 5 and Table 6 illustrate the comparative analysis of AUROC of CLIF-C OF scores computed on Days 1, 3, and 7 for predicting mortality at day 28 and day 90. The AUROC (95% CI) for the Day 3 CLIF-C OF score was 0.91 (0.83–0.99) for predicting 28-day mortality and 0.84 (0.71–0.96) for predicting 90-day mortality. The absolute AUROC value on Day 3 was higher than the other two scores (Days 1 and 7) for the mortality on both day 28 and day 90. No statistical significance was observed when comparing the AUROCs of Day 3 and Day 7 with those of Day 1.

Discussion

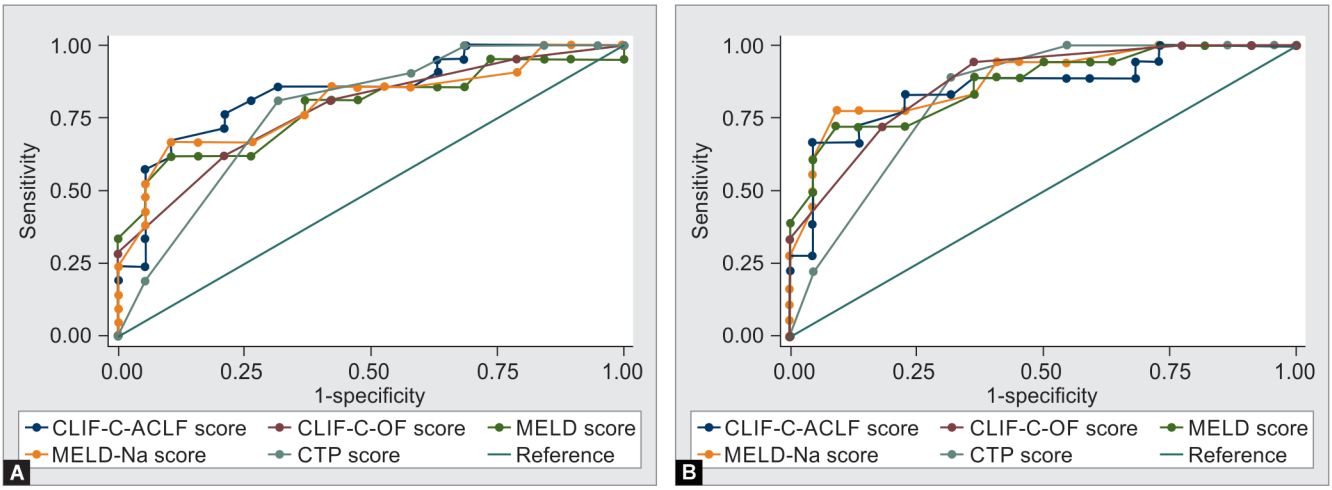
In our study, ACLF patients had a 28-day mortality rate of 45% and a 90-day mortality rate of 52.5%. As the ACLF grade increases, mortality rates correspondingly elevate. The AUROC of CLIF-C ACLF score to predict mortality on day 28 was 0.86, while for mortality on day 90, it was 0.84. Out of the five scores assessed in our study, MELD-Na and CLIF-C ACLF scores exhibited higher prognostic accuracy (AUROC) in predicting mortality on day 28 and day 90, respectively. However, none of the other four scores demonstrated statistical significance when compared with CLIF-C ACLF. The sequential analysis of CLIF-C OF scores revealed higher prognostic accuracy for Day 3 compared with both Day 1 and Day 7. However, neither the Day 3 nor the Day 7 scores demonstrated statistical significance in predicting mortality when compared with the Day 1 score.

The previously available scores, such as CTP, MELD, and MELD-Na consider the parameters associated with functions of the liver, kidney, brain, and electrolytes. During the CANONIC study, the Sequential Organ Failure Assessment (SOFA) score was modified and the CLIF-C OF score was formulated to diagnose and grade the severity of ACLF. It incorporates the functionality of the respiratory and circulatory systems into the prognostic evaluation of ACLF patients. The CLIF-C ACLF score aims to enhance the precision of mortality prediction. In addition to the CLIF-C OF score, age and total leukocyte count were considered in the computation of this score.[8]

Table 4: Prognostic accuracy of CLIF-C ACLF score in predicting 28-day and 90-day mortality and other diagnostic parameters for best cut-off score

Outcome	*AUROC (95% CI)*	*Cut-off of CLIF-C ACLF*	*Sensitivity*	*Specificity*	*PPV*	*NPV*
28-day mortality	0.86 (0.7–0.94)	48.5	83.3%	77.3%	74.4%	82.2%
90-day mortality	0.84 (0.7–0.96)	45.5	81%	73.7%	75.5%	79.5%

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CLIF-C ACLF, chronic liver failure-consortium acute-on-chronic liver failure; PPV, positive predictive value; NPV, negative predictive value



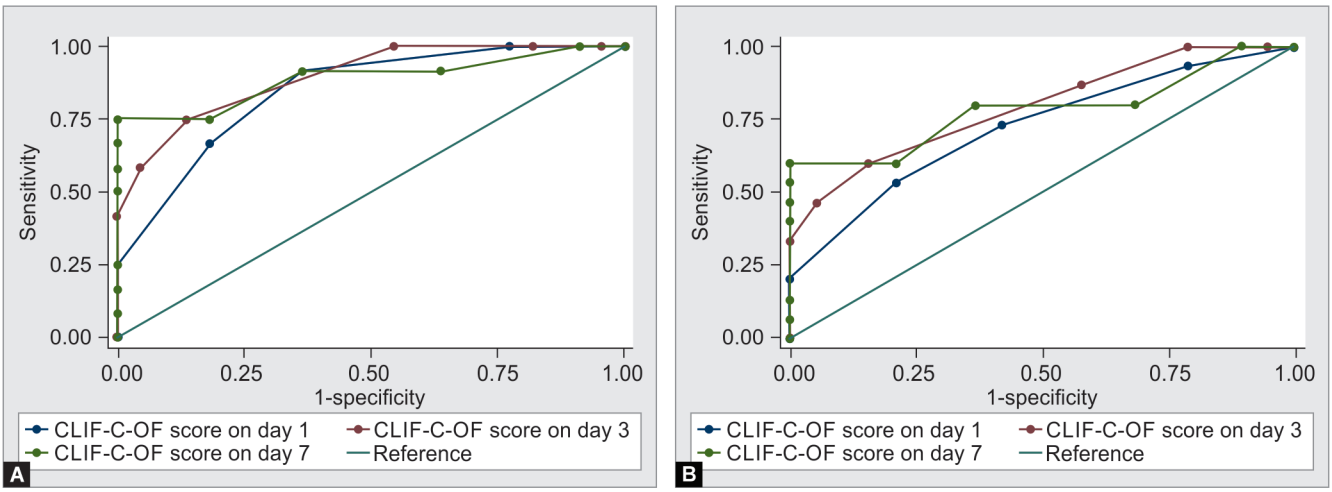
Figs 4A and B: (A) AUROCs of five different scores in predicting 28-day mortality; (B) AUROCs of five different scores in predicting 90-day mortality

CLIF-C ACLF, chronic liver failure-consortium acute-on-chronic liver failure; CLIF-C OF, chronic liver failure-consortium organ failure; CTP, Child-Turcotte-Pugh score MELD, Model for End-stage liver disease score; MELD-Na, model for end-stage liver disease – sodium score

Table 5: Comparison of prognostic accuracies of other scores with CLIF-C ACLF score in predicting 28-day and 90-day mortality

Scores	*AUROC for 28-day mortality*	*p-value (vs CLIF-C-ACLF)*	*AUROC for 90-day mortality*	*p-value (vs CLIF-C-ACLF)*
CLIF-C ACLF score	0.86 (0.73–0.94)	–	0.84 (0.71–0.96)	–
CLIF-C OF score	0.87 (0.77–0.98)	0.76	0.78 (0.63–0.92)	0.31
MELD score	0.87 (0.76–0.98)	0.87	0.78 (0.64–0.93)	0.49
MELD-Na score	0.88 (0.78–0.99)	0.71	0.80 (0.66–0.94)	0.62
CTP score	0.83 (0.70–0.95)	0.69	0.78 (0.63–0.93)	0.39

AUROC, area under the receiver operating characteristic curve; CTP, Child-Turcotte-Pugh score; CLIF-C ACLF, chronic liver failure-consortium acute-on-chronic liver failure; CLIF-C OF, chronic liver failure-consortium organ failure; MELD, model for end-stage liver disease score; MELD-Na, model for end-stage liver disease-sodium score



Figs 5A and B: (A) AUROCs of three different time-point CLIF-C OF scores in predicting 28-day mortality; (B) AUROCs of three different time-point CLIF-C OF scores in predicting 90-day mortality; CLIF-C OF, chronic liver failure-consortium organ failure

In our study, we observed the AUROC of CLIF-C ACLF for predicting the mortality on day 28 and day 90 to be 0.86 and 0.84, respectively. These values surpass the findings of the validation cohort in the CANONIC study, where they were reported as 0.74 and 0.736 for the respective time frames. In the CANONIC study, the sensitivity and specificity were reported as 64 and 75% at a cut-off score of 51. In our study, at a comparable cut-off of 51, we observed a sensitivity of 72% and a specificity of 86%. This could be due to the differences in baseline characteristics between the two studies. Our patients were younger (43.3 vs 55 years), predominantly men

Table 6: Comparison of prognostic accuracies of CLIF-C OF scores (Days 3 and 7) with CLIF-C OF (Day 1) in predicting 28-day and 90-day mortality

CLIF-C OF scores on	*AUROC at 28-day mortality (95% CI)*	*p-value (vs day 1 score)*	*AUROC at 28-day mortality (95% CI)*	*p-value (vs day 1 score)*
Day 1	0.87 (0.77–0.98)	–	0.77 (0.63–0.92)	–
Day 3	0.91 (0.83–0.99)	0.46	0.84 (0.71–0.96)	0.29
Day 7	0.89 (0.77–0.98)	0.62	0.78 (0.61–0.95)	0.46

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CLIF-C OF, chronic liver failure-consortium organ failure

(Men – 88 vs 76%), more patients with alcoholic cirrhosis (80 vs 70%), less proportion of high-grade ACLF (I, II, III – 32.5, 42.5, 25 vs 22.6, 31.6, 45.8%), had high level of inflammation [total leukocyte count (12500 vs 7800)] and less ICU admission (35 vs 100%). The 28-day and 90-day mortality rates were higher in that population (Europeans), reported as 52 and 62.7%, respectively, in contrast to our findings of 45 and 52.5%. The lower proportion of ACLF grade III patients in our study could explain the low mortality compared with the CANONIC study.[3]

In the CANONIC study's derivation cohort, the mortality rates at day 28 and day 90 for different grades of ACLF were 23.3 and 40.8% for grade I, 31.3 and 55.2% for grade II, and 74.5 and 78.4% for grade III. In our study, the corresponding mortality rates (28-day and 90-day) were 15 and 30% for grade I, 41 and 47% for grade II, and 90% and 90% for grade III. In a study involving ACLF patients (EASL criteria, $n = 132$) in eastern India, the observed mortality rates on day 28 and day 90 were 45.5 and 71.2%, respectively. Furthermore, the AUROC values of CLIF-C ACLF for predicting mortality on day 28 and day 90 in the same study were reported as 0.81 and 0.93.[5] Another South Indian study from Chennai (EASL criteria, $n = 150$ ACLF patients) reported an overall mortality of 83%.[9]

In our findings, MELD-Na and CLIF-C ACLF demonstrated superior AUROC values compared with other scores for predicting mortality on day 28 and day 90, respectively. In the CANONIC study, the CLIF-C ACLF score showed the highest predictive accuracy for both 28-day and 90-day mortality, and the difference was statistically significant when compared with other scores.[3] However, in our study, we did not observe a similar distinction when comparing the AUROC of CLIF-C ACLF with other scores. This deviation might be attributed to the disproportionate proportion of circulatory and respiratory failures in the study groups. In our study, 10% of patients had circulatory failure, 7.5% exhibited respiratory failure, and critical care support was required for only 35% of patients. Whereas in the validation cohort of the CANONIC study, these rates were 63.6 and 38.2%, respectively and all participants were enrolled from the ICU. The distinctive advantage of the CLIF-C ACLF score over other scores lies in its incorporation of parameters related to these two system functions. Since these two system failure rates were low in our study population, CLIF-C ACLF did not show any added benefit in predicting mortality. Other studies have reported that CLIF-C ACLF outperformed MELD and MELD-Na as a mortality predictor.[10–12] Grochot et al. reported a contrasting finding where the MELD-Na score demonstrated superior mortality prediction compared with CLIF-C ACLF.[13] Similarly, Maipang et al.'s study showed that CLIF-C OF outperformed CLIF-C ACLF as a predictor.[14]

A retrospective study was conducted in Germany involving 136 patients having acute decompensation of cirrhosis.[15] Among them, 117 patients had ACLF. The proportions of ACLF grades I, II, and III were 13, 25, and 48%, respectively, whereas, the respective grades were 32.5, 42.5, and 25% in our study. Consistent with our study, both CLIF-C OF and CLIF-C ACLF scores displayed statistical differences between survivors and non-survivors by day 28. Additionally, the AUROCs for MELD, CLIF-C ACLF, and CLIF-C OF in our research to predict 28-day mortality were higher compared with this study (MELD: 0.87 vs 0.767, CLIF-C ACLF: 0.86 vs 0.717, CLIF-C OF: 0.87 vs 0.652).

As ACLF is known for its dynamic nature, we computed serial CLIF-C OF scores on Days 1, 3, and 7 to ascertain which time-point score showed higher prognostic accuracy. The median score on Day 7 showed a marked contrast between survivors and non-survivors on Day 90 compared with the median scores on Days 1 and 3 (Fig. 3). While the AUROC of the Day 3 score exceeded the values of Days 1 and 7 for both 28-day and 90-day mortality, there was no statistical significance observed when comparing the AUROCs of Days 3 and 7 to that of Day 1. We did not calculate CLIF-C ACLF to assess the dynamicity of ACLF because it cannot be calculated serially for all patients (Day 3 and Day 7) if they recovered from ACLF to No ACLF as per the EASL criteria.[16] The CANONIC study computed serial CLIF-C ACLF scores and found that scores calculated between 3–7 days and 8–15 days following ACLF diagnosis significantly outperformed the score at ACLF diagnosis in predicting both 28-day and 90-day mortality.[3] There are studies in India assessing the predictive accuracy of various scores in acute liver disease and end-stage liver disease patients.[17,18] Our study specifically aimed to estimate the prognostic accuracy of various scores in ACLF cases.

The strengths of our study are: (1) it is one among very few studies done on EASL-criteria-based ACLF patients from India. (2) The predictive accuracy of the newly derived CLIF-C ACLF score for short-term mortality and its comparison with other scoring systems among ACLF patients in South India are studied. (3) The study investigated the dynamic changes in organ functions following ACLF treatment by computing the CLIF-C OF score at three-time points (Days 1, 3, and 7). Our study has a few limitations also. (1) As this is a single-center observational study involving a limited number of patients ($n = 40$) and a smaller representation of female patients (12.5%), the findings may not be generalizable. (2) Alcohol was the cause for 80% of patients in our study. So, further studies are required to compare the prognostic accuracy of scores across various etiologies of cirrhosis leading to ACLF.

Conclusion

Higher ACLF grades correlate with increased short-term mortality. The CLIF-C ACLF score shows strong prognostic accuracy for short-term mortality among ACLF patients, comparable to other scores (CLIF-C OF, MELD-Na, MELD, and CTP). Additionally, there was no difference in the prognostic accuracies of CLIF-C OF scores calculated on Days 1, 3, and 7 for predicting short-term mortality.

Supplementary Materials

All the supplementary materials are available online on the website of www.IJCCM.org.

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