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Assessment of Different Prognostic Scores in Predicting Short- Term Mortality in Cirrhotic Patients with ACLF

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Abstract

Background: Asia–Pacific Association for the Study of Liver (APASL) defined ACLF as acute hepatic insult manifesting as jaundice (serum bilirubin ≥5mg/dL) and coagulopathy (international normalized ratio [INR] ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. Several prognostic scores have been developed for patients with ACLF. Various scoring systems such as CTP, MELD Na+, CLIF SOFA CLIF C ACLF have been used to predict short- term mortality in patients with ACLF. Neutrophil to Lymphocyte ratio(NLR) also presented a good accuracy in predicting the outcome of patients with ACLF.

Method: The study included 153 cirrhotic patients diagnosed with ACLF according to APASL guidelines, conducted from April 2023 to March 2024. Sociodemographic data were collected using a predesigned proforma. Scoring systems such as CTP, MELD Na+, CLIF SOFA, CLIF C ACLF, and NLR were assessed at admission, 48 hours and 7 days, along with other lab parameters. The performance of these scoring systems at different time intervals was evaluated. Patients were followed up for one month, and mortality within this period was recorded.

Result: In this study, the total mortality was 64 (41.8%). Mortality within 48 hours was 13 patients (8.49%). Between 48 hours and 7 days, 26 patients (16.99%) died. Between 7 days and 1 month, 25 patients (16.33%) died. The highest mortality occurred between 48 hours and 7 days, with 26 patients (16.99%).When comparing scoring systems to predict mortality within 48 hours, all except the CTP score ($p > 0.05$) were significant. The significant scores were MELD Na+ (AUC = 0.970), CLIF SOFA (AUC = 0.983), CLIF C ACLF (AUC = 0.955), and NLR (AUC = 0.859). Likewise, for predicting mortality between 48 hours and 7 days, all scores except CTP ($p > 0.05$) were significant. The significant scores were MELD Na+ (AUC = 0.706), CLIF SOFA (AUC = 0.870), CLIF C ACLF (AUC = 0.837), and NLR (AUC = 0.865). However, for predicting mortality between 7 days and 1 month, only NLR was found to be significant ($p < 0.001$).

Conclusion: NLR, MELD Na+, CLIF SOFA, and CLIF C ACLF scores were superior to CTP in predicting early mortality (within 48 hours and up to 7 days). Only NLR was significant in predicting mortality from 7 days to 1 month.

Keywords: Inflammation; Deterioration; Diagnosed; Coagulopathy; Psychiatric

Abbreviations: AARC: APASL ACLF Research Consortium; AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on Chronic Liver Failure; AD: Acute Decompensation; AUC: Area Under Curve; APASL: Asian Pacific Association for the Study of the Liver; CTP: Child Turcotte Pugh; CLD: Chronic Liver Disease; CLIF C ACLF: Chronic Liver Failure Consortium Acute on Chronic Liver Failure; CLIF SOFA: Chronic Liver Failure Sequential Organ Failure Assessment; EASL: European Association for the Study of the Liver; HE: Hepatic Encephalopathy; MELD: Model for End Stage Liver Disease; MELD Na+: Model for End Stage Liver Disease Sodium; NASH: Nonalcoholic steatohepatitis; NLR Neutrophil to Lymphocyte Ratio

Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease [1]. Acute-on-chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease [1]. ACLF is characterized by its rapid progression, the requirement for multiple organ supports and a high incidence of short and medium term mortality of 50-90% [2]. Asia-Pacific Association for the Study of Liver defined ACLF as acute hepatic insult manifesting as jaundice (serum bilirubin ≥5mg/dL) and coagulopathy (international normalized ratio [INR] ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [3]. Similarly, European Association for the Study of the Liver-American Association for the Study of Liver Diseases (EASL-AASLD) 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 [4]. The definition given by EASL- AASLD implies that organ failure is a central component of this syndrome [5].

Several prognostic scores have been developed for patients with ACLF. The sequential organ failure assessment score (SOFAs), is widely used to track patient status during intensive care in order to determine the extent of organ dysfunction and failure over time [6]. The conventional scoring systems, the MELD score refined to take into account serum sodium level (MELD-Na+) and the Child-Pugh-Turcotte classification, were designed to predict the prognosis of chronic liver failure. These scoring systems are also commonly used to determine prognosis in ACLF [7]. CLIF SOFA and CLIF Consortium acute-on-chronic liver failure (CLIF-C ACLF) scores have been developed and validated to predict short-term mortality in patients with ACLF. Of these, the CLIF-C ACLF score has shown better accuracy in predicting mortality [8,9].

Neutrophil to Lymphocyte Ratio (NLR) is a novel surrogate marker of inflammation which takes into account both the polymorphonuclear count associated with inflammation and the lymphocyte count as a hallmark of immune impairment [10]. A normal range of NLR is between 1-2, the values higher than 3.0 and below 0.7 in adults are pathological. NLR between 2.3-3.0 may serve as early warning of pathological state or process such like cancer, atherosclerosis, infection, inflammation, psychiatric disorders and stress [11]. NLR presented a good accuracy in predicting the outcome of cirrhotic patients with ACLF [12]. NLR measured on hospital admission can serve as an independent predictor of the 3-month mortality rate in patients with acute-on-chronic liver failure (ACLF) [13,14]. This study was conducted because NLR is an easy, cost-effective, and reliable method for predicting mortality in cirrhotic patients with ACLF, as shown by several studies, and similar research has not been done to the best of my knowledge in Nepal.

Methodology

This is a hospital based prospective analytical study carried out in liver department. 153 consecutive cirrhotic patients with ACLF, diagnosed as per APASL criteria were enrolled in this study. Patients with hematological disorder, chronic infections (eg. Tuberculosis), active malignancies including hepatocellular carcinoma, patients on steroids and those unwilling to give consent were excluded from the study. All essential investigations required to calculate different scoring systems were sent. Prognostic scoring systems such as CTP, MELD Na+, CLIF SOFA, CLIF C ACLF and NLR were assessed at the time of admission, at 48 hrs and 7 days along with other lab parameters. Patients included in the study were followed up for a period of 1 month. Mortality during the time frame of 1 month was recorded. The study was approved by IRB of NAMS. Written informed consent was taken from patient or patient party. SPSS version 22 was used for statistical analysis. Mean, SD, median, and range was obtained for the quantitative data. P value was considered significant if it was less than 0.05. The discriminative ability of the liver-specific (Child-Pugh and MELD) and ACLF prognostic scores (CLIF-SOFA and CLIF C ACLF) and NLR at baseline (on admission), at 48 hours and at 7 days were evaluated using the area under a receiver operating characteristic (ROC) curve (AUROC). Significance was tested two sided and set to a P-value of less than 0.05.

Result

Over the course of one year, 167 patients were initially enrolled in the study. However, 5 patients withdrew consent, 2 were excluded, and 7 were lost to follow-up. Mean age of patients with CLD at presentation was 50±12 years and majority of them were male (68%).The main etiology of CLD was alcohol(92.15%) while other etiologies leading to CLD were chronic hepatitis B (4.57%), NASH (1.96%) and chronic hepatitis C (1.30 %). (Table 1) Mean bilirubin at the time of admission, at 48 hours and day 7 was 13.8± 4.9 mg/dl, 14.4±4.1 mg/dl and 13.1± 4.1 mg/dl respectively. Similarly, mean INR on admission, at 48 hours and at day 7 was 2.5 ± 0.6, 2.5± 0.6 and 2±0.6 respectively.(Table 2) Grade 2 ascites was seen in 75.2%, 75.7% and 74.6 % of the patients on admission, at 48 hours and 7days respectively. Majority of the patients had HE grade 2 on admission (68.6 %) and at 48 hours (47.9 %) while at day 7, most of them did not have HE (76.3%). Different prognostic scoring systems such as CTP, MELD Na+, CLIF SOFA, CLIF C ACLF and NLR were assessed at different time intervals (on admission, at 48 hours and at day 7).

Table 1: Demographic profile and etiology of CLD.

	Mean	SD
Age(yrs)	50.65	12.401
Sex	Frequency	Percent
F	49	32
M	104	68
Etiology of CLD		
Ethanol	141	92.15
Chronic Hepatitis B	7	4.57
Chronic Hepatitis C	2	1.3
NASH	3	1.96

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Table 2: Laboratory investigations and clinical parameters at different time intervals.

	Minimum	Maximum	Mean	SD
WBC count (cells/mm3) on admission	4560	35800	15542.75	6252.786
Neutrophil count (cells/mm3) on admission	3420	33652	12506.9	6170.3
Lymphocyte count (cells/mm3)on admission	912	4368	2577.5	546.1
Total bilirubin(mg/dl) on admission	5.5	34.9	13.826	4.9497
INR on admission	1.6	4.8	2.527	0.6567
Creatinine (mg/dl) on admission	0.4	5	1.298	0.7832
Serum Na+ on admission (mEq/L)	113	138	127.24	4.461
Serum Albumin (g/dl) on admission	1.8	3.9	2.746	0.4516
SpO_2/FiO_2 on admission	125	471	435.52	59.681
MAP on admission (mm/Hg)	50	86	71.56	6.471
WBC count (cells/mm3) at 48 hrs	7800	33000	15083.69	4717.061
Neutrophil count(cells/mm3) at 48 Hrs	5304	31020	11998.5	4780.6
Lymphocyte count (cells/mm3) at 48 Hrs	1524	4420	2640.1	473.7
Total bilirubin(mg/dl) at 48 Hrs	7	35.6	14.499	4.1771
INR at 48 Hrs	1.5	4.6	2.516	0.6411
Creatinine (mg/dl) at 48 Hrs	0.5	4	1.265	0.5781
Serum Na+ at 48 Hrs (mEq/L)	117	138	127.53	3.995
Serum Albumin at 48 Hrs (g/dl)	2	3.8	2.829	0.3635
SpO_2/FiO2 at 48 Hrs	122	466	433.74	57.485
MAP at 48 hrs (mm/Hg)	50	84	71.71	5.222
WBC count(cells/mm3) at Day 7	6600	23100	12488.6	3370.1
Neutrophil count(cells/mm3) at Day 7	4422	20328	9404	3295.6
Lymphocyte count (cells/mm3) at Day 7	1414	4104	2589.6	455.2
Total bilirubin(mg/dl) at Day 7	5.2	29	13.106	4.1405
INR at Day 7	1.1	5	2.043	0.6811
Creatinine (mg/dl) at Day 7	0.6	3.6	1.164	0.4016
Serum Na+ at Day 7 (mEq/L)	121	138	128.49	3.702
Serum Albumin at Day 7 (g/dl)	2.2	3.8	2.863	0.3023
SpO_2/FiO_2 at day 7	144	466	433.12	64.461
MAP at 7 days(mm/Hg)	63	84	73.68	3.531

Mean CTP score on admission, at 48 hours and at day 7 was 12, 12 and 10 (Class C) respectively. Similarly, mean MELD Na+ score on admission, at 48 hours and at day 7 was 31, 30 and 29 respectively. Another scoring system i.e. mean CLIF SOFA score on admission, at 48 hours and at day 7 was 11, 10 and 8 respectively. Mean CLIF C ACLF score which is another important prognostic score on admission, at 48 hours and at day 7 was 51, 51 and 44 respectively. Mean NLR on admission, at 48 hours and at day 7 was 4.9, 4.7 and 3.7 respectively.(Table 3). In this study, the total mortality was 64 (41.8%). Mortality within 48 hours was 13 patients (8.49%). Between 48 hours and 7 days, 26 patients (16.99%) died. Between 7 days and 1 month, 25 patients (16.33%) died. The highest mortality occurred between 48 hours and 7 days, with 26 patients (16.99%). (Table 4) When comparing scoring systems to predict mortality within 48 hours, all except the CTP score ($p > 0.05$) were significant. The significant scores were MELD Na+ (AUC = 0.970), CLIF SOFA (AUC = 0.983), CLIF C ACLF (AUC = 0.955), and NLR (AUC = 0.859) (Figure 1). Likewise, for predicting mortality between 48 hours and 7 days, all scores except CTP ($p > 0.05$) were significant. The significant scores were MELD Na+ (AUC = 0.706), CLIF SOFA (AUC = 0.870), CLIF C ACLF (AUC = 0.837), and NLR (AUC = 0.865) (Figure 2). However, for predicting mortality between 7 days and 1 month, only NLR was found to be significant ($p < 0.001$) (Figure 3).

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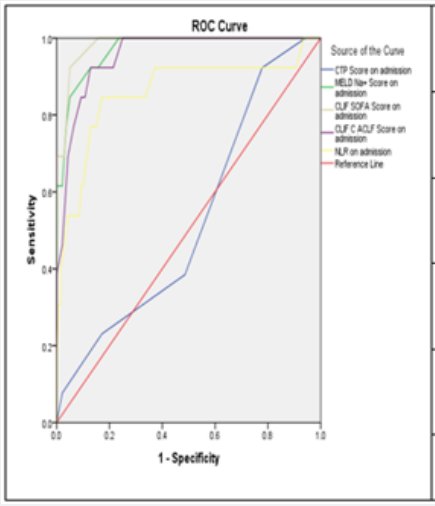
Table 3: Comparison of different scores at different time intervals.

	On admission	At 48 hours	At day 7
CTP	12	12	7
MELD Na+	31	30	29
CLIF SOFA	11	10	8
CLIF C ACLF	51	51	44
NLR	4.9	4.7	3.7

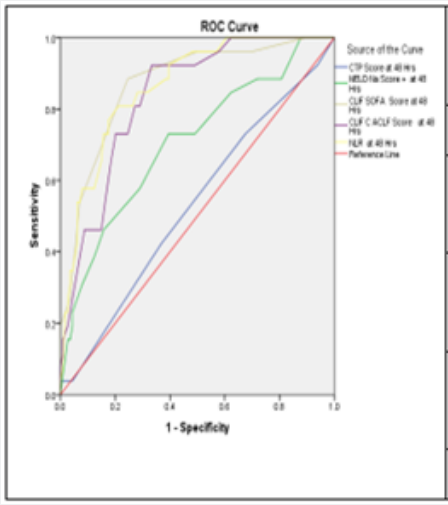
Table 4: Mortality at different time intervals.

Mortality	Frequency	Percent
Within 48 hours	13	8.49
Between 48 hours and 7 days	26	16.99
Between 7 days and 1 month	25	16.33
Total	64	41.8



Test Result Variable(s)	Area	P
CTP Score on admission	.527	.746
MELD Na+ Score on admission	.970	<0.001
CLIF SOFA Score on admission	.983	<0.001
CLIF C ACLF Score on admission	.955	<0.001
NLR on admission	.859	<0.001

Figure 1: Differentiating mortality within 48 hours.



Test Result Variable(s)	Area	P
CTP Score at 48 Hrs	.530	.630
MELD Na Score + at 48 Hrs	.706	.001
CLIF SOFA Score at 48 Hrs	.870	.000
CLIF C ACLF Score at 48 Hrs	.837	.000
NLR at 48 Hrs	.865	.000

Figure 2: Differentiating mortality between 48 hours and 7 days.

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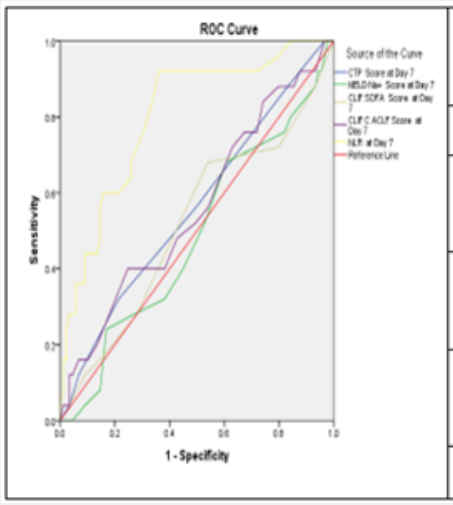

Test Result Variable(s)	Area	P
CTP Score at Day 7	.562	.343
MELD Na+ Score at Day 7	.487	.840
CLIF SOFA Score at Day 7	.520	.766
CLIF C ACLF Score at Day 7	.561	.352
NLR at Day 7	.802	<0.001

Figure 3: Differentiating mortality between 7 days and 1month.

Discussion

In this study, patients admitted with ACLF as per APASL guidelines were evaluated at different time intervals using various prognostic scoring systems. The overall mortality was 64 (41.8%) with majority of the mortality occurring between 48 hours and 7 days i.e. 26 (16.99%). Previously done studies have shown different mortality rates at different time intervals. In a study conducted by Mahmud et al the 28- and 90-day mortalities for APASL ACLF were 41.9% and 56.1%, respectively [15]. In this study ,CTP score was not found to be significant in predicting mortality when calculated at the time of admission, at 48 hours and at day 7. This is in contrast to a study conducted by Acharya et al where CTP score was superior to the MELD and MELD-Na+ scores in predicting 3-month mortality [16]. Other scoring systems such as MELD Na+, CLIF SOFA and CLIF C ACLF were found to be good predictors of mortality occurring within 48 hours and between 48 hours and 7 days when calculated at the time of admission and at 48 hours respectively. Ramzan et al showed that a CLIF-C ACLF score ≥ 70 at 48 hours predicts mortality more accurately and was significantly higher than MELD scores of 30, 40 and 50 at 48 hours.7 However, in contrast to previous studies, MELD Na+, CLIF SOFA and CLIF C ACLF were not found to be good predictors of mortality when calculated at day 7 to predict mortality between 7 days and 1 month in our study. In a study conducted by Barosa et al , the CLIF-C ACLF score was significantly superior to CTP, MELD, MELD-Na+ in predicting 28-day and 90-day mortality [17]. Similarly, in a study conducted by Rashed et al, CLIF-SOFA, CLIF-C ACLF, and CLIF-C AD were accurate short term and long-term prognosticating scores [18].

Neutrophil to Lymphocyte Ratio in few studies has shown to be a good predictor of mortality in patients of ACLF. Chiriac et al in their retrospective observational study concluded that NLR had a better accuracy in predicting mortality in patients with ACLF [12]. Similarly, another study by Bernsmeier et al showed that NLR and monocyte-lymphocyte ratio were elevated in patients with acute decompensation (AD) and ACLF who died during their hospital stay. NLR >30 was associated with an 80% 90-day mortality in patients with ACLF but not AD [19]. In this study, NLR was found to be superior to CTP in predicting mortality within 48 hours and between 48 hours and 7 days when measured at the time of admission and at 48 hours respectively. Furthermore, in this study NLR was found to be superior to CLIF SOFA score and CLIF C ACLF score in predicting mortality between 7 days and 1 month. This is in contrast to a study by Hareesh et al where CLIF-C ACLF had good short-term prognostic accuracy and it was as good as other available scores.9 In another study by Zakareya et al, CLIF C ACLF and CTP scores performed better in predicting in hospital mortality in patients with ACLF [20]. However, in one study by Nagel et al the predictive ability of CLIF-C OFs and CLIF-C ACLFs was relatively low to predict short- and long-term mortality in patients with ACLF with concomitant need for ICU treatment [21].

There are few limitations to the study. CLIF SOFA and CLIF C ACLF scores assess organ failures and help predict short-term mortality. Both these scores consider various extra-hepatic organ dysfunctions and failure to assess the severity of ACLF. In this study, patients were diagnosed with ACLF based on APASL criteria. Extra-hepatic organ failure is not required for diagnosis of ACLF as per APASL criteria. This could be the reason why CLIF SOFA and CLIF C ACLF scores were not found to be significant in predicting mortality between 7 days 1 month. Secondly, NLR, CLIF SOFA and CLIF C ACLF were not compared after 7 days. So, the probability of high CLIF SOFA and CLIF C ACLF score beyond 7 days due to multi-organ failure cannot be ruled out. AARC score is an important prognostic score in patients with ACLF diagnosed as per APASL criteria which was shown by several studies [22,23]. However, AARC score was not used in this study due to the requirement of lactate, which may not be available in resource limited settings.

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Conclusion

In conclusion, NLR, MELD Na+, CLIF SOFA, and CLIF C ACLF scores were superior to CTP in predicting early mortality (within 48 hours and up to 7 days). Only NLR was significant in predicting mortality from 7 days to 1 month. So, NLR can be taken as a cost effective and reliable score to predict short-term mortality in patients with ACLF especially in underdeveloped countries like ours where resources are limited.

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