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PROGNOSTIC PERFORMANCE OF 'INTEGRATED-MELD','MODIFIED-CTP' & OTHER PREDICTION MODELS IN A PROSPECTIVE COHORT OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) PATIENTS

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ABSTRACT

Background And Aim: Acute-on-chronic liver failure (ACLF) is a specific syndrome characterized by high short-term mortality. Identifying early and accurate prognostic factors is of critical importance. Different prognostic models like CTP, MELD, MELD-sodium (MELD-Na), MELD to sodium ratio (MESO), an integrated MELD (iMELD) and modified CTP (mCTP) have been studied for prognosis of ACLF. The Aim of the present study is to estimate the prognostic accuracy of these prediction models and to find out the most effective model to estimate the short term mortality risk in a cohort of ACLF.

Material & Methods: We prospectively evaluated a cohort of 100 patients, who satisfied the APASL criteria for ACLF, from June 2018 to july 2019, with 3-months follow up. All prognostic model scores were calculated based on clinical and laboratory results obtained at enrolment. The receiver-operator-curves(ROC) were drawn for Child-Turcotte-Pugh (CTP) score, Model for end-stage liver disease (MELD), MELD- sodium (MELDNa), MELD to sodium ratio (MESO), integrated MELD (iMELD) and Modified CTP(mCTP) score .Prognostic performance was assessed by the area under the receiver–operator curve (AUC).

Results: Out of the total 100 eligible patients,35% died within 3-months follow up. The AUCs of CTP,Modified CTP,MELD, MELDNa, MESO and iMELD were 0.769,0.884,0.875,0.897,0.898, 0.924 respectively for predicting the 3 month mortality. With the cut-off value of 51.45, iMELD had sensitivity of 85.7%, specificity of 89.2% and with the cut off value of 14.5,modified-CTP had sensitivity of 74.3% and specificity of 89.2%

Conclusion: In the present study, all the 6 scoring systems demonstrated good predictive accuracy for short term mortality in ACLF. However, the most accurate was the integrated-MELD. The modified CTP had a better performance than the original CTP score and was as efficient as the MELD based models.

KEYWORDS : Acute-on-chronic liver failure (ACLF), Child-Turcotte-Pugh (CTP) score, Model for end-stage liver disease (MELD), MELD- sodium (MELDNa)

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by severe acute hepatic abnormalities triggered by factors in patients with chronic liver disease and has high short-term mortality [1, 2]. It is estimated that the 28-day morality rate of ACLF ranges from 14.6% to 78.6%, depending on organ failures [3] . Acute-on-chronic liver failure (ACLF) is defined as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [1]. ACLF is a distinct entity separated from decompensated cirrhosis due to the acute precipitating event and a potential component of reversibility.[4]

Patients with ACLF often come with multiorgan failure (MOF), with poor survival rate. Treatment modalities are limited in patients with ACLF. The current primary treatment for ACLF is supportive care rather than targeted therapies. Liver transplantation is the only effective therapeutic intervention for ACLF patients who do not recover spontaneously from intensive care.

Therefore, it is important to predict the prognosis for these patients so that they can be included in various treatment protocols, such as liver transplantation. The past two decades have observed different prediction models apart from MELD & CTP, that have been developed to assess the prognosis in End stage Liver disease, including a model of MELD-sodium (MELD-Na) [5] , MELD to sodium ratio (MESO)[6], an integrated MELD (iMELD) [7] and modified CTP (mCTP)[8]. [Table 1] . Only a few studies have validated these models externally ,in patients with ACLF. In this study we assessed performance of these prognostic scores, in the prediction of short- term mortality in patients with ACLF.

MATERIAL & METHODS:

We prospectively evaluated a cohort of 100 patients, including 87 males and 13 females, with a median age of 48.8 years, who were treated for ACLF at the department of medical gastroenterology, Trivandrum medical college, from June 2018 to July 2019 ,with 3-months follow up. Written informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Institute.

ACLF was defined according to the Asian–Pacific Association for the Study of the Liver (APASL) criteria. Acute insult was defined as serum bilirubin >5 mg/dL and liver failure as international normalized ratio (INR) ≥1.5 ,complicated within 4 weeks by ascites and/or encephalopathy occurring in a patient with known or unknown CLD. Underlying CLD was defined as either the presence of cirrhosis or chronic hepatitis of any aetiology, cholestatic or metabolic liver disease.All patients were worked-up thoroughly for the possible aetiologies of their underlying CLD and acute precipitating events. Clinical manifestations including jaundice, ascites, encephalopathy or their combination were recorded. Routine blood parameters (routine blood tests with white blood cells and platelet counts, haematocrit, coagulation profiles including prothrombin time and INR, serum electrolyte levels, renal and liver function tests and arterial blood gas analysis) were analysed. All prognostic model scores were calculated based on clinical and laboratory results obtained at enrolment.

Statistical Analysis

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean. The performance of prognostic scores on the prediction of 3 month mortality was assessed by the receiver operating characteristic (ROC) curve. The receiver-operator-curves(ROC) were drawn for Child-Turcotte-Pugh (CTP) score, Model for end-stage liver disease (MELD), MELD- sodium (MELDNa), MELD to sodium ratio (MESO), integrated MELD (iMELD) and Modified CTP(mCTP) score (Figure 1).

TABLE 1-Models Description
CTP score-calculated based on serum bilirubin and albumin levels, PT, and the presence and severity of ascites and HE
Modified CTP- An additional 1 point was given to the traditional CTP score (3 at most) when the serum bilirubin level was > 8 mg/dL, PT prolongation > 11 sec or albumin level < 2.3 g/dL[8]
MELD = 11.2 x ln(INR) + 9.6 x ln[creatinine (mg/dL)] + 3.8 x ln[bilirubin (mg/dL)] + 6.4 (constant for liver disease etiology)
MELD-Na = MELD - Na - [0.025 x MELD x (140 -Na)] + 140.
MESO = (MELD/Na) x 10.
iMELD score = MELD + (age x 0.3) - (Na x 0.7) + 100.

RESULTS

Baseline characteristics, aetiology of cirrhosis and clinical presentations of the patients with ACLF are shown in Table 2. The median age of the patients was 49 years with a significant male predominance. All patients with ACLF had underlying cirrhosis based on serum biochemical examinations, imaging and gastroscopic evidence. Ascites (100%) and encephalopathy(39%) were the most common presentation . Alcoholic hepatitis (55%) was the most

common cause of acute deterioration in ACLF followed by Hepatitis B flare(22%) and DILI(13%).

Out of the total 100 eligible patients,35% died within 3-months follow up. IMELD had a higher AUROC than ,MESO, MELDNa, MELD, Modified CTP and CTP (0.924 *vs.* 0.898 for MESO, 0.897 for MELDNa ,0.884 for Modified CTP ,0.875 for MELD and 0.769 for CTP) for predicting 3 month mortality in all patients (Table 3, Fig. 1) .

With the cut-off value of 51.45, iMELD had sensitivity of 85.7%, specificity of 89.2% and with the cut off value of 14.5,modified-CTP had sensitivity of 74.3% and specificity of 89.2%

Table 2. Baseline Characteristics, Aetiology Of Liver Cirrhosis And Clinical Presentations In Patients With Acute-on-chronic Liver Failure (*n* = 100)

BASELINE CHARACTERISTICS	
Age	48.8 ± 11.5 (13-77)
Male	87(87%)
Aetiology of Cirrhosis	
Alcohol	57(57%)
HBV	24(24%)
NASH	11(11%)
HCV	2(2%)
Autoimmune Hepatitis	4(4%)
Wilsons	2(2%)
Precipitating Event	
Alcoholic Hepatitis	55(55%)
CHB Flare	22(22%)
DILI	13(13%)
Hepatitis A	3(3%)
Multiple	7(7%)
Clinical Parameters	
Ascites	100(100%)
HE	39(39%)
AKI	31(31%)
SBP	27(27%)
Laboratory Parameters	
Cr	1.2 (0.2-5.8)
Bili	13.7 (5.1-35.6)
INR	2.3 (1.5-8.6)
Na	131.0 (118-140)
Prediction Models	
MELD	26.4 (16-40)
MELD-Na	28.9 (19-40)
CTP	12.3 (10-15)
Modified CTP	13.7 (11-18)
MESO	2.0 (1.2-3.3)
integrated-MELD	49.5 (33-68)
Mortality	
@ 3 months	35(35%)

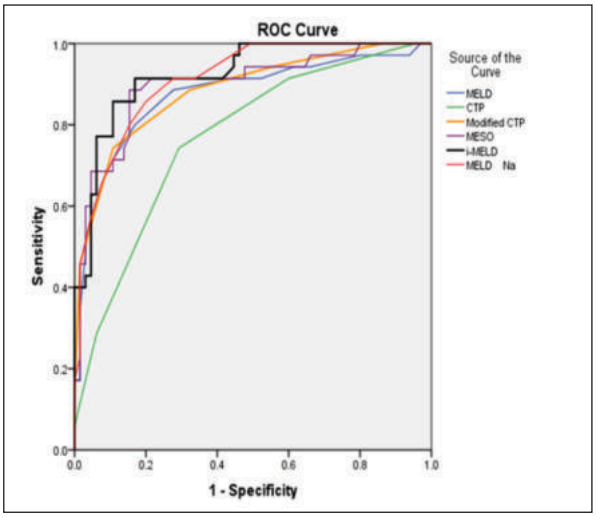

Figure 1. ROC Curves Of Six Models In Predicting The 3-month Mortality Of ACLF Patients

Table 3 Predictive accuracy of the six models for the 3-month mortality of ACLF patients

Prediction models	Optimal Cut Off	Sensitivity	Specificity	Area	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
MELD	26.5	0.800	0.831	.875	.795	.954
CTP	12.5	0.743	0.708	.769	.673	.865
Modified CTP	14.5	0.743	0.892	.884	.812	.955
MESO	2.035	0.886	0.846	.898	.829	.967
i-MELD	51.45	0.857	0.892	.924	.871	.977
MELD-Na	29.5	0.857	0.800	.897	.842	.952

DISCUSSION

ACLF is associated with high short-term mortality, which is confirmed in our current study. 35% of our patients died within 3-months follow up. This is similar to previous studies from different parts of the world[9,10,11,]. Alcohol was the most common cause of cirrhosis in our patients (57%) and around half of the patients had acute alcoholic hepatitis as the precipitating acute event. Patients with ALD had high risk of infection related to their neutrophil dysfunction [12]. Only few studies have been published on the use of prognostic scores in ACLF. Our results in patients with ACLF proves the superiority of IMELD in relation to other scores for predicting 3 month mortality. At admission patients with ACLF have both hepatic insufficiency and organ failures. The utility of various prognostic scores in patients with ACLF may vary with the type and severity of the acute precipitating insult and the underlying CLD.The use of various prognostic scores in patients with ACLF may help in categorizing these patients to limited ICU resources and evolving therapies.

Our study was limited by the fact that we used once only scores in predicting short-term mortality, whereas serial dynamic delta scores will be more useful in predicting the outcome in critically ill patients like ACLF.

CONCLUSION:

This study showed that ACLF had high short- term mortality. In the present study, all the 6 scoring systems demonstrated good predictive accuracy for short term mortality in ACLF. However, the most accurate was the integrated-MELD.The modified CTP had a better performance than the original CTP score and was as efficient as the MELD based models.

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