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Comparison of prognostic systems in cirrhotic patients with hepatic encephalopathy

Adnan TAŞ[1,*], Mehmet Suat YALÇIN[1], Bünyamin SARITAŞ[2], Banu KARA[1]
[1]Department of Gastroenterology, Adana Numune Research and Education Hospital, Adana, Turkey
[2]Department of Gastroenterology, Faculty of Medicine, Mersin University, Adana, Turkey

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Background/aim: There are various scoring systems for evaluating prognosis in patients hospitalized in intensive care units (ICUs) with hepatic encephalopathy. These include the Child–Turcotte–Pugh (CTP) classification, Model for End-stage Liver Disease (MELD), chronic liver failure–sequential organ failure assessment (CLIF-SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II). In this study, we aimed to compare the various scoring systems to determine the best system for showing the prognosis of patients with a prior diagnosis of cirrhosis who were hospitalized for hepatic encephalopathy.

Materials and methods: Patients with known cirrhosis hospitalized in the internal medicine ICU of the Adana Numune Education and Research Hospital with a diagnosis of hepatic encephalopathy were included in the study. Diagnosis and classification of hepatic encephalopathy were done according to the West Haven criteria. The etiology of hepatic encephalopathy was recorded for all patients. APACHE II, CLIF-SOFA, MELD, and CTP scores were calculated for all patients within the first 24 h. Outcomes of patients were recorded as either discharged or deceased. Demographic and biochemical data, duration of hospitalization, and prognostic factors were compared for both groups. Area under the receiver operating characteristic curve (AUROC) values were calculated for each scoring system.

Results: A total of 84 patients were included in the study. The etiologies of encephalopathy were infection (n = 35, 41.7%), variceal bleeding (n = 19, 22.6%), constipation (n = 15, 17.9%), consuming excessive protein (n = 8, 9.5%), hypokalemia (n = 6, 7.1%), and hepatocellular carcinoma (n = 1, 1.2%). Nine patients had grade 1 encephalopathy, 34 patients had grade 2, 27 patients had grade 3, and 14 patients had grade 4. AUROC values were 0.986 (0.970–1.003), 0.974 (0.945–1.003), 0.955 (0.915–0.996), and 0.880 (0.800–0.959) for CLIF-SOFA, APACHE II, CTP, and MELD scores, respectively.

Conclusion: We found the best prognostic model for patients who were hospitalized in the ICU for hepatic encephalopathy to be CLIF-SOFA, followed by APACHE II, CTP, and MELD scores.

Key words: Cirrhosis, hepatic encephalopathy, prognostic factors, CLIF-SOFA, APACHE II, CTP, MELD

1. Introduction

Hepatic encephalopathy (HE) is a reversible neurological disorder that is observed during the course of acute or advanced hepatic failure (1). Although the clear pathogenesis of HE is not evident, some mechanisms are suggested. It is thought to be caused by insufficiency in hepatocyte function. Patients with HE have increased gamma aminobutyric acid levels in the central nervous system, which leads to an increased inhibitor effect, and 90% of patients with HE have increased levels of ammonia in the arterial blood. Ammonia leads to deterioration in mitochondrial functions and causes swelling of astrocytes and vasodilatation. Vasodilatation may also be caused by increased nitrous oxide levels in patients with HE. Vasodilatation leads to increased intracranial pressure and deterioration in cognitive functions (1,2). Precipitating factors for HE include hypovolemia, hypokalemia, hyponatremia, gastrointestinal bleeding, consuming excessive protein, and hepatocellular carcinoma. HE is classified according to the West Haven criteria into four grades (3).

There are various prognostic models for evaluating patients with cirrhosis in the intensive care unit (ICU). These include Child–Turcotte–Pugh (CTP) classification, Model for End-stage Liver Disease (MELD), chronic liver failure–sequential organ failure assessment (CLIF-SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II). In the medical literature these prognostic systems have been evaluated in different patient groups, such as patients with burns, cardiovascular disease,

* Correspondence: dradnantas@gmail.com

pancreatitis, cirrhosis, and neurologic disorders in surgical or internal medicine ICUs (4–7). However, there has been no study investigating prognostic systems in patients with a prior diagnosis of cirrhosis with hepatic encephalopathy. In the present study we aimed to evaluate the different prognostic scoring systems in order to determine the best system for these patients.

2. Patients and methods

Our study included patients with a prior diagnosis of cirrhosis who were admitted to the Adana Numune Education and Research Hospital from January 2014 to January 2017 with hepatic encephalopathy. Diagnosis of cirrhosis was based on histological, clinical, laboratory, and radiological findings. Diagnosis and classification of HE were done according to the West Haven criteria (3). Patients with acute hepatic failure and hepatic encephalopathy after port-systemic shunt surgery were excluded. Causes of HE were recorded for all patients. APACHE II, CLIF-SOFA, MELD, and CTP scores were calculated for all patients within the first 24 h after admission to the ICU. Deceased and discharged patients' demographic data, laboratory parameters, duration of hospitalization, and prognostic scores were calculated. The area under the receiver operating characteristic curve (AUROC) was calculated for each prognostic system.

Statistical analyses were performed using SPSS 20 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to describe continuous variables. The χ^2 (Fisher's exact) test was used for categorical variables and expressed as observation counts (and percentages). Statistical significance was accepted when the two-sided P value was lower than 0.05. Comparison of noncontinuous variables between groups was done using the chi-square test, while continuous variables were compared using the t-test. In case of a skewed distribution, the Mann–Whitney U test was used for comparison of continuous variables, followed by ROC.

3. Results

A total of 84 patients (61 male (72.6%) and 23 female (27.4%)) were included in our study. Etiologies of encephalopathy were infection (urinary infection, spontaneous bacterial peritonitis, pneumonia) in 35 (41.7%) patients, esophageal variceal bleeding in 19 (22.6%) patients, constipation in 15 (17.9%) patients, consuming excessive protein in 8 (9.5%) patients, hypokalemia in 6 (7.1%) patients, and hepatocellular carcinoma in one patient. Nine (10.7%) patients had grade 1, 34 (40.5%) patients had grade 2, 27 (32.1%) patients had grade 3, and 14 (16.7%) patients had grade 4 hepatic encephalopathy.

Patients' demographic and laboratory data are summarized in Table 1. Comparison of prognostic models and duration of hospitalization in patients who were discharged or deceased are given in Table 2. AUROC, sensitivity, and specificity values are shown in Table 3 and the Figure.

4. Discussion

In the present study we aimed to evaluate prognostic scoring systems to determine the best system for patients with hepatic encephalopathy who had a prior diagnosis of cirrhosis. We found that the best prognostic scoring system was CLIF-SOFA, followed by APACHE II, CTP, and MELD (Table 3; Figure).

In a study conducted by Zhou et al. they included 730 patients in the ICU with cirrhosis and compared mortality at 30 days and 90 days. They found that the CLIF-SOFA score was superior to the MELD score for showing the prognosis. AUROC values were 0.768 (CI: 0.706–0.799) and 0.725 (CI: 0.691–0.757) for CLIF-SOFA and MELD scores, respectively (5). A total of 109 patients in the ICU with cirrhosis were included in a study conducted by Elzouki et al. and they observed that 27 (25%) patients died and 87 (75%) patients survived. They reported that the SOFA score was the best prognostic model for predicting mortality in all age groups but that the APACHE II and MELD scores were the best for patients who were over 60 years of age (P = 0.001 and P = 0.02, respectively). They reported that the CTP score was not a predictor of mortality (8). Hemida et al. conducted a study including 60 patients with hepatitis C-related cirrhosis who were undergoing surgery under general anesthesia except for liver surgery. They compared MELD and CTP scores to evaluate 30-day mortality. They found a sensitivity of 100% and specificity of 64% for a cut-off value of 13.5 for the MELD score and 75% sensitivity and 96.4% specificity for the CTP score. They concluded that the MELD score was more sensitive but less specific in comparison to the CTP score for predicting 30-day mortality in patients with hepatitis C-related cirrhosis who were undergoing surgery under general anesthesia (9). Radisavljevic et al. investigated the mortality of 126 patients with alcoholic cirrhosis after a follow-up of 29 months. In that study they reported the best predictor of mortality was a MELD score above 22.5 (AUC = 0.914, 95% CI: 0.849–0.978; P < 0.001) (10). Fan et al. conducted a study including 253 patients with cirrhosis and followed them up for 12 months. Mortality at 3 months and 12 months was 9.1% (n = 23) and 13.8% (n = 35), respectively. The AUC value for the CTP score was 0.838 at 3 months and 0.840 at 12 months. In that study they concluded that CTP was a perfect system for determining prognosis in Chinese patients with cirrhosis (11). In a study conducted by Peeraphatdit et al. including 830 patients who were admitted to the ICU, MELD scores were calculated on admission and on day

Table 1. Patients' demographic and laboratory data.

	Overall (n: 84)	Discharged (n: 41)	Deceased (n: 43)	P-value
Age (years)	65.62 ± 12.030	63.49 ± 12.87	67.65 ± 10.941	0.113
BUN (mg/dL)	106.70 ± 79.479	59.52 ± 44.313	150.58 ± 80.117	≤0.001
Cr (mg/dL)	2.0036 ± 1.51035	1.1623 ± 0.60607	2.8058 ± 1.67580	≤0.001
NA (mmol/L)	132.98 ± 8.712	134.00 ± 7.520	132.00 ± 9.703	0.296
K (mEq/L)	4.738 ± 1.0559	4.612 ± 0.9352	4.858 ± 1.1576	0.289
ALT (U/L)	47.17 ± 50.628	40.27 ± 42.181	53.74 ± 57.272	0.225
AST (U/L)	108.19 ± 127.690	79.88 ± 78.190	135.19 ± 157.702	0.047
DB (mg/dL)	5.0239 ± 6.68338	2.7656 ± 3.50959	7.1772 ± 8.17406	0.002
Albumin (g/dL)	2.6445 ± 0.59018	2.8983 ± 0.59874	2.4026 ± 0.47340	≤0.001
INR	3.6138 ± 17.06486	5.2432 ± 24.45433	2.0602 ± 0.94062	0.396
WBC	8779.64 ± 6386.062	6682.68 ± 2968.379	10,800.00 ± 7988.457	0.003
PLT	120,000.00 ± 86,724.09	118,000.00 ± 76,648.21	121,000.00 ± 96,247.20	0.877
HCT	30.800 ± 6.0766	32.285 ± 6.1110	29.384 ± 5.7618	0.028

BUN, blood urea nitrogen; Cr, creatinine; NA, sodium; K, potassium; DB, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelets;
INR, International normalized ratio; WBC, white blood cells; HCT, hematocrit

Table 2. Comparison of prognostic model scores and duration of ICU stay in patients with hepatic encephalopathy who died or were discharged from the ICU.

Prognostic model	Overall (n: 84)	Discharged (n: 41)	Deceased (n: 43)	P-value
CTP	10.80 ± 2.389	8.88 ± 1.452	12.63 ± 1.496	≤0.001
MELD	21.19 ± 9.428	14.83 ± 4.061	27.26 ± 9.098	≤0.001
CLIF-SOFA	9.04 ± 3.895	5.63 ± 1.685	12.28 ± 2.282	≤0.001
APACHE II	14.86 ± 7.241	8.80 ± 3.730	20.63 ± 4.530	≤0.001
DICU (days)	7.67 ± 5.347	5.88 ± 2.795	9.37 ± 6.554	0.002

CTP, Child–Turcotte–Pugh; MELD, Model for End-stage Liver Disease; CLIF-SOFA, chronic liver failure–sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; DICU, Duration of ICU

Table 3. Sensitivity, specificity, and accuracy of prognostic models based on cut-off values determined by receiver operating characteristic (ROC) curve analysis.

Prognostic model	Cut-off value	Sensitivity (%)	Specificity (%)	Accuracy	95% CI	P-value
CTP	≥9.5	97.7	26.8	0.955	0.915–0.996	≤0.001
MELD	≥10.5	97.7	87.8	0.880	0.800–0.959	≤0.001
APACHE II	≥9.5	97.7	34.1	0.974	0.945–1.003	≤0.001
CLIF-SOFA	≥7.5	97.7	14.6	0.986	0.970–1.003	≤0.001

CI, Confidence Interval; CTP, Child–Turcotte–Pugh; MELD, Model for End-stage Liver Disease;
APACHE II, Acute Physiology and Chronic Health Evaluation II; CLIF-SOFA, chronic liver failure–sequential organ failure assessment

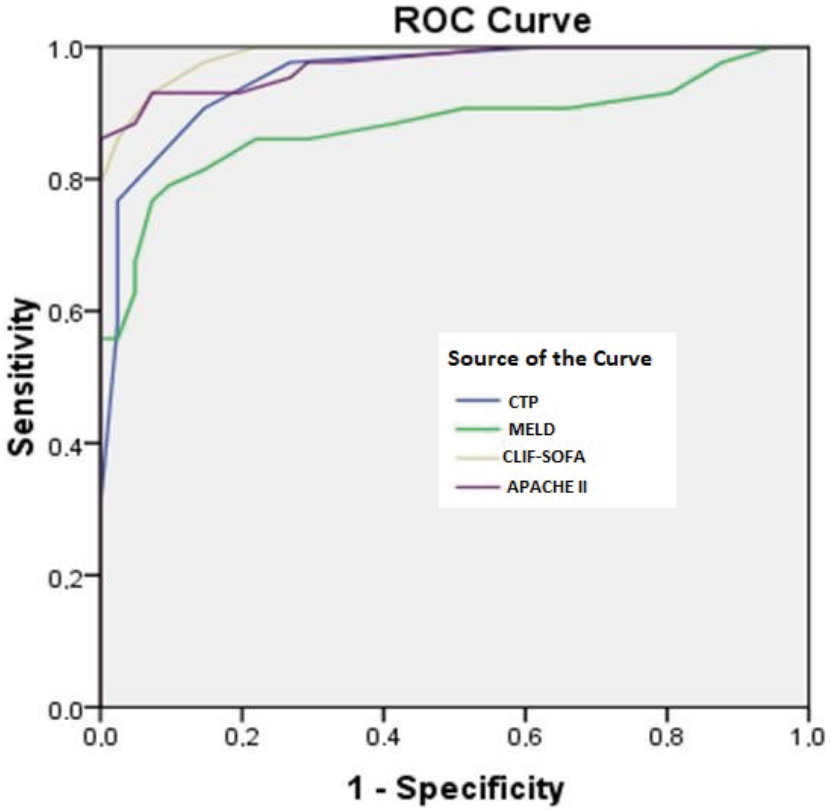

Figure. Comparison of ROC curves and ROC values of CTP, MELD, APACHE II, and SOFA scoring systems.

7 after admission. They reported a relationship between MELD score and 90-day mortality, and also MELD score was an independent predictor of mortality (OR 1.07, 95% CI, 1.05–1.10; P < 0.001). A consecutive calculation of MELD score on each day during 7 days of hospitalization was not superior to the MELD score on the first day (12). Dupont et al. investigated the relationship between SOFA, MELD, and CTP scores and mortality in a study including 281 patients with cirrhosis hospitalized in the ICU. They reported that mortality was 25.3%. AUROC values for SOFA, MELD, and CTP were 0.82 (0.77–0.88), 0.81 (0.76–0.87), and 0.76 (0.70–0.82), respectively. They reported that the best predictors of hospital mortality were SOFA and MELD scores (13). Peng et al. compared CTP and MELD scores as predictors of hospital mortality in 145 cirrhotic patients with upper gastrointestinal bleeding. AUROC values for MELD and CTP were 0.810 (95% confidence interval (CI): 0.736–0.870) and 0.796 (95% CI: 0.721–0.858). There was no statistically significant difference (P = 0.7241) (14). Zhang et al. investigated MELD and CTP scores to predict mortality in 77 patients with cirrhosis who had choledocholitiasis and were undergoing endoscopic retrograde cholangiopancreatography (ERCP). In that study, complications related to the ERCP procedure occurred in 21 (44.7%) patients whose MELD scores were above 11.5 and in three (10%) patients whose MELD scores were under 11.5 (P = 0.001). The cut-off value for MELD score to predict complications was >11.5 (AUC = 0.75, 95% CI = 0.63–0.87). The CTP score was not effective in predicting complications. They concluded that MELD score was superior to CTP score for predicting complications (15). Lee et al. investigated the CLIF-SOFA score as a predictor of short-term mortality in 345 patients with decompensated alcoholic cirrhosis. Supportive treatment was given to 262 patients and 83 patients had liver transplantation. Patient CLIF SOFA and MELD scores were compared. AUROC values for short-term (12 weeks) mortality were 0.978 (0.932–1.000) and 0.839 (0.668–1.000) for CLIF-SOFA and MELD scores, respectively. They concluded that CLIF-SOFA was superior to MELD score for predicting mortality at 12 weeks in patients with decompensated alcoholic cirrhosis (16). In the medical literature there is no study investigating prognostic systems in cirrhotic patients with hepatic encephalopathy. Our study included 84 patients. We compared CLIF-SOFA, APACHE II, CTP, and MELD scores as predictors of mortality. AUROC values were 0.986 (0.970–1.003), 0.974 (0.945–1.003), 0.955 (0.915–0.996), and 0.880 (0.800–

0.959), respectively, for CLIF-SOFA, APACHE II, CTP, and MELD scores (Table 3; Figure). We found there was a statistically significant difference in all prognostic models between deceased and discharged patients (Table 2).

In conclusion, we found the best scoring system to be CLIF-SOFA for cirrhotic patients with hepatic encephalopathy in the ICU.

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