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Comparative performance of prognostic models in predicting mortality in cirrhotic patients with spontaneous bacterial peritonitis

Chrisandi Yusuf Rizqiansyah[1*], Supriono Supriono[2,3]

[1]Department of Internal Medicine, Rumah Sakit Universitas Brawijaya, Malang, Indonesia; [2]Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia; [3]Division of Gastroenterohepatology, Department of Internal Medicine, RSUD Dr. Saiful Anwar, Malang, Indonesia.
Corresponding author: Chrisandi Yusuf Rizqiansyah (Email: chrisandi.yusuf@gmail.com)

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ABSTRACT

BACKGROUND: Prognostic models are widely used to predict mortality and management outcomes in liver cirrhosis patients with spontaneous bacterial peritonitis (SBP). However, it remains unclear whether these prognostic models can be applied to SBP.

OBJECTIVES: To determine the predictive value of prognostic models, including Child-Turcotte-Pugh (CTP), Model for End-stage Liver Disease score- Sodium (MELD-Na), Albumin to Bilirubin (ALBI), and Neutrophil-to-Lymphocyte Ratio (NLR) in cirrhotic patients with SBP.

METHODS: Seventy-four hospitalized cirrhotic patients with SBP were selected. Diagnosis was based on clinical, biochemical, ultrasonographic, and ascitic fluid analysis. CTP, MELD-Na, ALBI, and NLR scores at admission were calculated. The area under the ROC curve (AUC) was used to measure accuracy. Sensitivity and specificity were calculated for the optimal cut-off points.

RESULTS: Our results revealed that patients who died had higher scores in NLR (MD: 7.51; 95% CI: 1.46–13.56; p: 0.0150), MELD-Na (MD: 10.09; 95% CI: 6.91–13.27; p: 0.0000), CTP (MD: 2.57; 95% CI: 1.82–3.32; p: 0.0000), and ALBI (MD: 0.47; 95% CI: 0.22–0.73; p: 0.0000) compared to survivors. Among these scores, the highest AUC in univariate logistic regression analysis were CTP, MELD-Na, NLR, and ALBI with 0.87, 0.82, 0.73, and 0.72, respectively.

CONCLUSION: The combination of CTP and MELD-Na scores was superior to ALBI and NLR prognostic models. These can be used to assess liver function and prognosis in cirrhotic patients with SBP.

KEYWORDS: Liver cirrhosis; CTP; MELD-Na; NLR; spontaneous bacterial peritonitis.

INTRODUCTION

Liver cirrhosis is the final stage of chronic liver disease. This condition is one of the top 10 leading causes of death worldwide. More than 160 million people experienced cirrhosis globally in 2017, with over 0.8 million patients with cirrhosis dying each year.[1] Cirrhosis is characterized by fibrosis and the formation of nodules in the liver due to chronic damage, leading to a disruption of the normal lobular system of the liver. Various etiologies can cause liver damage, including viral infections, toxins, hereditary conditions, or autoimmune processes, which lead to the formation of tissue fibrosis, initially without loss of physiological function. Among the known etiologies, more than half of the patients are affected by hepatitis B and hepatitis C.[2]

Complications of cirrhosis result in approximately 150,000 hospital admissions of cirrhotic patients and cost USD 4 billion annually. Major complications of cirrhosis include variceal bleeding, ascites, peritonitis, hepatorenal syndrome (HRS), portopulmonary hypertension (PPH), and hepatic encephalopathy.[3] Ascites is the most common complication, defined as an excess of fluid in the peritoneal cavity caused by splanchnic vasodilation and activation of the renin-angiotensin-aldosterone system, leading to renal fluid and sodium retention.[4] Cirrhosis with ascites also results in impaired immune system defense mechanisms against bacteria, related to decreased bacterial clearance. Immune system defects facilitate bacterial translocation, triggered by increased intestinal permeability and bacterial overgrowth in the gut. This promotes bacterial infections, with spontaneous bacterial peritonitis (SBP) being the most common form.[5]

SBP contributes to high morbidity and mortality in cirrhotic patients with ascites. SBP is divided into three types: classical, culture-negative neutrophilic ascites (CNNA), and monomicrobial non-neutrocytic bacterascites (MNB).[6] SBP occurs in 12% of hospitalized patients with ascites, with a mortality rate of 20%. In certain cases, SBP may not show typical clinical characteristics, making it difficult to identify. Therefore, early non-invasive diagnosis of SBP in decompensated cirrhosis is recommended, particularly in cases with atypical clinical manifestations and newly diagnosed cases.[7] Several scoring systems have been used to predict mortality in cirrhotic patients, including the Child-Turcotte-Pugh (CTP) score, Model for End-stage Liver Disease score- Sodium (MELD-Na), and Albumin to Bilirubin (ALBI) score.[8] The Neutrophil-to-Lymphocyte Ratio (NLR) is a parameter commonly used as a marker of systemic inflammation and has been used as a predictor of outcomes in patients with cardiovascular disease, COVID-19, and malignancies.[9] This study aims to assess these scoring systems as predictors of prognosis and mortality in liver cirrhosis patients with SBP.

METHODS

Design and ethical approval

This study was a descriptive analytic study with a retrospective cohort design. The study analyzed clinical comorbidities, laboratory results, and SBP in cirrhotic patients with ascites, and their association with the severity of MELD-Na, CTP, ALBI, and NLR scores, length of hospital stay, the care unit (ICU or non-ICU), and the incidence of mortality during hospitalization. The study protocol was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies[10] and was approved by the local ethical committee. Additionally, the study adhered to the principles outlined in the Helsinki Declaration.[11] Informed consent from patients was not required for this study as it was a retrospective analysis.

Participants and eligibility criteria

The subjects in this study were all medical records of cirrhotic patients with ascites based on clinical criteria, laboratory results, and ultrasonography (USG) examinations, who were treated by the Department of Internal Medicine at the ICU and non-ICU wards of RSUD Dr. Saiful Anwar, Malang. Data for the study were obtained through a medical record review and determined using a consecutive sampling technique, where patient data were examined according to the inclusion and exclusion criteria. The inclusion criteria for this study were patients diagnosed with liver cirrhosis with ascites based on clinical criteria, laboratory results, and USG examination in their medical records from October 2020 to November 2023, diagnosed with SBP based on paracentesis examination with polymorphonuclear (PMN) cell count ≥ 250 cells/mm3,

with or without positive culture results, and having a history of risk factors including: Hepatitis B infection, Hepatitis C based on HBsAg and Anti-HCV serology results, alcohol consumption exceeding 2-3 bottles per week, and diabetes mellitus. The exclusion criteria for this study were incomplete medical records, patients diagnosed with hepatocellular carcinoma based on CT-scan results in three phases, and elevated alpha-fetoprotein (AFP) levels ≥ 200 U/L.

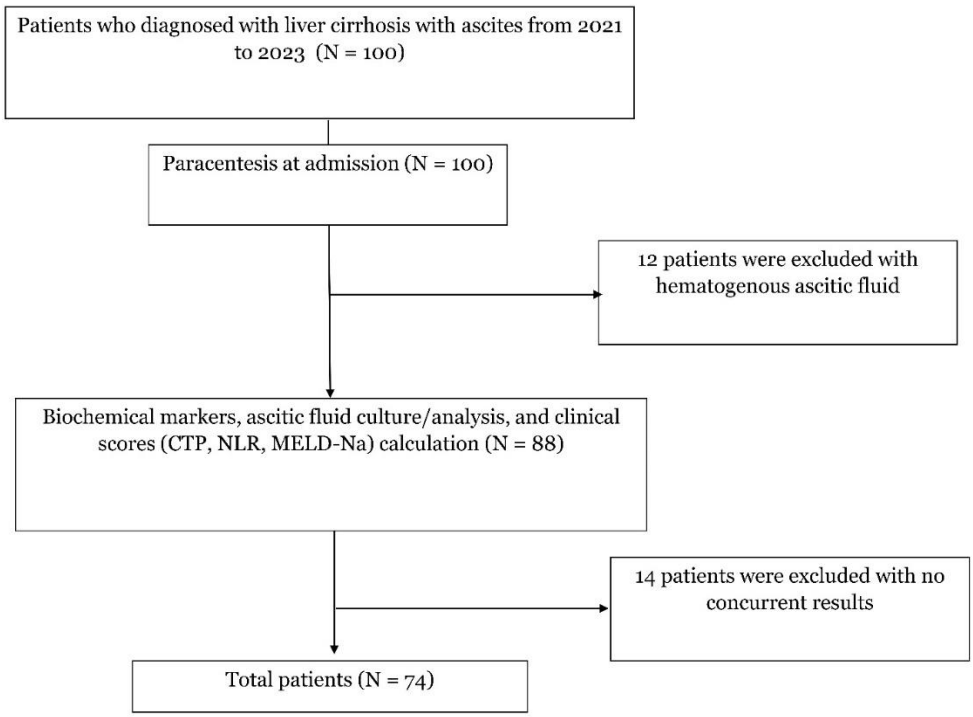

Figure 1. A flowchart of patient selection in our study.

Data collection

Data were obtained from the medical records of patients with liver cirrhosis and ascites who received care in both ICU and non-ICU wards at RSUD Dr. Saiful Anwar, Malang, from October 2020 to November 2023. The collected data included age, gender, length of stay, risk factors for liver cirrhosis, complications of liver cirrhosis, laboratory parameters, ascitic fluid analysis, mortality, and the MELD-Na, CTP, and ALBI scores.

Covariates

The predictor variables in this study were the prognostic scores of MELD-Na, CTP, ALBI, and NLR. The outcome variable in this study was mortality or death caused by liver cirrhosis or complications related to liver cirrhosis.

Statistical analysis

Categorical variable data were described as frequencies and percentages, while continuous variables were described as means, medians, and interquartile ranges (IQR). Data normality was tested using the Kolmogorov-Smirnov test. Normally distributed data were compared using the t-test for numeric variables, and the Mann-Whitney test was used for data that were not normally distributed. Categorical variables were tested using the chi-square test. To examine the relationships between risk factors, the collected data were analyzed using bivariate and multivariate analyses. Bivariate and multivariate analyses were used to determine the relationships between variables using bivariate and multivariate logistic regression models. The comparison of specificity and sensitivity was assessed using the Range of Curve (RoC) and the Area

Under Curve (AUC). Data analysis was performed using GraphPad Prism version 10.2 (GraphPad Software, LLC, San Diego, California, US).

RESULTS

Baseline characteristics of patients

The research data were obtained from the medical records of patients at RSUD Dr. Saiful Anwar, Malang, over a 26-month period from October 2020 to November 2023. The study sample was randomly selected using a consecutive random sampling method, consisting of 74 patients diagnosed with liver cirrhosis with ascites complicated by SBP, who came to the Emergency Department and were admitted to the isolation ward, according to the inclusion and exclusion criteria of the study. Patient selection for this study is outlined in Figure 1.

Table 1. Baseline characteristics of patients included in our study

Characteristics	Non-Survive (N = 45)	Survive (N = 29)	p
Age, y	56.13 ± 9.37	52.31 ± 10.05	0.0961
Male (n %)	37 (82.2)	18 (62.1)	0.0570
Length of stay, d	5.91 ± 4.07	8.10 ± 2.96	0.0124
Risk factors (n %)			
Hepatitis B infection	33 (73.3)	16 (55.2)	0.1100
Hepatitis C infection	6 (13.3)	8 (27.6)	0.1330
Alcoholic liver disease	1 (2.2)	3 (10.3)	0.1690
Other causes	5 (11.1)	2 (6.9)	0.5490
Complications (n %)			
UGIB	22 (48.9)	10 (34.5)	0.2240
HE	37 (82.2)	16 (3.5)	0.0000
Shock septic	34 (75.5)	2 (6.9)	0.0000
Laboratorium			
Hemoglobin (g/dL)	8.68 ± 2.14	10.26 ± 2.39	0.0039
Leukocyte (cell/uL)	15672 ± 8364.50	11054.48 ± 6951.54	0.0134
Hematocrit (%)	30.11 ± 6.75	26.42 ± 5.68	0.0148
Thrombocyte (cell/uL)	218184.44 ± 109274.36	187862.07 ± 129319.02	0.2784
ANC	13.30 ± 7.91	8.61 ± 6.30	0.0072
MPV (%)	10.21 ± 0.93	9.65 ± 0.68	0.0052
PDW (%)	11.26 ± 2.27	9.82 ± 1.08	0.0014
Albumin serum (g/dL)	2.41 ± 0.50	2.56 ± 0.61	0.2481
PT (sec)	16.71 ± 4.03	13.20 ± 2.02	0.0000
APTT (sec)	35.54 ± 11.15	28.28 ± 5.10	0.0010
INR (sec)	1.63 ± 0.41	1.28 ± 0.21	0.0000
SGOT (IU/L)	178.96 ± 118.68	129.55 ± 158.26	0.1256
SGPT (IU/L)	74.78 ± 54.18	94.45 ± 290.39	0.6569
NLR	14.04 ± 16.12	6.53 ± 4.84	0.0149
Urea (mg/dL)	103.46 ± 74.62	53.62 ± 34.37	0.0008
Creatinine (mg/dL)	2.17 ± 1.38	1.10 ± 0.60	0.0001
Procalcitonin	4.98 ± 6.62	3.97 ± 5.37	0.4914
CRP	6.29 ± 5.93	7.06 ± 4.77	0.5572
Total bilirubin (mg/dL)	10.55 ± 9.80	2.74 ± 2.65	0.0000
Direct bilirubin (mg/dL)	8.62 ± 8.15	1.97 ± 2.05	0.0000
Indirect bilirubin (mg/dL)	1.94 ± 1.95	0.75 ± 0.73	0.0017
Natrium (mmol/L)	127.20 ± 6.83	132.14 ± 6.10	0.0016
Potassium (mmol/L)	4.48 ± 0.85	4.09 ± 0.56	0.0291
Chloride (mmol/L)	103.47 ± 6.43	106.34 ± 6.23	0.0578
Ascitic fluid analysis			
Total protein	1.31 ± 0.88	1.39 ± 0.87	0.7014
Glucose	113.13 ± 47.94	139.31 ± 72.11	0.0604
Triglyceride	45.27 ± 37.72	39.52 ± 36.22	0.5156
Cholesterol	16.29 ± 19.86	24.83 ± 23.13	0.0906

LDH	229.51 ± 341.02	187.83 ± 323.23	0.6005
Erythrocyte	86187.90 ± 258682.81	255814.76 ± 862158.39	0.2149
Leukocyte	1160.31 ± 2940.99	656.92 ± 1233.66	0.3832
PMN	58.79 ± 29.07	31.17 ± 26.08	0.0000
MN	41.16 ± 29.12	68.83 ± 26.08	0.0000
Albumin ascites	0.58 ± 0.46	0.54 ± 0.36	0.6919
SAAG	1.63 ± 0.62	1.93 ± 0.75	0.0614
Albumin	2.29 ± 0.60	2.41 ± 0.74	0.4438
PMN cell count	23326.20 ± 144292.98	368.49 ± 975.46	0.3927
Scoring			
MELD-Na	28.40 ± 7.48	18.31 ± 5.62	0.0000
CTP	11.60 ± 1.74	9.03 ± 1.38	0.0000
ALBI	-0.73 ± 0.51	-1.20 ± 0.60	0.0003

Note, data were presented in n (%) or mean ± SD; UGIB, Upper Gastrointestinal Bleeding; HE, Hepatic Encephalopathy; ANC, Absolute Neutrophil Count; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; INR, International Normalized Ratio; SGOT, Serum Glutamate-Oxaloacetate Transaminase; SGPT, Serum Glutamate-Pyruvate Transaminase; NLR, Neutrophil-to-Lymphocyte Ratio; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase; PMN, Polymorphonuclear leukocytes; MN, Mononuclear Cells; SAAG, Serum-Ascites Albumin Gradient; MELD-Na, Model for End-Stage Liver Disease with Sodium; CTP, Child-Turcotte-Pugh; ALBI, Albumin-Bilirubin.

Based on the basic characteristic data of the study sample shown in Table 1, from a total of 74 patients confirmed with liver cirrhosis with ascites and SBP complications between October 2020 and November 2023, 45 patients did not survive and 29 patients survived. The average age of the study sample was 56.13 years (SD ± 9.37), with 37 male patients (82.2%) and 8 female patients (18.8%) in the non-survive group, and 18 male patients (62.1%) and 11 female patients (37.9%) in the survive group. The average length of stay in the non-survive group was 5.91 days (SD ± 4.07), and 8.1 days in the survive group (SD ± 2.96). The length of stay for the study sample with SBP complications was shorter compared to the survive group. Comorbidities included 48 patients with hepatitis B infection, 14 patients with hepatitis C infection, 4 patients with a history of alcohol consumption, and 7 patients with other diseases such as diabetes mellitus. Complications were more common in the non-survive group, with hepatic encephalopathy in 37 patients (82.2%), septic shock in 34 patients (75.5%), and gastrointestinal bleeding in 22 patients (48.9%). Laboratory results with low hemoglobin were found in the non-survive group with an average of 8.68 g/dL (SD ± 2.14), leukocytosis with an average of 15,672/uL (SD ± 8,364.50), lower albumin levels with an average value of 2.41 g/dL (SD ± 0.50), and hemostasis function values of PT 16.71 (SD ± 4.03), APTT 35.54 (SD ± 11.15), and INR 1.63 (SD ± 0.41). Higher liver enzyme levels were found in the non-survive group with an average SGOT of 178.96 U/L (SD ± 118.68) and SGPT of 74.78 U/L (SD ± 54.18). Renal enzyme function was also higher in the non-survive group with average urea levels of 103.46 (SD ± 74.62) and creatinine of 2.17 (SD ± 1.38). Bilirubin abnormalities were more prevalent in the non-survive group, and low sodium levels were found in the non-survive group with an average of 127.20 mmol/L (SD ± 6.83). Inflammatory markers such as procalcitonin and CRP were higher in the non-survive group with values of 4.98 (SD ± 6.62) and 6.29 (SD ± 5.93), respectively.

Based on the paracentesis examination, glucose levels were lower with an average of 113.13 (SD ± 47.94), LDH levels were high at 229.51 (SD ± 341.02), leukocytes averaged 1,160.31 (SD ± 2,940.99), PMN levels were 58.79 (SD ± 29.07), and the average PMN count was 23,326.20 (SD ± 144,292.98). The prognostic scores were higher in the non-

survive group, with MELD-Na averaging 28.40 (SD ± 7.48), CTP 11.60 (SD ± 1.74), ALBI -0.73 (SD ± 0.51), and NLR 14.04 (SD ± 16.12).

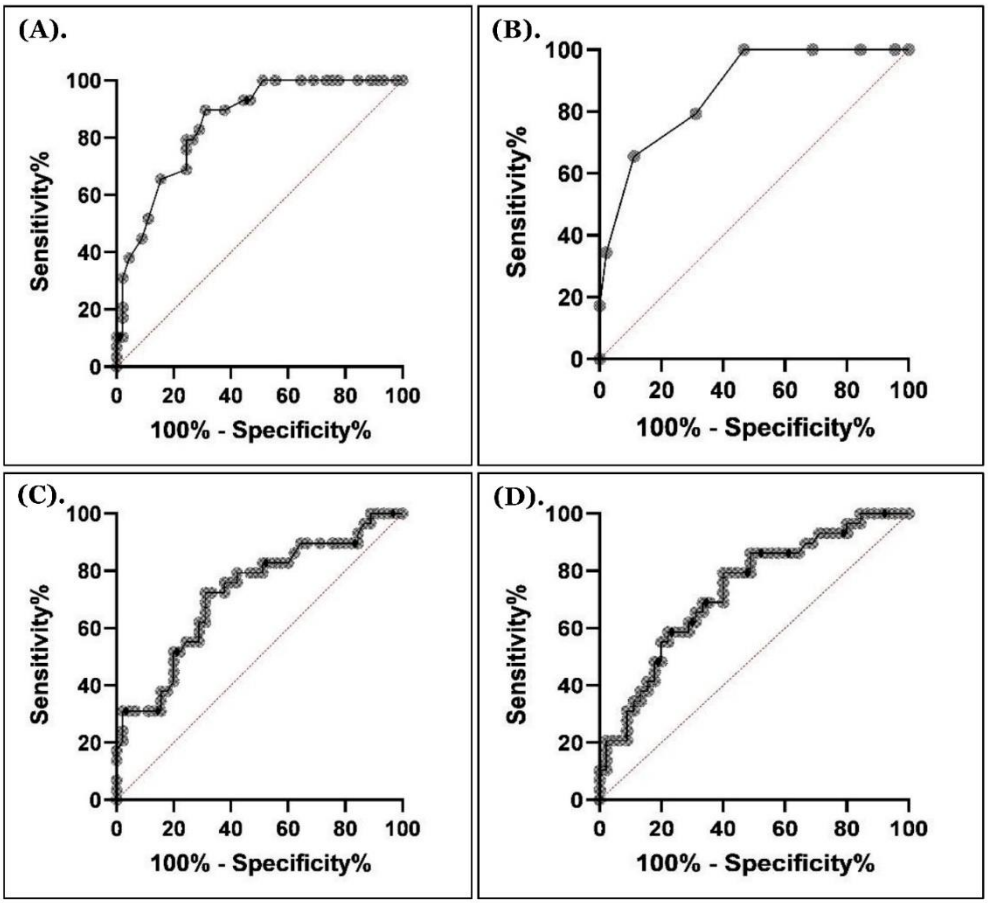

Figure 2. Comparison of ROC curves and AUC values for (A) MELD-Na, (B) Child-Turcotte-Pugh (CTP), (C) ALBI, and (D) Neutrophil-to-Lymphocyte Ratio (NLR) in predicting mortality risk in patients with liver cirrhosis and spontaneous bacterial peritonitis.

Comparison of prognostic scores MELD-Na, CTP, ALBI, and NLR in predicting mortality in liver cirrhosis patients with spontaneous bacterial peritonitis

In the next stage, we compared the prognostic scores of MELD-Na, CTP, ALBI, and NLR. The average prognostic scores are shown in Table 2. In the non-survive group, the MELD-Na score averaged 10.09 (28.40 ± 7.48), followed by CTP 2.57 (11.60 ± 1.74), ALBI 0.47 (-0.73 ± 0.51), and NLR 7.51 (14.04 ± 16.12). Higher prognostic scores were found in the non-survive group with MELD-Na (28.40 vs 18.31), CTP (11.60 vs 9.03), ALBI (-0.73 vs -1.20), and NLR (14.04 vs 6.53). Table 3 shows the mortality risk for each prognostic score. The group with MELD-Na scores > 25.5 had a significantly higher mortality risk (OR: 19.19; 95% CI 4.96-74.13; p: 0.0000), followed by NLR > 11.38 (OR: 5.0; 95% CI 1.49-16.73; p-value = 0.009), and ALBI > 0.615 (OR: 3.84; 95% CI 1.24-11.87; p: 0.019). In contrast, CTP > 14.05 had a higher risk but was not significant (OR: 3.39; 95% CI 0.15–73.2; p: 0.436).

Comparison of sensitivity and specificity of prognostic scores MELD-Na, CTP, ALBI, and NLR in predicting mortality in liver cirrhosis patients with spontaneous bacterial peritonitis

The comparison results of AUC and ROC for each prognostic score are depicted in Figure 2. The CTP prognostic score had an AUC of 0.87, followed by MELD-Na at 0.85, NLR at 0.73, and ALBI at 0.72, with all results being significant. Figure 2 shows the

sensitivity and specificity for each prognostic score: MELD-Na with a cut-off of 25.50 had a sensitivity of 89.6% and specificity of 68.9%, CTP with a cut-off of 9.50 had sensitivity of 65.5% and specificity of 88.9%, ALBI at -0.87 had sensitivity of 72.4% and specificity of 66.7%, while NLR with a cut-off of 9.17 had sensitivity of 79.3% and specificity of 60%.

Table 2. Mean difference of prognostic scores (MELD-Na, CTP, ALBI, and NLR) in predicting mortality risk in patients with liver cirrhosis and spontaneous bacterial peritonitis

Predictors	Non-Survive	Survive	MD	95% CI	p
NLR	14.04 ± 16.12	6.53 ± 4.84	7.51	1.46-13.56	0.0150
MELD-Na	28.40 ± 7.48	18.31 ± 5.62	10.09	6.91-13.27	0.0000
CTP	11.60 ± 1.74	9.03 ± 1.38	2.57	1.82-3.32	0.0000
ALBI	-0.73 ± 0.51	-1.20 ± 0.60	0.47	0.22-0.73	0.0000

Note, data were presented in mean ± SD; MD, mean difference; NLR, Neutrophil-to-Lymphocyte Ratio; MELD-Na, Model for End-Stage Liver Disease with Sodium; CTP, Child-Turcotte-Pugh; ALBI, Albumin-Bilirubin.

DISCUSSION

In this study, we successfully demonstrated that the CTP and MELD-Na models were the best prognostic indicators for cirrhotic patients with SBP. This was followed by the NLR and ALBI models, in that order (AUC values: 0.87, 0.85, 0.73, and 0.72). The CTP score, originally referred to as the CTP score, was initially designed to predict postoperative outcomes for portal hypertension.[12] It has been used for more than two decades to determine prognosis in cirrhosis patients. Higher CTP scores significantly predicted mortality and prognosis in hospitalized cirrhosis patients, as well as indicating a higher level of cirrhosis-related complications.[13]

Although there are subjective parameters for the CTP score, it remains the most commonly used scoring system for determining prognosis in cirrhosis patients.[14] A study by Piotrowski et al. demonstrated that the CTP score has the ability to distinguish between patients with higher and lower in-hospital mortality risks. It has also been applied to patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) and is increasingly important for determining the most appropriate therapeutic options for these patients. A higher CTP score in patients with SBP was also positively correlated with higher D-Dimer levels, which is an enzymatic breakdown of cross-linked fibrin, compared to lower CTP scores and non-cirrhotic patients.[15] This is significant because cirrhosis patients are often associated with hemostatic issues and blood clot lysis problems, which have previously been used for diagnosing diseases such as deep vein thrombosis and pulmonary embolism.[16]

Table 3. Odds ratios (OR) for prognostic scores (MELD-Na, CTP, ALBI, and NLR) in predicting mortality risk in patients with liver cirrhosis and spontaneous bacterial peritonitis.

Predictors	Non-Survive	Survive	OR	95% CI	p
NLR > 11.38	20 (44.4%)	4 (13.8%)	5.00	1.49-16.73	0.0090
MELD-Na >25.5	31 (68.9%)	3 (10.3%)	19.19	4.96-74.13	0.0000
CTP > 14.05	2 (4.44%)	0 (0%)	3.39	0.15-73.2	0.4360
ALBI >-0.615	20 (44.4%)	5 (17.2%)	3.84	1.24-11.87	0.0190

Note, data were presented in n (%); OR, odd ratio; NLR, Neutrophil-to-Lymphocyte Ratio; MELD-Na, Model for End-Stage Liver Disease with Sodium; CTP, Child-Turcotte-Pugh; ALBI, Albumin-Bilirubin.

MELD score was originally used to determine prognosis in cirrhosis patients treated with TIPS and later demonstrated excellent capability in predicting 90-day mortality.[17] The inclusion of modified hyponatremia was correlated with increased mortality risk, showing that MELD-Na was more predictive of death in patients with more severe

conditions. Hyponatremia has been identified as an independent risk factor for SBP in cirrhosis patients and a predictor of the development of hepatorenal syndrome.[18] A study by Bal et al. showed that MELD-Na helped predict 50-day in-hospital mortality in patients with decompensated cirrhosis and SBP, with a cut-off value of 27.53 ± 7.57. MELD-Na incorporates parameters such as bilirubin, creatinine, and INR, making it more objective and user-friendly.[19] Systematic reviews have previously reported that the MELD-Na and CTP prognostic scores have equivalent predictive value for cirrhosis prognosis.[8,20] On the other hand, NLR, as an inflammatory marker, does not accurately reflect the degree of liver function damage or the impact of various complications involved in cirrhosis.[21]

The combination of CTP and MELD-Na helps demonstrate a more robust prognostic model for short-term mortality, enabling physicians to gauge the aggressiveness of the management provided. Limitations of this study include the small sample size and the fact that it was conducted in a single center, suggesting the need for larger-scale studies involving multiple centers to validate these prognostic models. It is also important to apply these prognostic models to a broader range of cirrhosis patients, including those with different disease etiologies, and to assess their value not only in the short term but also in the medium and long term. The limitations of this study did not address the relationship between mortality and laboratory components, prior disease activity, or the duration and length of baseline treatment received before the first occurrence of SBP. The study was also conducted at a tertiary hospital with a relatively small sample size. Therefore, a cohort study with a larger sample size, multi-center participation, and classification of cirrhosis based on different etiologies should be conducted. Additionally, the inclusion of different microorganisms involved in the study should be considered to help determine subsequent therapy choices.

CONCLUSION

In conclusion, patients with hepatic cirrhosis, ascites, and SBP complications can benefit from prognostic scores such as MELD-Na and CTP to provide accurate identification of their prognosis. These scores can be used to guide treatment aggressiveness and assess disease progression during hospitalization. By utilizing prognostic scores, clinicians can improve the quality of life for patients and reduce mortality and morbidity rates in those with cirrhosis and ascites.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocols of our study have been approved by local ethical committee.

CONFLICTS OF INTEREST

We have no conflict of interest

FUNDING SOURCES

We have no source of funding

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AUTHOR CONTRIBUTION

Conceptualization: CYR; Data Curation: CYR; Formal Analysis: CYR; Investigation: CYR; Project Administration: CYR; Resources: CYR; Methodology: CYR; Software: CYR; Visualization: CYR; Supervision: SS; Validation: SS; Writing – Original Draft Preparation: CYR; Writing – Review & Editing: SS. All authors have critically reviewed

and approved the final draft and are responsible for the content and similarity index of the manuscript.

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