ORIGINAL ARTICLE

Predictors of Mortality in Patients with Spontaneous Bacterial Peritonitis

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Abstract

Introduction: Despite treatment with antibiotic therapy, spontaneous bacterial peritonitis (SBP) accounts for approximately 20–40% mortality in hospitalized patients. The data is scarce regarding mortality predictors in SBP. Recently, multiple factors have been studied for effectiveness in prognosis prediction in SBP. Therefore, in this study, our main objective was to evaluate the mortality predictors in SBP.

Materials and methods: This prospective observational study was conducted at the Department of Hepatogastroenterology, from January 2022 to June 2023. All the patients aged between 18 and 65 years having decompensated chronic liver disease and diagnosed with SBP were enrolled in the study. The excluded population comprised of those who were on hemodialysis, those having history of any solid organ malignancy or transplantation or patients suffering from infections such as those caused by human immunodeficiency virus (HIV) or infections other than SBP. These patients were followed during the hospital stay and after the discharge monthly for 3 months and then at 6 months to assess mortality.

Results: A total of 142 cirrhotic patients having SBP were enrolled in the study. Among them, most of them were males [98 (69%)]. Viral hepatitis (65.4%) was the most common cause of cirrhosis in studied population. On univariate analysis, serum total leukocyte count (TLC), international normalized ratio (INR), ascitic TLC, ascitic neutrophils, ascitic lactate, ascitic LDH, CTP score, MELD-Na were significantly higher while serum albumin was significantly lower in the patients who died as compared to those who survived. However, on multivariate cox regression analysis, high serum TLC ($p = 0.013$), ascitic fluid lactate ($p < 0.001$) along with high CTP ($p = 0.041$) and MELD-Na score ($p = 0.037$) at presentation were the factors that were identified as an independent poor prognostic factors in SBP population.

Conclusion: Cirrhotic patients with SBP are at increased risk of mortality. In our study we observed that high prognostic scores such as CTP and MELD-Na at presentation along with increased white blood cell counts and high ascitic fluid lactate levels at presentation are the potential and reliable predictors of mortality in SBP patients.

Keywords: Ascitic fluid lactate, Cirrhosis, Mortality, Predictor, Spontaneous bacterial peritonitis.

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Introduction

Cirrhotic patients being immunocompromised are prone to acquiring infections very easily. One of the most common infections in patients with decompensated chronic liver disease is spontaneous bacterial peritonitis (SBP) which is described by the presence of ≥250/uL neutrophil count in ascitic fluid.[1,2] In a study done by Piano et al., there was a 27% prevalence of SBP in the cirrhotic population.[3] The first episode associated of SBP is associated with a high mortality rate of 30%.[4]

Regarding the prompt diagnosis of SBP and predicting its recurrence, various different biochemical parameters have been analyzed in different studies. Ascitic calprotectin has been found to be an important marker of SBP diagnosis with a high negative predictive value (NPV).[5] Similarly, in another study, serum and ascitic homocysteine levels were utilized in making a diagnosis of SBP.[6] However, one study showed a significant association of ascitic calprotectin and ascitic fluid interferon-γ-induced protein (IP-10) with an increased rate of SBP recurrence.[7]

Recently, variable results have been obtained by multiple studies focusing on the evaluation of different markers of prognosis in SBP. Different serum and ascitic fluid parameters including various inflammatory markers along with Child Turcotte Pugh (CTP) score and model for end-stage liver disease (MELD) score have shown promise in establishing the prognosis in the SBP population.[8–11]

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Early identification of the factors predicting mortality in SBP patients is the best strategy for improving the overall survival in decompensated chronic liver disease (DCLD). Currently, the data is scarce in this regard and little research work has been done in this part of the world regarding the prognostic factors in the SBP population. Therefore, the main objective of our study was to identify the independent predictors of mortality in the SBP population.

Materials and Methods

This prospective observational study was carried out at the Department of Hepatogastroenterology, from January 2022 to June 2023 after approval from the institutional review board.

All the patients aged between 18 and 65 years having decompensated chronic liver disease and diagnosed with SBP were included in the study. The excluded population comprised those who were on hemodialysis, those having a history of solid organ malignancy or transplantation, or those patients suffering from infections such as those caused by human immunodeficiency virus (HIV) or infections other than SBP.

Patients were recruited by the non-probability consecutive sampling technique. Based on the estimation from previous studies, a total number of patients with SBP included in the study was 142.[12] During the initial 12 months' study period, 142 patients were enrolled for the study, i.e., from January 2022 to December 2022 and then these patients were observed for the next 6 months for the outcome.

Data Collection Procedure

After taking the informed consent, all the patients diagnosed with SBP admitted to a hepatobiliary unit of SIUT were enrolled in this study. At the time of admission, baseline characteristics including the demographics of the patients such as age and gender, cause of chronic liver disease, laboratory tests including the complete blood count (CBC), liver function test (LFT), urea, creatinine, electrolytes (UCE), serum albumin, international normalized ratio (INR), and ascitic fluid parameters [ascitic total leukocyte count (TLC)], ascitic neutrophils, ascitic lactate, ascitic glucose, ascitic LDH were obtained.

All the SBP patients were given IV antibiotics and IV albumin during hospitalization. These patients were observed during the period of hospitalization and were followed up after the discharge at the Outpatient Department or by telephonic communication with the patient or the relatives for 6 months. The outcome was assessed at 6 months for mortality in the SBP population.

Data Analysis Procedure

Statistical Package of Social Services (SPSS) version 23 was used for data entry and analysis. Quantitative variables were stated as mean ± standard deviation while frequencies and percentages were used to describe the categorical variables. The outcome was measured as 6 months' mortality. The stratification of continuous variables was performed using the student-*t* test while that for categorical variables was done using the Chi-square test. The variables that were statistically significant on univariate analysis then subsequently underwent multivariate logistic regression analysis to establish the independent mortality predictors in SBP. A *p*-value of ≤ 0.05 was considered statistically significant.

The optimal cut-off with an excellent sensitivity, specificity, and diagnostic accuracy for each statistically significant variable on multivariate analysis was obtained using the area under the receiver operating characteristic (AUROC) curves.

Results

A total number of cirrhotic patients having SBP was 142. Out of them, more than two-thirds of patients were males [98 (69%)] and more than two-thirds of patients [101 (71.1%)] had CTP class C at presentation. A most common cause of cirrhosis was viral hepatitis, i.e., hepatitis C followed by hepatitis B and then autoimmune hepatitis (Table 1). Out of 142 patients, 59 patients (41.5 %) did not survive the 6 months period while the majority (39/59) had mortality within the first 30 days.

Table 1: Baseline characteristics of the population included in the study (*n* = 142)

Study population	*N (%)*
Gender	
Male	98 (69)
Female	44 (31)
Child Turcotte Pugh score	
B	41 (28.9)
C	101 (71.1)
Cause of cirrhosis	
Hepatitis B (HBV)	19 (13.4)
Hepatitis C (HCV)	51 (35.9)
HBV and HCV coinfection	7 (4.9)
Hepatitis B and Hepatitis D (HDV) coinfection	14 (9.8)
HBV/HCV/HDV	2 (1.6)
Autoimmune hepatitis	18 (12.7)
Cryptogenic cirrhosis	14 (9.7)
Alcoholic liver disease	5 (3.3)
NASH	6 (4.1)
Wilson disease	6 (4.1)
Overall mortality	59 (41.5)
30 days	39 (27.6)
60 days	47 (33.3)
90 days	54 (38.2)
Six months	59 (41.5)
Age (years ± S.D)	45.1 ± 15.2
Hemoglobin (gm/dL)	9.6 ± 1.9
Serum total leukocyte count ($\times 10^9$/L)	8.9 ± 5
Platelet count ($\times 10^9$/L)	118 ± 81
Serum creatinine (mg/dL)	1.3 ± 1.0
Total bilirubin (mg/dL)	6.5 ± 7.5
Aspartate transaminase (AST) (IU/L)	120 ± 102
Alanine transaminase (ALT) (IU/L)	63 ± 63.4
Serum albumin (gm/dL)	2.3 ± 0.5
International normalized ratio (INR)	1.6 ± 0.6
MELD-Na	23.1 ± 7.5
Ascitic TLC ($\times 10^9$/L)	1414 ± 406
Ascitic lactate (mg/dL)	30.4 ± 20.1
Ascitic neutrophils ($\times 10^9$/L)	930 ± 320
Ascitic LDH (U/L)	105 ± 40

Table 2 shows a comparison of baseline characteristics of patients between the survivors and non-survivors groups. The mean age of patients in both groups was the same. The majority of the patients in both groups were males. On univariate analysis, serum TLC, INR, ascitic TLC, ascitic neutrophils, ascitic lactate, ascitic LDH, CTP score, MELD-Na were significantly higher while serum albumin was significantly lower in the non-survivor group as compared to the survivor group. However, on multivariate Cox regression analysis, high serum TLC ($p = 0.013$), ascitic fluid lactate ($p < 0.001$) along with the high CTP ($p = 0.041$) and MELD-Na score ($p = 0.037$) at presentation are the factors that were independently

Table 2: Comparison of baseline variables in terms of mortality in SBP patients ($n = 142$)

	Mortality		
Variable	*Yes (n = 59) N (%)*	*No (n = 83) N (%)*	*p-value*
Gender			
Males	36 (61.1)	62 (75)	0.929
Females	23 (38.9)	21 (25)	
Age (Years)	44.8 ± 16.1	45.5 ± 14.4	0.797
Hemoglobin (gm/dL)	9.6 ± 2.1	9.7 ± 1.8	0.243
Serum total leukocyte count ($\times 10^9$/L)	12.9 ± 7.2	7.8 ± 3.9	**0.015**
Platelet count ($\times 10^9$/L)	114 ± 76	123 ± 87	0.523
Serum creatinine (mg/dL)	1.4 ± 1.2	1.2 ± 0.8	0.215
Serum Na (mEq/L)	131 ± 5.9	131 ± 6.7	0.938
Total bilirubin (mg/dL)	7.1 ± 7.9	5.9 ± 7.1	0.188
Aspartate transaminase (AST) (U/L)	128 ± 17	109 ± 82	0.306
Alanine transaminase (ALT) (U/L)	53 ± 36	62 ± 82	0.151
Serum albumin (gm/dL)	2.2 ± 0.5	2.4 ± 0.54	**0.05**
International normalized ratio (INR)	1.7 ± 0.6	1.5 ± 0.49	**0.015**
Ascitic TLC (cells/mm^3)	2109 ± 5486	510 ± 163	**0.031**
Ascitic neutrophils (cells/mm^3)	1984 ± 5862	110 ± 62	**0.037**
Ascitic lactate (mg/dL)	38.5 ± 27.5	21.5 ± 12.3	**<0.001**
Ascitic LDH (U/L)	110 ± 108.5	78.3 ± 91.2	**0.013**
CTP score	13 ± 1	8 ± 2	**0.053**
MELD-Na score	26 ± 8	16 ± 7	**0.043**

Bold indicates statistically significant values of the variables on univariate analysis and multivariate analysis

Table 3: Multivariate cox regression analysis showing independent predictors of mortality in SBP

			95% CI for EXP (B)	
Variables	*p-value*	*Odds ratio*	*Lower*	*Upper*
TLC (>10 × 10^9/L)	**0.013**	1.126	1.025	1.238
INR	0.754	1.204	0.376	3.854
Serum albumin (gm/dL)	0.547	0.737	0.273	1.990
Ascitic neutrophils (cells/mm^3)	0.896	1.000	1.000	1.000
Ascitic lactate (mg/dL)	**≤0.001**	1.062	1.004	1.123
Ascitic LDH (U/L)	0.518	0.998	0.993	1.003
MELD-Na	**0.037**	1.153	1.067	1.245
CTP score	**0.041**	0.650	0.430	0.982

CTP, Child Turcotte Pugh; MELD-Na, model for end-stage liver disease-sodium; Bold indicates statistically significant values of the variables on univariate analysis and multivariate analysis

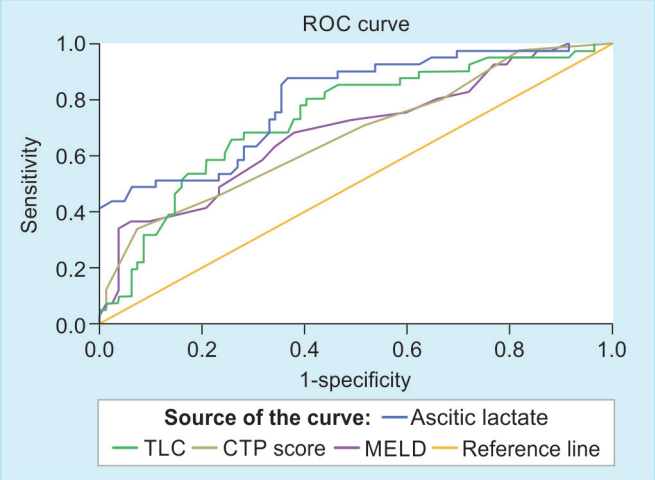

Fig. 1: Area under the receiver operating curve for ascitic fluid lactate (0.894) ($p < 0.001$), serum TLC (0.71) ($p < 0.001$), CTP score (0.64) ($p < 0.001$) and MELD-Na score (0.692) ($p < 0.001$) in predicting mortality in SBP

associated with an increased mortality in the patients having SBP (Table 3).

The AUROC was generated to evaluate the optimal cut-off of the variables found on multivariate analysis (Fig. 1). Serum TLC >12, ascetic fluid lactate >22.5 mg/dL, CTP score > 9 and MELD-Na >18 showed good sensitivity, specificity in predicting 6 months mortality in SBP population.

Discussion

Spontaneous bacterial peritonitis accounts for high morbidity and mortality rates in the cirrhotic population. It has high 1 month and 1 year mortality of around 30.3 and 63% respectively.[2] Many factors contribute to high mortality rates in patients with SBP including acute kidney injury (AKI), raised inflammatory markers, and severity of liver dysfunction.[10,13]

In our study, we found that high TLC, INR, and presence of increased neutrophil count in ascitic fluid along with high ascitic lactate, ascitic LDH, CTP score, and MELD-Na along with low serum albumin were associated with decreased survival in patients with SBP. However, on multivariate analysis, the raised serum TLC, ascitic lactate, CTP score, and MELD-Na were significantly associated with high risk of mortality in this population. Child purcotte pugh score and MELD-Na are the known prognostic scores that are used in cirrhotic patients to determine the severity of liver disease.

In one study, a model comprising MELD and age showed good discriminatory ability to predict prognosis and survival in SBP.[4]

The data regarding the role of high lactate levels in ascetic fluid as a prognostic marker in SBP patients is still scarce. Lactate is generated by the process of anerobic glycolysis during periods of stress, hypoxia, and sepsis.[14] The levels of lactate in the serum and its clearance have been utilized in the studies to determine the outcome in cirrhotic patients and those patients who are critically ill and admitted to ICU settings.[15,16] However, ascitic fluid lactate was first utilized by Mani and his colleagues showing a good sensitivity and specificity in predicting mortality in the SBP population.[12] In one of our previous studies, we also found that high levels of lactate in ascitic fluid were an excellent prognosticator of mortality in SBP patients with an overall diagnostic accuracy of 85%.[17] In concordance with previous studies, comparable results were also noted in the current study as along with other factors, ascitic fluid lactate showed an independent association with mortality in SBP patients (p-0.037).

In one study, done in the Spanish population by Poca and his colleagues, a model was developed to predict in-hospital deaths in patients with SBP that included serum urea, TLC, CTP, and mean arterial pressure.[8] However, in our study, we found that high serum

TLC and high CTP scores were independent predictors of mortality. In the former, patients suffering from HIV or HCC were included. However, we excluded these patients as both of these factors are confounders and can affect the outcome. These dissimilarities in the results can be best explained by the fact that the presence of either HIV or HCC in a cirrhotic patient can make them more susceptible to multi-organ failure resulting in raised serum urea levels, as explained by their model.

In the previous study done by Mani et al.,[12] alcoholic liver disease was the most common cause identified as the cause of chronic liver disease. However, in our study, viral hepatitis was found to be the predominant etiology of hepatitis C in more than one-third (51/142; 35.9%) of the patients reflecting the burden of hepatitis C in our region where Pakistan has the second highest number of hepatitis C cases globally.[18]

In our study, 1-month mortality was 27.6% and around 41% of the patients had mortality during 6-months' period after the first episode of SBP whereas Mani et al. observed that 6-months' mortality was found to be around 60% (38 patients out of 63) in patients with SBP which was much higher than in our study population.[12] One of the potential reasons for the decreased rates of mortality in our population can be explained by the difference in the population studied as the previously mentioned study was carried out in the European population while our population belonged to Asian ethnic origin.

In an Indian study, MELD-Na along with AKI and septic shock was found as independent predictors of 50 days in-hospital mortality in patients with SBP.[11] In one study from Egypt, MELD score, CTP score along with various clinical and biochemical parameters were associated with mortality in SBP.[9] Model for end-stage liver disease is found to be a common predictor in most of the studies predicting mortality in SBP patients.

In one study conducted in Turkey by Iliaz et al.,[10] 30 days mortality in SBP patients was found to be 26.1%. In the same study, authors determined the optimal cut-off value of MELD, i.e., 20.5 whereas in our study, we found similar 30-days mortality of 27.6% and MELD-Na of 18 as an optimal cut-off in determining mortality in SBP patients.

There were certain limitations that can be attributed to our study. At first, it was a single-centered study, with a small sample size and various etiologies of cirrhosis were included. For the further validation of our results, multi-centered studies with larger sample sizes are required.

Conclusion

Spontaneous bacterial peritonitis in cirrhotic patients is associated with a worse prognosis. In our study, we observed that prognostic scores such as CTP and MELD scores along with high serum TLC and Ascitic fluid lactate levels at presentation were associated with worse outcomes. Therefore, they can serve as the potential and reliable predictors of decreased survival in SBP patients. Hence, patients with SBP should be managed promptly with antibiotics with early listing and preference for early liver transplantation.

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