Original Article

Predictors of Spontaneous Bacterial Peritonitis in Patients with Cirrhotic Ascites

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Abstract

Background and Aims: Spontaneous bacterial peritonitis (SBP) is a serious complication of liver cirrhosis and a prognostic model to predict it is needed. This study was designed to test the ability of different laboratory tests and the new scoring system by Wehmeyer and colleagues (consisting of age, C-reactive protein (CRP) and platelet count) to predict it. ***Methods:*** Three-hundred patients admitted to the National Liver Institute, University of Menoufia, Egypt (2015–2016) with liver cirrhosis and ascites were included in our study. SBP was diagnosed if ascetic neutrophil count was ≥250/μL with no sign of secondary peritonitis. ***Results:*** The patient population had age range of 29–81 years old, was 60% men and showed a majority (91.7%) with primary cause of liver disease being hepatitis C. By univariate analysis, associations with age, total bilirubin, aspartate aminotransferase level, creatinine level, international normalized ratio, model for end-stage liver disease score, total leucocytic count, platelet count and CRP level were significant. By multivariate analysis, independent predictors were age, platelet count and CRP level (p = 0.004, 0.013 and <0.001, respectively). CRP at a cut-off point ≥13.5 mg/L could predict SBP (sensitivity of 86.4% and specificity of 66.0%). Wehmeyer's SBP scoring system was predictive (p < 0.001); only 4% of patients with 0 score developed SBP (CRP cut-off of 30 mg/L), while 92.8% with score of 3 or 4 developed SBP. By using our modified Wehmeyer score with CRP cut-off value of 13.5 mg/L, no patient with 0 score developed SBP. ***Conclusions:*** Age, CRP level and platelet count are independent predictors for SBP and a scoring system including them could easily predict the condition. SBP diagnosis could be excluded in patients with 0 score, using CRP cut-off value of 13.5 mg/L.

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Introduction

Liver disease burden is increasing all over the world, and in Egypt it is manifesting more frequently due to the high prevalence of hepatitis C virus (HCV).[1] Patients with advanced liver disease are at high risk of developing severe complications, one of which is spontaneous bacterial peritonitis (SBP). Its incidence was reported to reach 25%[2,3] among the cirrhotic patients with ascites, with mortality rates reported at 20–40%.[4,5] As such, there is a real need to find a noninvasive prognostic scoring system to predict patients more liable to develop SBP, as early treatment could reduce the mortality rate.[2] Multiple laboratory tests have been introduced as predictive for SBP, including C-reactive protein (CRP) level,[6,7] platelet count,[6–8] impaired prothrombin time,[9] serum creatinine level,[9] bedside liver disease scoring systems like Child-Pugh[8] and the model of end-stage liver disease (MELD) scores,[10] but only contradictory data are available. A new simple SBP prognostic scoring system consisting of age, platelet count and CRP level was recently developed by Wehmeyer *et al.*[7]

Our aim was to study the ability of different clinical and laboratory variables that could predict the development of SBP in Egyptian cirrhotic patients with ascites, and also to test the scoring system consisting of age, CRP level and platelet count and its cut-off values.

Methods

Adult patients (>18 years old) with liver cirrhosis and ascites admitted for various reasons to the National Liver Institute Hospital, University of Menoufia, from March 2015 to December 2016 were included in our study. Clinical examination findings and laboratory data were collected on admission. We excluded patients with malignancy, hemorrhagic ascites, evidence of secondary peritonitis or those receiving antibiotic treatment at the time of paracentesis, to exclude those patients with other systemic infections related to respiratory or urinary tract infection. Our study was approved by the ethical committee of the National Liver Institute, University of Menoufia.

Diagnostic paracentesis was carried out in all the patients and the samples were evaluated for polymorphonuclear cell (PMNs) count, total protein level, albumin level, Gram stain, bacteriological culture, and bedside pathologic assessment to exclude the presence of atypical cells. SBP was defined, according to the EASL Guidelines 2010,[11] as ascetic neutrophil count ≥250/μL with or without a positive culture of the ascetic fluid, in the absence of any finding suggestive of secondary peritonitis. The scoring system used by Wehmeyer and colleagues was tested in our patients, using a scale of 0 to 4, where we gave one point for age >60 years, one point if platelet count was <100,000/mL, one point if CRP was

Keywords: CRP; Predictors; SBP; Cirrhosis; Scoring.
Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; HCV, hepatitis C virus; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis.
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Table 1. Patients' characteristics

	SBP					
	Negative			Positive		
Variable	Mean ± SD	Range	Median	Mean ± SD	Range	Median
Age, y	54.5 ± 8.6	29–81	56	58.9 ± 8.3	33–70	60
Bilirubin, mg/dL	2.8 ± 2.7	0.5–26	2	5.1 ± 4.7	0.5–26	2
Albumin, g/dL	2.7 ± 0.5	1.2–4.1	3	2.6 ± 0.5	1.3–3.5	3
INR	1.8 ± 0.5	1.1–6.2	1.7	2.2 ± 0.8	1.3–5.9	2
MELD	18.7 ± 6.7	7–46	17	25.1 ± 7	12–49	23
Creatinine, mg/dL	1.5 ± 0.9	0.5–6.1	1	2.1 ± 1.7	0.5–8.9	2
TLC, mL	8,167.7 ± 3,858	580–28,400	7,500	10,005.1 ± 5,350.7	3,700–35,000	8900
Platelet, mL	113,257.3 ± 46,652.4	20,000–303,000	110,000	73,678 ± 31,110.7	21,000–174,000	67,000
CRP, mg/L	12.6 ± 6.6	5–44	11	29.1 ± 13.6	8–64	27
ALT, U/L	53.8 ± 153.6	10–2,004	33	85.4 ± 105.9	13–611	46
AST, U/L	62.5 ± 104.7	16–1,390	42	153.7 ± 242.7	24–1,374	79

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; SD, standard deviation; TLC, total leukocytic count.

between 30 and 60 mg/L, and two points if CRP was above 60 mg/L.[7]

Statistics

Patients were categorized into two groups according to the presence or absence of SBP. Data was statistically analyzed using SPSS version 20 for Windows, and p-value <0.05 was considered statistically significant for all the analyses. Data are shown as mean, range or value. Independent samples t-test was used to examine the difference between the two groups for continuously-distributed variables, while chi-square test was used for categorical variables. Significant factors were tested in a univariate binary logistic regression analysis, and then only significant variables were entered in a stepwise multivariate logistic regression analysis to identify the independent predictors for the occurrence of SBP.

Results

Our study included 300 patients with liver cirrhosis and ascites, of ages ranging 29–81 years old, and predominantly male (180 males and 120 females). The primary cause of liver disease was chronic hepatitis C (275 patients; 91.7%), hepatitis B (20 patients; 6.6%) and cryptogenic cause (5 patients; 1.7%). Diagnostic paracentesis revealed that 59 patients (19.6%) were diagnosed with SBP. Patients' characteristics are shown in Table 1.

Age had a highly statistically significant difference between patients with or without SBP (p = 0.001), while sex or the presence or absence of diabetes mellitus had no statistical

Table 2. Different variables and their statistical significant difference between patients with and without SBP

Variable	Independent sample t-test	p-value*	Variable	Chi-square	p-value*
Age, Y	3.51	0.001	Sex	0.17	0.67
Bilirubin, mg/dl	3.58	0.001	DM	2.05	0.15
INR	4.15	<0.001	Child-Pugh	0.61	0.73
Albumin, g/dl	−1.29	0.19	SBP scoring system	79.46	<0.001
Creatinine mg/dl	2.82	0.006			
ALT U/L	1.49	0.13			
AST U/L	2.85	0.006			
TLC, ml	3.02	0.003			
Platelet, ml	−7.84	<0.001			
CRP, mg/L	9.11	<0.001			
MELD	6.59	<0.001			

*p-value significant if <0.05.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DM, diabetes mellitus; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; TLC, total leukocytic count.

Table 3. Logistic regression analysis displaying independent predictors of the occurrence of SBP

Variable	B	S.E.	Wald	Sig.	Exp(B)
Age, Y	0.082	0.029	8.241	0.004	1.086
Bilirubin	0.010	0.072	0.020	0.89	1.010
INR	0.165	0.585	0.080	0.78	1.180
MELD	0.100	0.090	1.233	0.27	1.105
Creatinine	0.045	0.325	0.019	0.89	1.046
TLC, ml	0.000	0.000	0.944	0.33	1.000
Platelet, ml	0.000	0.000	6.110	0.013	1.000
CRP, mg/L	0.205	0.033	37.989	<0.001	1.228
AST U/L	0.002	0.001	1.936	0.16	1.002

Abbreviations: AST, aspartate transaminase; CRP, C-reactive protein; INR, international normalized ratio; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; TLC, total leukocytic count.

significant difference (p = 0.678 and 0.152, respectively). Table 2 shows the different variables with statistical significant difference between patients with and without SBP. Variables like serum total bilirubin, aspartate aminotransferase (AST), creatinine, international normalized ratio, total leukocytic count, platelet count and CRP showed a statistically significant difference between the two groups (p = 0.001, 0.006, 0.006, <0.001, 0.003, <0.001 and <0.001). On the other hand, variables like serum albumin and alanine aminotransferase had no statistical significant difference (p = 0.198 and 0.136). MELD score showed a highly statistically significant difference (p < 0.001) with positive correlation between the patients' MELD scores and the development of SBP, while Child-Pugh score failed to show such relation (p = 0.737).

By univariate analysis, nine variables had a p value of <0.05 as predictive factors of an episode of SBP: age, total bilirubin, AST, creatinine, international normalized ratio, MELD score, total leukocytic count, platelet count and CRP level. These variables were entered in a stepwise multivariate analysis, which showed that only age, platelet count and CRP (p = 0.004, 0.013 and <0.001, respectively) were independently correlated with the risk of developing SBP. Table 3 shows the logistic regression analysis results of the independent predictors of SBP. Our results showed that CRP and platelet count could significantly differentiate between patient groups at a cut-off point of ≥13.5 mg/L and ≤82,500/mL, respectively (sensitivity of 86.4% and 71.2%, and specificity of 66.0% and 71.4%, respectively).

Tables 4 and 5 show the diagnostic accuracy of CRP and platelet count in predicting SBP and the best cut-off values, as well as the receiver operating characteristic curves. When we tested our scoring system with a CRP cut-off value of 13.5 mg/L, we found that no patient with 0 score developed SBP. Table 6 shows our modified Wehmeyer's SBP scoring system and the incidence of SBP, where we gave one point if CRP value was between 13.5 and 30 mg/L, two points if between 30 and 60 mg/L, and three points if more than 60 mg/L.

Table 5. Best cut-off points of CRP and platelets to predict occurrence of SBP in the studied patients

	Coordinates of the Curve		
	Positive if greater than or equal to	Sensitivity	1-specificity
CRP, mg/L	13.5000	0.864	0.340
Platelet, ml	82500.0000	0.712	0.286

Abbreviations: CRP, C-reactive protein; SBP, spontaneous bacterial peritonitis.

Discussion

Cirrhosis increases the risk of developing bacterial infections and those patients are more vulnerable to death from sepsis than the normal population.[12,13] Mortality may reach 70% due to the development of shock or multiorgan failure.[14] Finding the prognostic factors that could evaluate the clinical condition of the hepatic patients and predict the occurrence of severe complications like SBP or even mortality is important for patient allocation on to the liver transplantation wait-list. The most widely used prognostic scoring systems for the general condition of such patients are the Child-Pugh and MELD, but still there is no agreement on a specific prognostic scoring system for the development of each severe complication. SBP is an example of such, a low ascetic fluid protein was found to be associated with high risk of its development but the search continues for a noninvasive scoring system. The new SBP prognostic scoring system developed by Wehmeyer *et al.,*[7] which depends on three parameters found to be related to SBP occurrence (age, platelet count and CPR level), is a simple and easy-to-use scoring system as it depends on routinely assessed parameters for admitted patients.

In our study which included Egyptian patients suffering advanced liver disease, mostly secondary to hepatitis C infection, the incidence of SBP was 19.6%, which shows how common it is to face this problem in this group of patients. We tested different variables, including the variables used in Wehmeyer's SBP scoring system, to see their relation to SBP prediction. The results showed that, although nine parameters

Table 4. Diagnostic accuracy of CRP and platelets to predict occurrence of SBP in the studied patients

				Asymptotic 95% confidence interval	
	Area under the curve	Std. error*	Asymptotic sig.†	Lower boundary	Upper boundary
CRP mg/L	0.875	0.029	<0.001	0.819	0.931
Platelet count, ml	0.767	0.032	<0.001	0.703	0.831

*Under the nonparametric assumption;
†Null hypothesis: true area = 0.5.
Abbreviations: CRP, C-reactive protein; SBP, spontaneous bacterial peritonitis.

Table 6. Our modified Wehmeyer's SBP scoring system and the incidence of SBP

	Modified Wehmeyer *et al.*[7] SBP scoring system, *n* (%)						
SBP	0	1	2	3	4	5	Total
Negative	58 (100)	120 (94.5)	55 (72.4)	6 (25)	2 (15.4)	0 (0)	241 (80.3)
Positive	0 (0)	7 (5.5)	21 (27.6)	18 (75)	11 (84.6)	2 (100)	59 (19.7)
Total	58	127	76	24	13	2	300
Chi-square test <0.001							

Abbreviation: SBP, spontaneous bacterial peritonitis.

had a statistical difference for SBP occurrence (age, total bilirubin, AST, creatinine, international normalized ratio, total leukocytic count, platelet count, CRP level and MELD score), only age, platelet count and CRP level could independently predict SBP.

Regarding age, there is an association between increasing age and the susceptibility to infections due to impaired immunity with aging.[15,16] Also, aging is an adverse prognostic factor in most liver diseases, with increasing morbidity and mortality compared to young patients.[17,18]

Low platelet count is common in chronic liver disease, due to splenic platelet sequestration, increase in its breakdown, or decrease in its production. It has been used as an indirect indicator of portal hypertension and liver disease severity.[19–22] Also, as infections and especially sepsis produce thrombocytopenia,[23] it was used as a predictor of SBP with low ascetic fluid protein.[8]

Measurement of CRP could be considered as a limitation to this study. Although CRP is a well-known parameter for detecting inflammation or infection in the general population,[24,25] it was considered by Le Moine *et al.*[26] as a weak predictor for infection in advanced liver disease because its basal level is commonly higher than normal in cirrhotics (owing to the underlying liver disease) and as it is produced mainly by hepatocytes (it does not increase so much with infection in patients with advanced cirrhosis). Our explanation is that, their study was conducted on 57 patients, 19 of which had infection on admission but only 7 of which had SBP and the other 12 had different causes of bacteremia; besides, they reported that CRP was correlated with interluekin-6 and they concluded that it was a marker for diagnosis of SBP. Also, Park *et al.*[27] reported that end-stage liver cirrhotic patients with bacteremia showed elevated CRP that was greater than in those without bacteremia, but these values were less than when there was bacteremia without cirrhosis. On the other hand, CRP was found to indicate a serious infection in cirrhotics if it was significantly high.[28] Also, Guler *et al.*[29] found significantly high CRP values in the SBP and the bacteriascites groups compared to the noninfected patient group (68.4, 68.3 and 6.5 mg/L, respectively). Wehmeyer *et al.*[7] found the same results and included such in their three-parameter scoring system by giving one point if its level is more than 30 mg/L and two points if it is more than 60 mg/L.

In our validation of the Wehmeyer SBP scoring system, we found higher scores (scores of 3 and 4) to be correlated significantly with the occurrence of SBP ($p < 0.001$). A 0 score was able to rule out SBP correctly in most cases; only 4 patients out of 100 with 0 score developed SBP. According to our modification to the scoring system (one point was given if the CRP value was between 13.5 and 30 mg/L, two points if between 30 and 60 mg/L, and three points if more than 60 mg /L), the results showed that scores of 4 or 5 are good predictors of SBP (only two patients with score of 4, out of 13 patients, did not have SBP, while both patients with score of 5 had SBP). On the other hand, scores of 0 or 1 could be used to exclude SBP diagnosis (only 7 patients with score of 1, out of 127 developed SBP, while no patient with score of 0, consisting of 58 patients, developed it).

Based on these results, we conclude that SBP as a serious complication could be diagnosed by a simple scoring system that depends on age, platelet count and CRP level. Patients with score of 0 are unlikely to have SBP, while we should start treatment once they have a score of 4 or 5. Ascitic sample testing and culture could be saved for patients with scores of 1, 2 or 3. Our results still need further work for validation in larger groups of patients.

Conclusions

Age, CRP level and platelet count are independent predictors for SBP, and a scoring system including them could easily predict the condition. SBP diagnosis could be excluded in patients with 0 score, using CRP cut-off value of 13.5 mg/L.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (KM, TF), acquisition of data (KM, TF, MA), analysis and interpretation of data (KM, MA), drafting of the manuscript (MY, EA, KM), critical revision of the manuscript for important intellectual content (KM, TF, MA, EA, MY), study supervision (MY, KM, MA).

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