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Predictors of Recurrence of Spontaneous Bacterial Peritonitis in Cirrhotic Ascitic Patients

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ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP) is widely common infection in cirrhosis. Deferral in diagnosis and treatment exposes the patients to a high risk of complications and death. Recurrence of SBP occurs in many patients however there is insufficient regional and no local data on factors responsible for its recurrence.

Objectives: The aim of the current work was to know the predictors of recurrence of SBP in cirrhotic ascitic patients and to evaluate the impact of some scores as predictors.

Patients and methods: The study was done in Tropical Medicine and Gastroenterology Department, Sohag University Hospital. All patients with liver cirrhosis, ascites and SBP were subjected to complete clinical, ultrasonographic and laboratory evaluation. The patients were followed up for one year after management of the 1st episode and categorized into 2 groups according to absence or presence of recurrence of SBP.

Results: Hundred patients with SBP were included. Univariate analysis showed that hematemesis, abdominal pain, multiple paracentesis, urinary tract infection, prolonged use of PPI, low serum sodium, high serum bilirubin and high MELD score were significant variables responsible for recurrence. Multivariate analysis showed that multiple paracentesis, urinary tract infection and low serum sodium were the highly risk factors for recurrence.

Conclusions: It could be concluded that multiple paracentesis, urinary tract infection and low serum sodium were the highly independent risk factors for recurrence of SBP.

Keywords: Liver cirrhosis, Ascites, Spontaneous Bacterial Peritonitis

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is one of the most widely recognized and life-threatening complications of liver cirrhosis which is characterized by infection of ascitic fluid without clear simultaneous intra-abdominal wellspring of infection [(1)]. It happens in 10-30% of cirrhotic ascitic patients with 30-50% in-hospital mortality rate. There is 10% likelihood of acquiring SBP in patients with terminal hepatic disease with ascites over a period of one year with chance of SBP recurrence around 70% per year [(2)].

Altered host immunity and translocation of the microorganisms from the gut to the extra intestinal sites are believed to be the reason for SBP [(3)]. Universally published information shows that raised serum bilirubin, higher serum creatinine, presence of hyponatremia and the utilizationof proton pump inhibitors (PPI) are the risk factors related to development of SBP [(4)]. However, there is lackingdata on factors responsible for SBP repeat. Long-term prophylaxis with antibiotics like quinolones (Norfloxacin, 400 mg per day orally) has decreased the rate of recurrence. However, emergence of quinolone resistant organisms has lowered its use [(5)]. Improvement in patients' management, including higher index of suspicion, clarity of diagnostic properties, safer and better antibiotics use, resulted in favorable prognosis and decreased in-hospital mortality [(6, 7)]. Available scores, for example Child-Pugh and model of end-stage liver disease (MELD) scores have been previously show favorable predictive accuracy in patients with advanced liver disease; but they less accurate in the prediction of SBP recurrence [(8)].

Another available score is AIMS65 score which consists of: albumin level <3.0 g/dL, international normalized ratio (INR>1.5), altered mental status, systolic blood pressure ≤90 mmHg, and age >65 years [(9)].

The aim of the current work was to know the predictors of recurrence of SBP in cirrhotic ascitic patients and to evaluate the impact of Child-Pugh grade, MELD score and AIMS65 score in prediction of recurrence of SBP.

PATIENTS AND METHODS

This study included a total of hundred patients (61 males and 39 females) with SBP, attending at Tropical Medicine and Gastroenterology Department, Sohag University Hospitals. This study was conducted between September 2017 to September 2019.

All patients were subjected to complete history taking, thorough clinical examination, abdominal ultrasonography and laboratory investigations including complete blood count (CBC), serum creatinine, serum electrolytes, liver profile, anti-hepatitis C virus (Anti-HCV) antibodies, hepatitis B surface antigen (HBsAg), and ascitic fluid study.

Diagnosis of liver cirrhosis was established by clinical, ultrasonographic and laboratory findings. Based on the results of ascitic fluid study, patients were diagnosed as SBP if polymorphonuclear leucocytes

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(PNLs) ≥ 250 cells/mm^3.Index cases of SBP were collected in the first year. Cure of SBP was documented by follow-up ascitic fluid study, then the patients were followed-up for one year.

Patients were divided into 2 groups according to absence or presence of recurrence of SBP. Group I is formed of 73 patients without recurrence of SBP and group II is formed of 27 patients who had recurrent SBP. Patients with secondary bacterial peritonitis, ascites unrelated to liver cirrhosis or ascitic fluid PNLs < 250 cells/mm^3, patients in whom the improvement of SBP was not documented at the time of discharge and those who were lost during the follow-up period were excluded.

***Ethical Consideration*:**

The study protocol was approved by the Ethical Committee of Scientific Research, Sohag University Hospital (Date: 2019/2020; No. 2). The study was performed according to the principles of the Declaration of Helsinkiand. Written informed consent were assigned by all patients prior to the study.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics for Windows version 20. Quantitative data was expressed as means ± standard deviation, median and interquartile range. Quantitative data was tested for normality by Shapiro–Wilk test. Independent Samples T test was used for normally distributed data. Mann–Whitney U test was used for data which wasn't normally distributed. Qualitative data was expressed as number and percentage. Chi-square (χ^2) test and Fisher's Exact Test were used for comparison of qualitative variables as appropriate. Univariate and multiple binary logistic regression analyses were used to determine predictors of recurrence of SBP. P-value of 0.05% or less is considered significant.

RESULTS

One hundred patients (100) with SBP were included. The age of patients ranged from 37-70 years with a mean of 59.54 ± 9.89 years, 61 (68.47%) were males and 39 (31.53%) were females. Recurrent SBP was found in 27% of cases (Figure 1).

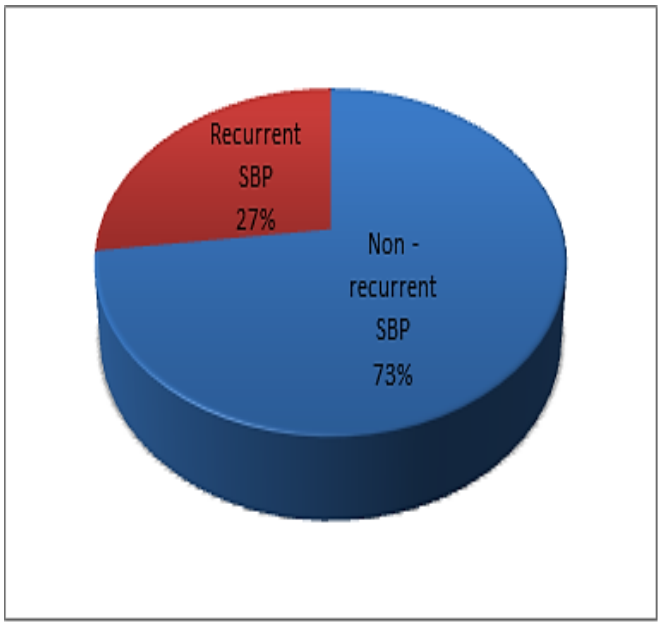

Figure (1): Seventy three percent of patients had non-recurrent spontaneous bacterial peritonitis (SBP) while 27% had recurrent SBP.

Comparison between patients with non-recurrent versus recurrent SBP:

Hematemesis, abdominal pain, multiple paracentesis, urinary tract infection (UTI), prolonged use of PPI, low serum sodium, high total bilirubin, Child-Pugh grade C and higher MELD score were significantly higher in patients with recurrent versus non-recurrent SBP. Patients with recurrent SBP were Child-Pugh C (100%) (Table 1).

In our study, univariate binary logistic regression analysis indicated that hematemesis, abdominal pain, multiple paracentesis, urinary tract infection, prolonged use of PPI, low serum sodium, high total bilirubin and higher MELD score were the highly significant variables responsible for recurrence of SBP (Table 2).

On doing multiple binary logistic regression analysis of the significant variables in univariate model we found that multiple paracentesis, urinary tract infection and low serum sodium were the highly risk factors for recurrence of SBP (Table 3).

Table (1): Comparison between patients with non-recurrent versus recurrent spontaneous bacterial peritonitis

Variable	Non-recurrent SBP Number=73	Recurrent SBP Number=27	P-value
Age (years)	58.11±11.69	59.15±7.03	0.96
Gender:			0.48
Male	43 (58.90%)	18 (66.67%)	
Female	30 (41.10%)	9 (33.33%)	
Hematemesis	30 (41.10%)	5 (18.52%)	**0.036**
Esophagogastroduodenoscopy and esophageal variceal band ligation	26 (35.62%)	5 (18.52%)	0.101 **0.025**
Abdominal pain	33 (45.21%)	19 (70.37%)	0.449
Fever	29 (39.73%)	13 (48.15%)	**<0.001**
Multiple paracentesis	21 (28.77%)	25 (92.59%)	**<0.001**
Urinary tract infection	17 (23.29%)	22 (81.48%)	0.169
Diabetes mellitus	17 (23.29%)	10 (37.04%)	0.225
Treatment of diabetes mellitus:			
Oral	5 (6.85%)	5 (18.52%)	
Insulin	12 (16.44%)	5 (18.52%)	
No	6 (8.22%)	17 (62.96%)	**<0.001**
Prolonged use of proton pump inhibitors	21 (28.77%)	23 (85.19%)	0.063
Encephalopathy	42 (57.53%)	21 (77.78%)	0.966
Hepatocellular carcinoma	24 (32.88%)	9 (33.33%)	
Red Blood cells (10^9/L)	9.7 ± 2.29	10.05 ± 2.03	
White blood cells (10^3/µL)	11.82 ± 2.28	12.49 ± 2.55	0.963
Platelets (10^3/µL)	135.45 ± 6.49	126 ± 5.86	0.336
Creatinine (mg/dL)	1.62 ± 0.24	1.49 ± 0.2	0.619
Serum sodium (mEq/L)	131.23±6.16	114.85±4.27	0.723
Serum potassium (mEq/L)	3.36±0.52	3.20±0.45	**<0.001**
Serum albumin (g/dL)	2.16 ± 0.46	2.06 ± 0.39	0.141
Total bilirubin (mg/dL)	3.51 ± 0.2	6.08 ± 1.59	0.304
Serology:			**<0.001**
Hepatitis B surface antigen	4 (5.48%)	2 (7.41%)	0.268
Antihepatitis C virus antibodies	66 (90.41%)	24 (88.89%)	
Hepatitis B surface antigen&antihepatitis C virus antibodies	0 (0.0%)	1 (3.70%)	
Negative	3 (4.11%)	0 (0.0%)	
Ascitic fluid protein[m]	1.43 ± 0.87	1.12 ± 0.65	0.101
Peritoneal fluid study–polymorphonuclearleucocytes[m]	3484.12± 5193.61	4803.89± 8693.37	0.529
Child-Pugh classification:			**0.003**
B	19 (26.03%)	0 (0.0%)	
C	54 (73.97%)	27 (100%)	**0.005**
Model of end stage liver diseasescore[m]	17.22 ± 5.87	20.26 ± 5.29	0.384
AIMS65 score:			
1	4 (5.48%)	0 (0.0%)	
2	33 (45.21%)	13 (48.15%)	
3	31 (42.47%)	10 (37.04%)	
4	5 (6.85%)	4 (14.81%)	0.228
Death	10 (13.70%)	7 (25.93%)	

SBP: spontaneous bacterial peritonitis. **[m]**:mean± standard deviation.
AIMS65: albumin <3.0 g/dL, international normalized ratio >1.5, altered mental state, systolic blood pressure ≤90 mmHg, and age > 65 years.
Significant p-values are in bold.

Table (2): Univariatebinary logistic regression analysis of predictors of recurrence of spontaneous bacterial peritonitis

Characteristics	Odds ratio (Confidence interval 95%)	P-value
Age	1.01 (0.97-1.06)	0.663
Gender: Male	1	
Female	0.72 (0.28-1.81)	0.481
Hematemesis	3.07 (1.05-9.01)	**0.04**
Esophagogastroduodenoscopy and esophageal variceal band ligation	2.4 (0.82-7.19)	0.107 **0.028**
Abdominal pain	0.35 (0.14-0.89)	0.450
Fever	0.71 (0.29-1.73)	< **0.001**
Multiple paracentesis	30.95 (6.72-142.49)	< **0.001**
Urinary tract infection	14.49 (4.77- 44.09)	0.173
Diabetes mellitus	1.94 (0.75-5.02)	0.099
Treatment of diabetes mellitus: Oral	3.11 (0. 81-11.98)	0.966
Insulin	1.04 (0.29-3.62)	
No	1	< **0.001**
Prolonged use of proton pump inhibitors	14.24 (4.39-46.18)	0.068
Encephalopathy	0.38 (0.14-1.07)	0.966
Hepatocellular carcinoma	1.02 (0.4-2.61)	
Red blood cells	1.08 (0.88-1.32)	0.487
White blood cells	1.01 (0.957-1.07)	0 .705
Platelets	0.98 (0.99-1.01)	0.491
Creatinine	0.89 (0.59-1.37)	0.62
Serum sodium	0.66 (0.54-0.79)	< **0.001**
Serum potassium	1.09 (0.19 – 5.97)	0 .923
Serum albumin	0.58 (0.2-1.64)	0.302
Total bilirubin	1.18 (1.05-1.34)	**0.008**
Serology: Hepatitis B surface antigen	8.1E+8 (NA)	0.999
Antihepatitis C virus antibodies	5.9E+8 (NA)	0.999
Hepatitis B surface antigen & antihepatitis C virus antibodies	3E+18 (NA)	0.999
Negative	1	0.098
Ascitic fluid protein	0.59 (0.31-1.1)	0.36
Peritoneal fluid study–polymorphonuclear leucocytes	1 (1-1)	
Child-Pugh classification: B	1	
C	8.1E+8 (NA)	0 .998
Model of end stage liver disease score	1.09 (1.01-1.18)	**0.026**
AIMS65 score	1.37 (0.74- 2.55)	0.322

NA: Not applicable.

AIMS65: albumin <3.0 g/dL, international normalized ratio >1.5, altered mental state, systolic blood pressure ≤90 mmHg, and age > 65 years.

Significant p-values are in bold.

Table (3): Multiple binary logistic regression analysis of significant variables in univariate model

Characteristics	Adjusted odds ratio (Confidence interval 95%)	P-value
Hematemesis	3.35 (0.89-12.68)	0.075
Abdominal pain	0.43 (0.13-1.4)	0.104
Multiple paracentesis	16.9 (2.61-109.59)	**0.003**
Urinary tract infection	10.79 (2.42-48.21)	**0.002**
Prolonged use of proton pump inhibitors	3.66 (0.78-17.24)	0. 1
Serum sodium	0.82 (0.73- 0.93)	**0.001**
Total bilirubin	0.9 (0.76-1.13)	0.434
Model of end stage liver disease score	1.02 (0.88-1.17)	0.821

DISCUSSION

In this study, 73% of patients had single episode of SBP while 27% had recurrent episodes of SBP. **Ginès and coworkers** [2] found the recurrence rate of SBP in one year 70% unless prophylactic antibiotics were given. We found that age and gender were not independent predictors of recurrence. This is in agreement with **Baland coworkers** [10] and in disagreement with **Thuluvathand coworkers** [11] who found the age an independent risk factor for recurrence. **Hematemesis** was significant for recurrence of SBP. Mucosal breaks, complements deficiency in cirrhotics with bleeding and hypovolemia may make them vulnerable to infections. This is in agreement with **Blaise and coworkers** [12]. Esophagogastroduodenoscopy (EGD) and variceal band ligation (VBL) were statistically insignificant between patients with recurrent and non-recurrent SBP. This could be attributed to the strict sterile conditions during EGD and VBL. This is in contrast with **Blaise and coworkers** [12] who said that the endoscopic procedures or instrumentations with invasive nature disturb and may breakdown the natural defenses.

We found that patients with **abdominal pain** were significantly associated with recurrent SBP and this agrees with many authors [13-15]. We found that history of fever had no role in recurrence of SBP and this disagrees with some authors who found that higher temperature is the most common symptom in patients with SBP and is found in about two thirds of them at the time of presentation [16, 17].

We found that **multiple paracentesis** was significantly associated with recurrent SBP, and this agrees with **Koulaouzidisand coworkers** [18] who found high incidence of SBP with tense ascites and paracentesis. This can be explained by the fact that large amount of ascitic fluid reduces the chance of contact between the phagocytic cells and bacteria and introduction of needle into the abdomen increases the number of bacteria and increases the incidence of peritonitis. Also, **urinary tract infection** was significantly associated with recurrent SBP and this result coincided with many other studies [11, 19].

In our study, we found that, DM and its treatment whether by oral anti-diabetic drugs or by insulin were not independent predictors of recurrence. **Guarner and Runyon** [4] found that DM was not significantly associated with recurrent SBP.

In our study, **prolonged use of PPI** was significantly associated with recurrent SBP and this agrees with **O'Leary and coworkers** [20] who found that patients hospitalized with cirrhosis who received PPIs for long periods were at high risk for subsequent infection. Severe hypochlorhydria generated by prolonged use of PPI increases the growth of gut microflora, increases susceptibility to enteric bacterial infection, increases bacterial translocation and alters various immuonomudularity and anti-inflammatory effects [21, 22].

In our study, hepatic encephalopathy was statistically insignificant between recurrent and non-recurrent cases of SBP. **Mandorferand coworkers** [23] reported that 65% of patients with SBP presented by hepatic encephalopathy. **Andreu and coworkers** [24] stated that SBP should be suspected if a known cirrhotic patient deteriorates particularly with encephalopathy. Bacterial infection was responsible for 34.7% of causes of acute hepatic encephalopathy and SBP was the most prevalent infection in acute hepatic encephalopathy [25].

We found that HCC, RBCs count, WBCs count, platelets count, serum creatinine and serum potassium were not independent predictors of SBP recurrence. Similar results were obtained by **Hassan and Abdel Rehim** [8]. We found that **hyponatremia** was significantly more frequent in patients with recurrent SBP and this is in agreement with **Ginès and coworkers** [2].

In our study serum albumin was insignificant between the two groups. **Huang and coworkers** [26] found low serum albumin a reliable predictor of first-time or recurrent SBP. We found that **high total bilirubin** was significantly associated with recurrent SBP and this agrees with some authors who found that serum bilirubin >4 mg was associated with recurrent SBP in both univariate and multivariate analyses [27]. We found the results of serological tests, ascitic fluid protein and ascitic fluid PNLs were insignificant between the two groups. This is in contrast to some authors who found ascitic fluid protein concentration < 1gm/dl was significantly associated with a high risk of SBP recurrence [28-29].

In our study, **Child-Pugh grade** was a significant predictor of SBP recurrence. The result was agreed with **Schwable and coworkers** [30] who found the same result. However, **Nobre and coworkers** [19] **and Wiesner and coworkers** [31] found that Child-Pugh score has short comings as it unable to differentiate between the patients as regard the severity of liver cell failure, moreover the assessment of ascites and encephalopathy is subjective.

MELD score was a significant factor for recurrence of SBP in our study. We found that MELD score is strongly predict short-term mortality in SBP patients, MELD score as an independent predictor of such mortality was supported by many studies [8, 19, 32]. Previous retrospective study showed that the presence of ascites, bleeding varices, SBP, and hepatic encephalopathy do not affect the ability of MELD score to predict survival [31]. Actually, it could reliably measure the short-term mortality risk in patients with advanced liver disease whatever its etiology, moreover it could be applied over a wide spectrum of disease severity [33]. The ability of this scoring system for prediction of short-term survival was previously confirmed in Indian and European series [34, 35].

AIMS65 score was insignificant factors in SBP recurrence in our study however it was a predictor of mortality in cases of upper gastrointestinal bleeding as reported by some authors [9]. We found that there was insignificant difference between the two groups regarding death rate and this is in agreement with **Ginès and coworkers** [2] who reported that the in-hospital mortality rate remains in the range of 20-40%, even though we can sterilize the ascitic fluid in about 70-90% of cases.

Univariate analysis showed that hematemesis, abdominal pain, multiple paracentesis, urinary tract infection, prolonged use of PPI, low serum sodium, high serum bilirubin and high MELD score were significant variables responsible for recurrence of SBP. Multivariate analysis showed that multiple paracentesis, urinary tract infection and low serum sodium were the highly risk factors for recurrence of SBP.

CONCLUSIONS

It could be concluded that recurrent SBP was found in 27% of cases. Multiple paracentesis, urinary tract infection and low serum sodium were the highly risk factors for recurrence of SBP. These factors offer a useful clue to identify high-risk patients for SBP recurrence who would benefit by intensive treatment, and to recommend prophylactic antibiotics.

Abbreviations: SBP: Spontaneous bacterial peritonitis, PPI: Proton pump inhibitors, MELD: Model of end-stage liver disease, INR: International normalized ratio, CBC: Complete blood count, HCV: Hepatitis C virus, PNLs: Polymorphonuclear leucocytes, UTI: Urinary tract infection, EGD: Esophagogastroduodenoscopy, VBL: Variceal band ligation

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

Mahmoud Saif-Al-Islam collected, analyzed, and interpreted the data. Usama M. Abdelaal, and Mohamed Malak shared and helped in the designing and conceptualization of the study. Salwa Mohammed, and Asmaa Naser Mohammad helped in the designing, editing, writing and publishing the study. All authors read and approved the final manuscript.

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