Brief Report

Bull Emerg Trauma 2018;6(4):363-366.

Bulletin of Emergency And Trauma

Spontaneous Bacterial Peritonitis in Afebrile Cirrhotic Patients; Report from a Referral Transplantation Center

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Received: June 23, 2018
Revised: August 29, 2018
Accepted: September 16, 2018

ABSTRACT

Spontaneous bacterial peritonitis (SBP) is a complication of liver cirrhosis with adverse effect on patient prognosis. Early diagnosis and treatment is highly important, especially in patients without remarkable manifestations. We designed this study to determine the prevalence of SBP among afebrile cirrhotic patients and identify high-risk subgroups in a referral center in southern Iran. This cross-sectional study evaluated all afebrile cirrhotic patients, admitted to the gastroenterology ward of Namazi hospital (affiliated with Shiraz University of Medical Sciences, Shiraz, Iran) over a 6-month period in 2017, for the presence and correlates of SBP. Demographic data, clinical findings, and comorbidities were recorded. Ascitic fluid white blood cells (WBC) count >500 and neutrophil count >250 indicated bacterial peritonitis. In total, 97 afebrile cirrhotic patients comprising of 63 (64.9%) men and 34 (35.1%) women were included. All patients had ascites and 89 (91.8%) had abdominal tenderness. Accordingly, abdominal distension was the top presentation. Confirmed etiologies or comorbidities such as HBS, HCV, and liver cancer or metastasis existed in 46 patients. Thirteen (13.4%) had SBP. The correlations of gender (p=0.331), decreased level of consciousness (p=0.145), tenderness (p=0.315). With regards to the type of presentations, only DLOC showed to be significantly higher in SBP negative patients (p=0.022, OR=0.09. 95%CI=0.01–0.62). Also, using binary logistic regression, the correlation of age with SBP was statistically non-significant (coefficient=-0.013, p=0.595). Our findings indicated that routine paracentesis in all cirrhotic patients regardless of fever can help diagnose a number of potentially neglected patients and improve their outcome.

Keywords: Ascites; Bacterial infections; Liver cirrhosis; Spontaneous bacterial peritonitis.

Please cite this paper as:
Mazloom SS, Khoramian MK, Mohsenian L. Spontaneous Bacterial Peritonitis in Afebrile Cirrhotic Patients; Report from a Referral Transplantation Center. *Bull Emerg Trauma*. 2018;6(4):363-366. doi: 10.29252/beat-060415.

Primary peritonitis or spontaneous bacterial peritonitis (SBP) is among the most common bacterial infections associated with advanced liver cirrhosis [1]. It is differentiated from secondary peritonitis based on the absence of any evident source for infection [2]. Although less prevalent in outpatient settings, SPB accounts for 10% to 30% of all bacterial infections in the hospitalized cirrhotic

patients [3]. The high mortality rate of 16% to 52% further reflects the significance of this complication [1, 4]. On a gross level, the color and clarity of the fluid may give clue to SBP; however, only with very poor sensitivity [5]. General consensus supports a cut-off of 250 PMN/μL count for optimal sensitivity. Unlike the well-established value of leukocyte count, biochemical analysis is less reliable [6, 7]. Regarding the population aging in our country, along with the upsurge of life-style related risk factors for liver cirrhosis, this challenging condition calls for urgent measurements. It is essential to determine the high-risk and potentially neglected subgroups of patients to implement optimal therapeutic approaches for enhancing their prognosis. Thus, we designed this study to determine the prevalence of SBP among afebrile cirrhotic patients and identify the predictive factors in a referral center in southern Iran.

In this cross-sectional study, we included all cirrhotic patients, who were admitted to the gastroenterology ward of Namazi hospital (affiliated with Shiraz University of Medical Sciences, Shiraz, Iran) over a six-month period in 2017. Patients were evaluated for the presence and predictive factors of SPB. Individuals younger than 15 years and those with fever (oral temperature >37.8°C) were excluded from the study, whereas ascites, abdominal pain, decreased level of consciousness (cirrhotic encephalopathy), hypovolemia, malnutrition, gastrointestinal bleeding, and diarrhea unrelated to lactose consumption were not considered as the criteria of exclusion. The study protocol was approved by the institutional review board (IRB) and medical ethics committee of the Shiraz University of Medical Sciences. As this was a retrospective review, no informed written consents were required.

The medical records of all the patients who were admitted with SBP were recruited from the hospital registry using the ICD-10 code of K65.2 Documents were reviewed to extract demographic data, clinical findings, presentations, and other comorbidities such as hypertension, diabetes, malignancies, hepatitis, and autoimmune disorders. Within the first 24 hours after admission and before initiation of any antibiotic therapy, abdominal paracentesis was performed under sterile conditions by inserting an 18-guague needle into the right or left lower quadrants to aspirate adequate amount of peritoneal fluid. White blood cells count >500 and neutrophil count >250 indicated bacterial peritonitis.

Windows statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 21.0 was used for statistical analysis. Data are represented as mean±standard deviation (SD) and frequency (%) as applicable. Binary logistic regression was used to assess the correlation of age with the presence of SBP. Chi-square test was applied to compare proportions between the SBP positive and SBP negative groups. For each proportional comparison, odds ratio (OR) with 95% confidence interval (CI) was reported. A two-sided p-value of less than 0.05 was considered statistically significant.

In total, 97 afebrile cirrhotic patients met the criteria of study. The majority of patients were male. All patients had ascites. Accordingly, abdominal distension was the leading initial presentation. Abdominal tenderness was present in over 90%. Forty-six (47.4%) patients had other comorbidities. SBP was confirmed in 13 (13.4%) patients. Table 1 summarises the characteristics of the study population.

Table. 1. Parameters of 97 afebrile patients with liver cirrhosis.

Parameters	Value
Age (years)	54.63±12.48 (22–84)
Gender	
Male (%)	63 (64.9%)
Female (%)	34 (35.1%)
DLOC[a] (%)	86 (87.6%)
Ascites (%)	97 (100%)
Abdominal tenderness (%)	89 (91.8%)
Presentations	
Abdominal distension (%)	66 (68%)
Fatigue (%)	12 (12.4%)
DLOC (%)	7 (7.2%)
Abdominal pain (%)	6 (6.2%)
Dyspnea (%)	3 (3.1%)
Others (%)	3 (3.1%)
Etiologies/ Comorbidities	
HBV[b] (%)	13 (28.3%)
HCV[c] (%)	7 (15.2%)
Liver cancer or metastasis (%)	10 (21.7%)
Others (%)	16 (34.8%)
Paracentesis (%)	
Positive	13 (13.4%)
Negative	84 (86.6%)

[a]DLOC: Decreased level of consciousness; [b]HBV: Hepatitis B virus; [c]HCV: Hepatitis C virus

The correlations of gender (p=0.331, OR=0.63, 95% CI=0.057–2.25), decreased level of consciousness (p=0.145, OR=3.66, 95% CI=0.96-8.97), tenderness (p=0.315, OR=0.36, 95% CI=0.03–3.61) with SBP were not significant as examined by chi-square test. With regards to the type of presentations, only DLOC showed to be significantly higher in SBP negative patients (p=0.022, OR=0.09. 95%CI=0.01–0.62), whereas it was not so for distension (p=0.281, OR=3.19, 95%CI=0.50–20.09), fatigue (p=0.098, OR=1.08, 95% CI=0.63-3.44), abdominal pain (p=0.696, OR=1.07, 95% CI=1.02–1.13), dyspnea (p=0.734, OR=1.06, 95%CI=1.01-1.12), and others (p=0.859, OR=1.03, 95%CI=0.99-1.0). Also, using binary logistic regression, the correlation of age with SBP was found to be statistically non-significant (coefficient= - 0.013, p=0.595) (Table 2).

The present study evaluated afebrile cirrhotic patients for SBP in a university-affiliated tertiary referral center in southern Iran. We found that over 13% of afebrile patients had SBP. Considering the

Table 2. Determinants of spontaneous bacterial peritonitis (SBP) in 97 cirrhotic patients who were included in the current study.

Variable	SBP		*p*-value	OR (95% CI)
	Positive (N=13)	Negative (N=84)		
Gender				
Male (%)	10 (10.3%)	53 (54.6%)	0.331	0.63 (0.057–2.25)
Female (%)	3 (3.1%)	31 (32%)		
DLOC[a] (%)	0 (0%)	12 (12.4%)	0.145	3.66 (0.96–8.97)
Tenderness (%)	2 (2%)	6 (6.2%)	0.315	0.36 (0.03–3.61)
Presentations				
Distension (%)	8 (8.2%)	58 (59.7%)	0.281	3.19 (0.50–20.09)
Fatigue (%)	4 (4.1%)	8 (8.3%)	0.098	1.08 (0.63–3.44)
DLOC (%)	0 (0%)	7 (7.3%)	**0.022**	**0.09 (0.01–0.62)**
Abdominal pain (%)	1 (1%)	5 (5.2%)	0.696	1.07 (1.02–1.13)
Dyspnea (%)	0 (0%)	3 (3.1%)	0.734	1.06 (1.01–1.12)
Others (%)	0 (0%)	3 (3.1%)	0.859	1.03 (0.99–1.0)

[a]DLOC: Decreased level of consciousness

malignant potential of infection in the preexisting state of liver cirrhosis, this figure can be interpreted as a serious warning. Although a number of patients are already affected by community-acquired infections at the time of admission, hospitalization renders patients subject to nosocomial infections, which are more difficult to treat. The impaired immune response in advanced cirrhosis can lead to rapid deterioration of patients' condition. Furthermore, infection indirectly exerts a negative impact on outcome by promoting gastrointestinal hemorrhage, renal dysfunction, and hepatic encephalopathy [8]. Thus, neglecting SBP in high-risk patients even without fever can be life-threatening and easily worsen their prognosis.

A nationwide study from the United States investigated the benefits of paracentesis and showed that patients, who did not undergo paracentesis, had significantly higher mortality of approximately two folds. Furthermore, early paracentesis was a protective measurement reducing the mortality rate as compared to late paracentesis. The other advantages were shorter length of hospital stay and lower hospitalization costs [9]. Similarly, Kim *et al*., compared the outcome of 239 patients with a mean age of 53 years, who had early (59%) vs. delayed (41%) paracentesis base on a cut-off point of 72 hours. Delayed group had a 2.7 times higher mortality along with prolonged overall hospital and ICU stay [10].

In our study, we noticed that most of the evaluated parameters were not predictive of SBP. Therefore, it seems that SBP does not show any tendencies with regards to age, gender, and comorbidities; however, we found that if patients presented with DLOC, they not likely to be SBP positive. It is noteworthy that despite the rise in alcohol consumption in our population over the past years, we only had one definite case with alcoholic hepatitis. However, considering the cultural stigma and the patients' fear about being announced ineligible for liver transplantation, it is possible that not all patients are willing to admit their alcohol abuse.

Most studies have focused on factors associated with outcome and mortality in patients with SBP. In a large study from the United States, the mortality rate in cirrhotic patients with SBP was reported 17.6%. Older age, female gender, hepatic encephalopathy, variceal hemorrhage, and acute kidney injury were associated with increased mortality [11]. Schwabel *et al*., identified Child-Pugh stage C, ascitic fluid PMN count ≥100 cells/µl, and hyponatremia <125 as independent risk factors for developing SBP, while mortality was correlated with MELD≥22 and elevated CRP levels [12]. Oladimeji identified low ascitic protein, hepatic encephalopathy, coagulopathy, creatinine above 2 mg/dl and leukocytosis as indicators of poor prognosis, and recommended diagnostic abdominal paracentesis for cell count and culture is necessary in cirrhotic patients with symptoms suggestive of SBP [13]. In a study by Musskopf et al in Brazil, the mean age of patients was 55 years with male predominance. Half of the patients had hepatitis C, and over one quarter had hepatocellular carcinoma. They found that bilirubin, creatinine, MELD and iMELD could predict hospital mortality [14]. In a report from Turkey, the average age of patients was 46 years and over 70% of were men. Around one third received prophylactic treatment for spontaneous bacterial peritonitis. The authors stated that existence of chronic renal failure, liver graft surgery, hepatocellular cancer, and albumin treatment did not have a significant effect on patient mortality [15]. Increased risk of mortality, gastrointestinal bleeding, and rehospitalization in SBP patients has been also documented in another study by Gunjača in Coratia [16].

According to a research conducted over a three-year period in Iran, Sheikhbahaei *et al*., cautioned that despite the relatively constant microbial etiology of SBP, the resistance particularly to the first-line antibiotics had elevated dramatically [17]. It is therefore imperative to possibly consider microbial sensitivity before initiation of empirical or decide

the best choices in each center based on common laboratory reports. Currently, only febrile patients receive antibiotics in our center. Our findings emphasize the need for reassessing this approach, as the incidence of SBP in afebrile patients cannot be ignored.

We note some limitations to our study. First, the cross-sectional design of the study does not shed light on the outcome of patients. In addition, adding the long-term follow up of the patients would be beneficial in understanding the natural course of the disease in different patients' population. Furthermore, it could be of interest to report the cultured bacterial strains and their sensitivity. Also, the status of prophylactic antibiotic therapy and its efficacy needs to be elucidated. This could help to choose best empirical antibiotic therapy protocol in our center. Increasing the sample size will also allow for more precise and reliable data analysis.

In conclusion, our findings indicate that routine paracentesis in all cirrhotic patients regardless of fever can help diagnose a number of potentially neglected SPB patients and improve their outcome by timely treatment.

Acknowledgement

The present article was extracted from the thesis written by Sara Sadat Mazloom (Number 10640010194) was financially supported by Shiraz University of Medical Sciences. We would like to acknowledge the editorial assistance of Diba Negar Research Institute for improving the English and style of the manuscript.

Conflicts of Interest: None declared.

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