Original article

Frequency of spontaneous bacterial peritonitis among cirrhotic ascitic patients and predictors for its outcome in Menoufia University Hospitals

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A R T I C L E I N F O

A B S T R A C T

Background: Cirrhosis often leads to spontaneous bacterial peritonitis (SBP) development, a condition with a poor prognosis warranting liver transplantation. This study aimed to identify SBP frequency among cirrhotic patients with ascites and to determine its risk factors and predictors for inadequate antibiotic response. **Methods:** This analytical cross-sectional study involved 78 cirrhotic patients with ascites. Patients' workup included: at-admission evaluation (clinical, laboratory, and imaging), treatment and follow-up for SBP patients, and re-evaluation after 48 hours of antibiotics with treatment modification according to response. **Results:** Ascitic fluid (AF) examination and microbiological cultures revealed that 24.4% of admitted cirrhotic patients with ascites had one of SBP variants with diabetes mellitus, high random blood sugar, and low AF albumin as independent risk factors for SBP development. 26.3% of SBP patients experienced inadequate antibiotic response. Inadequate response group showed delayed antibiotic initiation and history of prior SBP, lower AF albumin, higher C-reactive protein (CRP), and positive culture. After 48-hours, inadequate response patients experienced fever, disturbed conscious level, and abdominal tenderness in 20%, 60%, and 80%, respectively compared to 7.14%,0%, and 14.3% in those with adequate response. Nonetheless, 48-hour investigations revealed little decrease or even increase in total leucocyte count (TLC) in the blood, CRP, blood urea, and serum creatinine in patients with inadequate response. **Conclusion:** Delayed antibiotic initiation, positive culture, and clinical suspicion together with non-significant decrease or even increase in TLC in the blood, CRP, blood urea, and serum creatinine 48-hours of antibiotic initiation are potential predictors for inadequate response. This helps identify who would benefit from a second paracentesis and minimize unnecessary invasive procedures.

Introduction

Globally, cirrhosis is a prevalent condition caused by various factors, leading to either compensated or decompensated states. Decompensation manifests primarily through ascites, jaundice, and variceal hemorrhage. In cirrhotic patients, ascites development is linked to hepatic lymph leakage, hypoalbuminemia, portal hypertension, and retention of salt and water [1].

Arguably, one of the most significant side effects of cirrhosis is the emergence of spontaneous bacterial peritonitis (SBP), which carries a poor

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prognosis and serves as a key factor warranting liver transplantation. The main predisposing factor is often attributed to delayed intestinal transit time, fostering an overgrowth of intestinal bacteria. This bacterial overgrowth, coupled with compromised phagocytic function, diminished complement levels in both serum and ascitic fluid, and reduced activity of the reticuloendothelial system, results in an increased microbial count and a decline in the body's capacity to eliminate them from the bloodstream. Consequently, these microorganisms migrate into the ascitic fluid, where they proliferate over time [2].

The onset of the first episode of SBP marks a crucial turning point in the progression of cirrhosis and ascites, indicating further decompensation and significantly impacting survival, even following SBP resolution [3]. The in-hospital mortality rate for SBP within 30 days varies, ranging from 18% to as high as 31.9% [4,5]. A study suggests a long-term three-year mortality rate of approximately 66.5% for SBP, with a mortality risk 2.5 times higher compared to cirrhotic patients without ascites [6].

A noteworthy finding indicates that cirrhotic patients with ascites, who exhibit low levels of complement and ascitic fluid total protein below 1 g/dL, could face a tenfold increased risk of developing SBP compared to those with protein levels exceeding 1 g/dL [2].

A diverse array of signs and symptoms are evident in SBP, warranting a high level of suspicion, especially in cases of acute deterioration in the clinical condition. Remarkably, up to 30% of patients may present entirely asymptomatic. Increasing evidence indicates that both prompt diagnostic paracentesis (defined as conducted within the initial 11 hours of presentation) and early initiation of antibiotic therapy contribute to reduced lengths of stay in the intensive care unit (ICU) and hospital, as well as lower in-hospital and three-month mortality rates [4,7].

Proper handling of ascitic fluid (AF) is essential to enhance the accuracy of diagnosing SBP [8]. European guidelines propose performing a follow-up paracentesis 48 hours after initiating antibiotics to confirm resolution of SBP, indicated by a reduction in polymorphonuclear (PMN) cells by more than 25%, and to make any necessary adjustments to therapy [9].

The main objectives of this study were to investigate the frequency of spontaneous bacterial peritonitis in hospitalized cirrhotic patients with ascites and to identify the risk factors for SBP development and the predictors of an inadequate response to antibiotic treatment at Menoufia University Hospitals.

Methods

Study design and participants:

This analytical cross-sectional study involved 78 cirrhotic patients with ascites. These patients were selected from the inpatient cases of the Tropical Medicine and Internal Medicine Departments, in collaboration with the Clinical Pathology Department for laboratory investigations, at the Main Menoufia University Hospital over a period of 6 months, between August 2022 and January 2023. Among the patients, there were 47 males (60.3%) and 31 females (37.9%), with ages ranging from 45 to 70 years. These 78 patients were selected from a total of 171 patients with ascites requiring hospitalization for various reasons, based on predefined inclusion and exclusion criteria

Cirrhotic patients with ascites (hepatic ascites) and portal hypertension [serum ascites albumin gradient (SAAG) $\geq$ 1.1 gm/dl] based on imaging, laboratory, and clinical evidence were included. Patients with non-cirrhotic ascites or those with clinical, laboratory and imaging evidences consistent with secondary peritonitis or iatrogenic (poly-microbial) bacter-ascites, even if cirrhotic, and patients on antibiotic prophylaxis were excluded. All patients who lacked the necessary data, declined to participate in the study, or skipped the study were also not included.

Patients with secondary peritonitis have been identified if met at least two of the Runyon's criteria and/or the presence of a polymicrobial ascitic fluid culture. Among Runyon's requirements are A) glucose concentration in the ascitic fluid less than 50 mg/dL, B) Total protein content in the ascitic fluid was greater than 10 g/dL, and C) lactate dehydrogenase (LDH) level in the ascitic fluid greater than 225 U/mL (or greater than its upper limit of normal in the serum) [10].

Ethical considerations: After elaborating the research objectives and the research questions, each participant was given an explanation of the study and the chance to give written, informed consent before being enrolled. The research methodology and the sample size calculation were authorized by the Research Ethics Committee, Faculty of Medicine, Menoufia University, Egypt; with Institutional Review Board (IRB) approval number:

5/2022 TROP2, and was performed in accordance with the Helsinki Declaration.

Patients' work up included: I) At admission (baseline) evaluation, II) Treatment protocols and follow up for patients with one of the SBP variants, III) Treatment evaluation after 48 hours of antibiotic initiation for SBP patients with treatment modulation when required. IV) Management of patients according to antibiotic response and re-evaluation of treatment response.

I) **At admission (baseline) evaluation**

Clinical evaluation: A clinical evaluation, including history-taking, general and local examinations, was performed to identify the indication for admission, the etiology of ascites, the risk factors for SBP, and the risk factors for inadequate antibiotic response. History-taking includes assessment of i) Symptoms suggestive of systemic infection such as fever with or without rigor, abdominal pain, dysuria, rash, vomiting, diarrhea, cough, and hemoptysis. ii) Symptoms of hepatic decompensation as hematemesis and/or melena, hepatic encephalopathy, jaundice, abdominal enlargement, and lower limb edema. iii) History of previous hospitalization and the management provided. iv) History suggestive of previous SBP. v) History of gastrointestinal (GIT) endoscopy & previous endoscopic management. vi) History of regular proton pump inhibitors (PPI) use within the last few months of admission. vii) History of antibiotics including type, duration, and time of antibiotics used within two weeks before admission. viii) History of diuretics, beta blockers, analgesic, and steroids use. ix) History of diabetes mellitus (DM), alcohol consumption, and symptoms suggestive of cardiopulmonary diseases. General and local examinations were performed.

Laboratory investigations: Laboratory investigations were performed, including complete blood counts (CBC) and assessments of the liver, kidney functions, serum electrolyte levels, fasting blood sugar (FBS), and C-reactive protein (CRP). Furthermore, an enzyme linked immunosorbent assay (ELISA) test was employed to quantify serum Alpha fetoprotein (AFP).

Diagnostic imaging: the liver size, echogenicity, and hepatic focal lesions, spleen size and echogenicity, portal vein size and patency, dilated collaterals and grading of ascites were all assessed using abdominal ultrasonography.

Diagnostic abdominal paracentesis and ascitic fluid sample analysis: for all included patients, paracentesis was performed within 3 hours of admission. The paracentesis approach was explained for each patient, which involved using a wide-bore needle while adhering to aseptic precautions. The patient was lying supine as the needle was inserted in the lower right quadrant. The post-paracentesis leak was prevented by using the Z Tracking technique. Each patient had fifty milliliters of ascitic fluid aspirated, and these samples were sent to the Clinical Pathology Lab for evaluation, which included the following: a) Physical examination for color and aspect. b) Biochemical tests (5ml of ascitic fluid) for total protein, albumin, glucose, and lactate dehydrogenase (LDH). c) Total and differential white blood cell counts (WBCs) counting (5ml of ascitic fluid). d) Direct microscopic examination (5ml of ascitic fluid): Ascitic fluid was examined by direct microscopic examination of ascitic smear for the presence of bacteria. e) Microbiological cultures (35ml of ascitic fluid).

Cultures were done to detect any infecting organisms: The sample was centrifuged in a sterile tube at high speed for about 20 minutes to sediment the bacteria. The supernatant fluid was removed, and the sediment was cultured on blood, MacConkey and chocolate agar plates. The chocolate agar plate was incubated in a carbon dioxide enriched atmosphere at 35-37 °c for up to 48 hours. The blood and MacConkey agar plates were incubated aerobically and examined for growth after overnight incubation for up to 72 hours. The cultures were looked particularly for *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*), *Streptococcus pneumoniae (S. pneumonia)*, *Haemophilus influenzae (H. influenza)*, *Neisseria* species, *Enterobacteria* and *Pseudomonas aeruginosa* (*P. aeruginosa*).

Liver disease severity evaluation: Assessment of liver disease severity involved the use of the Child-Turcotte-Pugh (CTP) score and grade, as well as the MELD (Model for End-Stage Liver Disease) and Model for End-Stage Liver Disease-Na (MELD-Na) scores, to examine their correlation with the occurrence of SBP and the response to antibiotic treatment. The CTP score was calculated based on evaluations of ascites, history of hepatic encephalopathy, serum albumin, serum bilirubin, and prothrombin time. Additionally, the MELD score was determined using the formula:

MELD = 9.57 loge [Creatinine (mg/dL)] + 3.78 loge [Bilirubin (mg/dL)] + 11.2 loge [International Normalized Ratio] + 6.43 [11].

Patients grouping: Based on ascitic fluid examination, and ascitic fluid microbiological cultures patients were classified as patients with one of the three SBP variants (19 patients) and patients without SBP (59 patients). 19 SBP variants included; 5 patients with classic SBP were identified by polymorphonuclear (PMN) count in the ascitic fluid was ≥250 cells/mm^3, the culture results were positive, and secondary causes of peritonitis were ruled out, 14 patients with (culture-negative neutrocytic ascites (CNNA) who were diagnosed when ascitic fluid culture was negative and the PMN cell count is ≥250 cells/mm^3 and no one of the included patients was diagnosed as monomicrobial nonneutrocytic bacterascites (MNB) which is diagnosed if ascitic fluid culture was positive and the PMN cell count was < 250/mm^3 [10]

II) Treatment protocols and follow up for patients with SBP

SBP evidenced patients with PMN more than 250 cells/mm^3 received treatment according to the guidelines as following; intravenous Cefotaxime administered 2 grams every 8 hours in addition to, intravenous albumin, when available, (1.5 g/kg given within 6 hours of diagnosis and repeated as a 1.0 g/kg dose on day 3 [9].

III) Treatment evaluation after 48 hours of treatment

Clinical reevaluation: General as well as local examinations were performed, focusing on the presence of fever, fetor hepaticus, flapping tremors, abdominal tenderness, guarding, and rigidity.

Follow-up diagnostic paracentesis was done 48 hours after initiation of antibiotics: Patients were classified as having an adequate antibiotic response (14 cases) and an inadequate antibiotic response (5 cases) based on the ascitic fluid PMN count, which was measured 48 hours after the start of treatment. If the count declined by at least 25% after two days of antibiotic therapy, the patient had an adequate antibiotic response [12].

IV) Further management of patients according to antibiotic response

Further management of SBP patients was planned based on their individual antibiotic response; those who responded adequately to cefotaxime were kept on treatment, while those with inadequate response, antibiotic was modified regarding their antibiotic sensitivity results (2 cases received cefoperazone sulbactam and 3 cases received carbapenem; imipenem) with good antibiotic response.

Statistical analysis of the data

The computer was provided with the information, and IBM SPSS software package version 20.0 was implemented for assessment. (IBM Corp, Armonk, NY). The significance of the obtained results was judged at the 5% level. Numbers and percentages have been employed to express the qualitative data. The distribution's normality has been determined using the Kolmogorov-Smirnov test. In addition, the range (minimum and maximum), mean, standard deviation (SD), median, and interquartile range (IQR) have all been employed for characterizing quantitative data. For the sake of categorical variables, the chi-square test was implemented for comparing different groups of variables. Whenever over twenty percent of the cells displayed an anticipated count of fewer than 5, the chi-square was corrected applying either Fisher's Exact or Monte Carlo correction. The Student t-test was applied to compare two groups for quantitative variables that had a normal distribution, while, for abnormally distributed quantitative variables, Mann Whitney test was employed.

Results

A CONSORT flowchart of the study population was shown in **Figure 1**. Out of the 171 patients with ascites who were admitted to Tropical Medicine or Internal Medicine Departments for a variety of causes, 78 patients were chosen according to the inclusion and exclusion criteria.

Table 1 highlights the clinical and demographic characteristics of the studied patients. Patients were 47 (60.3%) males and 31 (37.9%) females with mean age of 55.52 ± 8.01 years. Of them 30 patients (61.5%) were diabetics on oral or insulin treatment, 48 (81.5%) patients had previous history of hematemesis and/or melena, 15 (19.2%) patients had history of previous SBP diagnosis and treatment, and 54 (69.2%) received proton pump inhibitors (PPI) treatment. According to the indication for hospital admission, the patients were presented by one or more of the following, uncontrolled ascites, hematemesis and/or melena, abdominal pain, fever, disturbed conscious level, vomiting, and diarrhea representing 44.9%, 21.8%, 17.9%, 11.5%, 10.3%, 6.4%, and 5.1% respectively.

Based on ascitic fluid examination and ascitic fluid microbiological cultures, patients were divided into 19 (24.4%) patients presented with one of the SBP variants patients and 59 (75.6%) patients without SBP. There were statistically non-significant differences between the two patient groups regarding the age and the sex (p value was 0.414 and 0.169).

With regard to the risk factors for SBP, **Table 1** shows that history of DM, history of hematemesis and/or melena, and prior history of SBP were all significantly different among the patient groups. They were more common in patients with SBP than in those without. While the two groups didn't differ regarding prior history of PPI consumption. Regarding the indication for hospital admission, patients with spontaneous bacterial peritonitis shows higher frequency of fever, abdominal pain, and uncontrolled ascites (*p*-value <0.001, <0.001, and 0.012 respectively) than those without SBP. However, there was statistically non-significant differences between the two groups regarding vomiting, diarrhea, distributed conscious level or hematemesis and/or melena as indication for hospital admission. Upon general examination, the patients showed symptoms of jaundice, edema of the lower limbs, disturbed conscious level, and pallor in 64.1%, 59%, 11.5%, and 10.3% of the cases, respectively. Notably, patients with SBP had a significantly higher prevalence of disturbance of the conscious level compared to those without. Furthermore, 24.4% of the patients had abdominal tenderness on local examination, which was more commonly found in SBP patients. On abdominal ultra-sonography (US) examinations, patients with and without SBP did not significantly differ concerning liver size, spleen size, portal vein (PV) diameter, or the presence of collaterals.

Regarding laboratory studies, there were no discernible variations between the two patient groups in any of the complete blood count parameters, liver, kidney function tests, MELD or MELD Na scores. However, in SBP patients, the CRP was more frequently positive with higher mean values *p* value was <0.001, in addition, fasting blood sugar was significantly higher in SBP patients 0.001 **(Table 2).**

For all patients included in our study, ascitic fluid aspiration was performed within the first 3 hours of admission. Ascitic fluid analysis reveals that while total leukocyte counts and polymorphonuclear (PMN) cells were significantly higher in SBP patients compared to the non-SBP group (p <0.001), ascitic fluid total protein and albumin were significantly lower (*p* = 0.031 and 0.019 respectively). However, the two patient groups did not differ in ascitic fluid glucose, or LDH levels. For all SBP patients, cefotaxime was administered (2 grams every 8 hours) within 5 hours of admission, as displayed in **Table 3**.

The ascitic fluid PMN count was measured 48-hours post-treatment, and patients were considered to have had an adequate antibiotic response if there was a decrease of at least 25% of their baseline values. Statistical analysis revealed that 5 out of 19 cases (26.3%) of SBP patients experienced inadequate antibiotic response after 48hrs treatment.

Table 4 demonstrates that there was no statistically significant difference in age, sex, or clinical findings between SBP patients with and without an adequate antibiotic response. However, individuals with inadequate antibiotic response had a higher frequency of prior SBP history. The time interval between the onset of symptoms and hospital admission (indicating the point at which antibiotics were started) was longer in patients who did not respond well to antibiotics. Clinical assessment follow-up (after 48 hours) for patients with an inadequate response reveals that one patient (20%) had fever, 3 patients (60%) had disturbed conscious level, and 4 patients (80%) had abdominal tenderness compared to 7.14%, 0%, and 14.3% in those with adequate response. These findings may give rise to clinical suspicion to identify patients who have inadequate response.

Regarding baseline laboratory investigations in SBP patients, there were no discernible variations between the two patient groups with different antibiotic response in any of the complete blood count parameters, liver, kidney function tests, CRP, MELD, or MELD Na scores. Patients with inadequate response had significantly higher CRP and TLC at the 48-hour laboratory assessment follow-up (*p* <0.001 and 0.014 respectively) (**Table 5**).

Baseline analysis of the ascitic fluid samples in patients with SBP revealed that patients with an inadequate antibiotic response had significantly lower ascitic fluid albumin and glucose (*p*-value = 0.014 and <0.001). However, total protein, SAAG, polymorph nuclear leucocytes, lymphocytes, or LDH did not differ from patients with an adequate response. Regarding the

microbiological examination, 4 patients (80%) in the inadequate response group showed bacterial growth on culture, of those 3 were Gram-positive cocci (1 case showed *staph. aureus* and 2 cases showed *enterococci*) and 1 was gram-negative bacilli (*Escherichia coli*). In contrast, only 1 case (7.14%) exhibited *Escherichia coli* growth in the group with adequate response showed bacterial growth ($p = 0.001$). When compared to patients with an adequate response, we noticed that those with an inadequate antibiotic response had a longer time interval between the onset of symptoms and the initiation of antibiotic treatment. Ascitic fluid analysis follow-up shows significantly higher values of TLC and PMN 48-hours as well as PMN 5-days post-treatment. Ascitic fluid TLC and PMN were decreased in both groups, with the adequate response group experiencing a significantly greater decrease ($p = 0.019$ and 0.049, respectively) as presented in **Table 6**.

Meanwhile, to determine the role of non-invasive laboratory investigations in predicting patients with inadequate responses, we calculated the degree of changes (Δ) in laboratory investigations. Δ lab investigation = the mean values measured at 48 hours of treatment minus their baseline levels. We observed statistically significant differences between the two groups. In contrast to the reduction in mean values of Δ TLC in CBC, Δ blood urea, Δ serum creatinine, and Δ CRP in

patients who had an adequate response, patients who had an inadequate response showed a non-significant decrease or even increase in their mean levels (**Table 7 and Figure 2**).

For the parameters (risk factors) influencing the development of SBP in cirrhotic patients, the univariate and multivariate logistic regression analyses revealed the following: with the univariate test diabetes mellitus had p value <0.001 and OR (LL – UL 95%C.I) 11.0(3.155 – 38.353), the history of hematemesis and/or melena had p= 0.027 OR 4.500(1.184 – 17.104), previous history of SBP had $p = 0.031$ OR 3.719(1.127 – 12.267), high random blood sugar had P = 0.001 OR 1.039(1.016 – 1.062), while total protein in ascitic fluid was protective had $p = 0.030$ OR 0.335(0.125 – 0.897). On the other hand, in the multivariate analysis only Diabetes mellitus and random blood sugar were independent predictors for SBP development and total protein in ascitic fluid was protective as displayed in **Table 8**.

Table 1. Demographic, clinical, and imaging data of studied patients.

		Total (n= 78)	No SBP (n = 59)	SBP variant (n = 19)	Test of sig.	*p*
Sex						
Male		47 (60.3%)	33 (55.9%)	14 (73.7%)	χ^2=1.891	0.169
Female		31 (37.9%)	26 (44.1%)	5 (26.3%)		
Age (years)						
Min. – Max.		45.0 – 70.0	45.0 – 69.0	45.0 – 70.0		
Mean ± SD.		55.52 ± 8.01	55.10 ± 8.22	56.84 ± 7.39	t=0.822	0.414
Median (IQR)		55.0(50.0 – 63.0)	52.0(48.5 – 62.5)	57.0 (50.0 – 62.5)		
Indication for admission						
Fever		9 (11.5%)	0 (0%)	9 (47.4%)	χ^2=31.593*	FEp<0.001*
Vomiting		4 (5.1%)	2 (3.4%)	2 (10.5%)	χ^2=1.504	FEp=0.248
Abdominal pain		14 (17.9%)	5 (8.5%)	9 (47.4%)	χ^2=14.762*	FEp<0.001*
Diarrhea		5 (6.4%)	2 (3.4%)	3 (15.8%)	χ^2=3.683	FEp=0.090
Disturbed conscious level		8 (10.3%)	4 (6.8%)	4 (21.1%)	χ^2=3.181	FEp=0.093
Hematemesis and/or melena		17 (21.8%)	11 (18.6%)	6 (31.6%)	χ^2=1.411	FEp=0.337
Uncontrolled ascites		35 (44.9%)	22 (37.3%)	13 (68.4%)	χ^2=5.631*	0.012*
Risk factors for SBP DM		30 (61.5%)	15 (25.4%)	15 (78.9%)	χ^2=17.395*	<0.001*
History of Hematemesis and/or melena		48 (81.5%)	32 (54.2%)	16 (84.2%)	χ^2=5.455*	0.020*
Previous history of SBP		15 (19.2%)	8 (13.6%)	7 (36.8%)	χ^2=5.016*	0.042*
Previous history of PPI		54 (69.2%)	40 (67.8%)	14 (73.7%)	χ^2=0.234	0.629
Antibiotic use within 2 weeks before admission						
Previous antibiotic (s)						
No		55 (70.5%)	44 (74.6%)	11 (57.9%)	χ^2=1.923	0.165
Yes		**23 (29.5%)**	**15 (25.4%)**	**8 (42.1%)**		
Type						
Quinolones		20 (25.6%)	13 (22%)	7 (36.8%)	χ^2= 2.328	MCp= 0.303
3rd generation cephalosporin		3 (3.8%)	2 (3.4%)	1 (5.3%)		
Duration (days)						
Min. – Max.		3.0 – 5.0	3.0 – 5.0	3.0 – 5.0	U=60.0	1.000
Median (IQR)		5.0(5.0 – 5.0)	5.0(5.0 – 5.0)	5.0(5.0 – 5.0)		
General examination						
Jaundice		50 (64.1%)	37 (62.7%)	13 (68.4%)	χ^2=0.204	0.652
Pallor		8 (10.3%)	8 (13.6%)	0 (0%)	χ^2=2.871	FEp=0.188
Disturbed conscious level		9 (11.5%)	4 (6.8%)	5 (26.3%)	χ^2=5.374*	FEp=0.034*
Lower limb edema		46 (59%)	34 (57.5%)	12 (63.2%)	χ^2=0.182	0.670
Local examination						
Ascites						
Grade 2		23(29.5%)	18 (30.5%)	5 (26.3%)	χ2=0.122	0.727
Grade 3		55 (70.5%)	41 (69.5%)	14 (73.7%)		
Abdominal tenderness						
No		59 (75.6%)	51 (86.4%)	8 (42.1%)	χ^2=15.332*	<0.001*
Yes		19 (24.4%)	8 (13.6%)	11 (57.9%)		
US	**Liver Size (cm)**					
	Min. – Max.	12.0 – 17.0	12.0 – 17.0	12.0 – 16.0	t= 0.207	0.837
	Mean ± SD.	14.60 ± 1.05	14.61 ± 1.10	14.55 ± 0.90		
	Median (IQR)	15.0(14.0 – 15.0)	15.0 (14.0 – 15.0)	15.0 (14.0 – 15.0)		
	Portal vein diameter					
	Normal	8 (10.3%)	6 (10.2%)	2 (10.5%)	χ^2= 0.002	FEp= 1.000
	Dilated	70 (89.7%)	53 (89.8%)	17 (89.5%)		
	Spleen size (cm)					
	Min. – Max.	10.50 – 26.0	10.50 – 23.0	13.50 – 26.0	U= 349.0*	0.028*
	Mean ± SD.	16.51 ± 2.87	16.10 ± 2.68	17.87 ± 3.12		
	Median (IQR)	15.90(15.0 – 18.0)	15.50 (14.0 – 17.50)	17.75 (15.5 – 19.70)		
	Spleen collaterals					
	No	65 (83.3%)	49 (83.1%)	16 (84.2%)	χ^2= 0.014	FEp= 1.000
	Yes	13 (16.7%)	10 (16.9%)	3 (15.8%)		

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, χ^2: Chi square test, FE: Fisher Exact test, t: Student t-test, p: p value for comparing between the two studied groups, *: Statistically significant at p < 0.05

Table 2. Laboratory investigations in studied patients

Lab parameters	Total (n= 78)	No SBP (n = 59)	SBP variant (n = 19)	Test of sig.	p
Hb (gm/dl)					
Min. – Max.	5.70 – 14.30	5.70 – 14.30	9.0 – 13.50	t= 1.351	0.181
Mean ± SD.	10.22 ± 1.57	10.08 ± 1.65	10.64 ± 1.23		
Median (IQR)	10.0 (9.20 – 11.40)	10.0 (9.0 – 11.35)	10.20 (9.80 – 11.6)		
TLC (×1000/ul)					
Min. – Max.	1.60 – 19.70	1.60 – 18.50	2.20 – 19.70	U= 407.0	0.074
Mean ± SD.	7.19 ± 3.99	6.61 ± 3.46	8.98 ± 5.0		
Median (IQR)	6.0(4.30 – 9.0)	5.90 (4.30 – 8.10)	8.0 (5.10 – 11.15)		
Platelet count (×1000/ul)					
Min. – Max.	38.0 – 353.0	38.0 – 353.0	47.0 – 180.0	t= 1.142	0.259
Mean ± SD.	133.33 ± 62.03	136.9 ± 67.55	122.4 ± 39.88		
Median (IQR)	122.0(87.0 – 165.0)	122.0(91.0 – 165.50)	119.0 (93.0 – 162.0)		
ALT (IU/L)					
Min. – Max.	4.0 – 348.0	4.0 – 65.0	8.0 – 348.0	U= 560.0	0.995
Mean ± SD.	31.08 ± 39.34	26.88 ± 14.44	44.11 ± 75.58		
Median (IQR)	24.0(16.0 – 33.0)	24.0 (17.5 – 33.0)	24.0 (17.5 – 33.0)		
Total bilirubin (mg/dl)					
Min. – Max.	0.30 – 18.0	0.30 – 18.0	0.70 – 7.0	U= 474.0	0.313
Mean ± SD.	2.17 ± 2.55	2.13 ± 2.77	2.29 ± 1.77		
Median (IQR)	1.35(0.90 – 2.10)	1.30 (0.90 – 2.10)	1.70 (1.0 – 3.15)		
Direct bilirubin (mg/dl)					
Min. – Max.	0.10 – 11.90	0.10 – 11.90	0.30 – 3.60	U= 457.50	0.229
Mean ± SD.	0.99 ± 1.54	1.0 ± 1.72	0.96 ± 0.81		
Median (IQR)	0.60(0.30 – 1.10)	0.60 (0.30 – 1.0)	0.70 (0.40 – 1.20)		
Serum albumin (g/dl)					
Min. – Max.	1.60 – 3.90	1.70 – 3.90	1.60 – 3.60	t= 0.446	0.657
Mean ± SD.	2.62 ± 0.49	2.63 ± 0.47	2.57 ± 0.57		
Median (IQR)	2.60(2.30 – 2.80)	2.60 (2.30 – 2.80)	2.60 (2.05 – 3.10)		
PT (seconds)					
Min. – Max.	25.0 – 95.0	25.0 – 95.0	27.0 – 83.0	t= 0.889	0.377
Mean ± SD.	57.24 ± 13.82	58.03 ± 13.30	54.79 ± 15.42		
Median (IQR)	56.0(50.0 – 63.0)	56.0 (51.5 – 61.5)	55.0 (43.0 – 64.0)		
INR					
Min. – Max.	0.90 – 2.40	0.90 – 2.40	1.10 – 2.30	U= 535.0	0.765
Mean ± SD.	1.45 ± 0.29	1.44 ± 0.27	1.50 ± 0.34		
Median (IQR)	1.40(1.30 – 1.60)	1.40 (1.30 – 1.58)	1.35 (1.30 – 1.70)		
Blood urea (mg/dl)					
Min. – Max.	20.0 – 222.0	20.0 – 222.0	20.0 – 142.0	U = 559.50	0.991
Mean ± SD.	59.09 ± 40.43	58.54 ± 40.81	60.79 ± 40.29		
Median (IQR)	44.0(29.0 – 77.0)	44.0 (31.0 – 68.0)	40.0 (28.0 – 84.0)		
Serum creatinine (mg/dl)					
Min. – Max.	0.40 – 7.0	0.40 – 7.0	0.50 – 3.90	U = 528.50	0.709
Mean ± SD.	1.49 ± 0.97	1.49 ± 0.98	1.51 ± 0.97		
Median (IQR)	1.20(0.90 – 1.70)	1.30 (0.90 – 1.70)	1.10 (0.90 – 1.75)		
Serum Na					
Min. – Max.	119.0 – 146.0	119.0 – 146.0	119.0 – 145.0	t= 0.446	0.657
Mean ± SD.	133.83 ± 5.78	134.0 ± 5.57	133.32 ± 6.52		
Median (IQR)	135.0(130.0 – 138.0)	135.0 (130.0 – 138.0)	135.0 (128.5 – 136.5)		
Serum K					
Min. – Max.	2.80 – 6.60	3.0 – 6.60	2.80 – 5.30	U= 436.50	0.148
Mean ± SD.	4.10 ± 0.69	4.07 ± 0.70	4.20 ± 0.66		
Median (IQR)	4.0(3.60 – 4.50)	4.0 (3.60 – 4.40)	4.30 (3.90 – 4.65)		
CRP					
Negative	48(61.5%)	46(80.7%)	2(10.5%)	χ²= 30.159*	<0.001*
Positive	28(35.9%)	11(19.3%)	17(89.5%)		
Min. – Max.	6.0 – 187.0	6.0 – 6.0	6.0 – 187.0	U= 57.0*	<0.001*
Mean ± SD.	17.80 ± 36.34	6.0 ± 0.0	25.0 ± 40.97		
Median (IQR)	6.0(6.0 – 12.0)	6.0(6.0 – 6.0)	12.0(12.0 – 12.0)		
RBS (mg/dl)					
Min. – Max.	89.0 – 325.0	89.0 – 200.0	130.0 – 325.0	t= 3.688*	0.001*
Mean ± SD.	148.47 ± 45.85	134.51 ± 24.74	191.84 ± 66.30		
Median (IQR)	140.0(120.0 – 160.0)	130.0(120.0 – 147.5)	160.0(152.5 – 225.0)		
MELD score					
Min. – Max.	6.0 – 27.0	6.0 – 27.0	7.0 – 26.0	U = 521.0	0.644
Median (IQR)	15.0 (12 - 19)	14 (12.0 – 19.0)	16.0 (12.0 – 21)		
MELD Na score					
Min. – Max.	6.0 – 43.0	6.0 – 43.0	7.0 – 43.0	U = 509.0	0.548
Median (I	19.0 (12 - 26)	19.0 (12 – 26)	21.0 (13 - 26)		

Table 3. Ascitic fluid analysis in studied patients

		Total (n= 78)	No SBP (n = 59)	SBP (n = 19)	Test of sig.	p
	Timing of AF sample aspiration (hours)					
	Min. – Max.	1.0 – 3.0	1.0 – 3.0	1.0 – 3.0	U=60.0	1.000
	Mean ± SD.	1.72 ± 0.70	1.69 ± 0.70	1.79 ± 0.71		
	Median (IQR)	2.0 (1.0 – 2.0)	2.0 (1.0 – 2.0)	2.0 (1.0 – 2.0)		
Ascitic fluid analysis	**Albumin**					
	Min. – Max.	0.10 – 3.60	0.30 – 3.60	0.10 – 1.80	U= 360.50*	0.019*
	Mean ± SD.	0.82 ± 0.48	0.87 ± 0.49	0.66 ± 0.42		
	Median (IQR)	0.80(0.50 – 1.0)	0.90 (0.60 – 1.0)	0.50 (0.40 – 0.75)		
	SAAG					
	Min. – Max.	1.10 – 3.30	1.10 – 3.30	1.20 – 3.30	U=429.50	0.126
	Mean ± SD.	1.83 ± 0.54	1.78 ± 0.52	2.0 ± 0.57		
	Median (IQR)	1.80(1.40 – 2.30)	1.60 (1.30 – 2.20)	1.80 (1.55 – 2.35)		
	Total protein					
	Min. – Max.	0.70 – 4.10	1.00 – 4.10	0.70 – 4.07	U=378.50*	0.031*
	Mean ± SD.	1.89 ± 0.66	1.99 ± 0.57	1.60 ± 0.83		
	Median (IQR)	2.0(1.50 – 2.0)	2.0 (1.75 – 2.0)	1.70(0.90 – 2.0)		
	TLC					
	Min. – Max.	20.0 – 6170.0	20.0 – 560.0	620.0 – 6170.0	U=0.000*	<0.001*
	Mean ± SD.	609.49 ± 1033.50	213.22 ± 148.45	1840.0 ± 1544.40		
	Median (IQR)	215.0(110.0 – 560.0)	190.0(100.0–300.0)	1300.0(830.0–1900.0)		
	PMN absolute count					
	Min. – Max.	6.0 – 4936.0	6.0 – 208.0	344.0 – 4936.0	U=0.000*	<0.001*
	Mean ± SD.	403.02 ± 839.53	89.43 ± 61.42	1376.79 ± 1296.01		
	Median (IQR)	117.0(43.0 – 208.0)	80.0(34.0 – 141.5)	876.0(607.5 – 1457.0)		
	Glucose					
	Min. – Max.	34.0 – 477.0	34.0 – 350.0	46.0 – 477.0	444.0	0.174
	Mean ± SD.	130.59 ± 58.16	130.07 ± 42.54	132.21 ± 92.92		
	Median (IQR)	120.0(111.0 – 135.0)	120.0 (112.0 – 135.5)	120.0 (98.0 – 126.0)		
	LDH					
	Min. – Max.	32.0 – 230.0	32.0 – 212.0	60.0 – 220.0	490.0	0.411
	Mean ± SD.	118.19 ± 33.51	115.07 ± 32.22	127.89 ± 36.45		
	Median (IQR)	120.0(111.0 – 130.0)	117.0(111.0 – 130.0)	120.0(111.50 – 131.0)		
	Timing of antibiotic initiations in SBP patients					
	Min. – Max.	2.0 – 5.0	2.0 – 5.0	2.0 – 4.0	U= 509.50	0.515
	Mean ± SD.	2.83 ± 0.75	2.81 ± 0.78	2.89 ± 0.66		
	Median (IQR)	3.0 (2.0 – 3.0)	3.0 (2.0 – 3.0)	3.0 (2.50 – 3.0)		

Table 4. Comparison between SBP patients with and without adequate antibiotic response according to demographic data, risk factors to SBP, and clinical examination .

	Antibiotic response		Test of sig.	*p*
	Inadequate response (n = 5)	Adequate response (n = 14)		
Sex				
Male	3 (60%)	11 (78.6%)	χ^2=0.655	FEp=0.570
Female	2 (40%)	3 (21.4%)		
Age (years)				
Mean ± SD.	56.60 ± 6.99	56.93 ± 7.78	t=0.083	0.935
Median (Min. – Max.)	57.0 (48.0 – 66.0)	57.50 (45.0 – 70.0)		
Risk factors for SBP				
DM	5 (100%)	10 (71.4%)	χ^2=1.810	FEp=0.530
Hematemesis and melena	4 (80%)	12 (85.7%)	χ^2=0.090	FEp=1.000
Previous history of SBP	4 (80%)	3 (21.4%)	χ^2=5.432*	FEp=0.038*
Previous history of PPI	2 (40%)	12 (85.7%)	χ^2=3.971	FEp=0.084
Antibiotic use within 2 weeks before admission				
Yes	**4 (80%)**	**4 (28.6)**	**χ^2=1.923**	0.165
Type				
Quinolones	4 (80%)	3 (21.4%)	χ^2=5.022	MCp=0.096
3rd generation	0 (0%)	1 (7.1%)		
Duration (days)				
Min. – Max.	5.0 ± 0.0	3.0 – 5.0	U=6.0	0.686
Median (IQR)	5.0 (5.0 – 5.0)	5.0(5.0 – 5.0)		
Clinical examination: Fever	2 (40%)	7 (50%)	χ^2=0.148	FEp=1.000
Conscious state				
Disturbed conscious level (DCL)	1 (20%)	4 (28.6%)	χ^2=0.140	FEp=1.000
Abdominal tenderness	3 (60%)	8 (57.1%)	χ^2=0.012	FEp=1.000
Time interval between onset of symptoms and admission in days (Median (Min. – Max.)	4.0 (3.0 – 5.0)	1.50 (1.0 – 2.0)	U=0.0*	<0.001*
Clinical assessment follow-up (post 48 hours)				
Fever	1 (20%)	1 (7.14%)	χ^2=0.647	FEp=0.468
Disturbed conscious level (DCL)	3 (60%)	0 (0%)	χ^2=9.975*	FEp=0.002*
Abdominal tenderness	4 (80%)	2 (14.3%)	χ^2=7.363*	FEp=0.017*

IQR: Inter quartile range, SD: Standard deviation, t: student t-test, χ^2: Chi square test, MC: Monte Carlo, FE: Fisher Exact, U: Mann Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at $p < 0.05$

Table 5. Relation between Antibiotic response and laboratory investigations

CBC	Antibiotic response		Test of sig.	p
	Inadequate response (n = 5)	Adequate response (n = 14)		
Hb (gm/dl)				
Mean ± SD.	10.42 ± 1.49	10.71 ± 1.18	t=0.449	0.659
Median (Min. – Max.)	9.90 (9.0 – 12.20)	10.60 (9.0 – 13.50)		
TLC (×1000/ul)				
Mean ± SD.	8.08 ± 3.83	9.31 ± 5.45	U=34.50	0.964
Median (Min. – Max.)	5.90 (4.80 – 13.10)	9.0 (2.20 – 19.70)		
Platelet count (×1000/ul)				
Mean ± SD.	115.8 ± 44.34	124.7 ± 39.69	t=0.419	0.680
Median (Min. – Max.)	119.0 (47.0 – 166.0)	123.0 (67.0 – 180.0)		
Serum albumin (g/dl)				
Mean ± SD.	2.70 ± 0.53	2.53 ± 0.60	t=0.563	0.581
Median (Min. – Max.)	2.60 (2.10 – 3.30)	2.45 (1.60 – 3.60)		
Blood urea (mg/dl)				
Mean ± SD.	54.80 ± 23.22	62.93 ± 45.42	U=33.0	0.893
Median (Min. – Max.)	60.0 (28.0 – 88.0)	40.0 (20.0 – 142.0)		
Serum creatinine (mg/dl)				
Mean ± SD.	1.18 ± 0.53	1.62 ± 1.08	U=29.0	0.622
Median (Min. – Max.)	1.0 (0.80 – 2.10)	1.25 (0.50 – 3.90)		
CRP				
Negative	1(20.0%)	1(7.1%)	χ^2=0.647	FEp= 0.468
Positive	4(80.0%)	13(92.9%)		
Mean ± SD.	45.80 ± 78.98	17.57 ± 13.41	U=32.50	0.823
Median (Min. – Max.)	12.0 (6.0 – 187.0)	12.0 (6.0 – 48.0)		
CRP				
Mean ± SD.	80.60 ± 64.98	9.0 ± 5.13	U=0.500*	<0.001*
Median (Min. – Max.)	48.0(24.0 – 187.0)	6.0(6.0 – 24.0)		
RBS (mg/dl)				
Mean ± SD.	219.0 ± 97.43	182.1 ± 52.72	t=0.805	0.458
Median (Min. – Max.)	160.0 (130.0 – 325.0)	160.0 (135.0 – 325.0)		
MELD score				
Mean ± SD.	15.80 ± 3.42	16.36 ± 6.21	U=32.50	0.823
Median (Min. – Max.)	15.0 (12.0 – 21.0)	17.0 (7.0 – 26.0)		
MELD score Na				
Mean ± SD.	20.80 ± 5.26	21.86 ± 11.70	U=34.0	0.964
Median (Min. – Max.)	22.0 (12.0 – 26.0)	19.0 (7.0 – 43.0)		
Laboratory investigations follow-up (post 48 hours)				
TLC after 48h				
Mean ± SD.	10.38 ± 2.43	6.23 ± 2.54	U=9.0*	0.014*
Median (Min. – Max.)	10.80(6.70 – 12.60)	5.40(2.70 – 12.80)		
Blood urea after 48h				
Mean ± SD.	69.0 ± 28.79	44.29 ± 20.53	U=15.50	0.070
Median (Min. – Max.)	54.0(44.0 – 112.0)	34.0(21.0 – 88.0)		
Serum creatinine after 48h				
Mean ± SD.	1.48 ± 0.61	1.36 ± 0.91	U=25.0	0.391
Median (Min. – Max.)	1.40(0.70 – 2.30)	1.0(0.70 – 3.40)		
CRP after 48h				
Mean ± SD.	80.60 ± 64.98	9.0 ± 5.13	U=0.500*	<0.001*
Median (Min. – Max.)	48.0(24.0 – 187.0)	6.0(6.0 – 24.0)		

Hb: hemoglobin concentration, TLC: total leucocyte count, CRP: C reactive protein, RBS: random blood sugar, MELD: Model for End-Stage Liver Disease, IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, U: Mann Whitney test, χ^2: Chi square test, FE: Fisher Exact, p: p value for comparing between the two studied groups, *: Statistically significant at $p < 0.05$

Table 6. Ascitic fluid analysis in SBP patients and its follow up

	Antibiotic response		U	p
	Inadequate response (n = 5)	Adequate response (n = 14)		
Timing of AF sample aspiration (hours)				
Mean ± SD.	1.40 ± 0.55	1.93 ± 0.73	U=21.0	0.219
Median (Min. – Max.)	1.0 (1.0 – 2.0)	2.0 (1.0 – 3.0)		
Albumin				
Mean ± SD.	0.36 ± 0.15	0.76 ± 0.44	9.0*	0.014*
Median (Min. – Max.)	0.40(0.10 – 0.50)	0.55(0.30 – 1.80)		
SAAG				
Mean ± SD.	2.36 ± 0.48	1.87 ± 0.56	15.50	0.070
Median (Min. – Max.)	2.50(1.60 – 2.80)	1.75(1.20 – 3.30)		
T. Protein				
Mean ± SD.	1.38 ± 0.77	1.68 ± 0.86	30.0	0.687
Median (Min. – Max.)	1.0 (0.70 – 2.40)	1.80 (0.70 – 4.07)		
TLC				
Mean ± SD.	2428.0 ± 2263.3	1630.0 ± 1243.4	30.0	0.687
Median (Min. – Max.)	1450.0 (620.0 – 6170.0)	1250.0 (660.0 – 5300.0)		
PMN absolute count				
Mean ± SD.	1949.8 ± 1870.2	1172.1 ± 1038.3	26.0	0.444
Median (Min. – Max.)	1160.0 (372.0 – 4936.0)	863.0 (344.0 – 4346.0)		
PMN (%)				
Mean ± SD.	75.80 ± 11.10	69.14 ± 15.37	26.50	0.444
Median (Min. – Max.)	80.0 (60.0 – 89.0)	73.0 (40.0 – 89.0)		
Lymphocytes (%)				
Mean ± SD.	27.0 ± 19.87	23.71 ± 10.84	33.0	0.893
Median (Min. – Max.)	20.0 (10.0 – 60.0)	20.50 (10.0 – 55.0)		
Glucose				
Mean ± SD.	73.20 ± 37.27	153.3 ± 98.54	1.0*	<0.001*
Median (Min. – Max.)	84.0 (8.0 – 102.0)	121.0 (94.0 – 477.0)		
LDH				
Mean ± SD.	115.8 ± 8.11	132.2 ± 41.74	19.50	0.156
Median (Min. – Max.)	112.0 (111.0 – 130.0)	121.5 (60.0 – 220.0)		
Microbiological examination				
No bacterial growth	1 (20%)	14 (100%)		
Gram positive	3 (60%)	0 (0%)	χ^2=12.049*	^{MC}p= 0.001*
Gram negative	1 (20%)	0 (0%)		
Duration between onset symptoms and admission (Starting antibiotic therapy)				
Mean ± SD.	3.80 ± 0.84	1.50 ± 0.52	U=0.0*	<0.001*
Median (Min. – Max.)	4.0(3.0 – 5.0)	1.50(1.0 – 2.0)		
Ascitic fluid analysis follow-up (post 48 hours and 5 days)			U	P
TLC after 48 h				
Mean ± SD.	2118.0 ± 1967.3	684.9 ± 517.6	8.0*	0.010*
Median (Min. – Max.)	1120.0 (700.0 – 5400.0)	532.0 (230.0 – 2110.0)		
PMN after 48 h				
Mean ± SD.	1631.0 ± 1521.2	397.4 ± 432.1	8.0*	0.010*
Median (Min. – Max.)	950.0 (290.0 – 4005.0)	239.5 (114.0 – 1780.0)		
PNL post 5 days				
Mean ± SD.	536.0 ± 511.2	113.2 ± 72.08	6.0*	0.005*
Median (Min. – Max.)	275.0 (120.0 – 1380.0)	78.50 (35.0 – 245.0)		
Delta (change) in AF TLC and PMN post 48 hours				
Δ TLC AF				
Mean ± SD.	-310.0 ± 318.0	-945.1 ± 739.9	10.0*	0.019*
Median (Min. – Max.)	-330.0 (-770.0 – 80.0)	-723.0(-3190.0– -0.340)		
Δ PMN AF				
Mean ± SD.	-310.80 ± 358.80	-774.79 ± 658.64	14.0	0.049*
Median (Min. – Max.)	-210.0(-931.0 – -50.0)	-527.0(-2566.0– -157.0)		

SAAG: serum ascites albumin gradient, TLC: total leukocyte count, PMN: polymorphenuclear, LDH: lactate dehydrogenase, IQR: Inter quartile range, SD: Standard deviation, t: student t-test, χ^2: Chi square test, FE: Fisher Exact, U: Mann Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at $p < 0.05$.

Table 7. Delta (change) in laboratory investigations in SBP patients with and without adequate antibiotic response for non-invasive predictors of inadequate response
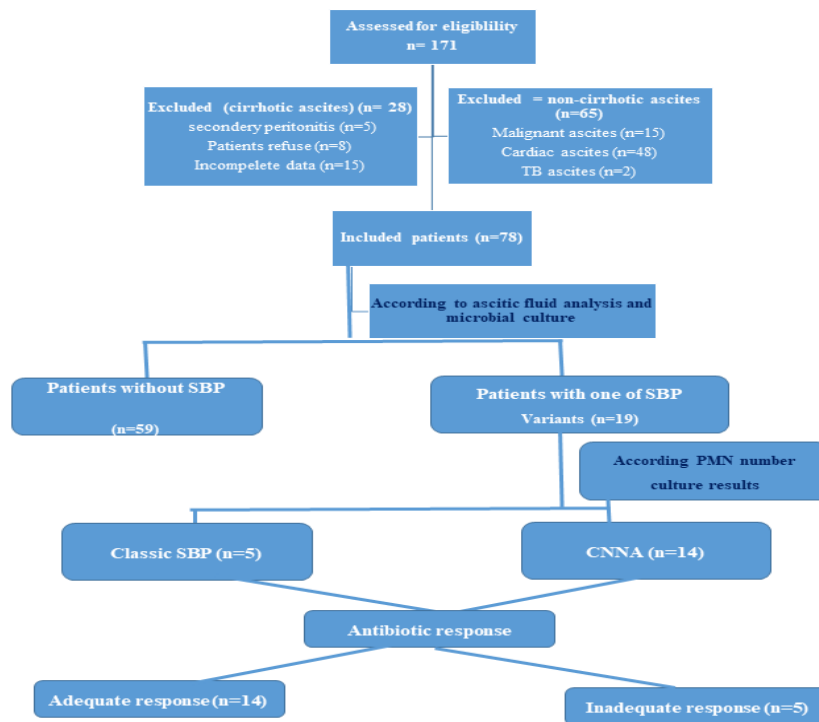
Delta change	Antibiotic response		U	p
	Inadequate response (n = 5)	Adequate response (n = 14)		
Δ TLC in CBC				
Mean ± SD.	2.30 ± 3.14	-3.08 ± 4.23	10.0*	0.019*
Median (Min. – Max.)	1.40 (-0.50 – 6.50)	-1.25 (-14.30 – 0.60)		
Δ Blood Urea				
Mean ± SD.	14.20 ± 17.24	-18.64 ± 26.01	9.0*	0.014*
Median (Min. – Max.)	22.0 (-16.0 – 25.0)	-6.50 (-74.0 – 5.0)		
Δ Serum Creatinine				
Mean ± SD.	0.30 ± 0.32	-0.26 ± 0.29	5.50*	0.003*
Median (Min. – Max.)	0.30 (-0.10 – 0.80)	-0.25 (-0.80 – 0.20)		
Δ CRP				
Mean ± SD.	34.80 ± 34.57	-8.57 ± 10.45	2.0*	0.001*
Median (Min. – Max.)	36.0 (0.0 – 90.0)	-6.0 (-36.0 – 0.0)		

Δ: the values measured at 48 hours of treatment – baseline levels, TLC: total leukocyte count, PMN: polymorphenuclear, IQR: Inter quartile range, SD: Standard deviation, t: student t-test, U: Mann Whitney test, p: p value for comparing between the two studied groups, *: Statistically significant at $p < 0.05$

Table 8. Univariate and multivariate Logistic regression analysis for the parameters (risk factors) for the development of SBP

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
Age	0.409	1.028(0.963 – 1.097)		
Sex (female)	0.175	0.453(0.145 – 1.422)		
Diabetes mellitus	<0.001*	11.0(3.155 – 38.353)	0.002*	27.924(3.235–241.026)
Hematemesis and/or melena	0.027*	4.500(1.184 – 17.104)	0.253	3.005(0.455–19.846)
Previous history of SBP	0.031*	3.719(1.127 – 12.267)	0.863	1.180(0.181–7.717)
Previous history of PPI	0.629	1.330(0.418 – 4.234)		
Random blood sugar	0.001*	1.039(1.016 – 1.062)	0.003*	1.060(1.020–1.101)
Albumin in ascitic fluid	0.072	0.223(0.044 – 1.142)		
SAAG	0.127	2.122(0.808 – 5.574)		
Total protein in ascitic fluid	0.030*	0.335(0.125 – 0.897)	0.005*	0.298(0.082–0.988)

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit, #: All variables with p<0.05 was included in the multivariate, *: Statistically significant at $p < 0.05$, Hosmer and Lemeshow Test= $\chi^2(p) = 2.026 (0.980)$
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Figure 1: A CONSORT flowchart of the study population

Figure 2: Degree of changes (Δ) in laboratory investigations A: Δ TLC in CBC in SBP patients with and without adequate antibiotic response, B: Δ blood urea in SBP patients with and without adequate antibiotic response, C: Δ creatinine in SBP patients with and without adequate antibiotic response, D: Δ CRP in SBP patients with and without adequate antibiotic response, E: Δ TLC AF in SBP patients with and without adequate antibiotic response, F: Δ PMN AF in SBP patients with and without adequate antibiotic response
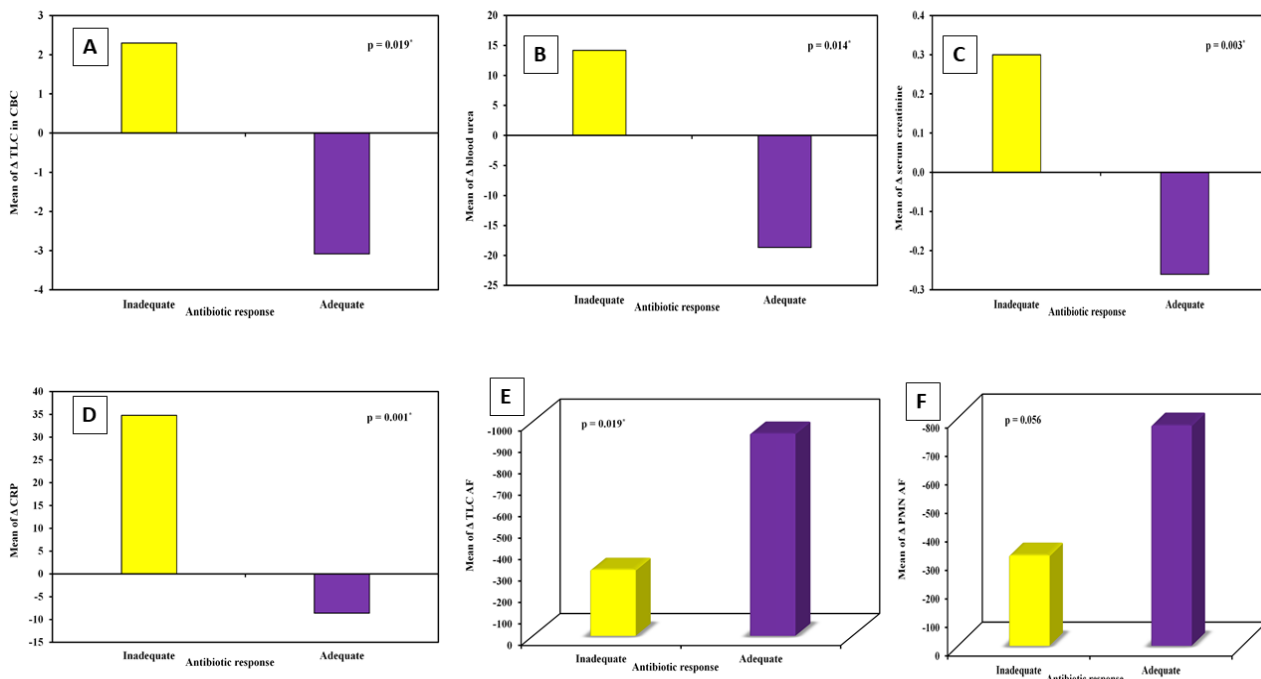
Discussion

Spontaneous bacterial peritonitisis a prevalent infection in patients with cirrhosis and ascites, affecting 10-30% of hospitalized and 3.5% outpatients, with in-hospital mortality ranging from 20-40%. SBP leads to kidney failure, acute on chronic liver failure, hepatic encephalopathy, gastrointestinal bleeding, hypervolemic hyponatremia, systemic sepsis, and poor survival [13].

According to European guidelines, diagnostic paracentesis is recommended for cirrhotic patients with (i) ascites requiring hospitalization, (ii) systemic or localized symptoms like fever, tachycardia, and/or tachypnea, vomiting, diarrhea, abdominal pain, tenderness and (iii) clinical deterioration, including hepatic encephalopathy, gastrointestinal bleeding, worsening renal or liver function. Besides, a new paracentesis should be performed 48 hours after the initial administration of antibiotics to show SBP resolution (defined as a drop in PMN cells of more than 25%) and modify therapy as necessary. Recent research suggests that this procedure may be tailored to each patient's unique needs based on their clinical and laboratory findings rather than being essential for all patients [9]. Furthermore, manually counting PMNs is tedious, time-consuming, and requires some experience to prevent variability among observers [14]. As a result, in clinical settings, there is still a significant demand to characterize patients who would benefit from a second paracentesis to adjust their antibiotic regimen and reduce unnecessary invasive procedures.

The study aimed to analyze the frequency of spontaneous bacterial peritonitis in cirrhotic patients with ascites and identify its risk factors and the predictors of inadequate antibiotic treatment response.

Based on ascitic fluid examination and ascitic fluid microbiological cultures in the current study, 19 (24.4%) patients of cirrhotic patients with ascites presented with one of the SBP variants patients. The body's response to infection may be inadequately expressed in cirrhosis because the disease is associated with immunosuppression known as cirrhosis-associated immune dysfunction (CAID). Thus, SBP should always be considered in the case of a sudden deterioration of liver function in all patients with liver cirrhosis, including those with mild ascites [15]. According to the current study, SBP was more common in men (73.7%) than in women (26.3%) and was unaffected by age. This finding was consistent with the research conducted by **Piano et al.,** which found that SBP was more common in men and not influenced by age [16].

Spontaneous bacterial peritonitisis is a cirrhosis complication that typically signifies a significant progression of the disease. For this reason, figuring out the risk factors for SBP is crucial to determine the progression of the condition. Regarding the risk factors for SBP, we noticed that patients with SBP had higher rates of diabetes mellitus, hematemesis and/or melena history, and prior history of SBP than did patients without SBP. Additionally, univariate and multivariate logistic regression analyses demonstrated that, total protein in ascitic fluid was protective, while DM, high random blood sugar, and prior history of SBP were significant risk factors.

In accordance with these results, **Tergast et al.** found that DM increases the risk of developing SBP in cirrhosis patients because it alters leukocyte function, and the immune system, and causes polyneuropathy. These alterations result in intestinal transit time extension and dyskinesia of the bowel muscles, raising the possibility of bacterial translocation from the gut [17]. According to **Dever and Sheikh,** hematemesis increases the risk of SBP occurring and recurring, which is explained by the presence of mucosal breaks. Deficits in complements in cirrhotic patients may also increase the risk of infection [18]. Furthermore, **Tandon and Garcia-Tsao,** noticed that a prior history of SBP increases the likelihood of a recurrence of SBP because of weakened immune systems, bacterial translocation from the gut [19].

In the current study, the SBP group reported a higher history of PPI intake than the non-SBP group, but with no significant difference; the majority of patients reported intermittent PPI intake. A meta-analysis clarifies the contradictory findings on the relationship between SBP and PPI use. This meta-analysis revealed a statistically significant but weak correlation between SBP and the use of PPI. The authors reported that the potential association's magnitude decreased when analysis was concentrated on more robust and higher-quality data, and recommended that cirrhotic patients with ascites should use PPIs carefully [20].

Clinically, patients with spontaneous bacterial peritonitis have higher frequency of fever and uncontrolled ascites than those without SBP, but no significant differences in vomiting, diarrhea, or hematemesis as the indications for hospital admission. Notably, patients with SBP had a significantly higher prevalence of disturbance of the conscious level compared to those without with statistically non-significant difference. Furthermore, 24.4% of the patients had abdominal tenderness on local examination, which was more commonly found in SBP patients.

Our findings aligned with the published results. According to a prior study by **Fernandez et al.,** ascitic fluid infection mostly developed when the volume of ascites was at its maximum [21]. According to **Nobre et al.,** there was no difference in the incidence of hepatic encephalopathy between patients who had SBP and those who did not [22]. Additionally, it was noted that patients with SBP frequently present with abdominal pain and tenderness (71–80% of patients) [23].

In terms of laboratory studies, we found no appreciable differences in any of the complete blood count parameters, liver, kidney, or MELD or MELD Na scores between patients with and without SBP. Nonetheless, there is still a tendency towards increased TLC in SBP patients, in addition to a higher mean CRP value that is more frequently positive. These results agreed with those of **Sheer and Runyon,** who observed no discernible variation in liver biochemistry between patients with SBP and those without. Furthermore, they reported that any disturbance in liver function as prolonged prothrombin time and hypoalbuminemia are linked to the underlying liver disease rather than the presence of SBP [24]. **Elsadek et al.** found that the CRP levels of cirrhotic patients with SBP varied significantly. They attributed this difference to the liver's production of CRP in response to infection and inflammation [25].

Ascitic fluid aspiration was done within the first three hours of admission for every patient in our study. Analysis of ascitic fluid shows that patients with SBP had higher TLC and PMN cells, but lower total protein and albumin. Higher ascitic fluid PMN cell count in SBP patients than in non-SBP patients was explained by the peritoneum's inflammatory response, which is indicated by PMN recruitment into the peritoneal cavity. As a sign of an active infection, an increase in the ascitic PMN count indicates the mobilization of PMNs in response to bacterial invasion. Moreover, reduced albumin impairs the opsonization of bacteria, reduces neutrophil function, and weakens the intestinal mucosal barrier integrity, which makes bacteria more likely to translocate increasing the susceptibility to SBP [26].

Regarding ascitic fluid culture findings in the present study, most patients with spontaneous bacterial peritonitis (14 out of 19 representing 73.7%) exhibit no bacterial growth (CNNA), while 5 cases (26.3%) showed bacterial growth (3 cases (60%) were gram positive cocci and 2 cases (40%) were gram negative bacilli). The culture negativity may be due to low concentration of bacteria in ascitic fluid.

Gharabawy et al. found that 179 patients (58.3 %) among 400 SBP Egyptian patients had CNNA while, 128 (41.7%) patients had positive cultures, and that patients with positive cultures experienced gram-negative bacteria in 60.2% and gram-positive in 39.8% [27]. Despite use of sensitive methods for culture approximately 60% of ascetic fluid samples with PMN more than 250 do not show evidence of bacterial growth this explained by prior antibiotic use before admission and wide use of antibiotic prophylaxis for SBP [28]. Conversely, **Oladimeji et al.,** found that culture-positive SBP was present in 66.7%, while CNNA was found in 33.3% [29]. The variation in study population, the timing of the ascitic fluid collection, the culture bottle used, and the facilities are all blamed for the discrepancy in the culture results.

A German study involving 311 cirrhotic patients with ascites. They observed SBP in 197 patients, of those 114 patients had positive cultures. 47.8% of the bacteria were gram-positive, of which 26.1% were *Enterococcus* and 13.8% were *Staphylococcus species* [30]. Other culture findings were found in the study conducted in the Central European region, where 80% of the bacteria causing SBP (in 4 out of 5 cases) proved to be G-positive [31].

48 hours after treatment, the ascitic fluid PMN count was measured; a decrease of at least 25% was deemed indicative of an adequate antibiotic response in patients. Statistical analysis revealed that 5 out of 19 cases (26.3%) of SBP patients experienced inadequate antibiotic response after 48hrs treatment. This might be explained by the fact that using antibiotics empirically increases antimicrobial resistance, making the eradication of SBP challenging. Furthermore, the bacterial profile varies by geographic location and can differ even within a single nation's hospitals. Consequently, the local epidemiology should be taken into consideration when selecting first-line empirical antibiotic therapy [32].

When we compared patients with and without adequate antibiotic response, we found no statistically significant difference in age, sex, or baseline clinical findings. However, patients with inadequate response had a longer time interval

between onset of symptoms and hospital admission and a higher frequency of prior SBP history. In line with our findings, **Rostkowska et al.** reported that, in cirrhotic patients with SBP, it is crucial to diagnose them and initiate an efficient antibiotic regimen as soon as possible. A delay in starting appropriate treatment is associated with worse outcomes and a higher death rate [8].

Clinical assessment follow-up (after 48 hours) for patients with an inadequate response reveals that one patient (20%) had fever, 3 patients (60%) had disturbed conscious level, and 4 patients (80%) had abdominal tenderness compared to 7.14%, 0%, and 14.3% in those with adequate response. All baseline laboratory results showed no statistically significant differences between the two groups, with the exception of lower ascitic fluid albumin and higher CRP. Nonetheless, in patients with insufficient antibiotic response, 48-hour laboratory results revealed little to no decrease in TLC in CBC, CRP, blood urea, and serum creatinine, or even an increase in these levels.

Taken together (clinical and laboratory follow-up findings), our findings suggest an individualized approach when following SBP cases. The current study identified certain clinical and non-invasive laboratory parameters that could point to a poor response to antibiotics 48 hours after therapy initiation. Some of these parameters were present at admission and the others were observed at follow-up. This could help identify who would benefit from a second paracentesis to modify antibiotic therapy (SBP patients with inadequate response) and avoid unnecessary invasive procedures (in patients with adequate response). When patients with inadequate response are identified, antibiotic should be modified as early as possible according to culture and antibiotic susceptibility results. This fact highlights the importance of providing AF for microbiologic analysis when there is a suspicion of SBP. Furthermore, AF needs to be cultured before antibiotic initiation.

Conclusion

A good clinical evaluation is necessary for the early identification of SBP patients and the early prediction of patients with inadequate antibiotic responses. Delayed antibiotic initiation, positive culture, and clinical suspicion together with non-significant decrease or even increase in TLC in the blood, CRP, blood urea, and serum creatinine 48-hours of antibiotic initiation are potential predictors for inadequate response. This helps identify who

would benefit from a second paracentesis and minimize unnecessary invasive procedures.

Limitations

A few limitations of the current study included its restriction to a single center, which resulted in a smaller patient pool. In addition, patients in our study require additional monitoring to detect those who had additional SBP episodes and those who developed SBP complications such as hepatorenal syndrome. It is important to acknowledge these limitations as they provide invaluable insights for future researches and reinforce the need to conduct longitudinal, multi-center.

Abbreviations

AF: Ascitic fluid

ALT: Alanine transaminase

CBC: Complete blood count

CRP: C-reactive protein

CTP: Child-Turcotte-Pugh

Hb: Hemoglobin concentration

INR: International normalized ratio

LDH: lactate dehydrogenase

MELD: Model for End-Stage Liver Disease

PMN: Polymorphonuclear

PPI: Proton pump inhibitors

PT: Prothrombin time

RBS: Random blood sugar

SAAG: Serum ascites albumin gradient

SBP: Spontaneous bacterial peritonitis

TLC: Total leucocyte count

Disclosure

Ethics approval and consent to participate: After elaborating the research objectives and the research questions, each participant was given an explanation of the study and the chance to give written, informed consent before being enrolled. The research methodology and the sample size calculation were authorized by the Research Ethics Committee, Faculty of Medicine, Menoufia University, Egypt; with Institutional Review Board (IRB) approval number: 5/2022 TROP2, and was performed in accordance with the Helsinki Declaration.

Consent for publication

Not applicable.

Authors' contributions

All authors made significant contributions to the work presented, whether in the areas of ideation, study design, implementation, data collection, analysis, and interpretation, or all of these. They also contributed to the article's writing, revising, or critical evaluation, gave final approval for the version to be published, chose the journal to which the article was submitted, and agreed to be responsible for all aspects of the work.

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