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Original article

Spontaneous fungal peritonitis is not a rare infection in cirrhotic patients with ascites: A cross-sectional study

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ABSTRACT

Background: In individuals with terminal-stage liver disease, spontaneous peritonitis, particularly spontaneous fungal peritonitis, is a serious fatal condition. We assessed different risk variables, microbiological results, and patient outcomes in SFP patients compared to patients with spontaneous bacterial peritonitis. **Objective:** We aimed to evaluate the frequency and risk factors for the development of SFP in cirrhotic patients with ascites. **Patients and methods:** We conducted a cross-sectional study on 154 cirrhotic patients with ascites (102 males and 52 females) who were admitted to the Tropical Medicine and Gastroenterology Departments in our Hospital. The samples were sent to the clinical and chemical pathology laboratory at Sohag university hospital. Detailed history, clinical examination, ascitic fluid analysis, laboratory investigations, abdominal ultrasonography, and bacterial and fungal cultures from ascitic fluid were performed. **Results:** The patients were categorized into 3 groups according to the ascitic fluid analysis and the bacterial and fungal culture. The first group included 69 patients (44.5%) who were diagnosed with SBP. The second group included 15 patients (9.7%) who were diagnosed with SFP. The third group included 71 patients (45.8%) who were diagnosed with liver cirrhosis without ascitic fluid infection. As regard the bacterial and fungal culture of ascitic fluid, *Escherichia coli* was the most reported bacterial infection (32.7%) followed by *Klebsiella pneumonia* (22.4%), while *Candida ciferrii* was the most reported fungal infection (10.2%) followed by *Candida albicans* (8.2%). **Conclusions:** SFP is not a rare complication of liver cirrhosis with ascites. It should be considered mainly in patients with high Model of End-stage Liver Disease and Child-Turcotte- Pugh scores.

Introduction

Liver cirrhosis is considered a risk factor for the emergence of certain infections as spontaneous bacterial peritonitis (SBP) or spontaneous fungal peritonitis (SFP) [1], which can be fatal in these patients [2]. SFP death rate ranges from 56% to 90% 2,3. Severe underlying chronic hepatic disease, high Child-Turcotte- Pugh (CTP) score, Model of End-stage Liver Disease (MELD) scores, antimicrobial prophylaxis, the occurrence of

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hepatorenal syndrome, reduced ascitic protein level, acute physiology and chronic health evaluation score, and septic shock are the most common risk factors linked to the hospital death rate in SFP [4].

Spontaneous peritonitis is known as infection of the peritoneal cavity without intra-abdominal inflammation or perforation, abdominal wall infections, or intra-abdominal surgery [5]. Diagnosis of SFP depends on the presence of 250 polymorphonuclear leukocytes (PMNs)/mm3 or more in the ascitic fluid and positive ascitic fungal culture with or without the presence of bacterial colonization. Positive ascitic fungal culture without bacterial co-colonization and less than 250 PMNs/mm3 in the ascitic fluid are considered to be fungi ascites [2, 6].

Cirrhotic patients are at high risk of fungal infection [7] as the antimicrobial drugs used in the treatment of SBP may cause fungal overgrowth in the gut flora with consequent fungal translocation into the peritoneum and development of SFP [8].

Fungal translocation may be enhanced by upper gastrointestinal haemorrhage, immunodeficiency, and malnutrition which are frequent in patients with advanced liver disease. Refractory ascites and a previous history of frequent paracentesis are considered predisposing factors for percutaneous inoculation of fungi [9].

A Fungal culture may be positive in about 0%-7.2% of spontaneous peritonitis cases, with *Candida albicans* being the most common isolate [8, 10]. *Candida glabrata*, *Candida krusei*, *Cryptococcus* species, *Aspergillus* species, and *Penicillium* species are some other fungi that can cause disease [4, 6].

Therapeutic recommendations for managing infections in cirrhotic patients contain suggestions for fungal infections but not for prophylactic or optimal treatment [7]. For cirrhotic individuals with nosocomial SFP or severely diseased cirrhotic persons with socially obtained SFP, echinocandins are advised as the primary line of treatment [6]. For less severe infections, fluconazole is advised. When a patient's medical status is stabilized and sensitivity testing is accessible, it is indicated to shift treatment from echinocandins to fluconazole [8].

The death rate in SFP is high due to late diagnosis, reduced symptoms, latency in treatment with antifungal drugs, and increased resistance of fungi to empirical specific antifungal drugs [4].

In the current study, we aim to estimate the frequency and risk factors of SFP in cirrhotic patients admitted to Sohag University Hospital.

Patients and methods

The current cross-sectional study was carried out on cirrhotic patients hospitalized at the Tropical Medicine and Gastroenterology Department in Sohag University Hospital during the period from September 2021 to February 2023.

Adult patients (>18 years old) with liver cirrhosis; diagnosed by ultrasound, and ascites who were hospitalized for different reasons met the inclusion criteria. The patients were chosen by simple random technique. Cirrhotic patients who were taking antibiotics at the time of paracentesis, those receiving continuous ambulatory peritoneal dialysis, those who test positive for the human immunodeficiency virus (HIV), or those with abdominal surgery or known cause of peritonitis were excluded from the study.

All included patients were subjected to

1.Detailed history, complete general and systemic examination.

2.Aspiration of peritoneal fluid samples: All samples were taken under a complete aseptic condition in a sterile container under aseptic precautions according to the standard protocol for further analysis. The samples were sent immediately to the clinical and chemical pathology laboratory to be processed. Each sample was examined physically for aspect, colour, and sediment, chemically for glucose and protein, and microscopically by using a haemocytometer for red blood cells (RBCs) count, white blood cells (WBCs) count, and their differential count.

3.Bacterial culture from ascitic fluid: The samples were cultured on different culture media as nutrient agar and blood agar and according to the results of growth on these culture media, subcultures were done on MacConkey's medium. According to the pattern of growth on these media, further identification was done Gram staining and subculture on selective media as EMB (Eosin Methylene Blue), and differential media as TSI (Triple Sugar Iron).

4.Bacterial strains identification: These bacterial strains were identified by the Vitek2 automated system (BioMérieux, Marcy l´Etoile, France). Pure subcultures of the isolated bacterial colonies, were dissolved in sterile saline and their turbidity was

measured by the DensiChek turbidity meter (bioMérieux) to obtain 0.5 McFarland turbidity, then was inoculated to the colorimetric ID-GN cards. These cards were filled with the diluted bacterial suspension, sealed, and incubated for the prescribed time according to the card protocol of Manufacture. Then these cards were loaded into the Vitek 2 compact instrument which is automatically filled. The results were compared to the database of the unknown organism. Final identifications of these bacterial suspensions were classified as "excellent," "very good," "good," "acceptable" or "low discrimination". Tubercle bacilli were excluded by staining the samples with Ziehl – Neelsen stain and culture on egg-enriched media as Lowenstein – Jensen media. Other media were used as, Middlebrook 7H10,7H11 agar and 7H9 broth.

5.Antibiotic sensitivity tests were done using Vitek 2 AST-GN cards performed according to the manufacturer's protocol and to be related with the isolated bacteria.

6.Fungal identification: Ascitic fluid samples were also cultured on Sabouraud Dextrose agar (Oxoid, UK), and were incubated for 48-72 hrs at 37 co. Colonies growth on this media was identified by gram staining, which revealed either yeast-shape large rounded cells. Staining also by methylene blue revealed thin, long branching filaments. Pure subcultures of fungal colonies were dissolved in sterile saline and their turbidity was measured by the DensiChek turbidity meter (bioMérieux) to obtain 1.8 to 2.1 McFarland turbidity, then inoculated to the colorimetric Vitek 2 YST cards. These cards were filled with the diluted fungal suspension, sealed, and incubated for the prescribed time according to the card protocol of Manufacture. Then these cards were loaded into the Vitek 2 (BioMérieux, Marcy l´Etoile, France) compact instrument automatically filled. The results were compared to the database of the unknown organism. Final identifications listed as "excellent," "very good," "good," "acceptable", or "low discrimination". Antifungal susceptibility tests were done using Vitek 2 AST-YS08 cards performed according to the manufacturer's protocol. Susceptibilities were determined for fluconazole, micafungin, caspofungin, flucytosine medications, voriconazole, and amphotericin B. These antifungal drugs were loaded into the AST-YS08 cards [11].

7.Ascitic fluid analysis interpretation: Diagnosis of SBP was determined with a threshold ascitic PMNs count of 250 cells/mm3 with or without positive bacterial culture, Bacterascites was defined as PMNs count less than 250/mm3 with positive bacterial culture [12]. SFP was diagnosed by PMNs count of at least 250 cells/mm3 and a positive fungal culture, irrespective of bacterial colonization, fungiascites was defined as PMNs count less than 250/ mm3 with positive fungal culture irrespective of bacterial co-colonization [2]. Patients with normal PMNs and negative bacterial and fungal cultures were diagnosed as having no ascitic fluid infection.

8.Other laboratory investigations: liver function tests, prothrombin time, prothrombin concentration, international normalized ratio (INR), fasting blood sugar, complete blood picture, serum electrolytes (Na+, K+, Ca++), and serum creatinine.

9.Abdominal ultrasonography: It was used to assess the liver size, surface, presence of hepatic focal lesion, portal vein diameter and patency, ascites, and splenic size.

•Liver size was measured as the span of the right lobe in mid-clavicular line on oblique view and classified as shrunken (<11 cm), average (11-15 cm), or enlarged (> 15 cm) [13].

• Portal vein diameter up to 13 mm was considered normal [14]

•Longitudinal spleen length greater than 13 cm was considered enlarged [15].

10. Estimation of the severity of liver cirrhosis by modified Child-Turcotte-Pugh (CTP) score [16], and MELD score was done for all patients [17].

Ethical consideration

After approval of the protocol by the Ethical Committee of Research (registration number: Soh-21-10-53), written informed consent was obtained from each participant. Clinical trial registration number: NCT05117073.

Statistical analysis design

The statistical evaluation was done using the Statistic Package for Social Science Version 22 (SPSS 22) for Windows. Quantitative data were presented as mean and standard deviation (mean ± SD) or median and interquartile range (IQR) and qualitative data were expressed as numbers and percentages. Comparing groups was done using the Chi-square test (X^2) for the comparison of qualitative data and independent Student's (t) test for the comparison of quantitative data of 2 independent

samples of normally distributed data and one-way ANOVA (f) test for the comparison of quantitative data of 3 independent sample of normally distributed data. Kruskal Wallis test was used for the comparison of non-normally distributed quantitative data of more than two groups. Binary logistic regression analysis was done to detect predictors of SFP in the studied population. The coefficient interval was set to 95%. The following probability (*P*) values were used to calculate the level of significance: Statistical significance was set at *p* 0.05.

Results

The current study was carried out on 155 cirrhotic patients, their mean age was 61± 12 years. One-hundred-two patients (66%) of the study population were male. Negative ascitic fluid culture; regardless PMNs count, was reported in 104 patients (67.5%). We categorized the patients into: SBP group (included 69 patients (44%)), SFP group (included 15 patients (10%)), and patients without ascitic fluid infection (included 71 patients (46%)) **(Figure 1).** Neither nor were found in the study subjects. Patients without ascitic fluid infection had a significantly higher frequency of hematemesis compared to those with SBP and SFP (*P*= 0.001). The SFP group had a significantly higher frequency of reduced liver size and portal vein thrombosis (*P*= 0.004, 0.001 respectively). Moderate amounts of ascites had a significantly higher frequency in the SFP group compared to the SBP group and non-ascitic fluid infection group (*p* = 0.34) **(Table 1).**

As regards the laboratory investigations, the total leucocytic count, total serum bilirubin, prothrombin time, and INR were significantly higher in cirrhotic patients with SFP than those with SBP and those without ascitic fluid infection (*p*=0.004, 0.011, 0.014, 0.016, respectively). Ascitic fluid analysis showed a highly significant increase in total WBCs count, neutrophilic count, and ascitic fluid protein in the SFP group compared to both SBP and non-infection groups (*p*=0.000). The MELD and CTP scores were significantly higher in cirrhotic patients with SFP than those with SBP and those without ascitic fluid infection (*p*=0.000, 0.012) **(Table 2).**

When assessing the results of bacterial and fungal cultures, *Escherichia coli* was the most reported bacterial infection (32.7%) followed by *Klebsiella pneumonia* (22.4%). *Candida ciferrii* was the most reported fungal infection (10.2%) followed by *Candida albicans* (8.2%) **(Figure 2).** All isolated fungi showed 100% sensitivity to fluconazole, micafungin, caspofungin, flucytosine, voriconazole, and amphotericin B medications **(Table 3).**

When assessing the risk factors of developing SFP, univariate logistic regression indicated that the serum leukocytic count, serum creatinine, total bilirubin, ascitic fluid WBCs, ascitic fluid neutrophils, ascitic fluid protein, high MELD score, and smaller liver size were independently related to the development of SFP **(Table 4).** However, by multivariate logistic regression, we found that ascitic fluid protein is the only factor related to the occurrence of SFP **(Table 5).**

Table 1. Clinical and imaging characteristics of the studied groups

		No Ascitic fluid infection N=71	**SBP N=69**	**SFP N=15**	***P*-value**
Age (years), Mean ± SD		60.55±9.76	60.88±14.39	63.60±10.53	0.672
Sex	Male	53 (74.60%)	41 (60.30%)	8 (53.30%)	0.109
	Female	18 (25.40%)	27 (39.70%)	7 (46.70%)	
Diabetes Mellitus	Yes	21 (29.6%)	25 (36.8%)	4 (26.7%)	0.585
Hematemesis	Yes	44 (62%)	22 (32.4%)	5 (33.3%)	0.001
Esophageal varices	Yes	35 (49.3%)	23 (33.8%)	5 (33.3%)	0.147
Encephalopathy	Yes	46 (64.8%)	52 (76.5%)	10 (66.7%)	0.308
Jaundice	Yes	34 (47.9%)	42 (61.8%)	9 (60%)	0.239
Hepatocellular carcinoma	Yes	27 (38%)	19 (27.9%)	2 (13.3%)	0.128
Previous history of Peritonitis	New	11 (78.6%)	37 (66.1%)	12 (80%)	0.445
	recurrent	3 (21.4%)	19 (33.9%)	3 (20%)	
Etiology	Unknown	15 (21.1%)	6 (10.5%)	0 (0%)	0.523
	HCV	48 (67.6%)	43 (75.4%)	11 (91.7%)	
	HBV	6 (8.5%)	5 (8.8%)	1 (8.3%)	
	HCV+HBV	2 (2.8%)	2 (3.5%)	0 (0%)	
	Autoimmune	0 (0%)	1 (1.8%)	0 (0%)	
Liver size	Average	62 (87.3%)	50 (73.5%)	9 (60%)	0.004
	Enlarged	8 (11.3%)	13 (19.1%)	2 (13.3%)	
	Reduced	1 (1.4%)	5 (7.4%)	4 (26.7%)	
Splenomegaly	Average size	13(18.30%)	22 (32.40%)	3 (20.00%)	0.118
	Mild	28 (39.40%)	17 (25.00%)	4 (26.70%)	
	Moderate	22 (31.00%)	19 (27.90%)	8 (53.30%)	
	Marked	8 (11.30%)	10 (14.70%)	0 (0.00%)	
Portal vein	Dilated, thrombosed	17 (24%)	36 (52.9%)	9 (60.0%)	0.001
	Dilated, patent	17 (24%)	13 (19.1%)	2 (13.3%)	
	Not dilated	37 (52.1%)	19 (27.9%)	4 (26.7%)	
Amount of Ascites	Minimal	6 (8.50%)	0 (0.00%)	0 (0.00%)	0.034
	Mild	10 (14.10%)	12 (17.60%)	3 (20.00%)	
	Moderate	13 (18.30%)	21 (30.90%)	7 (46.70%)	
	Marked	42 (59.20%)	35 (51.50%)	5 (33.30%)	

HBV: hepatitis B virus, HCV: hepatitis C virus. p-value was evaluated using the *Chi-square test [Write the statistical methods]*

Table 2. Laboratory characteristics, severity of liver disease, and outcomes of the studied groups

	No ascitic fluid infection N=71	**SBP N=69**	**SFP N=15**	***P*-value**
WBCs (10^9/l), Mean ± SD Median (IQR)	9.2±4.7 7.8(5-10.3)	9.7±4.6 9.5(7.2-12.5)	16± 11.5(9.7-18)	0.004
Hemoglobin (g/dl), Mean ± SD Median (IQR)	9.26±2.30 9.5(8-10.4)	10.15±2.60 10(8.7-11.5)	10.41±1.54 10.5(8.6-11.5)	0.046
Platelets (10^9/l), Mean ± SD Median (IQR)	130±76 116.5 (79-159)	144±88 124(83.5-180)	125±89 98(63-141)	0.395
Glucose (mg/dl), Mean ± SD Median (IQR)	133.03±59.46 109(98-160)	139.31±57.23 123(92-178)	142.93±38.35 145(117-180)	0.734
Creatinine (mg/dl), Mean ± SD Median (IQR)	1.4±0.7 1.1(0.8-1.9)	1.4±0.8 1.2(0.8-2)	1.95±1 1.9(1.1-2.2)	0.08
Albumin (g/dl), Mean ± SD Median (IQR)	2.34±0.58 2.3(2-2.7)	2.14±0.57 1.7(2.1-2.5)	2.27±0.67 (1.8-2.9)	0.112
Total bilirubin (mg/dl), Mean ± SD Median (IQR)	4.5±5.6 2.35(1.3-5.85)	4.8±4.6 3.9(1.4-6.5)	8.4±7.5 6.5(3-8.3)	0.011
AST (U/L), Mean ± SD Median (IQR)	99±133 55(37.5-120.5)	106±175 62(36-90)	98±127 69.7(41-87)	0.813
ALT (U/L), Mean ± SD Median (IQR)	49±57 26.5(15.8-60.3)	64±74 35(20.5-78.5)	52±45 39.8(20-67.5)	0.344
Prothrombin time (sec) Mean ± SD	17.15±5.26 16(14-20)	18.06±5.95 16(14-20)	22.08±7.81 20(18-22)	0.014
Prothrombin concentration (%), Mean ± SD Median (IQR)	58.79±23.03 16 (14-20)	55.82±20.82 53(39-72)	46.50±16.40 45(34-58)	0.133
INR, Mean ± SD Median (IQR)	1.50±0.49 56(42-74)	1.62±0.61 1.5(1.2-1.3)	1.97±0.77 1.8(1.6-20)	0.016
Na^+ (mmol/l), Mean ± SD Median (IQR)	125.61±5.09 150(110-170)	128 ±6.4 130(124-133)	128.36±6.10 130(122-134)	0.022
K^+ (mmol/l), Mean ± SD Median (IQR)	3.80±0.66 3.7(3.4-4)	3.71±0.69 3.7(3.3-4)	3.59±0.86 3.5(3.1-4.1)	0.518
Ca^{++}(mmol/l), Mean ± SD Median (IQR)	0.92±0.12 1.25(1.23-1.28)	0.97±0.13 0.9 (0.88-1)	0.97±0.10 0.98(0.9-1)	0.063
Ascitic fluid WBCs/mm^3, Mean ± SD Median (IQR)	233±274 108 (89-240)	884±1224 640 (487-920)	391±4221 1650 (1090-6878)	0.000
Ascitic fluid neutrophils/mm^3,	173±288	734±1320	714±13169	0.000

Mean ± SD Median (IQR)		87.5 (40-175)		459 (332-695)		1440 (872-6963)		
Ascitic fluid protein (mg/dl), Mean ± SD Median (IQR)		1.8±0.3 1.9 (1.8-2)		1.4±0.9 1.1(0.9-1.55)		2±2.4 1.7 (0.9-2.3)		0.000
MELD score, Mean ± SD Median (IQR)		16.28±7.58 16 (9.2-22)		18±7.65 18(12-23)		25.65±6.52 24(21-31)		0.000
CTP score, Mean ± SD Median (IQR)		10.80±2.10 9 (11-12)		11.53±2.16 12(10-13)		12.40±1.35 13(12-15)		0.012
		N	%	N	%	N	%	
Child class	A	0	0	0	0	0	0	
	B	19	(26.8%)	16	(23.5%)	1	(6.7%)	0.247
	C	52	(73.2%)	52	(76.5%)	14	(93.3%)	

ALT: alanine transaminase, AST: aspartate transaminase, CTP: Child-Turcotte- Pugh, INR: international normalized ratio, IQR: interquartile range, MELD: Model of End-stage Liver Disease, WBCs: white blood cells. The p- value of the non parametric data was evaluated using *Kruskal Wallis test*. The p-value of the parametric data using *one-way ANOVA.*

Table 3. Pattern of anti-fungal sensitivity according to anti-fungal sensitivity testing

Isolated organism	**Anti-fungal sensitivity**					
	Fluconazole	Micafungin	Capsufungin	Flucytocin	Voriconazole	Amphotracin B
Candida albicans	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4(100%)
Candida ciferrii	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)
Candida glabrata	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)
Triochosporon	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Cryptococcus laurentil	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)

Table 4. Univariate logistic regression of factors associated with the development of SFP

	Odds Ratio	**Confidence Interval**		***p*-value**
		Lower	Upper	
Age	0.07	-0.002	0.006	0. 4
Sex	0.09	-0.04	0.16	0.3
Diabetes Mellitus	-0.04	-0.13	0.08	0.6
Hepatorenal syndrome	0.14	-0.03	0.32	0.09
Hepatocellular carcinoma	-0.12	-0.18	0.02	0.12
WBCs	0.3	0.006	0.03	0.000
Ascitic fluid WBCs	0.5	0.05	1.08	0.000
Ascitic fluid neutrophils	0.48	0.38	3.8	0.000
Ascitic fluid protein	0.16	0.00	0.095	0.05
Serum creatinine	0.21	0.02	1.32	0.01
Serum albumin	0.01	-0.75	0.075	0.88
Total bilirubin	0.2	0.002	0.02	0.01
International normalized ratio	0.21	0.03	0.19	0.009
Child-Pugh score	0.13	-0.20	0.202	0.11
MELD score	0.33	0.006	0.018	0.000
Liver size	0.22	0.033	0.19	0.006

MELD: model for end-stage liver disease, WBCs: white blood cells *Statistical analysis was done using Binary logistic regression analysis*

Table 5. Multivariate logistic regression of factors associated with the development of SFP

	Odds Ratio	**Confidence Interval**		***p*-value**
		Lower	Upper	
WBCs	1.052	0.926	4.502	0.432
Ascitic fluid WBCs	1.000	1.000	1.001	0.188
Ascitic fluid neutrophils	1.000	1.000	1.001	0.163
Ascitic fluid protein	2.265	1.14	4.502	0.02
Serum creatinine	1.189	0.244	5.806	0.830
Total bilirubin	1.087	0.915	1.291	0.341
International normalized ratio	0.329	0.010	10.557	0.530
MELD score	1.148	0.826	1.597	0.411
Liver size	2.629	0.883	7.828	0.08

MELD: model for end-stage liver disease, WBCs: white blood cells. *Statistical analysis was done using Binary logistic regression analysis*.

Discussion

During this cross-sectional study, we evaluated the frequency and risk factors for the development of SFP in cirrhotic patients with ascites.

Our study was conducted on 155 cirrhotic patients with liver cirrhosis and ascites, 9.7% of them had SFP, 44.5% had SBP and 45.8% didn't have peritoneal infection. **Lahmer et al.** [18] performed a study on 250 cirrhotic patients, 10% of them were SFP, 14% were SBP, 24% had peritonitis with negative microbiological cultures, and 52% were without peritonitis. An Egyptian study made by **Gohar et al.** [19] detected one patient out of 141 patients with SFP. Another study conducted on 416 patients with SBP documented that 3.6% of them had SFP [6]. The low prevalence of fungal infection in individuals with liver cirrhosis may be attributed to the absence of persistent neutropenia and the presence of sufficient numbers of functioning neutrophils that are needed for increasing immunity against fungal infections [9].

Our study revealed significantly higher serum leukocytic count in patients with SFP than those with SBP and those without peritonitis. Our finding is supported by the results of **Lahmer et al.** [18], **Tariq et al**. [20], **Gravito-Soarse et al.** [21], **Cavigalia et al.** [22], and **Huang et al.** [23] who found the same observation. In contrast, **Hassan et al.** [9] found no significant difference in leukocytic count between SFP and SBP. Our finding may denote the increased systemic inflammatory activity in SFP against more organisms than just bacteria [24].

Data about the relation between serum creatinine level and SFP are conflicting. Our study did not find a significant difference in serum creatinine levels between the SFP group, SBP group, and non-infection group. Similar results were documented by **Hwang et al.** [6], **Hassan et al.** [9], **Lahmer et al.** [18], **Shizuma et al.** [25], **and Caviglia et al.** [22]. Moreover, despite being an independent risk factor for SFP related early mortality, raised serum creatinine was not significantly higher in SFP cirrhotic patients compared to those with either culture positive or negative SBP [23]. On the contrary, **Elkhateeb et al.** [26] documented that serum creatinine was significantly higher in cirrhotic patients with SFP compared to those with SBP. Despite the known impact of renal impairment on granulocyte function and cell-mediated immunity; which are the main host defenses against fungi [9], further research is required to establish the exact relationship between serum creatinine and SFP in liver cirrhosis.

As regards liver function, we found a significant elevation of total bilirubin, prothrombin time, and INR in patients with SFP compared to those with SBP and those without peritonitis, but there was no significant difference in serum albumin between our groups. This result was in agreement with **Lahmer et al.** [18] and **Tariq et al.** [20] who detected a significant elevation of serum bilirubin in SFP patients compared to SBP patients during their studies. In contrast, **Alexopoulou et al**. [27] and **Shizuma** [25] found no significant differences in total bilirubin, prothrombin time, INR, or albumin levels between SFP and SBP groups. Our results may be explained by the fact that high serum bilirubin and impaired INR indicate end-stage liver disease, which is associated with impaired innate and acquired immunity increasing the susceptibility to fungal infections [28,29].

To our knowledge, few reports documented the value of ascitic fluid WBCs count as a predictor of SFP in cirrhotic patients. The current study revealed that cirrhotic patients with SFP had significantly higher ascitic fluid neutrophilia compared to patients with SBP and those without ascitic fluid infection. **Roth et al.** [30] observed a trend toward significance in ascitic WBCs count in SFP cirrhotic patients compared to those with SBP. Similar to our results, **Huang et al.** [23] documented a significant rise in ascitic fluid neutrophilic count in SFP-associated liver cirrhosis compared to SBP-associated liver cirrhosis. On the other hand, **Gravito-Soares et al.** [21], **Hassan et al.** [9], and **Alexopoulou et al**. [27] did not find a significant difference in ascitic fluid neutrophilic count between cirrhotic patients with SFP and those with SBP. Nevertheless, more investigation is required to understand the distinction between the peritoneal immune response in SFP and SBP cirrhotic patients.

A surprising finding of the current study is the significantly higher ascitic fluid protein in SFP patients compared to SBP patients. Moreover, low ascitic fluid protein was the only independent predictor of SFP in cirrhotic patients. However, this level was still lower than that of patients without ascitic fluid infection. On the other hand, the previous literature did not find a significant difference in ascitic fluid protein between SFP and SBP patients [9,21,25,27]. This conflict may be attributed to the marked ascitic fluid leucocytosis observed in our series with SFP. Indeed, low ascitic fluid protein in SFP patients was identified as a risk factor for mortality [8] rather than a predictive factor for infection. Thus, in spite of the fact that ascitic fluid protein < 1.5 gm/ dl is associated with an increased risk of SBP [31,32], the cut-off value for SFP needs further investigation to be identified.

The current study revealed significantly higher CTP and MELD scores in patients with SFP and SBP than in those without peritonitis, and in patients with SFP than in those with SBP. This result is in agreement with many authors who found that higher CTP and MELD scores were considered risk factors in patients infected with bacteria or fungi during their studies [9,18,20]. In contrast, Shizuma [25] found no significant difference in CTP score between SFP and SBP patients during his study. Our results could be explained by the fact that fungi have larger diameters compared to bacteria. Thus, higher gut permeability is needed for fungal translocation through the intestinal wall, which is evident in patients with end-stage liver disease with severe malnutrition and immune dysfunction [3,8].

As regards the ascitic fluid culture, we found that *E. coli* was the most common bacterial species isolated from patients with SBP. Previous studies documented *Candida* species as the most common fungal isolate in patients with liver cirrhosis and SFP. This is in agreement with our results as we found that *Candida ciferrii* was the most common fungal isolate in cirrhotic patients with SFP followed by *Candida albicans* then *Candida glabrata*. **Lahmer et al.** [18] found that *Candida albicans* was the most common isolated fungal pathogen in SFP patients. Similar results were documented by **Karvellas et al.** [33] and **Hwang et al.** [6]. Moreover**, Bremmer et al.** [34] found that *Candida* was the only isolated fungal pathogen in 25 patients with liver cirrhosis and SFP, and most of them had *Candida albicans* species in their ascitic fluid cultures. The size difference between *Candida* and other fungal species is possibly one of the reasons why *Candida* is more prevalent in cirrhotic patients with SFP than other fungi, such as *Cryptococcus* [6]. The diameter of Cryptococcal species can reach up to 20 µm compared to 10-12 µm for *Candida* species. This relatively large size of Cryptococcal species hinders its ability to migrate through the intestinal wall [35].

Our results revealed that all isolated fungi had 100% sensitivity to fluconazole, micafungin, caspofungin, flucytosine, voriconazole, and amphotericin B medications. Similar results were documented by **Hwang et al.** [6] as they recommended echinocandins as the drug of choice in the treatment of cirrhotic persons with SFP. **Fiore et al.** [8] recommended the use of fluconazole in less serious illness. Nevertheless, these results should be confirmed by further research evaluating the response to antifungal therapy in clinical practice.

As the cases were recruited from a single healthcare center, this was considered a limitation of the study.

Conclusion

SFP is not a rare critical complication of liver cirrhosis with ascites. It should be considered mainly in patients with high MELD and CTP scores. The use of fungal culture should be considered in these patients, and empiric antifungal therapy may be considered in SBP-suspected patients with

clinical deterioration or increasing WBCs count despite proper antibiotic therapy, in order not to miss SFP cases.

Recommendations

Validation of our results in multicentre studies with large sample size is recommended. Using non-culture testing of SFP to increase the speed of diagnosis. Using another more accurate method in the diagnosis as polymerase chain reaction and fungal biomarker 1,3-Beta-D-Glucan.

Abbreviations

CTP: Child-Turcotte- Pugh, **HIV:** Human immunodeficiency virus, **INR:** International normalized ratio, **MELD:** Model of End-stage Liver Disease, PMNs: polymorphonuclear leukocytes. RBCs: Red blood cells. **SBP:** Spontaneous bacterial peritonitis. **SFP:** Spontaneous fungal peritonitis. **WBCs:** White blood cells.

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