

Effect of First Spontaneous Bacterial Peritonitis Event on the Survival of Cirrhotic Patients with Ascites and Predictive Factors of Recurrence

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Abstract

Spontaneous bacterial peritonitis (SBP) is a serious and frequent complication of cirrhosis. The aim of our study was to assess the predictive factors of recurrence and mortality after a first episode of SBP. We perform a retrospective monocentric study, in Gastroenterology department of Sahloul Hospital, Sousse-Tunisia. we include all patients with first SBP episode in a cirrhosis wick defined by the presence of more than 250 neutrophils/mm³ in ascitic fluid. Secondary peritonitis and positive culture of ascitic fluid and neutrophils < 250/mm³ were excluded from this study including 49 cirrhotic patients with first episode of SBP between January 2005 and December 2015.they were 32 men and 17 women, with a mean age of 58 years old. Virus B hepatitis was the most frequent etiology of cirrhosis (57%). Fever (69%) and abdominal (67%) were the most revealing symptoms of SBP. Thirty five patients were Child C cirrhosis. Renal impairment was observed in one third of patients. A germ was identified in ascitic fluid in 18% of cases. For treatment, Cefotaxime was prescribed in most cases (87%). 30-day mortality rate was 16%. The principle predictive factors of mortality were: sepsis, creatinine level > 120 micmol/l, Prothrombin time < 40% and hyperkalemia (> 5 mmol/l). Predictive factors of recurrence of SBP after first episode were: Absence of antibioprophylaxis and protein levels in ascitic fluid < 10 g/l. During the course of cirrhosis, 10% of patients developed hepatorenal syndrome and 24% had and hepatocellular carcinoma (HCC). Overall 5-year survival rate after first episode of SBP was 44%.

Keywords: Ascitic Fluid; Infection; Prognosis

Introduction

Spontaneous Bacterial Peritonitis (SBP) is associated with high rates of short-term mortality in cirrhotic patients who are always de-compensated in this case. So it is hard to differentiate whether mortality is due to infection itself or the altered liver function.

It was firstly described by Charrin and Veillon in 1893.

Few studies have been interested in this subject. It is well known that SBP related mortality is high in cirrhotic patients. When first described, its mortality exceeded 90% but it has been reduced to approximately 20% with early diagnosis and treatment. The risk of SBP

recurrence is around 70% per year. Many published data reported predictive factors of recurrence of SBP and risk factors for short and long-term mortality.

Thus, the aim of our study is to analyze the clinical, epidemiological, therapeutic characteristics of the 1st episode of SBP in cirrhotic patients, and evaluate the predicting factors of recurrence and mortality after a first SBP episode.

Materials and Methods

A monocentric retrospective study including 399 cirrhotic patients hospitalized in our Hepato-Gastro-Enterology unit in a period of 14 years (From January 2005 to December 2019). Among these patients, Forty-nine who had first episode of spontaneous bacterial peritonitis (SBP) were studied.

Two groups of patients were individualized in order to study factors of mortality:

- G1: Patients who recovered after treatment of first episode of SBP
- G2: Patients died during a follow up period of 30 days after SBP.

The term SBP refers to the presence of more than 250 neutrophils in ascitic fluid in the setting of cirrhosis, and in the absence of bowel or peritoneal perforation.

Detailed clinical examination was performed. Vital parameters like temperature, pulse, blood pressure, respiratory rate, mental status examination and presence or absence of signs of liver cell failure were noted.

Laboratory markers and parameters included in the study were total bilirubin, serum albumin, Prothrombin Time, platelet count, serum creatinine, random blood sugar and serum sodium. Presence of hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibodies by micro enzyme immunoassay (MEIA), history of alcohol intake and serum sodium were also documented.

Ascitic fluid analysis at the time of admission as well as repeat analysis done after 48 hours was also noted with culture and sensitivities report of both.

Statistical analysis

A descriptive analysis was done for demographic and clinical features and results are presented as mean standard deviation for quantitative variables and number (percentage) for qualitative variables. Differences in proportions for recurrence of SBP in cirrhotic patients with ascites were assessed by using the chi-square test or Fisher's exact test where appropriate. All significant factors on univariate analysis were considered for inclusion in the multivariable logistic model. All analyses were conducted by using the Statistical Package for Social Sciences (SPSS version 22.0). All p-values were two-sided and considered as statistically significant if < 0.05.

Results

A total of 399 cirrhotic patients with ascites were included in the study, among whom 49 patients were diagnosed with SBP (mean age: 58 years old). 65.3% were males and 34.7% were females. 24.5% had comorbidities: 8 patients (16.3%) had arterial hypertension, and seven (14.3%) had diabetes. Alcohol consumption was noted in 7 cases (14.3%).

Hepatitis B was the main etiology of cirrhosis in our patients (57%), Hepatitis C in 10%, autoimmune hepatitis in 8% of cases.

For SBP, clinical features were numerous, most frequently fever and abdominal pain (69.4%, and 67.3% of cases). (Table 1)

Symptoms	Number of cases	(%)
Fever	34	69,4
Abdominal pain	33	67,3
Fever + abdominal pain	22	44,9
Jaundice	15	30,6
BP < 10 mm Hg	11	22,4
Encephalopathy	11	22,4
Diarrhea	9	18,4
Sepsis	6	12,2
Vomiting	3	6,1

Table 1: Clinical Features.

Biological findings showed high CRP mean level (91 mg/L). Blood culture isolated a germ in 9 patients (18.3%) and five of our patients had a urinary tract infection. Cirrhosis was severe (CHILD C) in 75.1% of our patients. As for treatment of SBP, 87.8% of our patients were treated by Cefotaxime and 94% had albumin perfusion. 41 patients (83.7%) have been successfully treated with a decrease in PNN level of more than 50% (G1). 8 patients (16.3%) died during follow-up (G2).

In a univariate analysis, we found that signs of septic shock (p = 0.04), elevated creatinine levels more than 120 Micromol/ml (p = 0.03), prothrombin time (PT) less than 40% (p = 0.003), hyperkalemia > 4.9 mmol/l (p = 0.009) were the predictive factor of 30-day mortality (Table 2). A multivariate analysis showed that signs of septic shock (p = 0.018) and elevated creatinine levels (p = 0.015) were significantly predictive of 30-day mortality (Table 3).

Eighteen patients (44%), have relapsed after a mean follow-up period of 4 months and a half among whom 97% did not take prophylactic antibiotic treatment.

	Group 1 N = 41		Group 2 N = 8		P
	n	%	n	%	
WBC > 12000/mm ³	17	41,5	4	50	0.27
WBC < 4000/mm ³					
Platelets < 100000/mm ³	24	58.5	5	62.5	0.83
Hemoglobin < 10 g/dl	13	31.7	4	50	0.42
PT < 40%	13	31.7	7	87.5	0.003
Bilirubin > 40micmol/l	24	58.5	7	87.5	0.22
Creat > 120 micmol/l	12	29.2	6	75	0.03
Na ⁺ < 132 mmol/l	16	39	5	62.5	0.22
K ⁺ > 4.9 mmol/l	6	14.6	5	62.5	0.009
Elevated ALAT	11	26.8	5	62.5	0.09
Cholestasis	12	29.3	5	62.5	0.1

Table 2: Univariate Analysis for Biological Parameters Predicting Mortality in SBP.

	Univariate analysis	Multivariate analysis		
	P	Adjusted OR	HR (CI: 95%)	P
Sepsis	0,04	0,008	0,00 – 0,44	0,018
Blood sugar level	0,15	0,38	0,14 – 1,01	0,055
Creatinin level	0,02	1,04	1,009 – 1,083	0,015
CHILD score	0,12	2,6	0,992 – 6,886	0,05

Table 3: Multivariate Analysis for Factors Predicting 30-day Mortality.

Univariate analysis revealed 3 predictive factors of SBP recurrence: Absence of prophylactic treatment intake (p = 0.004), protein levels in ascites < 10g/l and younger age of diagnosis of cirrhosis (p = 0.027).

As for overall survival, 1 and 5 year survival in relapsing patients were respectively 92 and 52%. There was no significant difference between relapsing and non-relapsing patients according to Kaplan Meier curves (Log Rank: 0.58) (Figure 1).

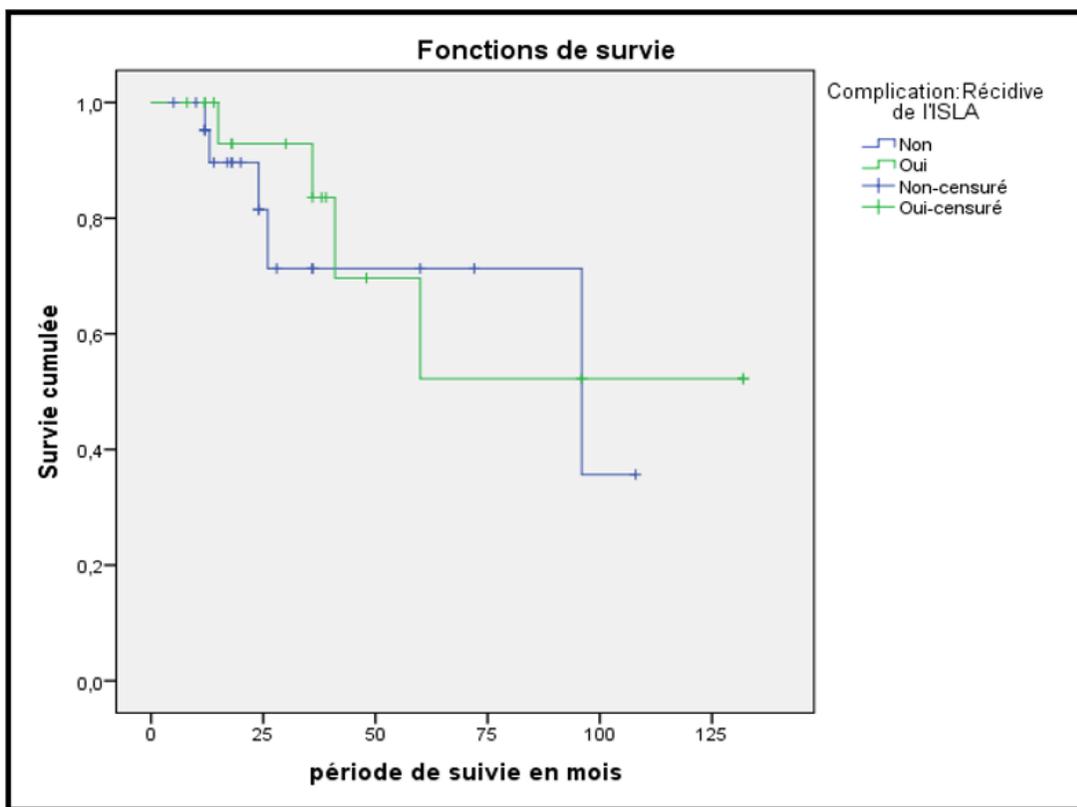


Figure 1: Overall Survival Rates in Relapsing and Non-Relapsing Patients.

Discussion

Cirrhosis is a condition where fibrosis is irreversibly installed and complications of portal hypertension and hepatic insufficiency are common. SBP is a major fatal complication of ascitic fluid. Most cases of SBP are caused by gram-negative enteric organisms, such as *Escherichia coli* and *Klebsiella pneumoniae*. However, many epidemiological changes made SBP due to gram positive cocci more and more frequent, as reported in a study by Alexopoulou, *et al*, where 55% of patients had cocci gram positive SBP [1]. In our study *E. Coli* was found in most cases (30%). Men were more concerned by SBP in our series (65.3%). Male predominance was confirmed in several studies [2-3]. The most frequent etiologies of cirrhosis were virus B (57%), hepatitis C (10%) and immune hepatitis (8%). These results were similar to those published by Dia D., *et al* and Kim JH., *et al* [4-5].

Fever (69%) and abdominal pain (67%) were the most common symptoms with which the patients presented. Jaundice was seen in 30% of cases, low blood pressure and hepatic encephalopathy were seen in 22%, diarrhea in 18%, sepsis signs were seen in 12%, and 6% had vomiting. In a study by Nadagouda SB., *et al* abdominal pain and fever were also the most frequent symptoms (77% and 66% respectively) [6]. Attia KA., *et al* published the same findings were abdominal pain and fever were preponderant. [7]. Biological findings showed a high mean bilirubin level (70 micromol/l), low Prothrombin Time (PT) (48%) and low medium albumin level (22g/l). These parameters (High bilirubin and low albumin level) were shown to be associated with high incidence rates of first episode and recurrence of SBP [8-9]. Ascitic fluid analysis was conducted in all patients. The ascitic fluid culture was positive in 9 cases among which *E. Coli* was predominant (30%), and medium ascitic protein concentration was 8.4 gr/l. 77% of patients had protein concentrations in ascitic fluid < 10 gr/l. The latter, was reported by some studies to be the best predictor of first episode of SBP.

In the present study, Child C was predominant (75.1%), but Child score was not significantly correlated with higher mortality rate (P = 0.12). These results were similar to those published by Kawale JB., *et al* and Kavita Paul., *et al*. [3-10].

Several previous studies showed SBP is associated with high long term mortality. Another study showed that one-year survival after first episode of SBP was 30% [11-13]. In our patients, overall 1 year and 5-year survival were 92% and 52%.

Prognostic factors in cirrhotic patients with SBP have recently been evaluated in several studies and many factors have been identified. A recent study has shown that CHILD score, elevated bilirubin and creatinin levels, hyponatremia, and resistance to antibiotics were independent predictive factors of high mortality rates in patients with first episode of SBP [14]. Another study by Tandon P., *et al* showed that renal impairment was the major predictive factor of high short-term mortality rates in SBP [15]. In the present study, univariate analysis of biological parameters showed that renal impairment (creatinin > 120 micromol/l) (P = 0.03), Hyperkalemia (K^+ > 4.9 mmol/l) (P = 0.009) and Prothrombin Time < 40% (P = 0.003) were predictive factors of high short-term mortality. In multivariate analysis, renal impairment was the only independent predictive factor of short-term mortality (P = 0.015). These results match with those previously published by Tandon P., *et al*.

High recurrence rates of SBP were shown in cirrhotic patients with ascites in many series [16]. In the present study, recurrence rates were comparable to those published in literature (44%). A Spanish study by Titó., *et al*. found serum bilirubin > 4 mg/dl, Prothrombin Time < 45% and protein concentration in ascitic fluid < 10g/l to be significantly (p < 0.05) associated with a high risk or recurrence of SBP in univariate analysis, but in multivariate analysis, only ascitic fluid protein concentration (p = 0.005) and prothrombin time (p = 0.009) were found to be independent predictors of recurrence of SBP [17]. Another study by Jamil S., *et al*, showed that independent predictive factors of recurrent SBP were: age > 55 years, bilirubin count > 1 mg/dl and presence of urinary tract infection. This Pakistani study also showed that HBV infection was a protective factor against SBP recurrence [18]. Absence of prophylactic treatment intake (p = 0.004), protein levels in ascites < 10 g/l and younger age of diagnosis of cirrhosis (p = 0.027) were independent predictive factors of recurrence of SBP in this study. Thus, International Ascites Club recommends Norfloxacin in patients with low protein concentration in ascitic fluid [19].

This study had several limitations that should be addressed. First, there is a potential for inaccurate and biased data collection because of the retrospective nature of the study. Further prospective studies including multiple centers are to be conducted. Second, it is a mono-centric study, making the results not superimposable to data of other centers. Third, Several parameters (MELD score, complete virus B markers, osteodensitometry) could have been included but in the case of a retrospective study, this was not possible.

Conclusions

In conclusion, our findings are in agreement with several other recent studies that reported a high mortality rate due to SBP inspite of progress in medical treatment. Our study showed that SBP had a predictable outcome on short-term mortality by identifying independent factors related to 30 -day mortality (Sepsis signs, renal impairment). Recurrence was also frequent as it was noted in 44% of cases. Absence of prophylactic treatment intake ($p = 0.004$), protein levels in ascites < 10 g/l and younger age of diagnosis of cirrhosis ($p = 0.027$) were predictive factors of recurrence of SBP. Further multicentric and prospective studies are to be conducted in order to identify other possible factors of mortality in SBP, to allow us to improve preventive measures for better survival rates.

What is already known on this topic

- Spontaneous bacterial peritonitis (SBP) is a serious complication of cirrhosis.
- SBP affects the survival course of the patients.
- The treatment is urgent.

What this study adds

- Sepsis sign and renal impairment are two factors which increase mortality in the first 30 days after infection.
- We confirm the high mortality rate due to SBP.
- The predictors factors of recurrence were Absence of prophylactic treatment intake ($p = 0.004$), protein levels in ascites < 10 g/l and younger age of diagnosis of cirrhosis.

Competing Interest

The authors declare no competing interests.

Authors Contributions

All authors actively participated in every step of the study from data collection, analysis to the redaction.

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