Spontaneous Bacterial Peritonitis in Cirrhotic Patients: Predictive Factors of Recurrence and Survival

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Abstract

Introduction: Spontaneous Bacterial Peritonitis (SBP) is a diagnostic and therapeutic emergency, which is a turning point in the natural history of the cirrhosis. Predictive factors of recurrence and survival after first episode of SBP in cirrhotic patients remain until now little known. Identifying these factors could improve the management of these patients. The aims of this study were to assess the prevalence and the risk factors for recurrence after a first episode of SBP in cirrhotic patients and to evaluate its impact on the prognosis.

Methods: We conducted a retrospective study including consecutive cirrhotic patients admitted in the Gastroenterology Department of Habib Thameur Hospital for the management of a first episode of SBP between January 2003 and December 2017. Patients, cirrhosis and first episode of SBP characteristics were studied. The occurrence of a recurrence during follow-up was investigated. Predictive factors for SBP recurrence and its impact on the survival were evaluated in patients who were on secondary prophylaxis.

Results: Eight hundred and twelve cirrhotic patients were collected. Our study focused on 90 patients who developed a first episode of SBP, meaning a prevalence of 11%. The mean age at diagnosis was 63 years. The sex ratio (M/F) was 0.66. Most of cirrhosis was due to viral hepatitis (54%). Child Pugh score was B in 51% of cases and C in 49% of cases. The average MELD score was 21 [range 9 to 41]. The infection was nosocomial in 18% of cases. The average protein concentration in ascitic fluid was 14.86 g/l. Antibiotic therapy was mainly based on third-generation cephalosporins (94%). Eighteen percent of patients required escalation of antimicrobial treatment. Hospital mortality following the first episode of SBP was 10%.

The SBP recurrence rate was 26% among patients who survived their first infectious episode. The average time to the occurrence of the first SBP recurrence compared to the first episode was 162 days. Predictive factors of SBP recurrence in univariate analysis were beta blocker use, refractory ascites, portal hypertensive gastropathy, the presence of hepatic encephalopathy at admission, high CRP level at admission with a cut off 30 mg/l and high MELD score with a cut off 17. In multivariate analysis, only portal hypertensive gastropathy was an independent factor of SBP recurrence (p=0.04). In terms of prognostic impact, SBP recurrence was associated with a decrease in survival, from 12.2 months in the absence of recurrence to 7.2 months in case of recurrence (p=0.6).

Conclusion: In these present study, prevalence of SBP recurrence was 2.58%. It was often early and greatly reduced survival. The presence of portal hypertensive gastropathy may be useful in predicting recurrence of SBP.

Keywords: Spontaneous bacterial peritonitis; Cirrhotic patients; Hepatitis

Introduction

Spontaneous Bacterial Peritonitis (SBP) is a severe and common complication of cirrhosis. SBP is a diagnostic and therapeutic emergency with hospital mortality approaching 20% to 40% and one year mortality between 31% and 93% [1,2]. Its prevalence among hospitalized patients for ascitic decompensation is between 10 and 30% [3-5].

After a first episode, the cumulative risk of recurrence at one year can reach 70% if no antibioprophylaxis is prescribed and 20% under prophylaxis [6].

Predictive factors of recurrence and survival after a first episode of SBP in cirrhotic subjects are poorly studied and remain little known. An identification of these risk factors could improve the management of the patients.

The aim of our study was to determine the prevalence and predictive factors of recurrence after a first episode of SBP and to study overall survival of these patients.

Methods

A retrospective study over a period of 14 years (January 2003 to December 2017), including all the cirrhotic patients hospitalized for a first episode of SBP in the department of gastroenterology of Habib Thameur hospital was conducted. Diagnosis of SBP was based on the cytological study of the ascites puncture fluid showing a Number of Neutrophils (PNN) up to 250 elements/mm³.

Were not included in our study cirrhotic patients with ascites of other origin (renal, cardiac, tuberculous or malignant), cirrhotic patients with bacterascites defined by a positive culture of ascites fluid associated with a number of PNN <250/mm³, cirrhotic patients treated for SBP without biological or bacteriological confirmation, patients presenting an empyema or bacterial peritonitis secondary to perforation or inflammation of an intra-abdominal organ, and hepatocellular complicated cirrhosis.

Patients with a follow-up of less than six months and cirrhotic patients who developed Hepatocellular Carcinoma (HCC) or other malignancy during the follow-up period were excluded from the study.

The prevalence of SBP recurrence in the study population as well as the time to onset and the number of recurrences were noted.

For all patients, duration of follow-up, overall survival in months after a first episode of SBP, as well as survival after recurrence and cause of death was specified.

The management of the ILA was carried out according to actual international guidelines [7-9].

Statistical analysis was performed by the SPSS Software version 21 for Windows. Descriptive analytic analysis was performed. Univariate analysis (based on student's quantitative variables test, the Pearson chi-square test and the exact test of Fisher for qualitative variables and calculating the odds ratio (OR) as a measure of risk, as well as their 95% confidence intervals, and ROC curves) was performed to determine predictors of recurrence of SBP. Multivariate logistic regression was conducted to identify independent predictors of recurrence of SBP. In all statistical tests, a p value <0.05 was considered statistically significant.

The survival analysis was performed according to the Kaplan-Meier method (Log Rank test).

The strict anonymity as well as the confidentiality of the individual data recorded was respected throughout the study.

Ethical Committee approval of Habib Thameur Hospital was obtained.

Results

During the study period, 812 decompensate cirrhotic patients were followed in the department. Our study focused on 90 cirrhotic patients with SBP (prevalence of 11%) (Figure 1).

Mean age at the time of SBP was 63 ± 13 years [22 to 90 years] and sex ratio female/male was 1.5.

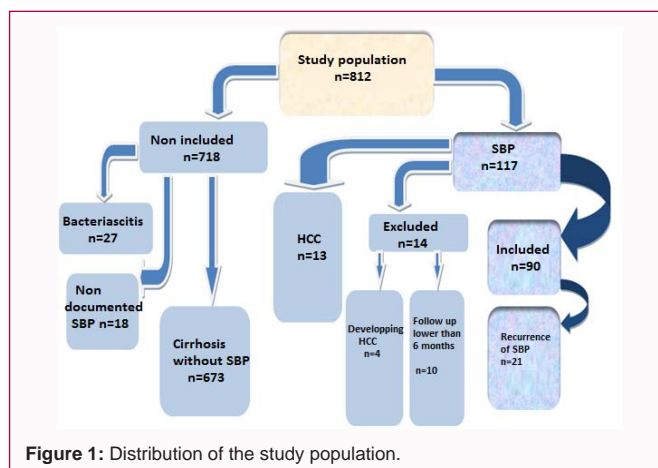Mean time to onset of SBP compared to the diagnosis of cirrhosis

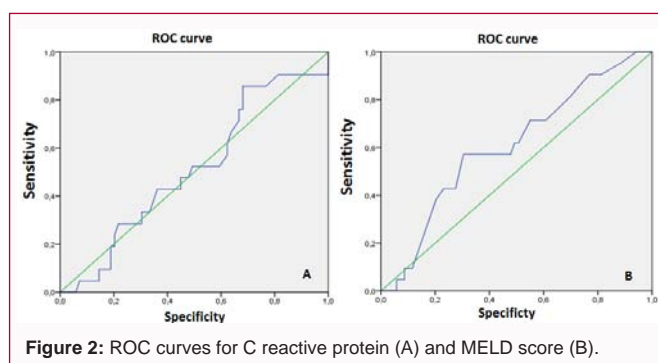**Figure 1:** Distribution of the study population.

Figure 2: ROC curves for C reactive protein (A) and MELD score (B).

was 38.4 ± 28 months [0 to 103]. Cirrhosis was inaugurated by SBP in 26% of cases.

Cirrhosis was due to hepatitis B or C in more than half of the cases, with a clear predominance of hepatitis C.

On admission, the patients had advanced cirrhosis; with Child Pugh score B in 51% of cases and C in 49% of cases. Average MELD score was 21 [range: 9 to 41]. Patients had already presented complications of their cirrhosis such as digestive bleeding due to esophageal varices (30%), refractory ascites (17%) and portal vein thrombosis (14%).

Eight percent of patients were on primary antibiotics prophylaxis at the time of diagnosis of the first episode of SBP.

SBP was associated with hepatic encephalopathy in 30% of patients and severe sepsis in 2%. SBP was generally of the communautary (82%). Nosocomial infection was noted in 18% of cases.

Average protein level in the ascites fluid was 14.86 ± 8 g/L. A responsible germ was identified in only 13% of cases. Escherichia coli were the most frequently isolated germ.

All patients received probabilistic antibiotic therapy. First line antibiotic therapy was based on third-generation cephalosporins (94% of patients). Eighteen percent of patients required to change antibiotics. The latter was guided by an antibiogram in 44% of cases.

The overall intra-hospital mortality rate following a first episode of SBP was about 10% in our cohort.

The mean hospitalization duration was 15.4 days [range 5 to 52]. Secondary antibiotics prophylaxis was prescribed for all patients who survived a first SBP episode.

Table 1: Predictive factors of recurrence of SBP in univariate analysis (qualitative variables).

Parameters	Recurrence of SBP			
	Yes (n=21)	No (n=69)	p value	OR [CI=95%]
Gender M/F	10/11	26/43	0.416	0.67
History	16	40	0.132	2.32
Diabetes	12	24	0.058	2.5
Hypertension	4	28	0.071	0.35
PPI	8	17	0.176	1.88
B Blockers	14	29	**0.041**	**2.7**
Post hepatitis B or C cirrhosis	13	35	0.259	1.6
Alcoholic cirrhosis	3	6	0.35	1.75
Non alcoholic steatohepatitis	1	9	0.267	0.33
Child Pugh B	8	37	0.159	0.53
Parameters	Oui (N=21)	Non (N=69)	P	OR [CI=95%]
Child Pugh C	13	31	0.133	2
Refractory ascites	7	8	**0.019**	**3.8**
History of digestive bleeding	9	18	0.117	2.12
Hypertensive gastropathy	18	44	**0.041**	**3.4**
Portal vein thrombosis	3	10	0.644	1
Communautary SBP	17	57	0.545	0.9
Nosocomial SBP	4	11	0.483	1.2
Positive culture of ascites	1	11	0.172	0.2
Fever	11	30	0.319	1.4
Hepatorenal syndrome	7	19	0.4	1.3
Hepatic encephalopathy	10	17	**0.043**	**2 .8**
Leucopenia	5	6	0.064	3.3
Hyperleucocytosis	7	24	0.561	0.9
Failure of antibiotics during SBP	3	13	0.455	0.7

OR: Odds Ratio; CI: Confidence Interval

Mortality at six months after SBP was 51% with an average follow-up of 5.13 years ± 3.48 [range 0.5 to 9 years]. The leading causes of death were dominated by hepatorenal syndrome (37%) followed by severe sepsis (31%).

Overall intra-hospital mortality rate following SBP was about 10% in our population.

In the first six months of follow-up after the diagnosis of the first episode of ISLA, 41 patients (51%) died.

Median overall survival after SBP was 12.2 months [0 to 96 months] [95% IC 7.7 to 21.8].

A recurrence of SBP was observed in 26% of patients despite the use of antibiotic prophylaxis in 81% of cases.

Predictive factors of recurrence of SBP in univariate analysis were: B blockers (p=0.041, OR [95% CI=2.7]), portal hypertension gastropathy (p=0.047, OR [95% CI=3.4]), refractory ascites (p=0.019, OR [95% CI=3.8]), hepatic encephalopathy (p=0.043, OR [95% CI=2.8]), C reactive protein level (p=0.04) with a cut off of 30 mg/l and the MELD score (p=0.023) with a cut off of 17.

In contrast, high bilirubin levels, low prothrombin time, and low levels of ascites fluid did not have a statistically significant relationship with the recurrence of SBP.

The results of the univariate analysis are summarized in Tables 1 and 2.

We determined the threshold values of admission C reactive protein level and MELD score via ROC curves. The cut-off value of CRP was 30 mg/l with respective sensitivity and specificity of 81% and 70% and an area under the curve of 0.511. The cut off value of the MELD score was 17 with a respective sensitivity and specificity of 71% and 60% and an area under the curve of 0.607 (Figure 2).

In multivariate analysis, only hypertensive gastropathy was an independent predictive factor of SBP recurrence (p=0.04).

Finally, SBP recurrence was associated with a decrease in survival, from 12.2 months in the absence of recurrence to 7.2 months in the case of recurrence (p=0.6).

Survival curve according to the recurrence of SBP are summarized in Figure 3.

Discussion

Our study focused on a delicate subject which remains at the origin of many questions so far unresolved.

Recent data on the natural history of patients who survived a SBP are limited. The recurrence of SBP is an emerging problem whereas its prevalence as well as its risk factors and its prognostic impact

Table 2: Predictive factors of recurrence of SBP in univariate analysis (quantitative variables).

Recurrence of SBP			
Parameters	**Yes (n=21)**	**No (n=69)**	**p value**
Age of diagnosis of cirrhosis (years)	56.9 ± 15	59.3 ± 13.6	0.493
Age of diagnosis of SBP (years)	60.81 ± 14.2	63.19 ± 12.5	0.462
Leucocytes (Elements/mm³)	7550 ± 4587	9323 ± 4901	0.136
Blood Neutrophils (Elements/mm³)	5989 ± 4277	7399 ± 4557	0.211
Hemoglobin (g/dl)	9 ± 2	10 ± 2	0.319
Hematocrit	29 ± 5	30 ± 6	0.294
Platelets (Elements/mm³)	136809 ± 147062	112843 ± 91720	0.371
CRP (mg/l)	76 ± 46	54 ± 39	**0.04**
Creatinin (µmol/l)	113 ± 59	123 ± 92	0.634
Urea (mg/l)	9 ± 2	12 ± 10	0.375
Natremia (mmol/l)	131 ± 4	132 ± 5	0.592
Albumin (g/l)	25 ± 3	25 ± 5	0.951
Prothrombin time (%)	44 ± 15	50 ± 15	0.136
INR	2.5 ± 1.3	2.2 ± 1.9	0.602
MELD Score	22.4 ± 5.4	19 ± 8	**0.023**
Ascitic protein level (g/l)	12.7 ± 7.7	13.2 ± 10.1	0.847
Ascitic leucocytes level (Elements/mm³)	3623 ± 9943	2046 ± 3118	0.629
Ascitic neutrophils (Elements/mm³)	3297 ± 9887	1256 ± 2651	0.36

Table 3: Results of the literature concerning predictive factors of recurrence of SBP.

Study Author Year (Reference)	First episode of SBP (n)	Survival after SBP (n)	Recurrence of SBP (n/%)	Predictive factors of recurrence of SBP (Univariate analysis)	p value	Predictive factors of recurrence of SBP (multivariate analysis)	p value
Tito et al. [10]	139	75	38 51%	Bilirubin >4 mg/dl Prothrombin time <45% Ascites protein level <10 g/l	0.005 0.043 0.031	Prothrombin time <45% Ascites protein level <10 g/l	0.009 0.005
Jamil et al. [12]	157		81	Female gender Hepatic encephalopathy Bilirubin >1 mg/l Creatinin >1.2 mg/l Post hepatitis B cirrhosis History of urinary infection	0.03 0.03 0.01 0.03 0.01 0.11	Age >55 ans Bilirubin >1 mg/l Post hepatitis B cirrhosis History of urinary infection	0.02 0.01 0.005 0.05
Huang et al. [13]	146	89	38 42.7%	Albumin level B blockers	10^{-4} 0.013	B Blockers	0.048
Naiv et al. [14]	111	111	45 40.5%	Fever Hepatic encephalopathy Diuretics Antibiotic prophylaxis Recent consumption of antibiotics <30 days paracentesis Child Pugh score C Hypertensive gastropathy	0.04 0.016 $<10^{-4}$ $<10^{-4}$ 0.04 $<10^{-4}$ 10^{-4} $<10^{-4}$	Hypertensive gastropathy	10^{-4}
Our study 2018	90	81	21 25.9%	B blockers Refractory ascites Hypertensive Hepatic encephalopathy C reactive protein >30 mg/l MELD Score >17	0.041 0.019 0.047 0.043 0.04 0.023	Hypertensive gastropathy	0.04

remain poorly understood.

The recurrence of SBP has been little studied. Historically, it was described by Tito et al. [10] in 1988 with a 43% 6 months survival, 69% 1 year survival and 74% 2 years survival without antibiotic prophylaxis, this rate being reduced to about 20% with norfloxacin in the only randomized trial conducted to date by Gines et al. [6] in 1990 (p=0.0063). This trial excluded patients with the most severe liver disease with TP<25%, serum bilirubin >10 mg/l or serum creatinine >2 mg/dl or with HCC [3].
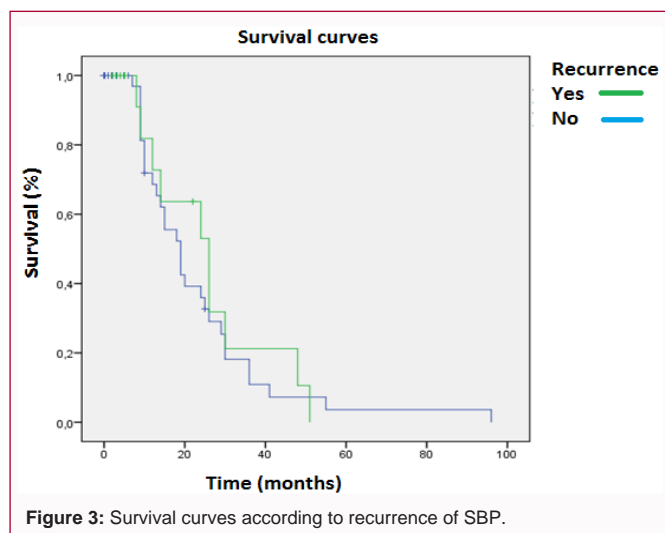
No other data on the prevalence of SBP recurrence in cirrhotic patients is currently available, as far as we know.

In our series, SBP recurrence was noted in 26% of patients.

Predictors of recurrence are poorly described and the prognostic impact of recurrence is poorly documented in the literature.

In the prospective study of Tito and al conducted in Spain from

Figure 3: Survival curves according to recurrence of SBP.

1981 to 1984 on 75 cirrhotic patients hospitalized for a first episode of SBP, 51% of patients presented a recurrence of the infection [10]. Multivariate analysis revealed that only low levels of ascites fluid and low prothrombin time were independent predictors of SBP recurrence. These results can be explained by the most accepted hypothesis on the pathogenesis of SBP. According to this hypothesis, SBP is the consequence of an increased bacterial translocation with a marked depression of the reticuloendothelial system [11], observed especially in case of advanced cirrhosis. The elements of this analysis were studied in our series but did not emerge as predictive factors of recurrence of SBP.

In addition, SBP recurrence was significantly associated with a decrease in survival compared to cirrhosis without SBP (p<0.01) [10].

In another more recent prospective series of Jamil et al. [12] published in 2011, the incidence of ISLA recurrence was 34%. In multivariate analysis, age >55 years (OR=0.45), bilirubin >1 mg/l (OR=7.03) and a history of urinary tract infection (OR=2.24) were predictive independent of SBP recurrence. In contrast, the hepatitis B etiology of cirrhosis was a protective factor against recurrence (OR=0.31).

Huang and al performed a study in order to limit the indications of secondary antibiotic prophylaxis due to increasing emergence of resistance to treatment [13]. Of the 146 patients included in this study, 89 survived to SBP, 42.7% of whom relapsed. SBP recurrence was associated with a decrease in survival (p=0.092). Sepsis was the leading cause of death in relapsing patients.

In this study, the authors showed that the albumin level could possibly have a prognostic value on the occurrence of recurrence of SBP. Indeed, the follow-up of patients who survived a first episode of SBP revealed that an albumin level <28.5 g/l was associated with a significantly higher risk of recurrence of infection in univariate (p=10-4) analysis with a sensitivity of 70.2%, a specificity of 76.3% and an area under the ROC curve (AUROC) of 0.78. This may suggest that albumin level may be a useful marker for predicting recurrence of ascites infection. In multivariate analysis, B blockers were an independent predictor of SBP recurrence (p=0.048).

B blockers also emerged in our series as a predictor of recurrence of SBP but only in univariate analysis.

Another more recent prospective observational unicentric study

published in 2018 by Nair and al assessed the determinants of SBP recurrence and its prognostic impact [14]. In this cohort a recurrence of SBP was noted in 40.5% of patients. In multivariate analysis, hypertensive gastropathy was an independent predictor of ISLA recurrence (p=0.001) as objectified in our study. This result could be explained by the hypothesis that portal hypertension plays a role in bacterial translocation [11] and thus predicts bacterial infections during decompensate cirrhosis. This study also showed that SBP recurrence was associated with higher mortality (p=0.009) with lower survival (p=0.04) compared with the first SBP episode.

Table 3 summarizes the results of the various studies concerning the predictors of recurrence of SBP.

Concerning SBP mortality, in the 1970s reports, it exceeded 90% [15]. Today, even with a better understanding of SBP physiopathology, its contributing factors and its management, its prognosis remains poor with a mortality rate around 20% to 40% in the most recent series [16-19]. In our work, the overall mortality rate following a first episode of SBP was significantly lower than the most recent data (about 10%).

Our study nevertheless has some weaknesses mainly due to methodological limitations. The retrospective and monocentric characters constitute the main limits. Indeed, the retrospective collection of data could include some biases in the collection of information. There may also be confounding factors that would not have been taken into account. Only a controlled prospective study would have corrected this selection bias. In the same way, the monocentric character considerably reduces the number of patients and consequently the power of the statistical results. Our work doesn't allow to evaluating the best therapeutic strategy since the treatment has been standardized.

Conclusion

In our study, SBP recurrence was relatively common as it involved a quarter of the patients who survived the first episode. Recurrence of SBP was associated with decreased survival hypertensive gastropathy is a simple endoscopic data that might be useful for recognizing patients who will have a recurrence of SBP.

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