The Negative Prognostic Impact of a First Ever Episode of Spontaneous Bacterial Peritonitis in Cirrhosis and Ascites

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Background: The prognostic impact of the first ever episode of spontaneous bacterial peritonitis (SBP) on patient outcomes is not well described. Our aim was to compare the clinical outcomes of cirrhotic patients with ascites, and with or without a first episode of SBP.

Methods: Consecutive patients with cirrhosis and ascites were prospectively enrolled. Demographics, liver and renal function, and hemodynamics were documented at baseline, at resolution of SBP, and thereafter at 4 monthly intervals for 12 months. Complications of cirrhosis and survival were noted.

Results: Twenty-nine cirrhotic patients with a first ever episode of SBP (group A) and 123 control patients slightly younger but similar in gender who never had SBP (group B) were enrolled. At SBP diagnosis, group A had worse liver and renal function (Model of End-Stage Liver Disease : 21.1 ± 10.6 vs. 14.4 ± 5.0), lower serum sodium concentrations, and a more hyperdynamic circulation compared with group B (all $P < 0.001$). SBP resolution resulted in improvement in all measures to baseline levels. During follow-up, group A required more frequent hospital admissions than group B (58% vs. 43%), developed more cirrhotic complications, including further SBP (31% vs. 3%*), hyponatremia (12% vs. 0.8%*), acute kidney injury (50% vs. 23%*), hepatorenal syndrome type 1 (46% vs. 7%*), liver transplantation (62% vs. 30%*), and had a worse overall 1-year survival (38% vs. 70%*) (*$P < 0.05$).

Conclusions: A first SBP episode is commonly followed by multiple complications, and overall worse prognosis. Consideration should be given to assess cirrhotic patients for liver transplant after the first episode of SBP.

Key Words: spontaneous bacterial peritonitis, cirrhosis, ascites

(*J Clin Gastroenterol* 2015;49:858–865)

Bacterial infections occur in 1/3 of all hospitalized patients with cirrhosis and ascites,[1–5] with spontaneous bacterial peritonitis (SBP) being one of the most common bacterial infections.[3,6–8] The presence of bacteria in SBP can trigger the release of various bacterial products and cytokines. Many of these have vasodilatory properties or they can induce the production of vasodilators, such as nitric oxide, leading to worsening of the already vasodilated systemic hemodynamics,[5] thereby predisposing the patient to further complications related to abnormal hemodynamics such as the development of acute kidney injury (AKI),[5] and other organ failures,[9] with in-hospital mortality ranging from 42% to as high as 67%.[9,10] AKI has the most negative impact on the survival of these patients.[10] AKI may be transient, persistent, or progressive,[11] and it can develop at the onset, during treatment, or even after resolution of SBP, potentially affecting prognosis beyond the SBP episode. Therefore, SBP remains a dreaded complication of cirrhosis.[12] However, the natural history of SBP beyond the first month is not well described. The only prospective study assessing 95 patients with a first episode of SBP showed a 1-year survival of 32.2%.[13]

It remains unclear as to whether the morbidity and the mortality of patients with cirrhosis and ascites who have recovered from a first episode of SBP differ from those of similar patients who have never had an SBP episode. We hypothesize that patients with a first ever episode of SBP will continue to show increased morbidity and mortality during follow-up despite recovery from their SBP. Therefore, the aim of this study was to compare the clinical outcomes of patients with cirrhosis and ascites and a first episode of SBP, to those with similar clinical characteristics, without ever had an SBP episode.

METHODS

The Research Ethics Board of University Health Network, which includes the Toronto General Hospital, approved the research study and each patient signed an informed consent. This is a prospective cohort study, enrolling consecutive consenting patients with cirrhosis and ascites from Toronto General Hospital, a quaternary referral hospital, between January 2008 and December 2010. Patients were recruited from outpatient general liver clinics and the pretransplant liver clinic, as well as several inpatient services of general internal medicine, hepatology, liver transplant, and general surgery. The control subjects (group B) were mostly recruited from outpatient clinics, with a small portion recruited as inpatients as they had other indications for admission; whereas all the SBP patients (group A) were recruited as inpatients. As all the cirrhotic patients with ascites who were outpatients were managed by hepatologists, and those admitted into the various inpatient services were either consulted or managed by the general hepatogists or transplant hepatologists, the care of these patients was fairly standardized. Cirrhosis was diagnosed either histologically or by a combination of biochemistry, endoscopic or radiographic findings, and the presence of ascites detected clinically and confirmed by ultrasound. Other inclusion criteria included age older than 18 years, and the ability to sign an informed consent. We excluded patients older than 75 years of age, or who had a previous episode of SBP, or a diagnosis of hepatocellular carcinoma, or intrinsic renal disease as evidenced by

Received for publication August 31, 2014; accepted February 14, 2015.
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abnormal urine findings and/or small kidneys on ultrasound, or those with a preexisting transjugular intrahepatic portosystemic shunt (TIPS) or a previous liver transplant. Patients who were scheduled for a live donor liver transplant or whose estimated survival was < 3 months were also excluded. The last group included patients who were under palliative care, patients who had organ failure, patients who were moribund, patients admitted into intensive care unit, and patients who had a Child-Pugh score of > 13 or a Model of End-Stage Liver Disease (MELD)[14] score of > 32. At the time of enrollment, patients were separated into their respective groups based on the confirmation of SBP. As this was the first ever episode, none of the patients was on prophylaxis for SBP. The diagnosis of index SBP was based only on ascitic fluid neutrophil count of $> 250 \times 10^6/\mu L$,[15,16] as ascitic fluid culture or blood culture may be negative in up to 60% of SBP cases.[17] Patients with suspected SBP and started on empirical antibiotics were not enrolled.

After obtaining consent, the patient's medical history was reviewed to ensure that all inclusion and exclusion criteria were met. In addition, patient demographics, comorbidities, etiology of liver disease, and clinical examination findings were recorded. All patients then underwent various laboratory investigations as documented in Table 1. In addition, the outpatient laboratory results within the past month in both the control and SBP patients were also recorded. Those for the SBP patients were taken as their baseline values, as the SBP episodes were often associated with acute changes in laboratory findings. Patients in the SBP group were treated with appropriate antibiotics and intravenous albumin infusion.[15,16] All inpatients were followed until hospital discharge for complications, including worsening ascites, electrolyte abnormalities, renal dysfunction including AKI, hepatorenal syndrome (HRS type 1 or 2) (see definitions below), hepatic encephalopathy, gastrointestinal bleed, and a new diagnosis of hepatocellular carcinoma. Clinical outcomes including death, liver transplant, and TIPS insertion were also recorded.

Upon discharge, all inpatients, like their outpatient counterparts, were reviewed at 4 monthly intervals, for at least 1 year. At each clinic visit, patients' overall condition and medications as well as any blood work done in the previous 4 months were recorded, and a complete physical examination including measurement of blood pressure and heart rate performed. Any complications, hospital admissions, or other clinical outcomes, as specified above that had occurred since the last visit were noted. All patients then received their regular 4 monthly laboratory investigations as per baseline. Other investigations such as abdominal ultrasound and gastroscopies were scheduled as per standard guidelines.[19,20] MELD score,[14] Child-Pugh score, and mean arterial pressure (MAP) were calculated. Patients who missed their follow-up appointments were contacted and rescheduled to ensure complete data collection.

Patients in both groups were censored upon receiving a TIPS or a liver transplant. Patients in the control group who developed SBP after enrollment were also censored.

Definitions

AKI

Absolute increase in serum creatinine of ≥ 0.3 g/dL (26.4 μmol/L) from baseline in ≤48 hours or increase in serum creatinine concentration of ≥50% from a stable baseline reading within a 6-month period.[21]

HRS

Increase in serum creatinine to > 1.5 mg/dL (133 μmol/L) that progresses over days to weeks, in the absence of intrinsic renal disease, as indicated by absence of hematuria (< 50 red blood cells per high-power field) and proteinuria (< 500 mg/d), and with a lack of improvement in renal function after withdrawal of diuretics and volume expansion with intravenous albumin (1 g/kg of body weight/d up to 100 g/d) for at least 2 days.[9]

Type 1 HRS. Rise in serum creatinine to ≥ 2.5 mg/dL (221 μmol/L) in < 2 weeks.

Type 2 HRS. A slow increase in serum creatinine to ≥ 1.5 mg/dL (133 μmol/L) but < 2.5 mg/dL (221 μmol/L) over weeks to months.[9]

Statistical Analysis

Statistical analysis was performed using Prism 6 (GraphPad Software Incorporated, La Jolla, CA). Continuous data are presented as mean ± SD, whereas discrete data are presented as median plus the interquartile range. Group comparisons for continuous variables were done with either a 2-sample *t* test or a 1-way ANOVA if > 3 samples are compared. Group comparisons for discrete data were done using a nonparametric Wilcoxon Rank-Sum test (Mann-Whitney *U* test) for 2 samples, or the Kruskal-Wallis for > 2 groups. Categorical data are presented as a percentage as well as the actual numbers used to calculate the percentages. Group comparisons for categorical variables were done using the χ^2 test. Survival curve was constructed using Kaplan-Meier analysis. All comparisons were 2 tailed and a *P* value of < 0.05 was considered statistically significant.

RESULTS

One hundred and eighty-nine patients signed informed consent, 37 patients were excluded (Fig. 1). Twenty-nine patients were recruited to the SBP group (19 males, 10 females; mean age, 57 ± 9 y), and 123 patients were recruited to the control group (95 males, 28 females; mean age, 59 ± 9 y). Patient demographics with laboratory results at enrollment and 1 month prior are shown in Table 1. Patients in the SBP group had similar laboratory data at 1 month before enrollment compared with controls whose laboratory data remained stable for the month before enrollment (Table 1), suggesting that the SBP group was fairly well matched to the control group before the first episode of SBP.

Initial Admission

Initial diagnosis of SBP consisted of 10 gram-positive cultures, 9 gram-negative cultures, and 10 culture-negative samples. The gram-positive cultures were 4 cases of *Streptoccocus viridans*, 2 of *Enterococcus faecium*, 1 each of *Staphylococcus aureus*, *Bacillus* species, *Clostridium difficile*, and Group B streptococcus. Gram-negative cultures included 7 cases of *Escherichia coli*, and 1 each of *Enterobacter aerogenes*, *Bacteroides fragillis* group (lactobacillus species), and *Enterobacter cloacae*. Patients with SBP at presentation had hyponatremia and worse renal and liver dysfunction, and therefore significantly higher Child-Pugh and MELD scores (Table 1), when compared with themselves at baseline, as well as compared with controls at

TABLE 1. Patient Demographics and Laboratory Data 1 Month Prior and at Enrollment

Variable	Controls		SBP	
n	123		29	
Age (y)	59 ± 9		57 ± 9*	
Sex (M:F)	95:28		19:10	
Etiology of cirrhosis (%)				
Alcohol	59 (48)		9 (31.5)	
Viral hepatitis	37 (30)		9 (31.5)	
NASH	13 (11)		3 (10)	
Cholestatic liver disease	4 (3)		5 (17)	
Other	10 (8)		3 (10)	
Comorbidities (%)				
Prior encephalopathy	55 (45)		14 (48)	
Prior rifaximin use	0 (0)		0 (0)	
Prior variceal bleed	47 (38)		12 (41)	
Prior β-blocker use	72 (59)		16 (55)	
Cirrhosis stage[18] [n (%)]				
Stage 3	76 (62)		17 (59)	
Stage 4	47 (38)		12 (41)	
	1 mo Prior	At Enrollment	1 mo Prior	At Enrollment
Hb (g/dL) (normal range, 14-18 g/dL)	11.4 ± 1.3	11.7 ± 1.4	11.3 ± 1.8§	10.5 ± 2.3#
WBC ($\times 10^9$/L) (normal range, 4-11 $\times 10^9$/L)	4.8 ± 3.2	5.5 ± 2.9	4.9 ± 3.0§	8.4 ± 5.0*
Platelet count ($\times 10^9$/L) (normal range, 150-400 $\times 10^9$/L)	119 ± 82	120 ± 80	118 ± 83	108 ± 107
INR (normal range, 0.8-1.2)	1.46 ± 0.47	1.53 ± 0.44	1.51 ± 0.41§	1.94 ± 0.56*
Serum Na (mmol/L) (normal range, 135-145 mmol/L)	134 ± 5	136 ± 4	135 ± 4§	131 ± 6*
Creatinine (mg/dL) (normal range, 0.8-1.3 mg/dL)	0.95 ± 0.31	0.99 ± 0.35	1.02 ± 0.51§	1.27 ± 0.72*
AST (U/L) (normal range, 5-34 U/L)	46 ± 31	55 ± 42	45 ± 35§	75 ± 56#
ALT (U/L) (normal range, 7-40 U/L)	38 ± 33	34 ± 26	37 ± 32§	51 ± 41#
Total bilirubin (mg/dL) (normal range, ≤1.3 mg/dL)	3.2 ± 1.8	3.2 ± 1.6	2.9 ± 1.4§	6.1 ± 4.4#
Albumin (g/dL) (normal range, 3.8-5.0 g/dL)	3.4 ± 0.5	3.4 ± 0.4	3.4 ± 0.5§	3.1 ± 0.7*
Child-Pugh score	8.2 ± 1.7	8.2 ± 1.7	8.5 ± 1.9§	10.5 ± 3.2*
Child-Pugh class	A = 20	A = 20	A = 5	A = 1
	B = 77	B = 77	B = 20	B = 7
	C = 26	C = 26	C = 4	C = 21
MELD	14.3 ± 5.3	14.4 ± 5.0	13.9 ± 5.6§	21.1 ± 10.6*

*$P < 0.001$ compared with controls at enrollment.
#$P < 0.05$ compared with controls at enrollment.
§$P < 0.05$ compared with enrollment of SBP group.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; INR, International normalized ratio; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; WBC, white blood cell count.

enrollment. In addition, SBP group had worse systemic hemodynamics as indicated by significantly lower MAP and significantly increased heart rate (Table 2) when compared with control group at enrollment.

Thirteen of the 29 patients with SBP had AKI at presentation with their mean serum creatinine having risen from 0.95 ± 0.32 mg/dL at baseline to 1.79 ± 0.81 mg/dL at SBP diagnosis. Six of the 13 patients with AKI fulfilled the diagnosis of type 1 HRS, with a mean serum creatinine of 2.84 ± 0.98 mg/dL at SBP diagnosis. All patients with SBP survived until SBP resolution, defined as ascitic fluid neutrophil count of $< 250 \times 10^6/\mu L$. Apart from the heart rate decreasing with the resolution of SBP, the patients continued to demonstrate evidence of renal and circulatory dysfunction as indicated by a high serum creatinine (1.36 ± 0.56 mg/dL), low serum sodium (133 ± 5 mmol/L), and low MAP (81 ± 12 mm Hg), all of which were significantly different ($P < 0.05$) from the control group at enrollment (Table 2). As a result, the Child-Pugh and MELD scores at SBP resolution remained elevated in the SBP group compared with the control group ($P < 0.001$) (Table 2).

Subsequent to the resolution of SBP, 2 patients with type 1 HRS died during the same admission. Another patient with HRS type 1 and SBP received a liver transplant during the same admission. The remaining 3 patients with type 1 HRS had improvement in renal function at hospital discharge. The other 7 SBP patients with AKI, not fulfilling criteria for type 1 HRS, survived the initial admission with recovered renal function, not requiring a liver transplant or TIPS insertion. Twenty-six SBP patients were eventually discharged from hospital and followed as outpatients.

In the control group, 3 of the 123 patients at enrollment had type 1 HRS and were admitted. Two of the type 1 HRS patients had persistent renal dysfunction despite treatment with albumin, midodrine, and octreotide, and both received liver transplants, while one had progressive renal dysfunction and died. Three other patients had non-HRS AKI at enrollment in the control group.

Follow-up Period

The follow-up period was 13 ± 14 months for the SBP group and 21 ± 12 months for the control group ($P < 0.05$).

Further Episodes of SBP

Twenty-five of the 26 patients in the SBP group who were discharged without a liver transplant were given SBP

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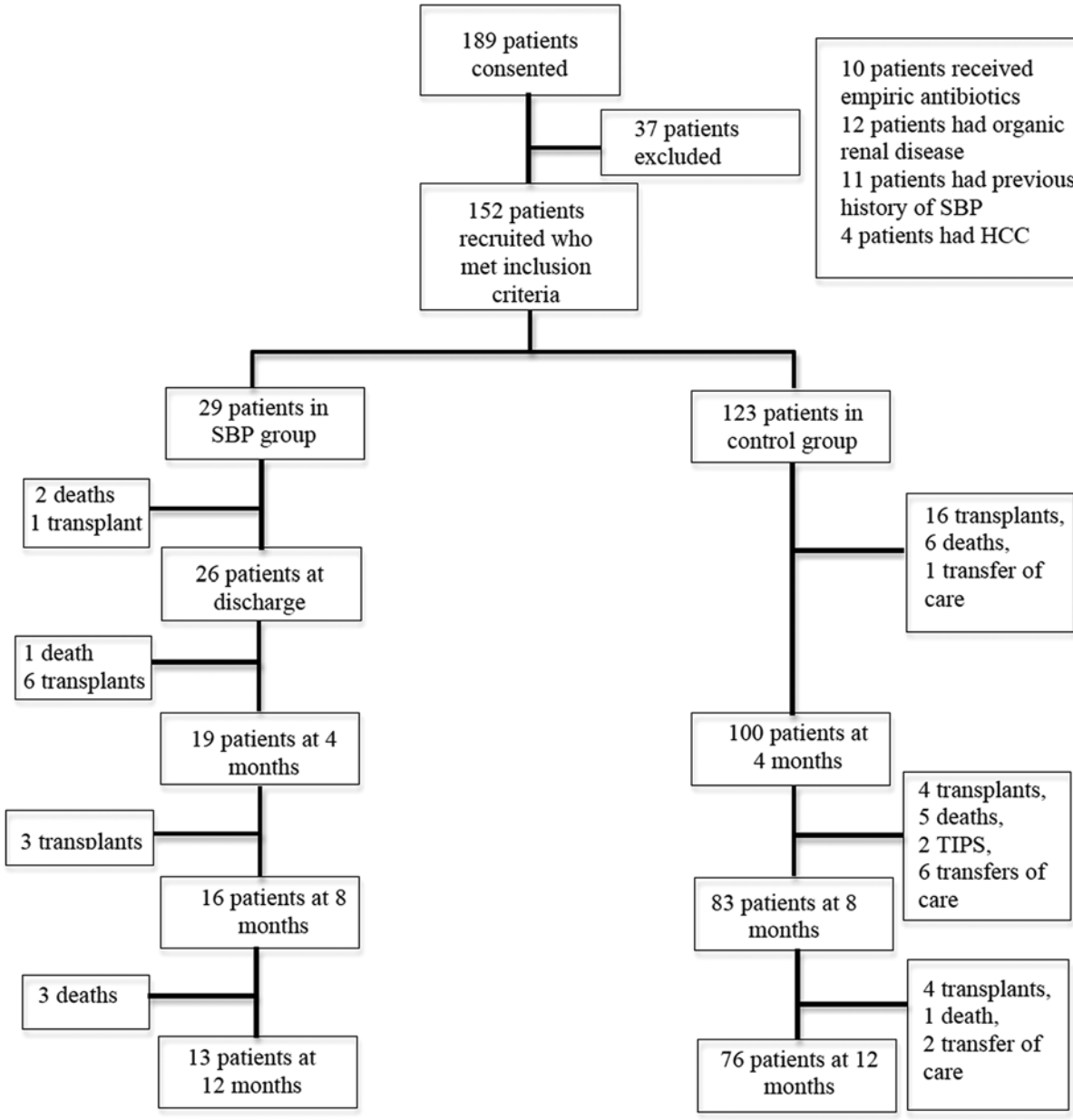

FIGURE 1. Disposition of all study patients. HCC indicates hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

prophylaxis. Twenty-two patients received ciprofloxacin 750 mg weekly, whereas 3 patients received norfloxacin 400 mg daily as secondary prophylaxis. The one patient who did not receive antibiotic prophylaxis (reason unclear) did not develop recurrent SBP.

Eleven episodes of recurrent SBP were seen in 8 patients (31%), with a mean of 1.4 episodes per patient. The organisms involved were: 3 gram-positive species (coagulase-negative *S. aureus*, 1 sensitive and 1 resistant to cephalosporins, and *C. difficile*), 2 gram-negative species (both with resistance/indeterminate sensitivity to ciprofloxacin), and 6 culture-negative samples.

Only 4 patients (3.3%) had 4 episodes of SBP in control group at 97 to 207 days during follow-up. At the time of diagnosis of SBP, they were censored; however, we continued to follow them with respect to clinical outcomes. The microbiology of the control group was 3 gram-positive cultures and 1 gram-negative culture with no evidence of antibiotic resistance.

Renal Function

In the SBP group, the 26 patients who survived the hospital admission without a liver transplant were discharged with normal renal function. During follow-up, there were episodes of AKI in between periods of normal serum creatinine. This occurred in 13/26 (50%) patients in the SBP group with a mean of 3.6 ± 3.1 episodes/patient, with 6 of these fulfilling the definition of type 1 HRS. The

TABLE 2. Follow-up Laboratory and Clinical Parameters in the SBP Group Versus Control Group

Parameter	1 Mo Prior	Enrollment	SBP Resolution	Month 4	Month 8	Month 12
n						
Controls	123	123	—	100	83	76
SBP	29	29	29	19	16	13
MELD score						
Controls	14.3 ± 5.3	14.4 ± 5.0	—	13.3 ± 6.3	12.6 ± 6.0	12.5 ± 5.6‖
SBP	13.9 ± 5.6§	21.1 ± 10.6*	21.3 ± 8.4*	15.3 ± 5.4§	16.0 ± 7.5†§	13.6 ± 4.2§
C-P score						
Controls	8.2 ± 1.7	8.2 ± 1.7	—	8.3 ± 1.6	8.2 ± 1.2	8.2 ± 1.1
SBP	8.5 ± 1.9§	10.5 ± 3.2*	10.5 ± 1.8*	9.1 ± 2.2§	8.6 ± 1.6§	8.4 ± 1.5§
Serum creatinine (0.8-1.3 mg/dL)						
Controls	0.95 ± 0.31	0.99 ± 0.35	—	1.06 ± 0.55	1.03 ± 0.43	1.00 ± 0.25
SBP	1.02 ± 0.51§	1.27 ± 0.72*	1.36 ± 0.56*	0.85 ± 10§	0.93 ± 0.35§	0.88 ± 0.17§
Serum (Na) (135-145 mmol/L)						
Controls	134 ± 5	136 ± 4	—	135 ± 4	136 ± 5	136 ± 4
SBP	135 ± 4§	131 ± 6*	133 ± 5#	134 ± 5§	136 ± 5§	135 ± 5§
MAP (mm Hg)						
Controls	83 ± 6	85 ± 7	—	83 ± 6	85 ± 6	87 ± 8
SBP	85 ± 7§	79 ± 12#	81 ± 12#	84 ± 9	83 ± 12	86 ± 14§
Heart rate (beats/min)						
Controls	74 ± 6	75 ± 10	—	75 ± 7	74 ± 8	73 ± 8
SBP	75 ± 9§	87 ± 14*	77 ± 14§	75 ± 11§	80 ± 11	79 ± 11

*$P < 0.001$ comparing SBP group to control group at enrollment.
#$P < 0.05$ comparing SBP group to control group at enrollment.
§$P < 0.05$ comparing SBP group at enrollment.
†Comparing SBP group to control group for month X.
‖$P < 0.05$ comparing to control group at enrollment.
C-P indicates Child-Pugh score; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis.

control group included 3 patients with non-HRS AKI at enrollment, which recovered to their baseline renal function, at a mean period of 16 ± 8 days. During follow-up, only 28/120 (23%) of controls developed AKI, with a mean of 1.8 ± 0.8 episodes/patient ($P < 0.05$ vs. SBP group), and only 2 episodes were type 1 HRS ($P < 0.001$ vs. SBP group) (Table 3). This is despite the fact that the mean serum creatinine before the AKI episodes was the same in both the groups. Most of the follow-up AKI episodes in the control group (93%) resolved. This contrasts with a resolution rate of 54% in the SBP group ($P < 0.001$), despite the peak serum creatinine and time to resolution of the AKI episode (in the patients with resolution) were comparable in both groups (Table 3). In the SBP group, 69% of AKI episodes were repeated AKI events compared with 32% in the control group ($P < 0.001$).

Clinical Outcomes and Mortality

Overall, there were an increased number of hospital admissions in the SBP group: 5.1 ± 3.6 hospitalizations per patient versus 2.0 ± 1.4 in the control group ($P = 0.015$). Other complications more frequent in the SBP group compared with the controls were: persistent hyponatremia of <130 mmol/L for >48 hours ($P = 0.022$), and AKI episodes ($P < 0.001$) (Table 3). More patients in the SBP group received a liver transplant (n = 10, 34%) compared with the control group (n = 24, 20%) ($P = 0.089$). There were 2 TIPS inserted only in the control group for the indication of refractory ascites at 12 months of follow-up. Subsequent follow-up beyond 12 months showed 1 TIPS in the SBP group and 5 TIPS in the control group, for the same indication.

With 10 patients of the initial SBP cohort censored during the initial 4 months due to either death or liver transplantation, there was an apparent improvement in the Child-Pugh and MELD scores. Follow-up in the survivors of the SBP group demonstrated gradual improvements and stabilization of the Child-Pugh ($P < 0.05$), and MELD scores ($P < 0.05$) beyond 4 months, associated with a reduction of serum creatinine ($P < 0.05$) (Table 2). The control group continued to maintain stable hemodynamics and renal function throughout the study period.

Associated with the higher complication and hospital admission rates in the SBP group, there was a significant increase in mortality compared with the control group ($P = 0.0019$) (Fig. 2). The 90-day mortality was 32% for the SBP group and 15% for the control group.

DISCUSSION

This study demonstrates that the occurrence of the first ever episode of SBP heralds in a stage of further decompensation in the natural history of cirrhosis and ascites. The SBP episode itself was associated with a significant deterioration in liver and renal function, albeit temporary in some patients, despite having been previously very stable. The deterioration in liver and renal function was sufficient to cause the demise of some patients despite resolution of SBP. In those who survived and were discharged from hospital, there remained evidence of liver and renal dysfunction, with higher Child-Pugh and MELD scores, together with a suggestion of worsening hemodynamics as indicated by the low MAP and the frequent episodes of hyponatremia, especially in the first few months following the episode of SBP. These changes may explain the higher likelihood of these patients developing AKI and type 1 HRS, and therefore leading to a worse survival and an increased need for liver transplantation. Although an overall poor survival with SBP has previously been reported,[22] our study is the first to report on the survival

TABLE 3. Complications During Follow-up

Complication	Controls (n = 120)	SBP (n = 26)
AKI episodes		
Proportion with acute kidney injury	28/120 (23%)	13/26 (50%)#
Episodes of AKI/patient	1.8 ± 0.8	3.6 ± 3.1*
Baseline creatinine before episode of AKI (μmol/L)	1.00 ± 0.31	0.98 ± 0.40
Maximum creatinine during episode of AKI (μmol/L)	1.63 ± 0.75	1.70 ± 0.98
Resolution creatinine after episode of AKI (μmol/L)	1.11 ± 0.32 (n = 26)	1.09 ± 0.43 (n = 7)
No. days until resolution of AKI	18 ± 9	17 ± 9
Resolved AKI	26/28 (93%)	7/13 (54%)*
Proportion with hepatorenal syndrome	2/28 (7%)	6/13 (46%)#
Bacterial infections as precipitant of AKI	20/28 (71%)	9/13 (69%)
Other complications		
No. patients who required admission	53/120 (44%)	15/26 (58%)
Total no. hospital admissions	102	63
No. hospitalizations/patient	2.0 ± 1.4	5.1 ± 3.6#
Further SBP	4/120 (3%)	8/26 (31%)*
Non-SBP infections	18/120 (15%)	7/26 (25%)
Worsening ascites	10/120 (8%)	6/26 (23%)
Hepatic encephalopathy (grade 2-4)	12/120 (10%)	6/26 (23%)
Gastrointestinal bleed	20/120 (17%)	6/26 (23%)
Persistent hyponatremia (serum Na < 130 mmol/L X > 48 h)	1/120 (0.8%)	3/26 (12%)#
AKI	28/120 (23%)	13/26 (50%)*
Hepatocellular carcinoma	17/120 (14%)	6/26 (23%)
Liver transplant	37/120 (31%)	16/26 (62%)#
TIPS	2/120 (2%)	0/26 (0%)
Others complications: umbilical hernia, falls, acute coronary syndrome, non–liver-related diagnosis	17/120 (14%)	6/26 (23%)

Worsening ascites: increase in frequency of large volume paracentesis (> 5 L).

*$P < 0.001$ SBP group versus controls.

#$P < 0.05$ SBP group versus controls.

AKI indicates acute kidney injury; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic stent.

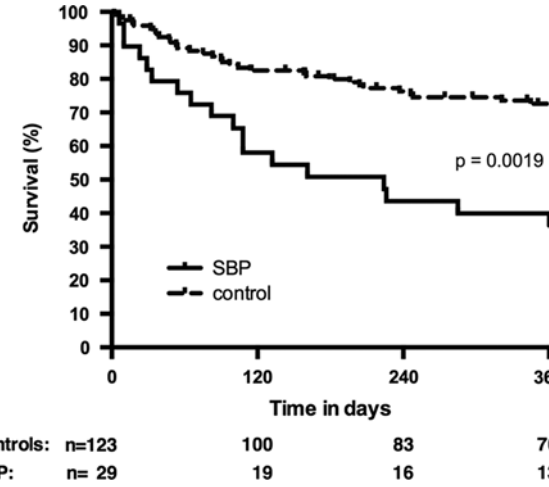

FIGURE 2. Survival of both groups during follow-up. SBP indicates spontaneous bacterial peritonitis.

and other outcomes following a first ever episode of SBP as compared with controls.

Decompensated cirrhosis is an immunocompromised state, associated with intestinal bacterial overgrowth, and increased intestinal translocation of bacteria and bacterial products,[23] which can stimulate an exaggerated proinflammatory response, with release of reactive oxygen species and nitric oxide.[23] These changes can modulate gut barrier function and impair mucosal bacteriocidal capability, thus predisposing these patients to the development of SBP.[24] Once SBP occurs, there is presumably an increased load of bacterial products and cytokines, many of these also have vasodilatory properties. The resultant augmented systemic vasodilatation[25] further increases the susceptibility of these patients to other complications such as renal dysfunction and other organ failure.[26] Despite appropriate antibiotic treatment, continued bacterial translocation can still occur.[27] Although bacterial DNAs and various cytokines were not measured in this study, this may explain why, after an initial episode of SBP, abnormal hemodynamics persisted, leading to incomplete resolution of renal dysfunction and hyponatremia.

Historically, the common microorganisms for SBP are gram-negative bacteria, thus various practice guidelines recommend the use of cefotaxime or another third-generation cephalosporin as first-line treatment for SBP.[15,16] However, our patients demonstrated a shift towards more gram-positive organisms as the causative agents. This has also been documented in several studies with increasing nosocomial infections in a high-risk population.[2,28,29] Our study patients were mostly outpatient decompensated cirrhotic patients whose SBP episodes were mostly community acquired. One would expect the bacterial profile to be largely gram-negative organisms sensitive to β-lactams.[30] The fact that we are observing a changing pattern of bacteria causing SBP may be related to their frequent visits to medical facilities. This changing microbiology pattern brings into question the appropriateness of current recommendations for antibiotic prophylaxis.[31] This may also explain the frequency of SBP recurrence during follow-up despite compliance with antibiotic prophylaxis, and the propensity for other cirrhotic complications, especially for renal dysfunction, that were observed in our study after an episode of SBP.

Indeed, we observed an AKI rate of 50% in the SBP group during follow-up, an incidence that was >2-fold higher than that observed in the control group. There were more AKI episodes per patient and more of these were type 1 HRS events. However, most of the AKI episodes did not result in a serum creatinine level high enough to qualify for a diagnosis of type 1 HRS, and therefore may escape the clinician's attention and are not treated. Fortuitously, most of these AKI episodes resolved, but the length of time required for resolution averaged at least 2 weeks. It has been previously reported in another cohort of cirrhotic patients that repeated episodes of mild AKI resulted in decreased survival, despite resolution of AKI.[32]

Indeed, decreased survival was observed in the SBP group after the index episode. Contributions to this

decreased survival may be related to increased prevalence of other complications of cirrhosis. The frequent occurrence of mild episodes of AKI that are left untreated may have also negatively impacted survival. Therefore, the development of the first ever episode of SBP may have identified patients who are at higher risk for further complications. Future management of patients with cirrhosis and ascites may need to include stratification depending on whether there has been a first ever episode of SBP.

Given the fact that a first ever episode of SBP has such a negative impact on the prognosis of these patients, the question arises as to whether we should universally provide primary prophylaxis against SBP in patients with decompensated cirrhosis. Various academic societies have provided strict guidelines for providing primary prophylaxis against SBP, namely, patients with advanced cirrhosis with a Child-Pugh score of ≥ 9, together with a bilirubin of ≥ 3 mg/dL, or the presence of impaired renal function (serum creatinine ≥ 1.2 mg/dL or a blood urea nitrogen of ≥ 25 mg/dL), or the presence of hyponatremia of ≤ 130 mmol/L, together with a low ascitic protein count of < 15 g/L.[15,16] Our patients who had their first ever episode of SBP did not have any of these features at baseline, and therefore would not qualify for primary prophylaxis according to the guidelines. Yet their first episode of SBP had such a negative impact on their clinical outcome. Therefore, it may be prudent to investigate other strategies of identifying patients for primary prophylaxis against the first episode of SBP. Further clinical trials may wish to assess for bacterial DNA or cytokines in ascitic fluid or serum as markers for primary prophylaxis.

We recognize that the sample size of the SBP population in this study is relatively small. It is plausible that some patients with cirrhosis and ascites, with no clinical signs or symptoms, would not have SBP diagnosed if diagnostic paracentesis was not performed. Nonetheless, we feel that it is unlikely that patients with undiagnosed SBP were included in the control group, given the poor outcome of untreated SBP that would eventually lead to the diagnosis declaring itself. We also did not collect any information on parameters such as bacterial DNA, cytokines, or nitric oxide—all of which have helped to explain the relationship between SBP in cirrhosis and clinical outcomes, as this was not planned to be a mechanistic study. Despite this, we were able to identify a timepoint in the natural history of decompensated cirrhosis that ushers in further deterioration of clinical outcome in these patients, namely after their first episode of SBP.

In conclusion, cirrhotic patients with even 1 episode of SBP need to be monitored regularly for the development of complications such as AKI and hyponatremia. In addition, patients with even a first episode of SBP need to be considered for liver transplantation promptly, given their high mortality during follow-up.

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