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ORIGINAL ARTICLE

Spontaneous bacteremia and spontaneous bacterial peritonitis share similar prognosis in patients with cirrhosis: a cohort study

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Abstract

Background and aims Spontaneous bacteremia is a poorly characterized infection in patients with cirrhosis. We compared the incidence of mortality and acute kidney injury in patients with spontaneous bacterial peritonitis and spontaneous bacteremia, and identified risk factors for mortality and acute kidney injury in patients with spontaneous bacteremia.

Methods We performed a retrospective cohort study of patients with cirrhosis and spontaneous bacteremia or spontaneous bacterial peritonitis from 2008 to 2016 at Hospital Italiano, Buenos Aires. We compared the cumulative incidence of acute kidney injury and death between the two infections, and identified risk factors for these outcomes in patients with spontaneous bacteremia.

Results Seventy-one patients with spontaneous bacteremia and 55 patients with spontaneous bacterial peritonitis were included. Most infections were nosocomial. Overall, 26% of bacteria were resistant and 11% multi-resistant. We found no significant association between acute kidney injury [subhazard ratio (sHR) 1.05 (95% confidence interval, CI 0.67–1.63, $p = 0.83$)] or death [sHR 1.15 (95% CI 0.60–2.20, $p = 0.68$)] and type of spontaneous infection in multivariate analyses adjusting for basal Model for End-Stage Liver Disease (MELD) score. In patients with spontaneous bacteremia, baseline MELD score was independently associated with acute kidney injury [sHR 1.07 (95% CI 1.03–1.11, $p = 0.001$)] and death [sHR 1.07 (95% CI 1.02–1.15, $p = 0.03$)].

Conclusions Short-term acute kidney injury and mortality rates were similar in patients with spontaneous bacteremia and spontaneous bacterial peritonitis. Risk assessment of patients with spontaneous bacteremia can be performed with baseline MELD score.

Keywords Spontaneous bacteremia · Spontaneous bacterial peritonitis · Outcome · Acute kidney injury · Mortality

Abbreviations

ACLF	Acute-on-chronic liver failure
AKI	Acute kidney injury
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile ratio

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CPE	Carbapenemase-producing *Enterobacteriaceae*
MELD	Model for End-Stage Liver Disease
MRSA	Methicillin-resistant *Staphylococcus aureus*
sHR	Subhazard ratio

Introduction

Spontaneous bacterial peritonitis is the most frequent and well-characterized infections in patients with cirrhosis [1, 2]. Due to its associated poor prognosis, specific recommendations for treatment and prophylaxis guide routine practice [3].

When analyzing other bacterial infections in patients with cirrhosis, risk stratification is difficult due to their heterogeneous prognosis: in a recent publication by Fernandez et al., bacterial infections showed strikingly different clinical outcomes (e.g., endocarditis was associated with 62% 90-day mortality, whereas cellulitis only showed 9.5% 90-day mortality in patients with cirrhosis) [4].

Spontaneous bacteremia in patients with cirrhosis is a poorly studied entity. Regarding prognosis, as much as 47% of patients may develop acute kidney injury and 22% may die within 30 days of diagnosis of the infection. However, prior studies assessing spontaneous bacteremia included patients with concomitant bacterial infections, and even grouped together patients with spontaneous and secondary bacteremia [4, 5]. Thus, it remains challenging to assess the clinical impact of this spontaneous infection.

Since spontaneous bacteremia shares pathophysiological pathways with spontaneous bacterial peritonitis [5], we hypothesized that these spontaneous infections may also share outcomes; thus, the main objectives of this study are to compare the incidence of mortality and acute kidney injury (AKI) in patients with spontaneous bacterial peritonitis and spontaneous bacteremia, and to identify risk factors for mortality and AKI in patients with spontaneous bacteremia.

Patients and methods

Study design, population, and follow-up

We designed a retrospective cohort study of consecutive patients with cirrhosis with either spontaneous bacteremia or spontaneous bacterial peritonitis, from 1 March 2008 to 31 March 2016, at Hospital Italiano, Buenos Aires, Argentina, a large teaching hospital.

The Clinical Research and Bioethics Committee of the aforementioned hospital approved the study, in accordance with the Declaration of Helsinki of 1975 as revised in 2008. Inclusion criteria were patients older than 17 years with cirrhosis (based on liver biopsy, or a combination of clinical signs and findings provided by laboratory tests, endoscopy, and radiological imaging) and diagnosis of a first episode of either spontaneous bacteremia or spontaneous bacterial peritonitis. Spontaneous bacteremia was defined as growth of a noncommon skin contaminant in $\geq$1 blood cultures, without evidence of infection located at another body site [5]. All patients with spontaneous bacteremia and ascites underwent ascitic fluid analysis and culture to rule out spontaneous bacterial peritonitis or bacterascites. Patients in whom analysis of ascitic fluid was not possible for technical reasons were excluded. Patients who fulfilled criteria for catheter-related bloodstream infection were also excluded [6]. Spontaneous bacterial peritonitis was defined as absolute polymorphonuclear count $\geq$250 cells/mm^3 in ascitic fluid without an evident intraabdominal, surgically treatable source of infection. Exclusion criteria included at least one prior episode of spontaneous infection (spontaneous bacterial peritonitis, spontaneous empyema, or spontaneous bacteremia), concomitant bacterial infection at time of inclusion, history of liver or other organ transplantation, advanced hepatocellular carcinoma according to Barcelona Clinic Liver Cancer classification, and infection with human immunodeficiency virus. Patients were followed for 90 days from day of infection diagnosis or until liver transplant or death, whichever occurred first.

Diagnostic and treatment strategies in the Liver Unit of the Hospital Italiano were as follows: Whenever an infectious episode was suspected in a patient with cirrhosis (based on worsening of clinical status such as hepatic encephalopathy, fever, or laboratory abnormalities), complete work-up was carried out, including ascitic, urine, and blood cultures and chest X-rays, within 2 h. Antibiotic therapy was promptly initiated when infection was suspected, after cultures were obtained. In patients with community-acquired spontaneous infection, third-generation cephalosporin was the antibiotic of choice. When the infection was health related or of nosocomial origin, piperacillin/tazobactam was used as first-line empiric therapy (in those patients previously exposed to piperacillin/tazobactam, carbapenems were used). Since the appearance of carbapenemase-producing *Enterobacteriaceae* (CPE) in our hospital in 2011, colistin was included in the empirical treatment in high-risk patients (pretreatment with carbapenems, colonization by CPE, prior broad spectrum antibiotic therapy). Coverage with vancomycin was considered when patients had predefined risk factors, such as colonization with methicillin-resistant *Staphylococcus aureus* (MRSA), central venous catheter, and history of prior infection with MRSA or shock. In patients with spontaneous bacterial peritonitis, intravenous albumin infusion was used according to treatment guidelines [7].

Table 1 Baseline characteristics of entire study population, and according to type of infection (spontaneous bacteremia or spontaneous bacterial peritonitis), at Hospital Italiano from 2008 to 2016 ($n = 126$)

Variable	All ($n = 126$)	Spontaneous bacteremia ($n = 71$)	Spontaneous bacterial peritonitis ($n = 55$)	p
Age (years)	63 (53–69)	62 (53–69)	65 (51–69)	0.83
Male gender	73 (58%)	42 (59%)	31 (56%)	0.75
Cirrhosis etiology				
Viral hepatitis	39 (31%)	27 (38%)	12 (22%)	0.17
Alcohol	28 (22%)	15 (21%)	13 (24%)	
Autoimmune hepatitis	16 (13%)	9 (13%)	7 (13%)	
Primary biliary cholangitis	13 (10%)	5 (7%)	8 (15%)	
Other	30 (24%)	15 (21%)	15 (26%)	
HCC	23 (18%)	12 (17%)	11 (20%)	0.65
Ascites	106 (84%)	51 (72%)	55 (100%)	< 0.001
Creatinine (mg/dL)	1.1 (0.8–1.6)	1 (0.8–1.4)	1.3 (0.8–1.9)	0.041
Leukocyte count ($\times 10^3/mm^3$)	7.6 (5.0–10.1)	7.3 (4.7–9.4)	7.8 (5.6–12.1)	0.24
Total bilirubin (mg/dL)	4.4 (2.1–7.6)	3.8 (1.9–6.1)	6.4 (3.1–9.0)	0.003
Serum albumin (g/dL)	2.6 (2.2–2.9)	2.6 (2–3)	2.6 (2–3)	0.74
INR	1.8 (1.5–2.2)	1.8 (1.4–2.1)	1.95 (1.6–2.8)	0.03
Serum sodium (mEq/L)	133 (129–137)	134 (129–137)	132 (127–136)	0.10
SIRS*	70 (56%)	38 (54%)	32 (58%)	0.66
MELD score	20 (16–26)	19 (14–25)	24 (18–31)	0.001
Child–Pugh score	10 (9–12)	10 (9–12)	11 (9–12)	0.34

All variables collected at time of diagnosis of infection. All qualitative variables expressed as absolute numbers and percentages. All quantitative variables expressed as median and interquartile range (IQR)

HCC hepatocellular carcinoma, *INR* international normalized ratio, *SIRS* systemic inflammatory response syndrome, *MELD* Model for End-Stage Liver Disease

* Available in 125 patients

Data collection and definitions

At Hospital Italiano, all medical care interventions are registered centrally in a computerized data repository, with only one electronic health record per person. Data were extracted by a hepatologist from the electronic clinical records using a standardized data collection form. Variables included patient demographics (sex, age), date of spontaneous bacteremia or spontaneous bacterial peritonitis diagnosis, and cause and severity of liver disease according to baseline Child–Pugh and Model for End-Stage Liver Disease (MELD) scores [8, 9]. Acute kidney injury (AKI) was considered present when increase in serum creatinine $\geq$0.3 mg/dL or $\geq$50% in two measurements 48 h apart occurred at admission or during follow-up, reaching a final peak value of $\geq$1.5 mg/dL [10]. Laboratory and clinical data were used to identify systemic inflammatory response syndrome at admission [11], and acute-on-chronic liver failure (at admission or during follow-up) [12]. Information regarding bacteria identification and antibiotic susceptibility (sensitive, resistant, multiresistant) [13], initial antibiotic treatment and further change in therapy (if needed), and type of infection according to site of acquisition (community acquired, healthcare associated, and nosocomial) [14] was collected and recorded by a specialist in infectious diseases. Adequate initial antibiotic therapy was defined as initiation of antibiotics within 24 h, with at least one in vitro active antibiotic against the isolated pathogen [15]. Blood cultures were obtained by venipuncture from two or more different peripheral veins. Blood samples were collected in BacT/ALERT^{TM} 3D culture aerobic/anaerobic vials; the BacT/ALERT^{TM} 3D automated microbial detection system was used according to manufacturer's instructions.

Sampling and sample size calculations

Since spontaneous bacteremia is an infrequent infection, we included all consecutive identified cases. We included a simple random sample of consecutive patients with spontaneous bacterial peritonitis that fulfilled selection criteria using high-quality validated databases of previous

published and unpublished studies conducted by the same research team [16, 17]. Since these studies considered consecutive patients with spontaneous bacterial peritonitis treated at the same hospital and over the same period, the sample was considered random and representative. We estimated the minimal detectable difference between both groups with the observed sample size. Considering 71 patients with spontaneous bacteremia and 55 patients with spontaneous bacterial peritonitis as the obtained sample size, 90% power and α error of 5% would allow identification of a hazard ratio of at least 1.78. This estimation of the minimum detectable effect was performed with the objective of comparing the incidence of mortality and AKI in patients with spontaneous bacterial peritonitis and spontaneous bacteremia, without considering competing events. STATA software (version 14.2; StataCorp) was used for these calculations.

Statistical analysis

Qualitative variables are presented as absolute and relative frequencies (percentages). Quantitative variables are shown as median and interquartile range (IQR: 25th centile and 75th centile). Bivariate analysis was performed with chi-squared for categorical data and Mann–Whitney test for quantitative variables.

Outcome analysis

To estimate the cumulative incidence of AKI, we calculated the time from date of inclusion to the date when previously detailed dynamic changes in serum creatinine with final value $\geq$1.5 mg/dL were detected, in presence of competing events of death and liver transplantation. To estimate the cumulative incidence of death, we calculated the time from date of inclusion to date of death in presence of the competing event liver transplantation. We estimated the cumulative incidence of AKI and death at 28 and 90 days with their corresponding 95% confidence intervals in patients with spontaneous bacteremia and in patients with spontaneous bacterial peritonitis, considering their corresponding competing events. We present Kaplan–Meier survival estimation considering respective competing risks. We evaluated the effect of each spontaneous infection on AKI or death, and risk factors for AKI and death in patients with spontaneous bacteremia using a bivariate and multivariate Fine–Gray regression model to consider the respective competing events [18]. The following variables with known clinical relevance from literature, or statistical significance on bivariate analyses, were considered as potential confounders and were included in multivariable analyses: age, MELD score, serum sodium, and infection by resistant/multiresistant bacteria. Since some variables contained the same information, such as Child–Pugh and MELD score, only the most relevant from a clinical point of view was included in the multivariable model in order to avoid multicollinearity. We chose the models with the lowest Akaike information criterion. Estimated subhazard ratios (sHR), crude and adjusted, are presented with their 95% confidence intervals.

Results

Overall patient characteristics

A total of 84 patients with spontaneous bacteremia were identified during the study period, of whom 13 were excluded (6 for history of transplantation, 4 for advanced hepatocellular carcinoma, and 3 for human immunodeficiency virus infection). Simple random sampling of 55 patients with spontaneous bacterial peritonitis was performed over 122 patients who were known to fulfill the selection criteria. Overall, 126 patients were included in the study: 71 patients with spontaneous bacteremia and 55 patients with spontaneous bacterial peritonitis (Fig. 1). Overall, patients were predominantly male; their median age was 63 years. Chronic viral hepatitis and alcohol-related liver disease were the leading causes of cirrhosis in the entire cohort. Systemic inflammatory response syndrome at moment of infection was present in only 56% of patients. Regarding disease severity, most patients had advanced liver disease. Median MELD score was 20 (IQR 16–26), being significantly different between patients with spontaneous bacteremia [19 (IQR 14–25)] and spontaneous bacterial peritonitis [24 (IQR 18–31)]. Of the 71 patients with spontaneous bacteremia, 51 (71.8%) had ascites; their median polymorphonuclear cell count was 26/mm^3 (IQR 15–44/mm^3), and their median ascitic protein content was 1.4 g/dL (IQR 0.44–2.15 g/dL). Patients with spontaneous bacterial peritonitis had median polymorphonuclear cell count of 2030/mm^3 (IQR 590–3440/mm^3), and their median ascitic protein content was 1.3 g/dL (IQR 0.8–1.6 g/dL). The baseline characteristics of the entire study population, and according to the type of infection are detailed in Table 1.

Microbiological characteristics according to type of spontaneous infection

Overall, 55% of infections were classified as nosocomial (63% and 45% of patients with spontaneous bacteremia and spontaneous bacterial peritonitis, respectively).

In 71 patients with spontaneous bacteremia, a single microorganism was isolated in all cases. In cases of spontaneous bacterial peritonitis, bacterial isolation in

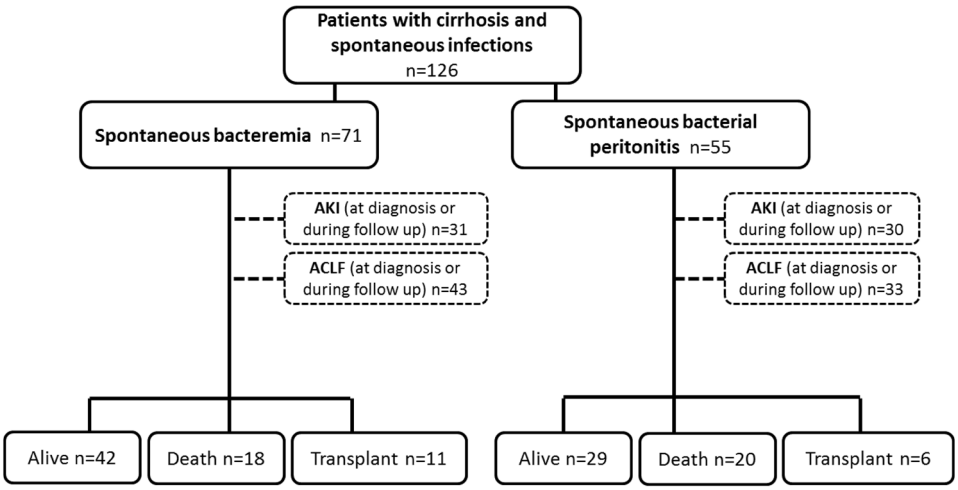

Fig. 1 Study population outcomes during 90-day follow-up period according to type of infection (spontaneous bacteremia or spontaneous bacterial peritonitis) at Hospital Italiano from 2008 to 2016 ($n = 126$). *AKI* acute kidney injury, *ACLF* acute-on-chronic liver failure

ascitic fluid was registered in 19 (34.5%) patients (Table 2).

Overall, the distribution between Gram-positive and Gram-negative bacteria was equal among the 90 patients with positive cultures. In patients with spontaneous bacteremia, Gram-positive bacteria accounted for 52% of isolates; the most prevalent isolated microorganism in this group was *Streptococcus viridans*, identified in 24% of episodes; whereas, in the Gram-negative bacteria group, the most prevalent isolated microorganism was *Escherichia coli*, identified in 24% of episodes. In patients with spontaneous bacterial peritonitis, Gram-positive bacteria accounted for 42% of isolates in ascitic fluid; the most prevalent microorganism in this group was also *S. viridans*, identified in 27% of episodes. In the Gram-negative bacteria group, the most prevalent isolated microorganism was *E. coli*, identified in 32% of episodes.

No differences were found in the resistance patterns between patients with spontaneous bacteremia versus spontaneous bacterial peritonitis. Overall, 63% of bacteria were susceptible, 26% resistant, and 11% multiresistant. Of 71 patients with spontaneous bacteremia, 4 (5.6%) were on antibiotic prophylaxis with norfloxacin. None of the 19 patients with spontaneous bacterial peritonitis who had bacterial isolation were receiving antibiotic prophylaxis.

Adequate initial antibiotic therapy was achieved in a similar proportion in both groups (85% in patients with spontaneous bacteremia, 78% in patients with spontaneous bacterial peritonitis, $p = 0.49$).

Outcome analysis: acute kidney injury and mortality

Of the 71 patients with spontaneous bacteremia, 18 died and 11 were transplanted during 90 days of follow-up. Of the 55 patients with spontaneous bacterial peritonitis, 20 died and 6 were transplanted during 90 days of follow-up.

Either at the moment of diagnosis or during follow-up, AKI and ACLF were diagnosed in 31 and 43 patients with spontaneous bacteremia, and in 30 and 33 patients with spontaneous bacterial peritonitis, respectively (Fig. 1).

Acute kidney injury

The cumulative incidence of AKI in patients with spontaneous bacteremia was 36.8% (95% CI 25.7–47.9%) and 44.5% (95% CI 32.6–55.7%) at 28 and 90 days, respectively. The cumulative incidence of AKI in patients with spontaneous bacterial peritonitis was 54.5% (95% CI 40.5–66.6%) at 28 days and remained constant until the end of follow-up (90 days).

We found no significant association between time to AKI and type of spontaneous infection in bivariate analyses [sHR 1.37 (95% CI 0.89–2.12, $p = 0.151$)] or in multivariate analysis adjusting for MELD score [sHR 1.05 (95% CI 0.67–1.63, $p = 0.83$)] (Fig. 2a).

Mortality

The cumulative incidence of death in patients with spontaneous bacteremia was 22% (95% CI 13–32 %) and 26% (95% CI 18–37%) at 28 and 90 days, respectively. The cumulative incidence of death in patients with spontaneous bacterial peritonitis was 22% (95% CI 12–34%) and 38% (95% CI 25–51%), at 28 and 90 days, respectively.

We found no significant association between time to death and type of spontaneous infection in bivariate [sHR 1.47 (95% CI 0.78–2.76, $p = 0.232$)] or in multivariate analyses adjusting for MELD score [sHR 1.15 (95% CI 0.60–2.20, $p = 0.68$)] (Fig. 2b).

Table 2 Site of infection acquisition, etiology, and antimicrobial resistance patterns of entire study population, and according to type of infection (spontaneous bacteremia or spontaneous bacterial peritonitis) at Hospital Italiano from 2008 to 2016 ($n = 126$)

Variable	All ($n = 126$)	Spontaneous bacteremia ($n = 71$)	Spontaneous bacterial peritonitis ($n = 55$)	p
Bacterial isolation	90 (71.4%)	71 (100%)	19 (34.5%)	–
Gram-negative bacteria	45 (50%)	34 (48%)	11 (58%)	0.43
Type of Gram-negative bacteria				
Escherichia coli	17 (19%)	11 (15.5%)	6 (32%)	0.33
Escherichia coli FQR	5 (6)	5 (7%)	0	
Escherichia coli ESBL	1 (1%)	1 (1.2%)	0	
Kleb. pneumoniae	7 (8%)	3 (4.1%)	4 (21%)	
Kleb. pneumoniae ESBL	1 (1%)	1 (1.2%)	0	
Pseudomonas sp.	2 (2%)	2 (3%)	0	
Acinetobacter sp.	2 (2%)	2 (3%)	0	
Enterobacter sp.	2 (2%)	2 (3%)	0	
Proteus spp.	2 (2%)	2 (3%)	0	
Other	6 (7%)	5 (7%)	1 (5%)	
Gram-positive bacteria	45 (50%)	37 (52%)	8 (42%)	0.43
Type of Gram-positive bacteria				
Streptococcus viridans	22 (25%)	17 (24%)	5 (27%)	0.50
Streptococcus spp.	7 (8%)	6 (9%)	1 (5%)	
Streptococcus agalactiae	1 (1%)	1 (1.2%)	0	
Streptococcus pneumoniae	1 (1%)	1 (1.2%)	0	
Staphylococcus aureus	1 (1%)	0	1 (5%)	
S. aureus MRSA	5 (6%)	5 (7%)	0	
S. aureus MSSA	1 (1%)	1 (1.2%)	0	
Enterococcus faecium	2 (2%)	1 (1.2%)	1 (5%)	
Staphylococcus spp.	2 (2%)	2 (3%)	0	
Staphylococcus epidermidis	2 (2%)	2 (3%)	0	
Other	1 (1%)	1 (1.2%)	0	
Type of infection*				
Community acquired	37 (30%)	20 (28.5%)	17 (31%)	0.04
Healthcare associated	19 (15%)	6 (8.5%)	13 (24%)	
Nosocomial	69 (55%)	44 (63%)	25 (45%)	
Antimicrobial resistance pattern**				
Susceptible bacteria	56 (63%)	48 (68%)	8 (45%)	0.12
Resistant bacteria	23 (26%)	17 (24%)	6 (33%)	
Multiresistant bacteria	10 (11%)	6 (8%)	4 (22%)	
Resistant/multiresistant bacteria**	33 (37%)	23 (32%)	10 (56%)	0.06
Adequate initial therapy***	64 (83%)	50 (85%)	14 (78%)	0.48

Qualitative variables expressed as absolute numbers and percentages

*Available in 125 patients; **available in 89 of the 90 patients with positive cultures; ***available in 77 patients

ESBL extended-spectrum beta-lactamase, *FQR* fluoroquinolone resistant, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*

Risk factors for acute kidney injury and transplant-free mortality in patients with spontaneous bacteremia

The risk factors for AKI in patients with spontaneous bacteremia are presented in Table 3. Only age [sHR 1.04 (95% CI 1.01–1.07, $p = 0.004$)] and MELD score [sHR 1.07 (95% CI 1.03–1.11, $p = 0.001$)] were associated with AKI after adjusting for potential confounders.

The risk factors for mortality in patients with spontaneous bacteremia are presented in Table 4. Only MELD score [sHR 1.07 (95% CI 1.00–1.15, $p = 0.03$)] and serum

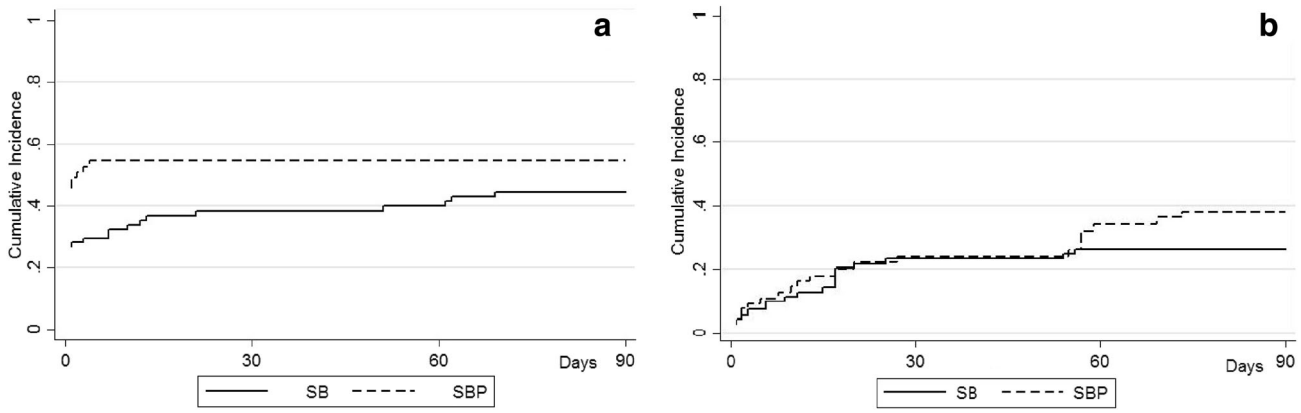

Fig. 2 Cumulative incidence of acute kidney injury and death in 126 patients with cirrhosis and either spontaneous bacterial peritonitis or spontaneous bacteremia at Hospital Italiano from 2008 to 2016. **a** Cumulative incidence of acute kidney injury in both study groups. We found no significant association between time to AKI and type of spontaneous infection in bivariate analyses ($p = 0.151$). **b** Cumulative incidence of death in both study groups. We found no significant association between time to death and type of spontaneous infection ($p = 0.232$). *SB* spontaneous bacteremia, *SBP* spontaneous bacterial peritonitis

Table 3 Risk factors for acute kidney injury at 90 days of follow-up in patients with cirrhosis and spontaneous bacteremia at Hospital Italiano from 2008 to 2016 ($n = 71$)

Risk factor	Crude sHR			Adjusted sHR		
	sHR	95% CI	*p*	sHR	95% CI	*p*
Age (years)	1.02	1.01–1.04	0.006	1.04	1.01–1.07	0.004
HCC	0.84	0.47–1.53	0.57	–	–	–
Leukocyte count ($\times 10^3/mm^3$)	1.00	1.00–1.00	0.11	–	–	–
Platelet count ($\times 10^3/mm^3$)	1.00	1.00–1.00	0.71	–	–	–
SIRS	1.11	0.72–1.72	0.63	–	–	–
Serum sodium	1.01	0.97–1.04	0.74	–	–	–
Child–Pugh score	1.20	1.07–1.35	0.003	–	–	–
MELD score	1.06	1.04–1.09	< 0.001	1.07	1.03–1.11	0.001
Community-acquired infection	0.93	0.57–1.52	0.76	–	–	–
Resistant/multiresistant bacteria	1.25	0.71–2.23	0.43	1.21	0.69–2.09	0.50
Adequate initial therapy*	0.71	0.34–1.49	0.36	–	–	–

* Information available in 58 patients

sHR subhazard ratio, *CI* confidence interval, *HCC* hepatocellular carcinoma, *SIRS* systemic inflammatory response syndrome, *MELD* Model for End-Stage Liver Disease

sodium [sHR 1.10 (95% CI 1.02–1.18, $p = 0.008$)] were associated with death after adjusting for potential confounders.

Discussion

There are two main findings of this study. First, patients with spontaneous bacteremia and spontaneous bacterial peritonitis had high and comparable rates of 28- and 90-day AKI and mortality. Second, we were able to identify independent predictors of AKI (MELD and age) and death (MELD and serum sodium) in patients with spontaneous bacteremia.

To the best of the authors' knowledge, no cohort studies comparing outcomes between patients with spontaneous bacteremia and spontaneous bacterial peritonitis have been published. A systematic review reported survival of 53% and 44% at 30 days in patients with bacteremia (primary or secondary) and spontaneous bacterial peritonitis, respectively, but those data arose from independent studies, limiting the ability to compare the two populations [1].

Previous studies analyzing patients with cirrhosis and spontaneous bacteremia reported mortality rates ranging from 18.6% at 3 months to 29–32% during hospitalization or at 30 days of follow-up [4, 5, 19]. However, most of those studies grouped together primary and secondary bloodstream infections or considered spontaneous bacteremia together with other nonspontaneous bacterial

Table 4 Risk factors for transplant-free mortality at 90 days of follow-up in patients with cirrhosis and spontaneous bacteremia at Hospital Italiano from 2008 to 2016 ($n = 71$)

Risk factor	Crude sHR			Adjusted sHR		
	sHR	95% CI	*p*	sHR	95% CI	*p*
Age (years)	1.01	0.97–1.04	0.51	1.02	0.99–1.06	0.15
HCC	0.59	0.13–2.57	0.48	–	–	–
Leukocyte count ($\times 10^3/mm^3$)	1.00	0.99–1.00	0.71	–	–	–
Platelet count ($\times 10^3/mm^3$)	0.99	0.99–1	0.35	–	–	–
SIRS	0.85	0.84–2.12	0.73	–	–	–
Serum sodium	1.06	0.97–1.17	0.17	1.10	1.02–1.18	0.008
Child–Pugh score	1.32	1.02–1.31	0.03	–	–	–
MELD score	1.08	1.02–1.15	0.005	1.07	1.00–1.15	0.03
Community-acquired infection	0.50	0.14–1.84	0.30	–	–	–
Resistant/multiresistant bacteria	1.75	0.67–4.55	0.24	1.57	0.58–4.22	0.37
Adequate initial therapy*	0.55	0.15–1.96	0.36	–	–	–

* Information available in 58 patients

sHR subhazard ratio, *CI* confidence interval, *HCC* hepatocellular carcinoma, *SIRS* systemic inflammatory response syndrome, *MELD* Model for End-Stage Liver Disease

peritonitis infections, making it difficult to generalize their results to patients with spontaneous bacteremia alone [5, 19–21].

In the study by Bartoletti et al. which assessed epidemiological characteristics and outcomes of patients with cirrhosis and bloodstream infections, a 30-day mortality rate of 22.9% was reported for the subgroup of patients with spontaneous bacteremia, a result that is in line with ours. Similarly, both the 30-day mortality rate (22%) and the incidence of AKI at 30 days (35%) in patients with spontaneous bacteremia in a recent paper by Fernandez et al. were almost identical to our results, despite the fact that, in the aforementioned study, outcomes were measured in patients with prior or concomitant infections, which could cause overestimation of results [4], whereas in our study patients with prior or concomitant spontaneous infections were excluded.

Both multiresistant bacteria and adequacy of initial antibiotic therapy are known to predict mortality in patients with spontaneous bacterial peritonitis [5]. The bacteriology of patients with cirrhosis and spontaneous bacteremia has not been extensively described. We found that, in more than one-third of patients with spontaneous bacteremia, a resistant/multiresistant bacterium was isolated. This is important since understanding the local bacterial epidemiology is essential for selection of an adequate initial antibiotic regimen.

In daily practice, when treating patients with spontaneous bacteremia, no consensus exists regarding ideal antibiotic selection, treatment duration, and/or necessity to use albumin to prevent renal failure. Moreover, it is not clear whether primary and secondary prophylaxis should be indicated. It has been suggested that patients with spontaneous bacteremia should be treated as patients with spontaneous bacterial peritonitis, but the rationale for this recommendation is not evidence based. In our study, both spontaneous infections showed similar mortality and incidence of ACLF and AKI. This might suggest that a common treatment approach for both infections should be considered, although this requires further exploration.

In our study, we identify MELD score as a predictor of both AKI and death in patients with spontaneous bacteremia; this finding is consistent with previous knowledge, since this specific score has been extensively validated for mortality assessment in patients with cirrhosis, and even for AKI prediction in patients with bacterial infection [5, 22]. We also found that age was independently associated with AKI in patients with spontaneous bacteremia. Older age had also been described as an independent predictor for AKI in a recent trial by Thévenot et al. assessing the impact of albumin infusion in renal function and mortality in patients with cirrhosis and sepsis [23]. Most of these variables (age, creatinine, and bilirubin analyzed separately from MELD score) were also found to be independent predictors of death and AKI in a recent paper discussing prognosis in nonspontaneous bacterial peritonitis in cirrhosis [4]. We did not find age to be independently associated with death in patients with spontaneous bacteremia. This could be explained by the fact that MELD score and serum sodium might have greater effect on death than age during an acute event in patients with cirrhosis. Since the sample size was relatively small, it is also possible that this study is underpowered to detect a significant effect of age on mortality in the multivariate model.

Our study has several strengths. First, it addresses an important clinical situation, which has not been studied in depth. Second, it only considered patients without prior episodes of spontaneous infection, which is important to adequately evaluate the effect of spontaneous bacteremia or spontaneous bacterial peritonitis on mortality and other outcomes. Third, even though the number of patients included was relatively small, this is the largest series to compare patients with spontaneous bacteremia and spontaneous bacterial peritonitis. Moreover, our study was powered to detect differences in incidence of AKI and death between the two groups of patients, and used a competing-risk analysis approach, which is recommended for multistage diseases such as cirrhosis [24].

Our study also has some limitations. First, its retrospective design precludes analysis of additional clinical and biochemical data in an orderly fashion. Also, the study design did not allow us to estimate the ratio between the two spontaneous infections, since we only sought to include a random sample of patients with spontaneous bacterial peritonitis to compare their outcome/prognosis. Finally, this study was performed at a single center and thus may not represent epidemiology at other institutions. However, this study was conducted in a large hospital that accepts referrals from many centers in other cities and regions of Argentina.

In summary, short- and mid-term AKI and mortality rates were found to be similar in patients with spontaneous bacteremia and spontaneous bacterial peritonitis. Whether patients with spontaneous bacteremia would benefit from specific treatments and prophylactic strategies such as those used in patients with spontaneous bacterial peritonitis should be analyzed in controlled trials.

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Author contributions Sebastián Marciano and Melisa Dirchwolf designed the research study and wrote the paper; Carla S. Bermudez, Natalia Sobenko, Leila Haddad, Federico Genre Bert, Laura Barcán, and Astrid Smud performed the research and collected the data; Maria L. Posadas-Martínez and Diego Giunta analyzed the data and provided critical insight; Adrián Gadano contributed to study design and revised/corrected the final manuscript. All authors approved the final version of the manuscript including the authorship list.

Compliance with ethical standards

Conflict of interest Sebastián Marciano, Melisa Dirchwolf, Carla S. Bermudez, Natalia Sobenko, Leila Haddad, Federico Genre Bert, Laura Barcán, Astrid Smud, Maria Lourdes Posadas-Martínez, Diego Giunta, and Adrián Gadano declare that they do not have any conflicts of interest.

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