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BRIEF REPORT

# Epidemiological characteristics of bloodstream infections in patients with different degrees of liver disease

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**Abstract** Observational retrospective study to evaluate the etiology, the outcome and the risk factors of bloodstream infections (BSIs) in patients with liver disease. One hundred and forty-eight BSIs were diagnosed (infection rate: 0.60 per 100 days of hospital stay), 62 BSIs (41.9 %) were associated with Gram-positive bacteria (infection rate: 0.25 per 100 days of hospital stay) and *80* (54.4 %) with Gram-negative bacteria (infection rate: 0.32 per 100 days of hospital stay). Admission-associated mortality was higher in patients with BSI than in those without BSI (20.6 versus 5.0 %, $p < 0.001$). Patients with cirrhosis had an increased risk to develop a BSI compared with patients with chronic hepatitis, specifically for Gram-positive (and *Staphylococcus* spp)-related BSI.

**Keywords** Bloodstream infection · Liver cirrhosis · Chronic hepatitis

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## Introduction

Patients with liver diseases have impaired immunity and are more susceptible to infections [1–3]. Multiple immunologic defects are responsible for this form of acquired immunodeficiency [4]. The cirrhotic patient has low complement and opsonin levels, a dysfunctional reticuloendothelial system and a gut mucosa that are unusually permeable to bacteria. The more advanced is the liver disease, the higher is the propensity to infection and mortality associated with infections [4, 5]. The epidemiology of BSIs in patients with hepatic disease reported in the literature is not homogeneous [6–9], in particular an increasing prevalence in Gram-positive bacteria has been reported, being Gram-negative bacteria still the leading cause. The aim of this study was to evaluate the epidemiological characteristics of BSIs in patients with different degrees of liver disease admitted to a single teaching hospital.

## Methods

This was an observational retrospective study to evaluate the etiology, outcome and risk factors of BSIs in patients with liver disease who were admitted to the Fondazione IRCCS Policlinico San Matteo, Pavia. The study period was comprised from January 1st 2011 to December 31st 2012. The study was approved by the local Ethics Committee of the Fondazione IRCCS Policlinico San Matteo Hospital (approval may 26, 2014, protocol number 2014-0012443).

Diagnosis codes obtained through administrative data (international classification of disease (ICD-9), codes number 571.4/8/9 for chronic hepatitis and 571.2/5/6 for cirrhosis) were utilized to identify patients with liver disease

(chronic hepatitis and/or liver cirrhosis). Other risk factors associated with BSIs (diabetes, cancer, chronic kidney disease, and HIV infection) were identified with the diagnosis code. Outcome was divided into two categories: discharged alive or deceased.

The AST–platelets-ratio-index (APRI) score [10] and Mayo End-Stage Liver Disease score (MELD) [11] were used for staging the severity of liver disease in patients with cirrhosis and matched with administrative data to confirm the diagnosis of cirrhosis.

Blood culture results were collected through a surveillance program. BSI was defined as having one blood culture positive for Gram-negative bacteria or *Streptococcus* spp or *Enterococcus* spp or *Staphylococcus aureus* or *Candida* spp or at least two sets of blood cultures positive for identical coagulase negative *Staphylococcus* (CoNS). BSIs acquired >48 h after hospital admission were defined as hospital acquired. Blood cultures were collected by venipuncture from two or more different sites or from a central venous catheter and peripheral vein. Blood samples were collected in BD BACTEC™ culture aerobic/anaerobic vials and were incubated in the BACTEC™ 9240 or 9120 automated blood culture system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), according to the manufacturer's instructions. Gram's stain was performed on positive samples to differentiate Gram-positive and Gram-negative microorganisms. Automated real-time PCR technology GeneXpert® system (Cepheid, Sunnyvale, CA), performed according to the manufacturer's instructions, was used to detect methicillin/oxacillin resistance for blood cultures growing Gram positive (Staphylococci morphology on Gram stain). Concurrently, all isolates were identified and tested for antimicrobial susceptibility using the Phoenix 100™ (BD) automated system. Phenotypic screening for carbapenemases was performed for Enterobacteriaceae exhibiting reduced susceptibility to carbapenems (Meropenem MIC >0.12 g/mL and Imipenem MIC >1 g/mL) by the combined disk tests using carbapenems with and without dipicolinic acid or boronic acid or cloxacillin (Rosco Diagnostica, Taastrup, DK) and Temocillin (Liofilchem S.r.l., Rosetodegli Abruzzi, IT).

## Statistical analysis

Data are reported as medians (1-3 IQR). The BSIs incidence rate and corresponding 95 % confidence interval (95 % CI) are reported for 100 days of hospital stay. BSI incidence is reported as the rate per 100 days of hospital stay.

A preliminary analysis to evaluate the BSI rate among patients with liver disease versus all patients admitted was performed (period from July 1st 2012 to December 31st 2012). The incidence rate in patients with BSI was compared with the incidence rate of all the remaining admitted patients. Once the relevance of liver disease as risk factor for BSI was proved, the analysis was focused only on patients with liver disease.

Poisson regression model was fitted to evaluate in univariable and multivariable analyses the association between independent variables such as age (IRR was calculated for each year increase), gender (male versus female), chronic kidney disease (CKD), cancer, HIV infection, diabetes (IRR was calculated for the presence versus absence of each variable), cirrhosis versus chronic hepatitis and BSIs in patients with liver disease. Successively, a second model was fitted to evaluate the role of APRI and MELD scores in patients with cirrhosis (IRR was calculated for each score unit increase).

Multiple imputation of missing data for biochemical parameters was used to calculate the APRI and MELD scores, as exclusion of subjects with missing data is inefficient and can lead to biased results and multiple imputation can both increase efficiency and reduce bias in such settings [12]; the number of BSI, age, gender, length of stay, CKD, cancer, HIV infection, diabetes were included in the model. A total of five imputations were used to stabilize the results and to ensure negligible loss of statistical power.

Analyses were performed using STATA 13.

## Results

In the preliminary analysis, the rate of BSIs in patients with liver disease was compared with those in patients without liver disease admitted to the hospital. The rate was, respectively, 0.70 (0.52–0.93) per 100 days of hospital stay versus 0.30 (0.27–0.34) per 100 days of hospital stay. Liver disease was independently associated with BSI (IRR 1.83, 95 % CI 1.23–2.73, $p = 0.003$), as well as age (IRR 1.16 95 % CI 1.09–1.22, $p < 0.001$ for 10-year increase), CKD (IRR 3.12, 95 % CI 2.02–4.81, $p < 0.001$), cancer (IRR 1.46, 95 % CI 1.14–1.88, $p = 0.003$), and diabetes (IRR 1.48, 95 % CI 1.06–2.05, $p = 0.027$).

Once the independent role of liver disease on the risk of BSI was documented, the analysis was focused on patients with liver disease. A total of 1161 patients with liver disease (40.4 % females), aged 69 years (53–78) were enrolled accounting for 2207 hospital admissions (total of 24,871 days of hospital stay); median number of admissions for each patient was 2 [1–4].

The median length of stay was 8 days [5–15]. Liver disease was due to HBV in 69 (6 %) patients, HCV in 582 (50 %) and alcohol abuse in 248 (21 %) and unknown for 262 patients (23 %). Four hundred and eighty-seven (41.9 %) had a diagnosis of cirrhosis, accounting for 965

**Table 1** Patient characteristics

| | All patients | Patients with chronic hepatitis | Patients with cirrhosis | $p^a$ |
|---|---|---|---|---|
| Diabetes *N* (%) | 221 (19.0 %) | 121 (17.9 %) | 100 (20.5 %) | 0.269 |
| HIV infection *N* (%) | 85 (7.3 %) | 56 (8.3 %) | 29 (6.0 %) | 0.129 |
| Cancer *N* (%) | 441 (38.0 %) | 185 (27.4 %) | 266 (52.6 %) | <0.001 |
| CKD *N* (%) | 62 (5.3 %) | 46 (6.8 %) | 16 (3.3 %) | 0.008 |
| Age median (IQR) | 69 (53–78) | 66.5 (49–78) | 71 (60–77) | <0.001 |
| Female *N* (%) | 469 (40.4 %) | 293 (43.5 %) | 176 (36.1 %) | 0.012 |
| APRI score median (IQR) | | | 1.88 (0.76–3.86) | |
| MELD score median (IQR) | | | 14 (10–23) | |
| BSI | 0.60 (0.50–0.70) | 0.54 (0.43–0.77) | 0.67 (0.52–0.85) | <0.001 |
| Gram pos BSI rate (95 % CI) | 0.25 (0.19–0.32) | 0.19 (0.13–0.28) | 0.33 (0.23–0.46) | 0.038 |
| Gram neg BSI rate (95 % CI) | 0.32 (0.26–0.40) | 0.25 (0.18–0.35) | 0.42 (0.30–0.57) | 0.024 |

[a] Comparison between patients with chronic hepatitis and cirrhosis

admissions (43.7 %), the median MELD value was 14 [10–23] and APRI was 1.88 (0.76–3.86). Patient characteristics according to the degree of liver disease are reported in Table 1. CKD was more frequent among patients with chronic hepatitis than among those with cirrhosis ($p = 0.008$), while cancer was more frequent among those with cirrhosis ($p < 0.001$). CKD was more frequent among patients with BSI compared with those without ($p = 0.003$), other risk factors were comparable among the two groups.

One hundred and forty-eight BSIs were diagnosed (infection rate: 0.60 per 100 days of hospital stay; 95 % CI 0.50–0.70) in 107 patients. Sixty-two BSIs (41.9 %) were associated with Gram-positive bacteria (infection rate: 0.25 per 100 days of hospital stay; 95 % CI: 0.19–0.32) (20 *Staphylococcus aureus*, 11 CoNS, 17 *Enterococcus* spp, 14 *Streptococcus* spp). Methicillin resistance was detected in 10 (90.9 %) out of 11 BSIs sustained by CoNs and in 4 (20 %) out of 20 BSIs sustained by *Staphylococcus aureus.* Eighty (54.4 %) BSIs were associated with Gram-negative bacteria (infection rate: 0.32 per 100 days of hospital stay; 95 % CI: 0.26–0.40) (Table 2). Among Gram-negative bacteria, ESBL *E. coli* was isolated in 8 cases (10 %), and carbapenem-associated resistance was detected in 9 cases (11.3 %) (*Acinetobacter baumanii* 3, *Klebsiella pneumoniae* 4, *Pseudomonas aeruginosa* 2). Six BSIs (4.1 %) were associated with *Candida* spp.

Eighty-five BSIs (57 %) were hospital acquired; the breakdown of hospital acquired BSIs per species is as follows: *Staphylococcus* spp 54.8 % (17/31 cases; 5 out of 17–29.4 % were methicillin resistant and hospital acquired), *Pseudomonas* spp all cases (2/2 were carbapenem resistant and hospital acquired), *Acinetobacter* spp all cases (3/3 were carbapenem resistant and hospital acquired), *Candida* 100 % (6/6 cases), *Enterobacteriaceae* 50.8 % (32/63 cases, 4/4 *K. pneumoniae* carbapenem resistant, of these 3 were hospital acquired), *Enterococcus* spp 64.7 % (11/17 cases), *Streptococcus* spp 30.8 % (4/13 cases). Six (19.4 %) out of 31 *Staphylococcus* spp BSIs were considered as central line associated (of these 4 were detected in cirrhotic patients).

Length of hospital stay was longer for patients with a BSI versus those without (20 days (12–31) versus 8 [4–14], $p < 0.001$). Moreover, admission-associated mortality was higher in patients with BSI than in those without BSI (22 deaths, −20.6 % versus 105, −5.0 %, $p < 0.001$), the corresponding mortality rate was 0.88 versus 0.5 per 100 days of hospital stay. The mortality rate was not different between Gram-positive and Gram-negative BSIs. The *Candida* BSI mortality was 83.3 %. Complication of BSI was infective endocarditis in 7 cases (4.7 %) and meningitis in 1 case (0.7 %).

The infection rate was 0.67 per 100 days of hospital stay (95 % CI 0.52–0.85) in patients with cirrhosis and 0.54 (95 % CI 0.43–0.77) in patients with chronic hepatitis ($p < 0.001$). Risk factors associated with BSIs in patients with chronic hepatitis compared with those with cirrhosis are reported in Tables 3, 4 and 5. Patients with cirrhosis had an increased risk to develop a BSI compared with patients with chronic hepatitis, specifically for Gram-positive (and *Staphylococcus* spp)-related BSI. Furthermore, among cirrhotic patients, the worsening of liver disease, documented by APRI score, was associated with an increased risk to develop Gram-positive (and *Staphylococcus* spp)-related BSI (IRR 1.05, 95 % CI 1.00–1.10, $p = 0.04$ and IRR 1.06, 95 % CI 1.01–1.11, $p = 0.01$, respectively).

## Discussion

The analysis of data reported in the present study on BSI incidence in patients with liver disease compared with

**Table 2** Types of bacteria isolated from blood cultures in patients with liver disease

| Type of isolate | *N* | % | Community acquired | Hospital acquired |
|---|---|---|---|---|
| Gram negative—enterobacteriaceae | | | | |
| *Escherichia coli* | 34 | 23.0 | 20 | 14 |
| *Klebsiella pneumoniae* | 9 | 6.1 | 1 | 8 |
| *Proteus mirabilis* | 6 | 4.1 | | 6 |
| *Enterobacter aerogenes* | 3 | 2.0 | 2 | 1 |
| *Serratia marcescens* | 3 | 2.0 | 1 | 2 |
| *Enterobacter cloacae* | 2 | 1.4 | 2 | |
| *Pantoea agglomerans* | 2 | 1.4 | 2 | |
| *Enterobacter spp.* | 1 | 0.7 | 1 | |
| *Klebsiella oxytoca* | 1 | 0.7 | | 1 |
| *Salmonella group B* | 1 | 0.7 | 1 | |
| *Citrobacter spp.* | 1 | 0.7 | 1 | |
| Gram negative—non-fermenting bacteria | | | | |
| *Pseudomonas aeruginosa* | 9 | 6.1 | 1 | 8 |
| *Acinetobacter spp.* | 4 | 2.7 | 0 | 4 |
| *Stenotrophomonas maltophilia* | 1 | 0.7 | | 1 |
| Gram positive | | | | |
| *Staphylococcus aureus* | 20 | 13.5 | 11 | 9 |
| *CoNS* | 11 | 7.4 | 3 | 8 |
| *Enterococcus faecalis* | 8 | 5.4 | 5 | 3 |
| *Enterococcus faecium* | 6 | 4.1 | 1 | 5 |
| *Enterococcus casseliflavus* | 2 | 1.4 | | 2 |
| *Enterococcus spp.* | 1 | 0.7 | | 1 |
| *Streptococcus viridans group* | 6 | 4.1 | 3 | 3 |
| *Streptococcus bovis group* | 2 | 1.4 | 1 | 1 |
| *Beta hemolytic streptococcus group a* | 2 | 1.4 | 2 | |
| *Beta hemolytic streptococcus group b* | 1 | 0.7 | 1 | |
| *Streptococcus pneumoniae* | 2 | 1.4 | 2 | |
| *Corynebacterium striatum* | 1 | 0.7 | | 1 |
| Fungi | | | | |
| *Candida albicans* | 5 | 3.4 | | 5 |
| *Candida krusei* | 1 | 0.7 | | 1 |
| Gram negative—Anaerobic bacteria | | | | |
| *Bacteroides fragilis* | 3 | 2.0 | 2 | 1 |

**Table 3** Bacterial and fungal BSI risk factors in patients with liver disease

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | IRR | *p* | 95 % CI | IRR | *p* | 95 % CI |
| Gender | 0.91 | 0.59 | 0.66–1.27 | 0.99 | 0.99 | 0.61–1.61 |
| HIV infection | 0.96 | 0.89 | 0.53–1.73 | 0.88 | 0.72 | 0.43–1.81 |
| Cancer | 0.88 | 0.43 | 0.63–1.21 | 0.89 | 0.57 | 0.57–1.37 |
| Diabetes | 0.97 | 0.86 | 0.66–1.41 | 0.88 | 0.62 | 0.51–1.49 |
| CKD | 1.99 | 0.003 | 1.26–3.13 | 2.14 | 0.04 | 1.03–4.44 |
| Age | 0.99 | 0.14 | 0.98–1 | 0.99 | 0.13 | 0.98–1.00 |
| Cirrhosis | 1.52 | 0.01 | 1.1–2.1 | 1.63 | 0.03 | 1.04–2.58 |

Age (IRR was calculated for each year increase), gender (male versus female), chronic kidney disease (CKD), cancer, HIV infection, diabetes (IRR was calculated for the presence versus absence of each variable), cirrhosis versus chronic hepatitis and BSIs in patients with liver disease

**Table 4** Gram-positive BSI-associated risk factors in patients with liver disease

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | IRR | *p* | 95 % CI | IRR | *p* | 95 % CI |
| Gender | 0.75 | 0.28 | 0.44–1.26 | 0.88 | 0.65 | 0.50–1.54 |
| HIV infection | 1.38 | 0.42 | 0.63–3.04 | 1.23 | 0.59 | 0.58–2.63 |
| Cancer | 1.18 | 0.51 | 0.72–1.95 | 1.22 | 0.46 | 0.72–2.09 |
| Diabetes | 0.72 | 0.31 | 0.38–1.35 | 0.68 | 0.29 | 0.34–1.39 |
| CKD | 1.93 | 0.07 | 0.95–3.92 | 2.32 | 0.02 | 1.17–4.58 |
| Age | 0.99 | 0.1 | 0.97–1 | 0.99 | 0.10 | 0.97–1.00 |
| Cirrhosis | 1.7 | 0.04 | 1.03–2.8 | 1.86 | 0.04 | 1.04–3.33 |

Age (IRR was calculated for each year increase), gender (male versus female), chronic kidney disease (CKD), cancer, HIV infection, diabetes (IRR was calculated for the presence versus absence of each variable), cirrhosis versus chronic hepatitis and BSIs in patients with liver disease

**Table 5** Staphylococcus spp. BSI-associated risk factors in patients with liver disease

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | IRR | *p* | 95 % CI | IRR | *p* | 95 % CI |
| Gender | 0.69 | 0.34 | 0.332–1.47 | 0.82 | 0.62 | 0.38–1.79 |
| HIV infection | 2.09 | 0.13 | 0.8–5.43 | 2.31 | 0.09 | 0.89–6.04 |
| Cancer | 0.91 | 0.79 | 0.44–1.87 | 0.97 | 0.94 | 0.43–2.20 |
| Diabetes | 1.04 | 0.11 | 0.47–2.34 | 0.88 | 0.80 | 0.34–2.28 |
| CKD | 3.32 | 0.005 | 1.43–7.7 | 4.18 | <0.01 | 1.61–10.84 |
| Age | 0.99 | 0.48 | 0.97–1.01 | 1.00 | 0.76 | 0.97–1.02 |
| Cirrhosis | 2.21 | 0.03 | 1.07–4.56 | 2.46 | 0.04 | 1.04–5.83 |

Age (IRR was calculated for each year increase), gender (male versus female), chronic kidney disease (CKD), cancer, HIV infection, diabetes (IRR was calculated for the presence versus absence of each variable), cirrhosis versus chronic hepatitis and BSIs in patients with liver disease

those without liver disease showed that liver disease represents an independent risk factor for BSI, as well as CKD, cancer or diabetes. The occurrence of BSI in patients with cirrhosis is associated with a poor outcome; thirty-day mortality rates were roughly 30 % in patients with liver disease with BSI and 20 % in patients with other diseases as risk factors [7, 13, 14] and the severity of underlying liver dysfunction in patients with liver disease is an independent predictive factor associated with BSI increased mortality [5]. In our series, the hospital stay mortality was 20 % in patients with liver disease who developed a BSI and 5 % in those without BSI.

Considering the etiology of BSI, no difference in mortality rates was observed between Gram-positive or Gram-negative bacteria associated BSIs, as reported elsewhere [7, 8, 15], while others have reported an increased mortality associated with Gram-positive bacteremia in cirrhotic patients [14, 16]. In our experience, Gram-positive BSI was more frequent in patients with cirrhosis than in patients with chronic hepatitis, and in particular in those with a worse APRI score, the progressive worsening of hepatic function represented a risk factor for Gram-positive bacteria.

Among bacteria isolated by blood cultures, Gram-negative bacteria were responsible for 55 % of BSIs, Gram positive for 40 % of BSIs and Candida for roughly 5 % of BSIs. The epidemiological data for BSIs in patients with liver disease reported in this paper are in agreement with those recently reported in another Italian cohort [8]. Compared with previous reports, a variation in bacterial patterns has been observed since the 1980s when Gram-negative bacilli accounted for the majority of all infections [17–19]. Even if Gram-negative bacteria remain important pathogens in patients with liver disease, and the primary source of bacteremia in cirrhotic patients is abdominal, followed by the urinary tract [7], Gram-positive bacteria are becoming increasingly recognized as the etiologic cause of BSIs in liver disease [15, 16]. Among Gram-positive bacteria, *S aureus* is recognized as an important pathogen in cirrhotic patient, the most common infections sustained by *S.aureus* in these patients being bacteremia, followed by pneumonia, soft tissue infection and spontaneous bacterial peritonitis [16, 20]. *S.aureus* plays also an important role as cause of bacteremia in patients who have end-stage liver disease and are awaiting transplantation [16]. *Staphylococcus* colonization of single or multiple sites (nose, groin, axilla and

rectal perineum) in cirrhotic patients usually precedes an episode of bacteremia [18, 21]. Studies on mucous-cutaneous decontamination procedures with mupirocin (and chlorhexidine) in patients with liver disease have shown the recurrence of *Staphylococcus* nasal colonization [22], but an overall reduction of subsequent infections [23]. In our series roughly 5 % of patients had a Candida associated BSI, these episodes were associated with the highest mortality. As reported also by others, fungal infection shows the worse prognosis in patients with liver disease [8]. It is, therefore, important to keep in mind the possibility of fungal infection when approaching a suspected case of BSI and evaluate the presence of other risk factors for candidemia [24].

About 15–35 % of patients with liver disease develop nosocomial infections during their hospital stay as compared with 5–7 % in the general hospital population [22]. In our series, the majority of BSIs (57 %) were hospital acquired. In particular all cases of non-fermenting Gram-negative bacteria BSIs were hospital acquired and 50 % of those associated with Enterobacteriaceae and *Staphylococcus* spp. For this reason, prophylactic antibiotics may be suggested for patients with hepatic disease who undergo invasive procedures such as endoscopic variceal ligation or endoscopic sclerotherapy or transjugular Intrahepatic portosystemic shunts. Antibiotic resistance is frequently observed in health care associated infections, in particular for Gram-negative BSIs and this is true also for patients with liver disease [8, 16]. Inappropriate empirical antimicrobial therapy for Gram-negative BSIs is a recognized risk factor associated with an increased mortality; thus it is important to reconsider the empirical antimicrobial therapy for BSI according to site-specific bacterial ecology [8]. Roughly, 20 % of *Staphylococcus* BSI were observed in patients with a central line, improving the measures of asepsis on insertion and after care of catheter, and removing the unnecessary catheters could have a very important impact to reduce these serious events in patients with hepatic disease. Advanced liver disease represents a risk factor for infective endocarditis [26], and patients with cirrhosis have a higher risk to develop IE, that is frequently acquired during hospitalization as a consequence of invasive diagnostic or therapeutic procedures, with *Staphylococcus* being the leading cause [27]. In our experience 4.7 % of BSI were in fact associated to an episode of infective endocarditis. Because most of the factors facilitating the development of bacterial infections in cirrhotic patients are unchangeable and many cases occur during hospitalization, prevention should focus on measures to avoid bacteremia and other nosocomial infections [27].

This study has several limitations. First, the use of administrative discharge data and the lack of clinical details and the relatively broad classification of cirrhosis and chronic hepatitis may not be entirely accurate, as they may have been misclassified. In particular, we might have included some early-stage cirrhosis in the group of chronic hepatitis, nevertheless even considering the possibility of a classification bias of 5–20 % among the two groups, the results clearly demonstrate that patients with liver disease are at high risk of BSIs. Furthermore, the availability of clinical data, such as the occurrence of acute renal insufficiency, hepatic coma, variceal bleeding or worsening of pre-existing conditions would have added more information to the study. The monocentric nature of the study might furnish data representative of our cohort of patients, although the results are comparable with the most recent analysis on BSI epidemiology in patients with liver disease.

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**Conflict of interest** The authors have no competing interests to declare.

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