Bacterial distributions and prognosis of bloodstream infections in patients with liver cirrhosis

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Bloodstream infections (BSIs) are a frequently observed complication in liver cirrhosis patients. This study aimed to investigate the microbiological characteristics and outcomes of BSIs in patients with liver cirrhosis. We retrospectively studied 852 patients with liver cirrhosis who developed a BSI. Patient outcome was evaluated using 30-day mortality and assessed using multivariate stepwise logistic regression analysis. Antibiotic sensitivity of the pathogens was tested. Gram-negative bacteria were responsible for 59.6% of BSIs, and Gram-positive bacteria caused 40.4% of the episodes among liver cirrhosis patients. The bacterial distribution significantly differed between hospital-acquired and community-acquired infections, especially in cases caused by Gram-negative pathogens. The results of the drug sensitivity test suggested that amikacin, cefoperazone/sulbactam, and piperacillin/tazobactam highly suppressed Gram-negative infections, while vancomycin and teicoplanin strongly inhibited Gram-positive BSIs. Liver failure, liver cancer, complications, Child-Pugh grade, septic shock, administration of appropriate antibiotics within 24 h, ICU admission, nosocomial infection, and Gram nature of the bacteria were independent risk factors for 30-day mortality (P < 0.05). The choice of initial empirical antibiotics should be based on the type, severity and origin of infection and on the local epidemiological data on antibiotic resistance. Accurate evaluation of risk factors for mortality may improve appropriate therapeutic choice.

Liver cirrhosis is one of the leading causes of death worldwide1. Hepatitis B virus (HBV), hepatitis C virus, alcoholism, and non-alcoholic fatty liver disease are the most common conditions leading to liver cirrhosis2. China has the highest HBV infection burden in the world. According to statistics, there are approximately 120 million hepatitis B surface antigen (HBsAg) carriers, and nearly 300,000 individuals die from HBV-related liver diseases each year in China3. Patients with liver cirrhosis have been found to be more likely to acquire bacterial infections due to their dysregulated immune function4. Bloodstream infections (BSIs) are frequently observed complications in liver cirrhosis patients5. BSIs in cirrhosis patients are associated with prolonged hospital stay, rapid progression of liver disease, poor prognosis, and an increased risk of mortality6. Timely and appropriate empirical antibiotic therapy is pivotal for BSI management7. However, the heterogeneous epidemiology of BSI may increase the difficulty of empirical antibiotic management, especially with the increasing prevalence of Gram-positive and multidrug-resistant bacteria8,9.

A growing body of evidence indicates that the source of infection may influence the bacterial distribution and sensitivity of these bacteria to antibiotics in liver cirrhosis patients who develop BSIs10,11. Several studies have found that liver cirrhosis patients who have nosocomial infections exhibit high resistance to empirical antibiotic treatments12–14. Therefore, the choice of antimicrobial coverage should be taken into account local epidemiology and the site of infection onset. Improved knowledge of the local epidemiology of bacterial infections is necessary. However, few such retrospective studies with a large sample size have been reported in China.

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In this study, we aimed to investigate the distribution of both Gram-negative and Gram-positive bacteria and their sensitivity to commonly used antibiotics in liver cirrhosis patients who develop BSIs. In addition, we defined the risk factors for 30-day mortality in the study population.

Results

Basic characteristics of the study population. Patients with liver cirrhosis who developed BSIs during the study period were recruited to participate in this study. In total, 852 liver cirrhosis patients participated in the present study, including both men (78.8%) and women (21.2%), with an average age of 50.80 ± 11.78 years. Of these, 155 (18.2%) were admitted to the ICU (Table 1).

We evaluated the types of liver cirrhosis based on the study population. Hepatitis B was the most common cause of liver disease in the study population (64.3%), followed by alcoholic liver disease and hepatitis C. Furthermore, 22.1% of the patients with liver cirrhosis presented with liver failure, while 29.3% had hepatocellular carcinoma. Few patients were classified as Child-Pugh class A (12.8%), with the majority of patients classified as class B (35.4%) or class C (51.8%) chronic liver disease (Table 1).

We summarized the medical information of BSI in liver cirrhosis patients. In our study, 61.4% of patients were diagnosed with nosocomial infection. Approximately half of the patients (53.4%) had a history of infection within two years. Primary infection was the major reason for BSI, accounting for 60.2% of the cases, followed by spontaneous bacterial peritonitis (32.5%), lung infection (5.6%), and urinary tract infection (0.8%). The most frequent complications of BSI in liver cirrhosis were ascites, hepatic encephalopathy, upper gastrointestinal bleeding, and hepatorenal syndrome. In addition, 172 patients presented with more than one type of complication. The occurrence rate of septic shock was 18.9% (Table 1).

| Features                                      | Total (n = 852) | Survivors, n = 660 (77.5%) | Non-survivors, n = 192 (22.5%) | P value |
|-----------------------------------------------|----------------|-----------------------------|--------------------------------|---------|
| Demographic characteristics                  |                |                             |                                |         |
| Male (n, %)                                   | 671 (78.8)     | 528 (80)                    | 143 (74)                       | 0.04    |
| Age (years)                                   | 50.8 ± 11.8    | 50.6 ± 11.4                 | 51.5 ± 13.2                    | 0.366   |
| Hospitalization unit                          |                |                             |                                | <0.001  |
| General ward (n, %)                           | 697 (81.8)     | 595 (90.2)                  | 102 (53.1)                     |         |
| ICU (n, %)                                    | 155 (18.2)     | 65 (9.9)                    | 90 (46.9)                      |         |
| Liver diseases                                |                |                             |                                | 0.631   |
| Single Hepatitis B (n, %)                     | 548 (64.3)     | 429 (65.0)                  | 119 (62.0)                     |         |
| Single Hepatitis C (n, %)                     | 85 (10.0)      | 68 (10.3)                   | 17 (8.9)                       |         |
| Combined with Hepatitis B and C (n, %)        | 8 (0.9)        | 7 (1.1)                     | 1 (0.5)                        |         |
| Alcoholic (n, %)                              | 107 (12.6)     | 80 (12.1)                   | 27 (14.1)                      |         |
| Others (n, %)                                 | 104 (12.2)     | 76 (11.5)                   | 28 (14.6)                      |         |
| Combined with liver failure (n, %)            | 188 (22.1)     | 95 (14.4)                   | 93 (48.4)                      | <0.001  |
| Combined with hepatocellular carcinoma (n, %) | 250 (29.3)     | 202 (30.6)                  | 48 (25.0)                      | 0.133   |
| Child-Pugh classification                     |                |                             |                                | <0.001  |
| Class A (n, %)                                | 109 (12.8)     | 105 (15.9)                  | 4 (2.1)                        |         |
| Class B (n, %)                                | 302 (35.4)     | 267 (40.5)                  | 35 (18.2)                      |         |
| Class C (n, %)                                | 441 (51.8)     | 289 (43.8)                  | 152 (79.2)                     |         |
| BSI data                                      |                |                             |                                |         |
| Nosocomial infection (n, %)                   | 523 (61.4)     | 390 (59.1)                  | 134 (69.8)                     | 0.007   |
| Infection history within 2 years              | 455 (53.4)     | 347 (52.6)                  | 108 (56.3)                     | 0.369   |
| BSI source                                    |                |                             |                                | <0.001  |
| Primary (n, %)                                | 513 (60.2)     | 427 (64.7)                  | 86 (44.8)                      |         |
| Lung (n, %)                                   | 48 (5.6)       | 21 (3.2)                    | 27 (14.1)                      |         |
| Abdominal (SBP) (n, %)                        | 277 (32.5)     | 199 (30.2)                  | 78 (40.6)                      |         |
| Urinary tract (n, %)                          | 7 (0.8)        | 7 (1.1)                     | 0 (0.0)                        |         |
| Complications                                 |                |                             |                                | <0.001  |
| Ascites (n, %)                                | 486 (57.0)     | 325 (49.2)                  | 161 (83.9)                     |         |
| Upper gastrointestinal bleeding (n, %)         | 58 (6.8)       | 28 (4.2)                    | 30 (15.6)                      |         |
| Hepatic encephalopathy (n, %)                 | 118 (13.9)     | 72 (10.9)                   | 46 (24.0)                      |         |
| Hepato-renal syndrome (n, %)                  | 27 (3.2)       | 7 (1.1)                     | 20 (10.4)                      |         |
| More than one complication (n, %)             | 172 (20.2)     | 46 (7.0)                    | 126 (65.6)                     |         |
| Septic shock                                  | 161 (18.9)     | 58 (8.8)                    | 103 (53.7)                     | <0.001  |
| Appropriate antibiotics within 24 h (n, %)    | 612 (72.8)     | 501 (75.9)                  | 111 (57.8)                     | <0.001  |

Table 1. Basic characteristics of the study population. Note: ICU: Intensive care unit; BSI: Bloodstream infection.
Additionally, empirical therapy was considered adequate when at least one active antibiotic against the isolated pathogen, according to the species identification and susceptibility test, was administered during the first 24 h after blood cultures were drawn (before microbiological results were available). Overall, 72.8% of the patients received adequate empirical antibiotics within 24 h (Table 1).

Comparison of clinical characteristics between survivors and non-survivors. The 30-day mortality was used to estimate the primary clinical outcomes of liver cirrhosis patients developing BSIs. Among the study subjects, the mortality rate was 22.54%. We also analysed the clinical characteristics of the patients according to their survival status within 30 days after BSI. The results demonstrated that gender and ICU admission combined with liver failure, Child-Pugh score, nosocomial infection, BSI source, complications, and septic shock significantly differed between survivors and non-survivors (P < 0.05). Furthermore, markedly higher percentages of patients received adequate antibiotics within 24 h after infection in the survival group (P = 0.000; Table 1). Additionally, types of liver disease and occurrence of hepatocellular carcinoma did not significantly differ between the survivor and non-survivor groups (P > 0.05; Table 1).

Bacterial distribution. In total, 852 cultures were isolated from the blood specimens. Of these, 59.6% were confirmed to be Gram-negative, while 40.4% were Gram-positive. The Gram-negative bacteria mainly included Escherichia coli, Klebsiella pneumoniae, Aeromonas species, Enterobacter cloacae, Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and others. Furthermore, 138 isolated Gram-negative bacteria were identified as extended-spectrum beta-lactamase (ESBL)-positive, and 215 cultures were confirmed as ESBL-negative. Overall, 40.2% of Escherichia coli and Klebsiella pneumoniae presented as ESBL-positive, and the rest (59.8%) were negative. Gram-positive organisms included coagulase-negative staphylococci, Streptococcus spp., Staphylococcus aureus, and Enterococcus spp. Table 2 presents a detailed distribution of the bacteria.

We analysed the methicillin resistance of coagulase-negative staphylococci and S. aureus. Overall, 74 coagulase-negative staphylococcal cultures and 8 S. aureus isolates were confirmed to be methicillin-resistant (Table 2). In Gram-positive bacteria, 23.8% were methicillin-resistant, and 9.3% were Enterococcus spp.

The results suggested that the distributions of Gram-positive and Gram-negative bacteria (P = 0.006), Acinetobacter baumannii (P = 0.001), and MRSA (P = 0.027) significantly differed between the survivor and non-survivor groups (Table 2).

Effects of acquisition sites of infection on bacterial distribution. Epidemiological analyses were performed according to their acquisition sites of infection. As shown in Table 3, we found that the distributions of Klebsiella pneumoniae (P = 0.047), Pseudomonas aeruginosa (P = 0.011), Enterobacter cloacae (P = 0.022), Stenotrophomonas maltophilia (P = 0.039), and Streptococcus spp. (P = 0.035) significantly differed between nosocomial and community-acquired infections.

Drug sensitivity analysis. We then investigated the sensitivity of the isolated cultures to commonly used antibiotics. The isolated Gram-negative bacterial strains were highly sensitive to amikacin, cefoperazone/sulbactam, meropenem, imipenem, and piperacillin/tazobactam, regardless of their ESBL status (Table 4).

Drug sensitivity analysis of Gram-positive bacteria showed that these strains were highly sensitive to vancomycin and teicoplanin. In addition, methicillin-resistant coagulase-negative staphylococci and MRSA were also sensitive to vancomycin and teicoplanin (Table 4).

Risk factors for 30-day mortality in liver cirrhosis patients combined with BSIs. In the current study, a stepwise logistic regression model was used to evaluate the prognostic significance of the clinical parameters for BSI in liver cirrhosis patients. The results of the univariate analyses demonstrated that gender, liver failure, non-primary infection source, presence of complications, Child-Pugh grade, septic shock, administration of appropriate antibiotics within 24 h, ICU admission, nosocomial infection, and Gram nature of the bacteria were significantly correlated with outcomes of liver cirrhosis patients who develop BSIs (Table 5).

Results of the multivariate stepwise logistic regression analyses identified liver failure, liver cancer, presence of complications, Child-Pugh grade, septic shock, administration of appropriate antibiotics within 24 h, ICU admission, nosocomial infection, and Gram nature of the bacteria as independent risk factors for 30-day mortality in the study population (Table 6).

Discussion

BSIs are a prevalent complication in liver cirrhosis patients and cause severe mortality. Compared to non-cirrhotic patients, cirrhotic patients have poor prognoses in BSIs15,16. BSIs lead to poor patient outcomes17,18, prolonged patient stays in the ICU and in the hospital, and substantial extra medical costs19-21. BSIs are associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis22. Timely and appropriate empirical antibiotic treatment is pivotal for the prognosis of liver cirrhosis patients suffering from BSIs. However, antibiotic management represents a great challenge in the clinical setting due to the heterogeneous aetiology of BSIs, the increasing prevalence of Gram-positive bacterial pathogens in BSIs, and the emergence of multidrug-resistant organisms23,24. To improve the management of empirical antibiotic therapy, we investigated the clinical and epidemiological characteristics of BSIs in liver cirrhosis patients.

We found that Gram-negative bacteria were responsible for 59.6% of BSIs, and 40.4% of infection episodes were caused by Gram-positive bacteria. Escherichia coli and K. pneumoniae were the most frequently observed Gram-negative bacteria. Coagulase-negative staphylococci and Streptococcus spp. were the most prevalent Gram-positive pathogens associated with BSI in liver cirrhosis patients. In our early study, Escherichia coli and coagulase-negative staphylococci were the main pathogens in SBP23. The results of the present study are consistent with those of previous investigations. Brandolini et al. reported that 41.9% of BSI cases in patients with liver
disease were associated with Gram-positive bacteria, and Kang et al. reported that *S. aureus* represented the main pathogen for bacteraemia. Thus, from the view of antibiotic management, it is necessary to consider that Gram-positive bacteria are responsible for infection.

Nosocomial infections continue to pose a major challenge in the clinical setting. There is growing evidence indicating that nosocomial infections are associated with high drug resistance and poor prognosis. This may be attributed to the diverse epidemiology, causative pathogens, and the immunocompromised nature of the patients themselves. In a similar study, Hoenigl et al. demonstrated that *E. coli* and *S. aureus* were the most frequently isolated pathogens, while Enterococcus spp., Candida spp., *Pseudomonas* spp., Enterobacter spp., and coagulase-negative staphylococci were isolated more frequently among those with hospital-acquired BSIs. The results of our analysis demonstrated that the distribution of Gram-negative bacteria clearly differed between the two groups (community-acquired and nosocomial infection groups). In addition, we found that the distribution of Gram-positive bacteria did not significantly differ according to the infection source, except for that of *S. pneumoniae*.

Empirical antibiotic management is critical for good clinical outcomes of BSIs in liver cirrhosis patients. Generally, intravenous third generation cephalosporins are recommended as an empirical antibiotic therapy for cirrhotic patients. However, in this study, we investigated the sensitivity of the isolated pathogens to commonly used antibiotics. The results revealed that Gram-negative pathogens exhibited high sensitivity to imipenem, meropenem, amikacin, cefoperazone/sulbactam, and piperacillin/tazobactam, regardless of their ESBL status. Vancomycin and teicoplanin strongly suppressed Gram-positive bacterial infections. Thus far, carbapenems represent the last line of treatments of multidrug-resistant Gram-negative pathogens in empirical treatment. However, various studies have reported that carbapenems are associated with severe nephrotoxicity and bone marrow toxicity.

### Table 2. Comparison of bacterial distributions between survivors and non-survivors based on the study population.

| Bacterial distributions | Total, *n* = 852 | Survivors, *n* = 660 (77.5%) | Non-survivors, *n* = 192 (22.5%) | *P* value |
|-------------------------|------------------|-----------------------------|-------------------------------|----------|
| **Gram-negative bacteria** | 508 (59.6) | 377 (57.1) | 131 (68.2) | 0.006 |
| *Escherichia coli* | 245 (28.8) | 185 (28.0) | 60 (31.3) | 0.519 |
| *Klebsiella pneumoniae* | 98 (11.5) | 72 (10.9) | 26 (13.5) | 0.851 |
| *Pseudomonas aeruginosa* | 9 (1.1) | 5 (0.8) | 4 (2.1) | 0.197 |
| *Enterobacter cloaceae* | 19 (2.2) | 14 (2.1) | 5 (2.6) | 0.957 |
| *Aeromonas species* | 30 (3.5) | 24 (3.6) | 6 (3.1) | 0.455 |
| *Acinetobacter baumanii* | 16 (1.9) | 6 (0.9) | 10 (5.2) | 0.001 |
| *Stenotrophomonas maltophilia* | 6 (0.7) | 3 (0.5) | 3 (1.6) | 0.173 |
| Others | 75 (8.8) | 61 (9.2) | 14 (7.3) | 0.127 |
| **Mixed** | 10 (1.2) | 7 (1.1) | 3 (1.6) | 0.758 |
| **ESBL status of the isolated pathogens** | | | | 0.061 |
| ESBL (+) | 138 (16.2) | 97 (14.7) | 41 (21.4) | |
| ESBL (−) | 215 (25.2) | 170 (25.8) | 45 (23.4) | |
| **Gram-positive organisms** | 344 (40.4) | 283 (42.9) | 61 (31.8) | 0.006 |
| *Coagulase-negative staphylococci* | 158 (18.5) | 131 (19.9) | 27 (14.1) | 0.398 |
| *Staphylococcus epidermidis* | 61 (7.2) | 47 (7.1) | 14 (7.3) | |
| *Staphylococcus hominis* | 32 (3.8) | 29 (4.4) | 3 (1.6) | |
| *Staphylococcus haemolyticus* | 19 (2.2) | 16 (2.4) | 3 (1.6) | |
| Others | 46 (5.4) | 39 (5.9) | 7 (3.7) | |
| **Methicillin resistance** | | | | 0.235 |
| Methicillin-resistant groups | 74 (8.7) | 60 (9.1) | 14 (7.3) | |
| Methicillin-sensitive groups | 61 (7.2) | 54 (8.2) | 7 (3.7) | |
| **Streptococcus species** | 96 (11.3) | 86 (13.0) | 10 (5.2) | 0.160 |
| *Streptococcus pneumoniae* | 12 (1.4) | 9 (1.4) | 3 (1.6) | |
| *Streptococcus gallolyticus* | 23 (2.7) | 22 (3.3) | 1 (0.5) | |
| Others | 61 (7.2) | 55 (8.5) | 6 (3.1) | |
| **Staphylococcus aureus** | 58 (6.8) | 46 (7.0) | 12 (6.3) | — |
| Methicillin resistance | | | | 0.027 |
| MRSA | 8 (0.9) | 4 (0.6) | 4 (2.1) | |
| Methicillin-sensitive | 45 (5.6) | 38 (5.8) | 7 (3.7) | |
| **Enterococcus spp.** | 32 (3.8) | 20 (3.0) | 12 (6.3) | 0.475 |
| *Enterococcus faecium* | 22 (2.6) | 13 (2.0) | 9 (4.7) | |
| *Enterococcus faecalis* | 4 (0.5) | 2 (0.3) | 2 (1.0) | |
| Others | 6 (0.7) | 3 (0.8) | 1 (0.5) | |
ototoxicity, and excessive use of carbapenems may promote the prevalence of pathogens resistant to these drugs, resulting in serious outcomes\(^\text{28, 29}\). Thus, cefoperazone/sulbactam and piperacillin/tazobactam should be used for the initial empirical treatment of BSIs. However, the methicillin resistance rate was 23.8%, and *Enterococcus spp* accounted for 9.3% of the Gram-positive bacteria in our study. The recently issued Infectious Diseases Society of America clinical practice guidelines recommend vancomycin for the treatment of bacteraemia caused by MRSA\(^\text{30}\). Thus, in the case of response failure, initial empirical antibiotics should be changed, and vancomycin or teicoplanin may be suitable choices.

In the current study, 30-day mortality was used to estimate the outcomes of BSI in liver cirrhosis patients. The results of this study suggested that both liver disease and infection played pivotal roles in the prognosis of the study population. Stepwise logistics regression analysis demonstrated that presentation with liver failure, liver cancer, septic shock, presence of complications, Child-Pugh grade, administration of appropriate antibiotics within 24 h, ICU admission, nosocomial infection, and Gram nature of the bacteria were independent factors correlated with clinical outcomes of BSI in liver cirrhosis patients.

Our study has several limitations. First, the study was purely observational, and clinical parameters, such as hepatic encephalopathy, depended on the judgement of physicians. Second, this study was conducted from data at a single centre. Therefore, the results obtained from this study need to be verified in a prospective multicentre study with a large sample size. Lastly, antibiotic resistance patterns might be different in other parts of the world (restricted generalizability).

In conclusion, the 30-day mortality of liver cirrhosis patients presenting with BSIs was independently correlated with liver failure, liver cancer, septic shock, presence of complications, Child-Pugh grade, administration of appropriate antibiotics within 24 h, ICU admission, nosocomial infection, and Gram nature of the

| Bacterial distributions | Total, n = 852 | Nosocomial infection, n = 523, 61.4% | Community-acquired infection, n = 329, 38.6% | P value |
|-------------------------|--------------|------------------------------------|---------------------------------|--------|
| **Gram-negative bacteria** | 508 (59.6) | 299 (57.2) | 209 (63.5) | 0.058 |
| *Escherichia coli* | 245 (28.8) | 135 (25.8) | 110 (33.4) | 0.097 |
| *Klebsiella pneumoniae* | 98 (11.5) | 49 (9.4) | 49 (14.5) | 0.047 |
| *Pseudomonas aeruginosa* | 9 (1.1) | 9 (1.7) | 0 (0.00) | 0.011 |
| *Enterobacter cloacae* | 19 (2.2) | 16 (3.1) | 3 (0.9) | 0.022 |
| *Aeromonas species* | 30 (3.5) | 15 (2.9) | 15 (4.6) | 0.309 |
| *Acinetobacter baumannii* | 16 (1.9) | 14 (2.7) | 2 (0.6) | 0.018 |
| *Stenotrophomonas maltophilia* | 6 (0.7) | 6 (1.2) | 0 (0.00) | 0.039 |
| Others | 75 (8.8) | 52 (9.9) | 23 (7.0) | 0.046 |
| Mixed | 10 (1.2) | 3 (0.6) | 7 (2.1) | 0.061 |
| **ESBL status of the isolated pathogens** | | | | 0.302 |
| ESBL (+) | 138 (16.2) | 79 (9.3) | 59 (17.9) | |
| ESBL (−) | 215 (25.2) | 111 (13.0) | 104 (31.6) | |
| **Gram-positive organisms** | 344 (40.4) | 224 (26.3) | 119 (36.2) | 0.058 |
| *Coagulase-negative staphylococci* | 158 (18.5) | 111 (13.0) | 47 (14.3) | 0.828 |
| *Staphylococcus epidermidis* | 61 (7.2) | 43 (5.1) | 18 (5.5) | |
| *Staphylococcus hominis* | 32 (3.8) | 23 (2.7) | 9 (2.7) | |
| *Staphylococcus haemolyticus* | 19 (2.2) | 15 (1.8) | 4 (1.2) | |
| Others | 46 (5.3) | 30 (3.5) | 16 (4.9) | |
| Methicillin resistance | | | | 0.185 |
| Methicillin-resistant groups | 74 (8.7) | 54 (6.3) | 20 (6.1) | |
| Methicillin-sensitive groups | 61 (7.2) | 38 (4.5) | 23 (7.0) | |
| **Streptococcus species** | 96 (11.3) | 43 (5.1) | 43 (13.1) | 0.035 |
| *Streptococcus pneumoniae* | 12 (1.4) | 5 (0.6) | 7 (2.1) | |
| *Streptococcus galilolyticus* | 23 (2.7) | 18 (2.1) | 5 (1.5) | |
| Others | 61 (7.2) | 30 (3.5) | 31 (9.4) | |
| *Staphylococcus aureus* | 58 (6.8) | 38 (4.5) | 20 (6.1) | — |
| Methicillin resistance | | | | 0.164 |
| MRSA | 8 (0.9) | 7 (0.8) | 1 (0.3) | |
| Methicillin-sensitive | 45 (5.3) | 28 (3.3) | 17 (5.2) | |
| *Enterococcus spp.* | 32 (3.8) | 20 (3.8) | 12 (3.6) | 0.115 |
| *Enterococcus faecium* | 22 (2.6) | 14 (2.7) | 8 (2.4) | |
| *Enterococcus faecalis* | 4 (0.5) | 3 (0.6) | 1 (0.3) | |
| Others | 6 (0.7) | 4 (0.8) | 2 (0.6) | |

Table 3. Characteristics of isolated bacteria in liver cirrhosis patients suffering from nosocomial and community-acquired infections. Note: —: Indicates no available data; MRSA: methicillin-resistant *Staphylococcus aureus*. 
bacteria. Gram-negative bacteria were the major pathogens responsible for BSIs in liver cirrhosis patients, but Gram-positive pathogens have become increasingly common. The choice of initial empirical antibiotics should be based on the type, severity and origin of the infections and on the local epidemiological data on antibiotic resistance.

Methods

Study population. This was a retrospective cohort study. The study protocol was approved by the Ethics Committee of our hospital, and informed consent was waived. This retrospective study included the records of patients with liver cirrhosis patients who developed BSIs in Beijing 302 Hospital from October 2010 to January 2015. The following inclusion criteria were applied for the patients screened for recruitment to this study: (1) the study population was adults over 18 years of age; (2) the patients visited the hospital for liver cirrhosis and presented with community-acquired or nosocomial (after 48 h or more since admission) BSIs; and (3) the clinical and demographic data of the patients, such as age, gender, hospitalization information, and BSI data, were available. In cases of patients who developed multiple BSIs during their hospital stay, only the first episode was used for analysis. All methods were performed in accordance with the relevant guidelines and regulations.

Diagnosis standard. Diagnosis of liver cirrhosis was established by histological examination or by clinical, analytical, and ultrasonographic findings. Non-infectious complications of cirrhosis (ascites, hepatorenal syndrome, hepatic encephalopathy) and hepatocellular carcinoma were defined in patients using criteria from the European Association for the Study of the Liver and International Ascites Club. BSI was defined as the growth of a non-common skin contaminant from ≥1 BCs (Blood Cultures) and of a common skin contaminant (e.g., diphtheroids, Bacillus species, Propionibacterium species, or micrococci) from ≥2BCs drawn on separate sites. To distinguish between true BSIs and contamination, each positive BC was analysed during review of the medical and microbiology records to confirm that it represented true infection. Spontaneous bacterial peritonitis (SBP) was defined as the presence of ≥250 PMN/mm³ in ascitic fluid along with/without a positive ascitic fluid culture.

Patients who showed infection within 48 h of hospital admission were considered to have community-acquired infections, while those who presented with infection after 48 h of admission were considered as having nosocomial infections. The source of the BSI in each patient was determined on a clinical basis. Sources of BSI, such as lung, urinary tract, and abdomen, were defined as previously described. Sources of BSI were designated as culture confirmed (if the same organism was isolated from another site) or suspected (if clinical findings of infection were seen without microbiological proof). A case was regarded as a primary bacteraemia when no overt infection focus other than the bloodstream was identified.

Blood culture and antibiotic susceptibility test. Blood samples were drawn from the subjects for antimicrobial susceptibility testing (AST). Briefly, 10 mL of blood was drawn under aseptic conditions, and the blood sample was cultured both aerobically and anaerobically with both Bact/Alert3D anaerobic and aerobic blood culture bottles (bioMerieux) at the patients’ bedside. Bacteria were inoculated into Columbia blood agar and China blue agar plates. After culture, a single colony was isolated and identified using an automated VITEK2 system (bioMerieux). The cells were tested for antimicrobial susceptibility using the Kirby-Bauer or MIC method.

| Antibiotics               | Isolated bacterium | ESBL + E. coli | ESBL + K. pneumonia |
|--------------------------|--------------------|----------------|---------------------|
| Cefepime                 | 462 (76.0)         | 27/121 (22.3)  | 4/8 (50.0)          |
| Ceftazidime              | 480 (73.3)         | 21/122 (17.2)  | 1/8 (12.5)          |
| Ceftriaxone              | 470 (63.2)         | 1/126 (0.8)    | 0/9 (0.0)           |
| Levofloxacin             | 474 (63.2)         | 39/121 (32.2)  | 3/8 (37.5)          |
| Ceftoperazone/sulbactam  | 405 (69.9)         | 77/103 (74.8)  | 1/5 (20.0)          |
| Piperacillin/tazobactam  | 467 (62.1)         | 100/118 (84.8) | 6/9 (66.7)          |
| Imipenem                 | 485 (64.6)         | 126/126 (100)  | 9/9 (100)           |
| Meropenem                | 387 (57.3)         | 104/105 (99.1) | 8/9 (89.0)          |
| Amikacin                 | 473 (54.6)         | 119/125 (95.2) | 8/9 (89.0)          |

| Gram-positive bacteria   |                      | Methicillin-resistant Coagulase-negative staphylococci | MRSA |
|--------------------------|----------------------|----------------------------------|------|
| Penicillin               | 324 (40.7)           | 0/74 (0.0)                       | 0/8 (0.0) |
| Ceftriaxone              | 182 (36.1)           | 0/47 (0.0)                       | 0/4 (0.0) |
| Levofloxacin             | 334 (31.1)           | 36/74 (48.7)                     | 1/8 (1.3) |
| Erythromycin             | 316 (28.2)           | 11/74 (14.9)                     | 4/8 (50.0) |
| Vancomycin               | 331 (29.1)           | 75/73 (100)                      | 8/8 (100) |
| Teicoplanin              | 200 (19.9)           | 71/72 (98.6)                     | 8/8 (100) |

Table 4. Drug resistance analysis for the isolated organisms.
Escherichia coli (ATCC25922) and Staphylococcus aureus (ATCC25923) were used as the strains for quality control. Antimicrobial susceptibility testing were performed according to the recommendations of the Clinical and Laboratory Standard Institute (CLSI)34.

Treatment. Empirical antimicrobial therapy was defined as the administration of antimicrobial agents after collecting the first set of positive blood cultures. In most cases, patients received a third-generation cephalosporin or piperacillin/tazobactam. In patients with a history of colonization or multidrug-resistant bacterial infection, carbapenem and vancomycin were the preferred drugs of choice. Antimicrobial therapy was considered appropriate if the drug used could inhibit the activity of the isolated pathogens in the antimicrobial sensitivity test in vitro. In case the drugs were not effective against the selected pathogen, a different antimicrobial agent was administered.

Data collection. Data were collected from the medical records of the patients. The collected information included the demographic characteristics (gender and age), hospitalization unit, cause of cirrhosis, Child-Pugh score, BSI data (history of the past two years, source of BSI, days hospitalized before BSI onset, initial symptoms, complications, septic shock), bacterial distribution, drug sensitivity test results, and empirical antibiotic regimens. The 30-day mortality was counted from the first day of positive blood cultures and then used to evaluate the outcomes of BSI in liver cirrhosis patients. If the patients were discharged before 30 days, the author would call the patients at home at 30 days after infection.

Statistical analyses. SPSS version 18.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses in this study. Continuous data are presented as the means ± standard deviation and were analysed using Student’s t test. The chi-square test was used for categorical data analyses. Patient information was recorded in a standardized

| Factor                                | Group | N   | OR    | 90% CI | P value |
|---------------------------------------|-------|-----|-------|--------|---------|
| Gender                                | M     | 671 | 1.000 (Reference) |       |
|                                       | F     | 181 | 1.479 | 1.018  | 2.149   | 0.0402  |
| Age (years)                           | < ≤ 44| 251 | 1.000 (Reference) |       |
|                                       | 45–59 | 519 | 1.014 | 0.700  | 1.467   | 0.9429  |
|                                       | ≥ 60  | 182 | 1.160 | 0.755  | 1.782   | 0.4930  |
| Pathogen                              | Hepatitis B | 548 | 1.000 (Reference) |       |
|                                       | Hepatitis C | 85  | 0.840 | 0.483  | 1.460   | 0.5361  |
|                                       | Alcoholic | 107 | 1.095 | 0.669  | 1.791   | 0.7193  |
|                                       | Other   | 104 | 1.374 | 0.866  | 2.181   | 0.1773  |
| Combined with liver failure           | No     | 664 | 1.000 (Reference) |       |
|                                       | Yes    | 188 | 5.949 | 4.164  | 8.499   | <0.0001 |
| Combined with liver cancer            | No     | 602 | 1.000 (Reference) |       |
|                                       | Yes    | 250 | 0.749 | 0.519  | 1.080   | 0.1216  |
| Infection history within 2 years      | No     | 397 | 1.000 (Reference) |       |
|                                       | Yes    | 455 | 1.122 | 0.756  | 1.667   | 0.5679  |
| Source of infection                   | Primary| 513 | 1.000 (Reference) |       |
|                                       | Non-Primary | 339 | 2.360 | 1.703  | 3.271   | <0.0001 |
| Complication                          | No     | 163 | 1.000 (Reference) |       |
|                                       | Yes    | 689 | 11.717 | 8.996  | 16.957   | <0.0001 |
| Child-Pugh grade                      | A      | 109 | 1.000 (Reference) |       |
|                                       | B      | 302 | 3.098 | 1.068  | 8.987   | 0.0375  |
|                                       | C      | 441 | 14.528 | 5.256  | 40.154   | <0.0001 |
| Septic shock                          | No     | 691 | 1.000 (Reference) |       |
|                                       | Yes    | 161 | 12.602 | 8.511  | 18.658   | <0.0001 |
| Appropriate antibiotics within24 h    | Yes    | 612 | 1.000 (Reference) |       |
|                                       | No     | 240 | 6.060 | 4.282  | 8.576   | <0.0001 |
| ICU                                   | No     | 697 | 1.000 (Reference) |       |
|                                       | Yes    | 155 | 9.092 | 9.092  | 13.396   | <0.0001 |
| Nosocomial infection                  | No     | 329 | 1.000 (Reference) |       |
|                                       | Yes    | 523 | 1.428 | 1.018  | 2.005   | 0.0392  |
| Gram stain                            | Negative| 508 | 1.000 (Reference) |       |
|                                       | Positive| 344 | 0.633 | 0.451  | 0.888   | 0.0082  |

Table 5. Univariate analysis of risk factors for 30-day mortality in liver cirrhosis patients suffering from BSIs. Note: Complication: including ascites or hepatoportal syndrome or hepatic encephalopathy or upper gastrointestinal bleeding. Combined with liver failure: cirrhosis with liver failure. Non-Primary: Sources of BSI including lung or urinary tract or abdomen.
Table 6. Multivariate analyses for 30-day mortality in the study population. Note: Complication: including ascites or hepatorenal syndrome or hepatic encephalopathy or upper gastrointestinal bleeding. Combined with liver failure: cirrhosis with liver failure.

| Factor                        | Group | N    | OR   | 90% CI  | P value |
|-------------------------------|-------|------|------|---------|---------|
| Combined with liver failure   | No    | 664  | 1.000 (Reference) |        |         |
|                               | Yes   | 188  | 2.288 | 1.451   | 3.609   | 0.0028  |
| Combined with liver cancer    | No    | 602  | 1.000 (Reference) |        |         |
|                               | Yes   | 250  | 2.196 | 1.366   | 3.529   | 0.0064  |
| Complication                  | No    | 163  | 1.000 (Reference) |        |         |
|                               | Yes   | 689  | 4.663 | 3.057   | 7.113   | <0.0001 |
| Child-Pugh grade              | A     | 109  | 1.000 (Reference) |        |         |
|                               | B     | 302  | 5.483 | 1.914   | 15.708  | 0.0078  |
|                               | C     | 441  | 10.499| 3.687   | 29.894  | 0.0002  |
| Septic shock                  | No    | 691  | 1.000 (Reference) |        |         |
|                               | Yes   | 161  | 3.959 | 2.457   | 6.380   | <0.0001 |
| Appropriate antibiotics within 24h | Yes | 612  | 1.000 (Reference) |        |         |
| I.C.U.                        | No    | 697  | 1.000 (Reference) |        |         |
|                               | Yes   | 155  | 2.363 | 1.447   | 3.861   | 0.0039  |
| Nosocomial infection          | No    | 329  | 1.000 (Reference) |        |         |
|                               | Yes   | 523  | 1.670 | 1.107   | 2.520   | 0.0402  |
| Gram stain                    | Negative | 508 | 1.000 (Reference) |        |         |
|                               | Positive | 344 | 0.465 | 0.305   | 0.710   | 0.0029  |

data form and compared based on the patient’s survival status within 30 days of the occurrence of infection. The stepwise logistic regression model was applied to identify the risk factors and independent risk factors for 30-day mortality. Variables in the univariate analysis (P < 0.1) and variables with clinical significance were entered into a multivariate logistic regression analysis using stepwise selection. The goodness of fit was tested with the Hosmer–Lemeshow test, which revealed that the model was of adequate fit (P = 0.813). P values less than 0.05 were considered statistically significant.

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Author Contributions
Yangxin Xie and Bo Tu participated in the literature search, study design, data collection, data analysis, and data interpretation and wrote the manuscript. Zhe Xu, Xin Zhang, and Jingfeng Bi carried out the data collection and analysis and provided the critical revision. Min Zhao, Weiwei Chen, Lei Shi, Peng Zhao, and Chunmei Bao conceived of the study and participated in its design and coordination. Enqiang Qin and Dongping Xu participated in the study design and provided the critical revision. All authors read and approved the final manuscript.

Additional Information

Competing Interests: The authors declare that they have no competing interests.

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