

Clinical risk factors and predictive tool of bacteremia in patients with cirrhosis

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Abstract

Objective: We aimed to analyze the risk factors and to establish a predictive tool for the occurrence of bloodstream infections (BSI) in patients with cirrhosis.

Methods: A total of 2888 patients with cirrhosis were retrospectively included. Multivariate analysis for risk factors of BSI were tested using logistic regression. Multivariate logistic regression was validated using five-fold cross-validation.

Results: Variables that were independently associated with incidence of BSI were white blood cell count (odds ratio [OR] = 1.094, 95% confidence interval [CI] 1.063–1.127), C-reactive protein (OR = 1.005, 95% CI 1.002–1.008), total bilirubin (OR = 1.003, 95% CI 1.002–1.004), and previous antimicrobial exposure (OR = 4.556, 95% CI 3.369–6.160); albumin (OR = 0.904, 95% CI 0.883–0.926), platelet count (OR = 0.996, 95% CI 0.994–0.998), and serum creatinine (OR = 0.989, 95% CI 0.985–0.994) were associated with lower odds of BSI. The area under receiver operating characteristic (ROC) curve of the risk assessment scale was 0.850, and its sensitivity and specificity were 0.762 and 0.801, respectively. There was no significant difference between the ROC curves of cross-validation and risk assessment.

Conclusions: We developed a predictive tool for BSI in patients with cirrhosis, which could help with early identification of such episodes at admission, to improve outcome in these patients.

Keywords

Liver, cirrhosis, bacteremia, bloodstream infection, outcome, cross-validation, risk assessment

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Introduction

Bacterial infection is an important factor leading to acute decompensation (AD) in patients with cirrhosis and is associated with higher mortality than in patients without cirrhosis.¹ During the course of cirrhosis, bacterial infection develops as a consequence of immune dysfunction, portal hypertension, gut microflora damage, and bacterial translocation.² Bloodstream infection (BSI) is a common type of infection in patients with cirrhosis and is associated with acute organ failure and a high risk of short-term death, ranging between 23% to 58%.^{3,4} The epidemiology and outcomes of BSI in patients with cirrhosis have been reported in many prospective, multicenter studies.⁵ Several scoring systems have also been developed, such the Model for End-Stage Liver Disease (MELD), MELD Sodium (MELD-Na), and Chronic Liver Failure Consortium Acute Decompensation (CLIF-C AD) score, to predict short-term mortality among patients with cirrhosis and BSI.^{5,6} However, early identification of BSI and management of infection before the development of BSI is important to reduce morbidity and mortality. In the current study, we analyzed the clinical data of patients with cirrhosis and developed a predictive tool for bacteremia (BSI) in patients with cirrhosis at the time of hospitalization.

Methods

Study design

This was a retrospective, single-center, observational cohort study. We retrospectively included patients with cirrhosis (age >18 years) from September 2000 to May 2018 in Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. This study conformed to the principles of the Declaration of Helsinki and was

approved by the Ethics Committee of Sir Run Run Shaw Hospital. Written consent was obtained from each participant or their legal surrogate at admission.

Definitions

In patients with chronic liver diseases, the diagnosis of liver cirrhosis was based on liver biopsy, endoscopic signs of portal hypertension, radiologic imaging evidence of liver nodularity, or clinical signs of hepatic decompensation such as ascites, upper gastrointestinal bleeding, or hepatic encephalopathy.

BSI was defined as the growth of an uncommon skin contaminant in more than one blood culture and of a common skin contaminant (e.g., diphtheroids, *Bacillus* species, coagulase-negative staphylococci, *Propionibacterium* species or micrococci) in more than two blood cultures drawn from separate sites, with signs of infection.⁷ If a patient experienced multiple episodes of BSI, only the first BSI was included in the analysis. Each positive blood culture was independently reviewed by a clinician and a microbiologist to confirm a true BSI, and any discrepancies were resolved in discussion.

Patients with disseminated malignancy or malignant blood diseases were excluded, as were patients with systemic immunosuppressive diseases.

Data collection

We collected data using a clinical database available on the hospital website. All data were systematically checked by two investigators independently before enrollment. The following variables were collected: demographic variables, regular vital signs, etiologies of cirrhosis, presence of complications (diabetes, hepatocellular carcinoma (HCC)), and previous antibiotic exposure within the past 3 months. We also collected

the following initial laboratory biochemical data after admission: albumin, alanine aminotransferase, aspartate aminotransferase (AST), white blood cell (WBC) count, platelets, C-reactive protein (CRP), serum sodium, serum creatinine, bilirubin, international normalized ratio (INR), data of blood cultures, and severity of cirrhosis according to MELD, MELD-Na, and CLIF-C AD scores.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) if normally distributed or as median and interquartile range if non-normally distributed. Categorical variables were expressed as frequency and percentage. Continuous variables were compared using a Student *t*-test or Wilcoxon rank-sum test. Categorical variables were compared using the χ^2 test. Multivariate analysis of patients with cirrhosis and BSI were tested using logistic regression and forward stepwise regression. Independent variables in multivariate analysis were those with $P < 0.2$ in the univariate analyses. The regression model was depicted using a nomogram. The power of the model was tested using five-fold cross-validation. The receiver operating characteristic (ROC) curves were compared with DeLong's test. The analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) or R version 3.2.3 (The R Project for Statistical Computing, Vienna, Austria). All tests were two-sided with a significance level of 0.05.

Results

Demographic and clinical characteristics

A total of 4001 patients with cirrhosis were enrolled between January 2004 and March 2018 from the Department of Infectious

Diseases of Sir Run Run Shaw Hospital. We excluded 672 patients with missing data, and 441 patients were excluded owing to infections other than BSI. Finally, 2888 patients with cirrhosis were included in the analysis, among which 303 had BSI (Figure 1). Of all the patients enrolled in the study, 855 patients (29.5%) were women; the mean patient age was 58.3 ± 12.5 years. The most common etiology of cirrhosis was hepatitis B virus (HBV) infection, accounting for 39% of cases. Complication with diabetes and HCC accounted for 19.3% and 35.5% of cases, respectively. Overall, 14.6% patients had a history of antibiotics treatment within 3 months prior to admission. The enrolled patients were divided into two groups, the non-combined BSI group and the combined BSI group. A comparison of the clinical features and laboratory indicators between the two groups is shown in Table 1.

Analysis of risk factors for BSI

We compared patients with and without BSI to identify possible risk factors for BSI in univariate analysis (Table 1). The results showed that patients with cirrhosis and BSI were more likely to have etiologies of HBV, autoimmune liver diseases, and previous antimicrobial therapy within the past 3 months. Patients with cirrhosis and BSI had higher levels of AST, WBCs, CRP, total bilirubin (TBIL), and higher INR than those without BSI, and lower levels of albumin, platelets, serum sodium, and serum creatinine than patients without BSI. We also found that high MELD score, MELD-Na score, and the initial CLIF-C AD score were independently associated with BSI in patients with cirrhosis.

Based on multivariate analysis, low levels of albumin, platelets, and serum creatinine were predictive of BSI in patients

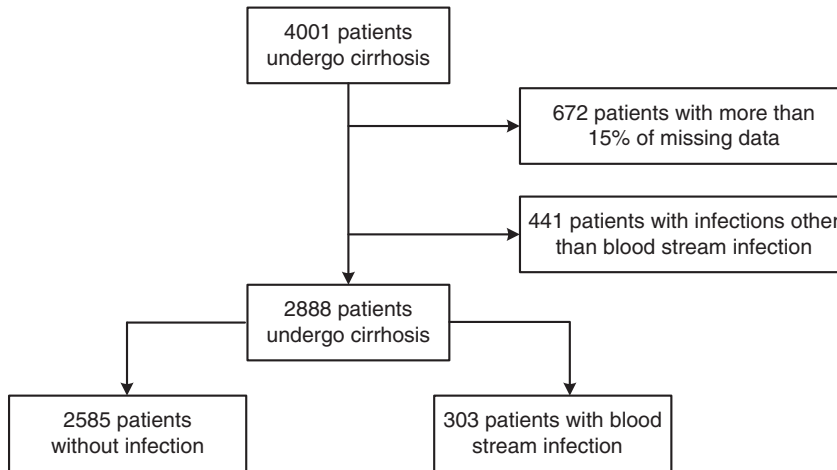


Figure 1. Flow chart of patient selection in this study.

Table 1. Comparison of demographic and related clinical data between patients with and without BSI.

Variables	BSI status		Statistics	P
	Without BSI (N = 2585)	With BSI (N = 303)		
Age (years), mean \pm SD	58.4 \pm 12.43	57.6 \pm 13.00	$t = 1.043$	0.297
Sex (male)	765 (70.4%)	91 (70.0%)	$\chi^2 = 0.025$	0.874
Diabetes	496 (19.2%)	62 (20.5%)	$\chi^2 = 0.283$	0.591
Liver cancer	944 (36.5%)	81 (26.7%)	$\chi^2 = 19.610$	<0.001
Etiology of cirrhosis				
HBV	983 (38.0%)	146 (48.2%)	$\chi^2 = 11.753$	0.001
HCV	10 (0.4%)	3 (1.0%)	$\chi^2 = 2.203$	0.149
Schistosomiasis	157 (6.1%)	20 (6.6%)	$\chi^2 = 0.131$	0.717
Autoimmune liver diseases	35 (1.4%)	18 (5.9%)	$\chi^2 = 31.671$	<0.001
Antimicrobial exposures	290 (11.2%)	132 (43.6%)	$\chi^2 = 227.421$	<0.001
First laboratory data after admission, median (P ₂₅ , P ₇₅)				
Albumin (g/L)	33.3 (28.6, 38.0)	28.0 (24.0, 32.0)	$Z = -13.300$	<0.001
ALT (U/L)	32.0 (20.0, 55.0)	35.0 (20.0, 60.5)	$Z = -1.074$	0.283
AST (U/L)	44.0 (28.0, 77.0)	52.5 (34.0, 97.5)	$Z = -3.891$	<0.001
WBC count ($10^9/L$)	4.5 (3.1, 6.2)	7.1 (3.85, 11.00)	$Z = -9.247$	<0.001
Platelet count ($10^9/L$)	93.0 (58.0, 152.0)	71.0 (42.5, 128.5)	$Z = -5.396$	<0.001
CRP (mg/L)	4.6 (1.2, 18.2)	22.0 (7.7, 58.0)	$Z = -13.205$	<0.001
Serum sodium (mmol/L)	140.0 (137.9, 142.0)	137.0 (133.1, 137.0)	$Z = -8.262$	<0.001
Creatinine ($\mu\text{mol/L}$)	70.0 (59.0, 82.0)	60.0 (48.0, 75.0)	$Z = -7.692$	<0.001
Serum bilirubin ($\mu\text{mol/L}$)	22.3 (14.3, 39.2)	48.7 (21.2, 142.0)	$Z = -11.301$	<0.001
INR	1.2 (1.1, 1.4)	1.4 (1.2, 1.7)	$Z = -10.362$	<0.001
MELD score	7.0 (3.8, 10.9)	10.7 (4.9, 16.1)	$Z = -6.501$	<0.001
MELD-Na score	-0.7 (-6.0, 5.8)	5.8 (-1.1, 15.8)	$Z = -9.325$	<0.001
CLIF_C_AD score	42.4 (37.7, 48.1)	48.5 (42.1, 54.7)	$Z = -9.380$	<0.001

Note: Values are n (%), unless otherwise noted.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BSI: bloodstream infection; CLIF_C_AD: chronic liver failure-consortium acute decompensation; CRP: C-reactive protein; HBV: hepatitis B virus; HCV hepatitis C virus; INR: international normalized ratio; MELD: model for end-stage liver disease; SD: standard deviation.

Table 2. Risk factors associated with BSI in patients with cirrhosis.

Variables	B	SE	P	OR (95% CI)
Albumin	-0.101	0.012	<0.001	0.904 (0.883, 0.926)
WBC count ($10^9/L$)	0.090	0.015	<0.001	1.094 (1.063, 1.127)
Platelet count ($10^9/L$)	-0.004	0.001	<0.001	0.996 (0.994, 0.998)
CRP (mg/L)	0.005	0.002	0.001	1.005 (1.002, 1.008)
Serum sodium (mmol/L)	-0.011	0.002	<0.001	0.989 (0.985, 0.994)
Serum bilirubin ($\mu\text{mol/L}$)	0.003	0.001	<0.001	1.003 (1.002, 1.004)
HBV	0.894	0.149	<0.001	2.444 (1.826, 3.271)
HCV	1.776	0.769	0.021	5.908 (1.308, 26.683)
Autoimmune liver diseases	1.910	0.351	<0.001	6.755 (3.398, 13.431)
Antimicrobial exposures	1.516	0.154	<0.001	4.556 (3.369, 6.160)
Constant	0.378	0.414	0.361	-

Statistical analysis was performed using multivariate logistic regression analysis.

BSI, bloodstream infection; CRP, C-reactive protein; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval.

with cirrhosis (Table 2). High levels of WBC, CRP, TBIL, and antimicrobial therapy within the previous 3 months were indicative of a risk of BSI (Table 2). Furthermore, the above model had a predictive value with area under the ROC curve (AUC) of 0.851 (95% CI 0.828–0.875, $P < 0.001$, Figure 2). The sensitivity and specificity were 0.746 and 0.815, respectively. The AUC, internally validated using five-fold cross-validation for the ability of the predictive model, was 0.844 (Figure 3). DeLong's test showed that there was no significant difference between the above ROC curves.

Development of a predictive model for BSI in patients with cirrhosis

We constructed a nomogram for the prediction of BSI in patients with cirrhosis, using the independent variables including albumin, WBC, CRP, serum creatinine, TBIL; etiologies of HBV, HCV and autoimmune liver diseases; and previous exposure of antimicrobial therapy (Figure 4). A risk assessment scale for BSI was calculated using the nomogram (Table 3).

Validation of a predictive model for BSI in patients with cirrhosis

An ROC curve for validation of the predictive model was constructed using risk assessment (Figure 5) The AUC of the risk assessment scale was 0.850. The sensitivity and specificity were 0.762 and 0.801, respectively. DeLong's test showed that there was no significant difference between the cross-validation curve and risk assessment curve.

Discussion

Patients with cirrhosis are susceptible to bacterial infections owing to a variety of complex pathogenic mechanisms.¹ Infection might lead to the natural history of cirrhosis entering a rapidly progressive phase, termed AD of cirrhosis, even acute-on-chronic liver failure (ACLF) and death. BSI are a lethal type of infection in patients with cirrhosis and are the common precipitating event of severe sepsis and short-term mortality.⁸ The clinical presentation of BSI in some patients with cirrhosis may be not specific; therefore, early detection and

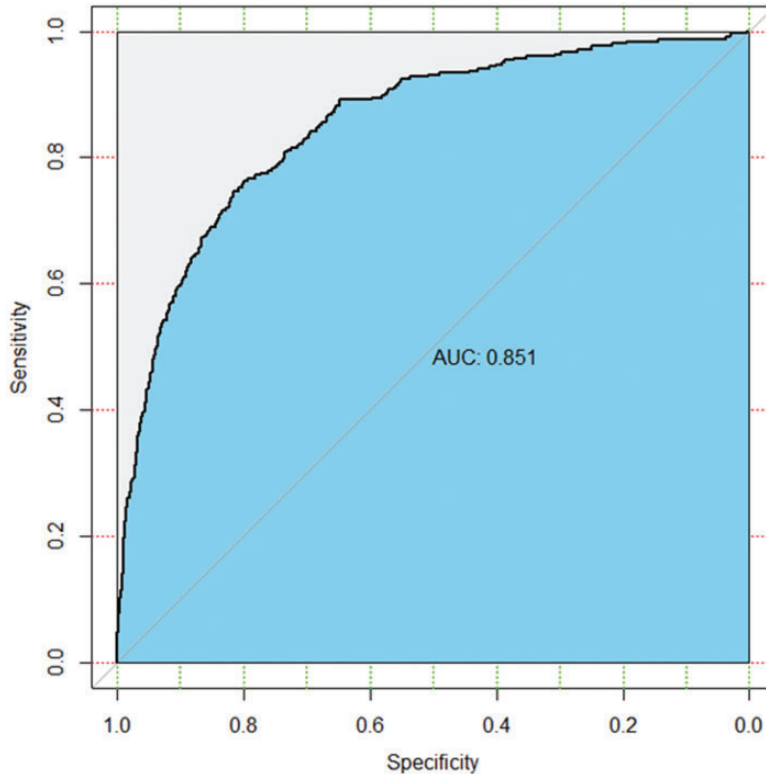


Figure 2. ROC curve of logistic regression model for patients with cirrhosis and BSI. AUC, area under ROC curve; BSI, bloodstream infection; ROC, receive operating characteristic.

diagnosis of BSI is a crucial step in the management of patients with cirrhosis.

Similar to earlier studies among Asian populations, we found that HBV infection was the main underlying disease in our patients.⁹ The incidence rate of BSI in patients with cirrhosis was 7.9%, which was significantly higher than that associated with BSI in the general population. The presence of diabetes mellitus is an independent factor of the occurrence of BSI.¹⁰ However, we did not identify an association between complication with diabetes and the occurrence of BSI in patients with cirrhosis. It should be noted that clinical information of diabetes was collected from the medical history and not the actual blood sugar value at admission, which may explain the above

discrepancy. Future studies are needed to clarify the clinical characters of patients with liver cirrhosis who develop diabetes and sepsis. Although higher creatinine levels are associated with worse renal function and poor prognosis in BSI, it should be noted that lower levels of serum creatinine were predictive of BSI in the current study. This finding might be owing to the values of serum creatinine being collected at the time of admission, when the episode of BSI had not yet occurred. A recent study demonstrated that sarcopenia can damage the immune system, decrease organ tolerance, and increase the risk of infection.¹¹ We speculated that lower levels of creatinine may be related to atresia in our patients, and infections were more likely in those

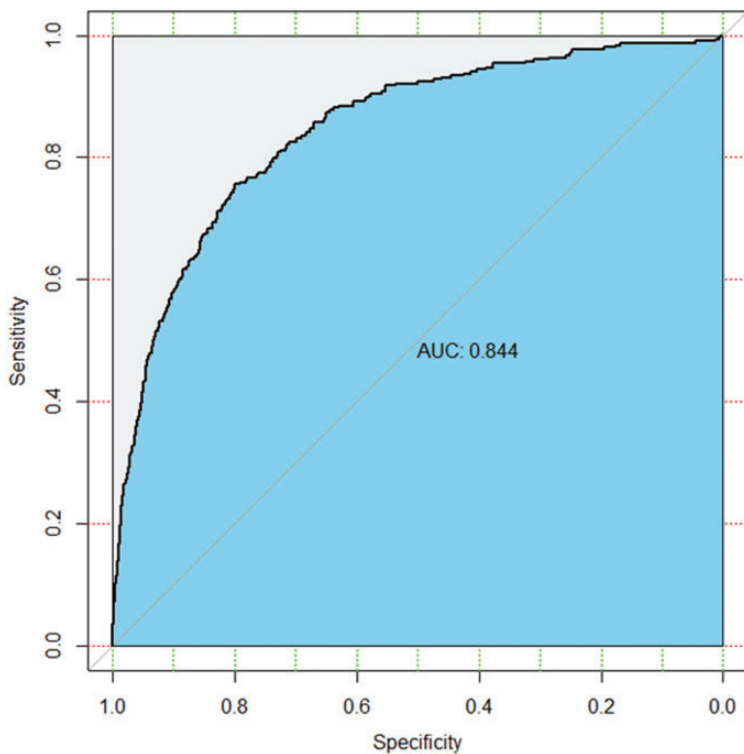


Figure 3. ROC curve of logistic regression model validated using five-fold cross-validation for patients with cirrhosis and BSI. AUC, area under ROC curve; BSI, bloodstream infection; ROC, receive operating characteristic.

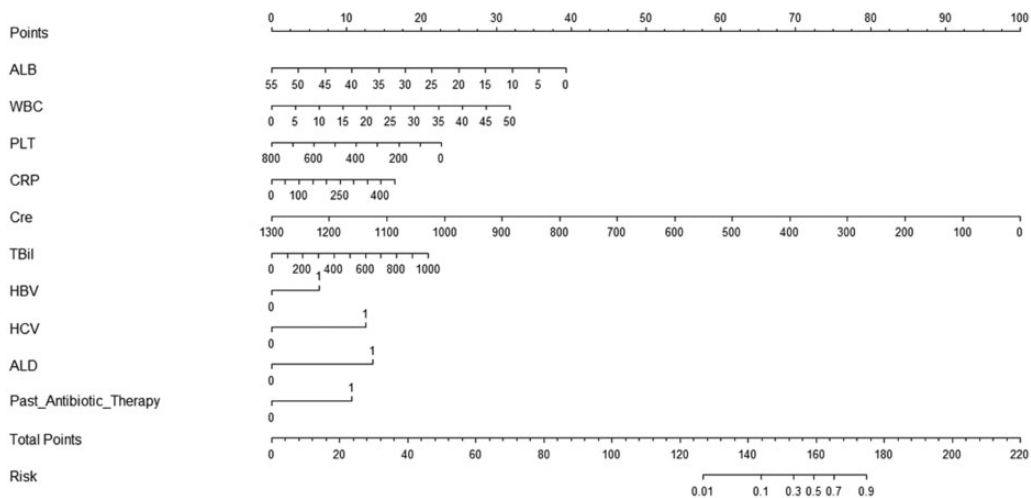


Figure 4. Nomogram of logistic regression model for patients with cirrhosis and BSI. ALB, albumin; ALD, autoimmune liver diseases; Cre, creatinine; CRP, C-reactive protein; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet; TBil, total bilirubin; WBC, white blood cell.

Table 3. Risk parameters of different variables in the scoring system.

Risk factors	Points
ALB	-6/per 10 unit
WBC count	0.6/per 1 unit
PLT count	-3/per 100 unit
CRP	1/per 25 unit
Cre	-2/per 25 unit
TBIL	1/per 50 unit
HBV	Yes = 6, No = 0
HCV	Yes = 13, No = 0
ALD	Yes = 13, No = 0
Past antibiotic therapy	Yes = 11, No = 0
Constant	162

ALB, albumin; ALD, autoimmune liver diseases; Cre, creatinine; CRP, C-reactive protein; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet; TBIL, total bilirubin; WBC, white blood cell.

with malnutrition. Therefore, dynamic monitoring of changes in serum creatinine may be important to investigate in future studies. Another important finding of this study is that a risk factor associated with BSI was previous antimicrobial exposure. The use of antibiotics might be owing to prior decompensation of cirrhosis or to misuse of antibiotics. Therefore, recent exposure to antibiotics in patients with cirrhosis should be routinely evaluated at the time of hospitalization.

Many prognostic scoring systems have been developed recently to predict the mortality of ACLF. However, few studies have focused on the occurrence of BSI in patients with cirrhosis, which are recognized as a lethal precipitating event of ACLF. In this

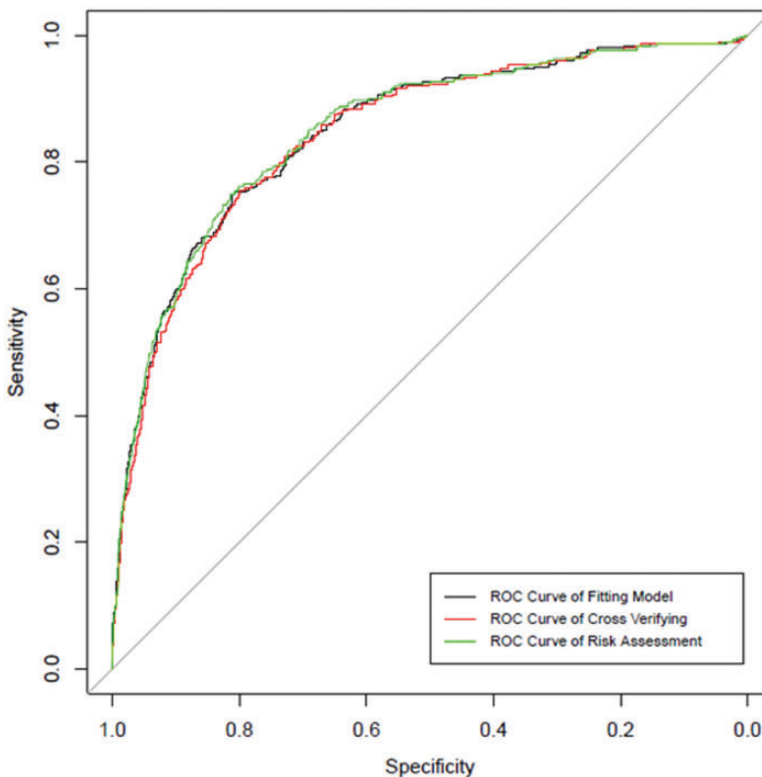


Figure 5. ROC curves of the fitting model, cross-validation, and risk assessment. ROC, receive operating characteristic.

study, we developed a predictive model for BSI based on a nomogram. Our analysis showed that the predictive model, which includes albumin, WBC, platelets, CRP, creatinine, TBIL, and previous antimicrobial therapy, had good predictive value for BSI. An internal cohort further validated the diagnostic accuracy. An early diagnosis of BSI may permit patients with cirrhosis to receive timely clinical management and earlier antibiotics therapy, which may help to reduce mortality in these patients.

Our study had some limitations. This was a retrospective, single-center, observational cohort study in which most cases of cirrhosis were caused by HBV. Thus, the findings of our study may not be representative of other patient populations at other institutions. Second, prospective follow-up data were lacking. Additionally, development of a more accurate risk model for predicting BSI in patients with cirrhosis was limited by the number of study participants in our dataset. Nevertheless, our findings suggest a growing proportion of patients with cirrhosis have previous antibiotics exposure, raising concerns about whether empirical antimicrobial regimens in these patients with a high risk of BSI should be considered in the presence of resistant organisms, thereby creating the need to tailor antibiotics therapy to include piperacillin/tazobactam or carbapenem rather than third-generation cephalosporins.

In conclusion, we developed a predictive tool for BSI in patients with cirrhosis, which could help in developing a multifaceted clinical risk score to guide clinicians in identifying patients with the highest risk who might benefit from earlier empiric therapy.

Trial registration number

This study was approved by the Ethics Review and Scientific Investigation Board of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University in Hangzhou, Zhejiang, China (Ethics Code No. 20140219-1).

Author contributions

Lv Fangfang and Yang Qiao conceived and designed the manuscript, Jiang Xianzhong analyzed the data, Yang Qiao and Zhu Yongfen wrote the manuscript, and Lv Fangfang revised and checked the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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