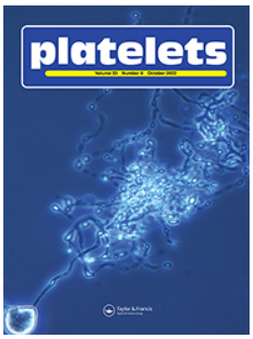

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Platelet index on admission as a predictor of bacteremia in acute cholangitis: a 7-year retrospective observational study

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Abstract

Bacteremia frequently occurs in patients with acute cholangitis, which could increase the risk of mortality. This single-center retrospective observational study was conducted from July 2013 to July 2020 to evaluate the predictive value of platelet index for bacteremia at admission for acute cholecystitis. A total of 285 patients with acute cholangitis were divided into bacteremia group and non-bacteremia group. The incidence of bacteremia in acute cholangitis was 48.42%. The bacteremia group had more grade III patients, higher 30d mortality rate [17(12.32%) vs 8(5.44%), p = .040] and higher incidence of thrombocytopenia [76(55.07%) vs 35(23.81%), p < .001]. Platelet counts and plateletcrit were significantly lower in the bacteremia group [84.5(60, 180) vs 162(102,225) $\times 10^9$/L and 0.10(0.07, 0.21)% vs 0.18(0.12, 0.25) %, both p < .001]. ROC analysis indicated a high predictive value of platelet count and plateletcrit for bacteremia in patients with acute cholangitis and the area under the ROC curve (AUC) were 0.649 and 0.655, respectively. These results support the value of platelet count and plateletcrit in early prediction of bacteremia at admission for acute cholangitis.

Plain Language Summary

What is the context?

- Acute cholangitis is a fatal infectious disease. Bacteremia frequently occur in patients with acute cholangitis, which could increase the risk of mortality.
- The positive rate of blood cultures in patients with acute cholangitis ranged from 21% to 71%.
- Platelets play key roles in thromboembolism, inflammation, and immune regulation.
- To the best of our knowledge, whether platelet index facilitates to the diagnosis of bacteremia in acute cholangitis has not been investigated.

What is new?

- In this study, we designed this 7-year retrospective, observational study to verify that platelet index could contribute to the early diagnosis of bacteremia in acute cholangitis.
- The results showed that:
- The patients with bacteremia had a higher incidence of thrombocytopenia.
- Thrombocytopenia, platelet count, plateletcrit, and procalcitonin were independent risk factors for bacteremia in acute cholangitis
- Platelet count and plateletcrit had positive predictive value for bacteremia in acute cholangitis.

What is the impact?

- This study presents clinical characteristics of acute cholangitis complicated by bacteremia, and provides evidence that platelet index can be used to predict bacteremia in acute cholangitis.

Keywords

Acute cholangitis, bacteremia, platelet, thrombocytopenia

History

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Introduction

Acute cholangitis is a fatal infectious disease, which has a high mortality rates if left untreated [1]. Especially in patients classified Grade III according to TG18 with severe acute cholangitis, the 30-day mortality rate as high as 8.4% [2]. Factors such as biliary barrier damage, increased biliary pressure, and liver

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immunity are all involved in the progression of cholangitis, and bacteria can enter the bloodstream through the biliary tract to cause bacteremia [2], which could increase the risk of mortality [3]. Early diagnosis of bacteremia is helpful for cholangitis condition and prognosis evaluation.

Currently, diagnosis of bacteremia by blood culture or metagenomic next-generation sequencing technology still require a relatively long time. Methods for early prediction of bacteremia need investigation.

Clinical observation found that some patients with acute cholangitis were accompanied by thrombocytopenia [4,5]. Infection is an important factor causing thrombocytopenia, but the mechanism is still unclear, it may be that patients with bacteremia induce platelet activation and aggregation in vivo [5–8]. Some studies have found that platelet characteristics may be helpful for the diagnosis of bacteremia. Research shows platelet count-mean platelet volume (MPV) ratio contribute to diagnosis of bacteremia in children in pediatric emergency settings [9]. The pathophysiological mechanism of biliary tract infection is different from that of other systemic infections, involving factors such as biliary tract, liver, and intestine. The mechanism of thrombocytopenia in patients with cholangitis is different from that of other systemic infections. Clinical platelet-related data are simple, easy to obtain, and fast. Whether the changes in platelet characteristics in acute cholangitis are related to bacteremia and whether they can be used as early predictors of cholangitis bacteremia have not yet been studied. To verify that platelet index could contribute to the early diagnosis of bacteremia in acute cholangitis, we designed this 7-year retrospective, observational study.

Material and methods

Definition

Tokyo Guidelines 2018 (TG18) diagnostic criteria for acute cholangitis [10]:

A. Systemic inflammation (A-1. Fever and/or shaking chills, A-2. Laboratory data: evidence of inflammatory response)

B. Cholestasis (B-1. Jaundice, B-2. Laboratory data: abnormal liver function tests)

C. Imaging (C-1. Biliary dilatation, C-2. Evidence of the etiology on imaging).

Definite diagnosis: one item in A, one item in B and one item in C.

Diagnostic criteria for bacteremia: Aerobic and anaerobic bacteria were cultured with peripheral venous blood from two different sites of the patient, the bacteria were cultured within 5 days, and the type of bacteria was identified.

Diagnostic criteria for Thrombocytopenia and severe thrombocytopenia [11,12]:

Thrombocytopenia is defined as a platelet count less than 100×10^9/L, and severe thrombocytopenia as a platelet count less than 50×10^9/L when the patient take the blood routine examination on admission.

Inclusion and exclusion criteria and grouping

The research was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Ethical approval number 2022-K132. This retrospective observational study investigated all patients diagnosed with cholangitis, acute cholangitis, obstructive suppurative cholangitis, and severe cholangitis in the First Affiliated Hospital of Chongqing Medical University from July 2013 to July 2020. The datas are extracted from the medical record information database according to the ICD code of our hospital. A total of 1289 patients, of which 1230 patients screened to meet the TG18 Diagnostic criteria for acute cholangitis [10].

The following patients were excluded:

1. <18 years old n = 3,
2. Treatment in other hospitals before admission n = 229,
3. Organ failure before onset n = 97,
4. Inability to assess the prognosis due to abandoned treatment or transfer n = 141,
5. No blood culture or used antibiotics before blood culture n = 337,
6. With other potential causes of bacteremia n = 81,
7. With previous history of thrombocytopelemia n = 22,
8. With previous history of blood diseases or autoimmune diseases n = 35,

Total 285 patients were enrolled in the study eventually. The included patients were divided into Bacteremia group and non-

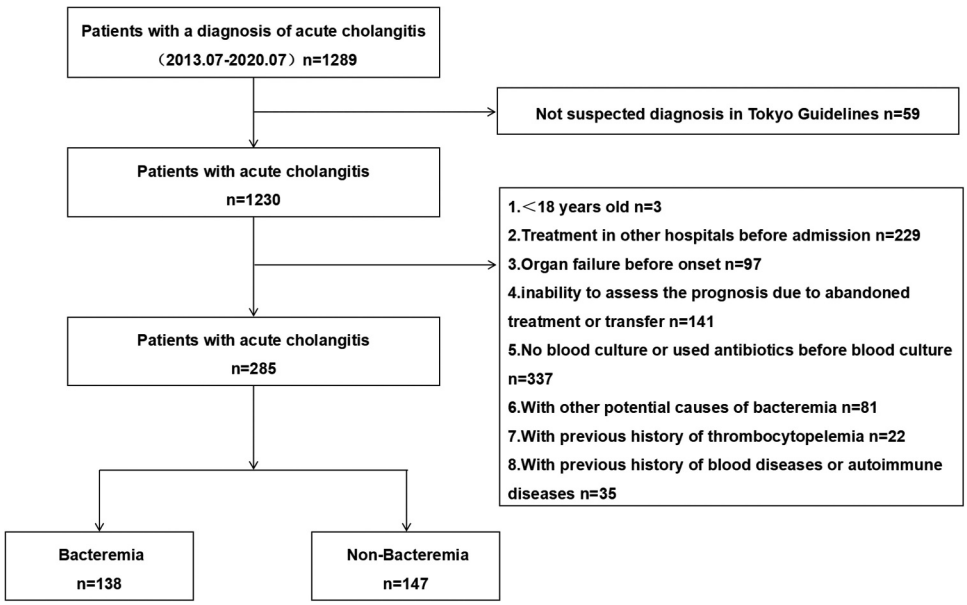


Figure 1. Patient selection flowchart.

bacteremia group according to whether bacteremia occurred or not (Figure 1).

Clinical data collection and laboratory examination

The general clinical datas of the patients which enrolled in this research were collected after admission, including age, gender, past medical history, etiology of cholangitis, 30-day survival, and clinical sign within 48 hours of admission (Fever, Abdominal pain, Jaundice, Lethargy or mental confusion, Shock). Blood routine examination, biochemical examination of liver and renal function were detected in all patients within 24 h of admission, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) Score were calculated. The patients which included in this research were underwent risk classification according to TG18 Severity assessment standard [10].

Statistical analysis

Data were expressed as mean ± standard deviation or medians (interquartile range) for continuous variables and counts and frequencies [number (percentage)] for categorical variables. The Shapiro-Wilk normality test was used to test whether the continuous variables conformed to a normal distribution. The independent t test or Mann–Whitney U test were used to compare differences in continuous variables between the two groups depending on whether the data conformed to a normal distribution. A comparison of categorical variables between the two groups was performed using Pearson's $\chi 2$ test with continuity correction or Fisher's exact test, where appropriate. The binary logistic regression model was used to analyze risk factors for. The bivariate and multivariate logistic regressions were used to investigate the risk factors for bacteremia in acute cholangitis involving the indicators with significant differences between two groups on admission, and the odds ratio (OR) with 95% confidence interval (95%CI) were calculated. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive ability of the independent risk factors. A value of $P < .05$ represented statistical significance. Statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL, USA). Generation of figures were carried out using the SigmaPlot 10.0 software (Systat Software, SPSS Inc., USA) and Excel software.

Results

Comparison of baseline and laboratory characteristics between bacteremia group and non-bacteremia group

A total of 285 patients with acute cholangitis were enrolled in this study and all enrolled patients received general supportive care, biliary drainage, organ support including noninvasive/invasive positive pressure ventilation, vasopressors, and antimicrobial therapy according to Tokyo guidelines after admission. The median age of the patients was 70.00 (55.00, 78.00) years. Of the 285 patients, 143 patients (55.43%) were male. The etiology of 268 patients (94.04%) was bile stones, and 15 patients (5.26%) were caused by tumor. According to the TG18 Severity assessment, the severity of patients was grade I in 42 cases (14.74%), grade II in 128 cases (44.91%), and grade III in 115 cases (40.35%). Altogether 25 patients (8.77%) died within 30 days of hospitalization. (Severity grade: I = mild, II = moderate, III = severe).

Bacteremia was diagnosed in 138 patients (48.42% of all patients with acute cholangitis). The baseline characteristics of the patients between bacteremia group and non-bacteremia group were summarized in Table I. The results showed differences in the past medical history of diabetes mellitus and clinical manifestations of fever, jaundice, lethargy or mental confusion, and shock. Compared with the non-bacteremia group, the bacteremia group contained more patients which were classified grade III($p < .001$) and fewer patients which were classified Grade I($p = .001$). The patients in bacteremia group had a higher APACHE II Score [12.50(9.00, 19.00) vs 11.00(9.00, 15.00), $p = .004$] and SOFA Score[12(9, 13.5) vs 6(3, 12), $p < .001$] and 30d mortality[17 (12.32%) vs 8(5.44%), $p = .040$]. In terms of laboratory examination, the bacteremia group had significantly higher levels of neutrophil percentage, procalcitonin, glutamic-pyruvic transaminase, and glutamic-oxaloacetic transaminase than non-bacteremia group. And significant decrease of absolute lymphocyte count and lymphocyte percentage were observed in the bacteremia group.

The distribution of microbiology of bacteremia in acute cholangitis

In this research, we investigated the microbiota profiles of 138 patients with bacteremia (Figure 2). The findings showed there were 106 cases of single bacterial infection (76.81%) and 32 cases of more than one kinds bacterial infection (23.19%) in the patients with bacteremia. Of all the samples of the patients in the bacteremia group, 124 grew gram-negative bacilli (89.86%), which included Escherichia coli (78,56.52%), Klebsiella pneumoniae (31, 22.46%), Enterobacter cloacae (10, 7.25%), Pseudomonas aeruginosa (9, 6.52%), and other Gram-negative bacilli (5, 3.62%). Thirty-nine grew gram-positive cocci, which included Enterococcus faecium (11,7.97%), Enterococcus faecalis (10, 7.25%), Enterococcus casseliflavus (5, 3.62%), Enterococcus gallinarum (3, 2.17%), other Gram-positive cocci (6, 4.35%). No fungi were found in our study.

Comparison of platelet index between bacteremia group and non-bacteremia group in acute cholangitis

Of all the patients, thrombocytopenia occurred in 111 patients (38.95%). The number of patients with thrombocytopenia in the bacteremia group was higher than that in the non-bacteremia group [76(55.07%) vs 35(23.81%), $p < .001$]. We performed a comparison of platelet index between bacteremia and Non-bacteremia group in acute cholangitis (Table II). The results reveal that compared with the non-bacteremic group, platelet counts, and plateletcrit were significantly lower in the bacteremic group [84.5(60, 180) vs 162(102,225) ×10^9/L and 0.10(0.07, 0.21) vs 0.18(0.12, 0.25) %, both $p < .001$]. However, no significant differences were found in the MPV, PDW, platelet count-to-plateletcrit ratio and PLCR between the two groups.

Risk factors of bacteremia in acute cholangitis

The bivariate logistic regression was performed to analyze the independent risk factors of bacteremia (Table III). As a result, thrombocytopenia, platelet count, plateletcrit, and procalcitonin were independent risk factors for developing bacteremia in acute cholangitis. However, platelet count-to-plateletcrit ratio, neutrophil percentage, absolute lymphocyte count, lymphocyte percentage, and APACHE II score may not constitute independent risk factors for predicting the bacteremia in acute cholangitis.

We analyzed the occurrence of bacteremia in different platelet count stratifications of the patient with acute cholangitis (Figure 3). And found that a total of 174 patients with platelet count $>100 \times 10^9$ /L, of which 62 patients developed bacteremia (35.63%). There were 70 patients with platelet count between 50×10^9 /L and 100×10^9 /L ($50 \times 10^9 <$ PLT$\leq 100 \times 10^9$ /L), and bacteremia occurred in 50 patients of these patients (71.43%). In addition to these, the number of patients with platelet count $\leq 50 \times 10^9$ /L was 41 and 26 patients suffered from bacteremia (63.41%). Compared with patients with platelet count $> 100 \times 10^9$ /L the proportion of patients with

Table I. Comparison of baseline and laboratory characteristics between bacteremia and non-bacteremia group in acute cholangitis.

Characteristics	Total (n = 285)	Bacteremia group (n = 138)	Non-Bacteremia group (n = 147)	*P*
Age, years	70.00(55.00, 78.00)	70.00(53.00, 78.00)	71.00(58.00, 78.00)	0.880 ^{U}
Male, n(%)	143(55.43%)	70(50.72%)	73(49.66%)	0.857 $^{\chi 2}$
Co-morbidities/past medical history				
Cardiovascular disease, n (%)	84(29.47%)	41(29.71%)	43(29.25%)	0.932 $^{\chi 2}$
Chronic pulmonary disease, n (%)	21(7.37%)	11(7.97%)	10(6.80%)	0.706 $^{\chi 2}$
History of malignancies, n (%)	22(7.72%)	11(7.97%)	11(7.48%)	0.877 $^{\chi 2}$
Diabetes mellitus, n (%)	44(15.44%)	15(10.87%)	29(19.73%)	0.039 $^{\chi 2}$
Chronic liver disease, n (%)	19(6.67%)	9(6.52%)	10(6.80%)	0.924 $^{\chi 2}$
Chronic renal insufciency, n (%)	8(2.81%)	2(1.45%)	6(4.08%)	0.179 $^{\chi 2}$
Neurologic disorder, n (%)	15(5.26%)	6(4.35%)	9(6.12%)	0.503 $^{\chi 2}$
Clinical sign				
Fever, n(%)	178(62.46%)	96(69.57%)	82(55.78%)	0.016 $^{\chi 2}$
Abdominal pain, n(%)	264(92.63%)	127 (92.03%)	137(93.20%)	0.706 $^{\chi 2}$
Jaundice, n(%)	222(77.89%)	116(84.06%)	106(72.11%)	0.015 $^{\chi 2}$
Lethargy or Mental confusion, n(%)	50(17.54%)	34(24.64%)	16(10.88%)	0.002 $^{\chi 2}$
Shock, n(%)	62(21.75%)	41(29.71%)	21(14.29%)	<0.001 $^{\chi 2}$
Cause of cholangitis				
Bile stones, n(%)	268(94.04%)	126(91.30%)	142(96.60%)	0.059 $^{\chi 2}$
Tumor, n(%)	15(5.26%)	12(8.70%)	3(2.04%)	0.012 $^{\chi 2}$
Biliary tract drainage				
ERCP, n (%)	144(%)	72(52.17%)	72(48.98%)	0.846 $^{\chi 2}$
Choledochotomy and T-tube drainage, n (%)	141(%)	66(47.83%)	75(51.02%)	0.846 $^{\chi 2}$
Laboratory data				
White blood cell count, ×10^9 /L,RV: 3.50–9.50	11.36(8.40, 16.48)	12.34(8.95, 17.60)	10.63(8.01, 15.70)	0.106 ^{U}
Absolute neutrophil count, ×10^9 /L,RV: 1.80–6.30	10.08(7.38, 14.90)	10.80(8.08, 15.8925)	9.11(7.05, 14.37)	0.064 ^{U}
Neutrophil percentage, %,RV: 40.0–75.0	90.6(85.30, 93.60)	91.70(87.00, 94.20)	89.60(84.20, 92.90)	0.012 ^{U}
Absolute lymphocyte count, ×10^9 /L, RV: 1.10–3.20	0.63(0.41, 0.92)	0.59(0.37, 0.785)	0.65(0.43, 1.03)	0.045 ^{U}
Lymphocyte percentage, %,RV: 20.0–50.0	4.90(3.00, 8.20)	4.10(2.50, 6.75)	6.00(3.40, 8.70)	0.002 ^{U}
Absolute monocyte count, ×10^9 /L, RV: 0.10–0.60	0.47(0.26, 0.76)	0.455(0.24, 0.83)	0.49(0.28, 0.71)	0.998 ^{U}
Monocyte percentage, %,RV: 3.0–10.0	4.10(2.35, 5.75)	3.85(2.18, 5.50)	4.20(2.80, 6.20)	0.288 ^{U}
Procalcitonin, mmol/L, RV: 0.00–0.05	6.32(1.83, 30.79)	12.37(2.58, 56.88)	4.14(0.82, 20.76)	0.001 ^{U}
Total bilirubin, μmol/L, RV: 3.4–20.5	89.5(43.65, 142.90)	90.45(54.05, 144.4)	89.50(36.70, 141.6)	0.265 ^{U}
Direct bilirubin, μmol/L, RV: 0.0–6.8	67.60(29.20, 108.80)	71.00(35.23, 108.20)	65.20(23.60, 110.50)	0.404 ^{U}
ALT, U/L, RV: 13–69	128.00(62.00, 239.00)	137.50(69.00, 299.50)	111.00(60.00, 211.00)	0.028 ^{U}
AST, U/L, RV: 15–46	127.00(62.50, 244.50)	149.00(79.25, 286.00)	105.00(49.00, 199.00)	0.001 ^{U}
BUN, mmol/L, RV: 3.1–8.0	5.80(4.10, 7.90)	5.80(4.40, 8.35)	5.60(4.00, 7.80)	0.349 ^{U}
Creatinine, μmol/L, RV: 57–97	69.00 (57.00, 95.00)	69.00 (57.00 109.00)	68.00(57.00, 90.00)	0.370 ^{U}
INR, RV: 0.8–1.2	1.13(1.03, 1.32)	1.17(1.03, 1.36)	1.10(1.03, 1.25)	0.037 ^{U}
Child-Pugh-score	6(5, 7)	6(5, 7.25)	6(5, 7)	0.006 ^{U}
Child-Pugh Classification(A, B, C), n	174, 108, 3	74, 62, 2	100, 46, 1	—
APACHE II Score	11.00(9.00, 16.00)	12.50(9.00, 19.00)	11.00(9.00, 15.00)	0.004 ^{U}
SOFA Score	4(2, 7.25)	12(9, 13.5)	6(3, 12)	<0.001 ^{U}
TG18 Severity assessment				
Grade I (mild)	42(14.74%)	10(7.25%)	32(21.77%)	0.001 $^{\chi 2}$
Grade II (moderate)	128(44.91%)	57(41.30%)	71(48.30%)	0.235 $^{\chi 2}$
Grade III (severe)	115(40.35%)	71(51.45%)	44(29.93%)	<0.001 $^{\chi 2}$
Mortality(%)	25(8.77%)	17(12.32%)	8(5.44%)	0.040 $^{\chi 2}$

RV: Reference Values. APACHE II Score: Acute Physiology and Chronic Health Evaluation II Score. SOFA Score:Sequential Organ Failure Assessment Score. TG18: Tokyo guideline 2018. ERCP:.endoscopic retrograde cholangiopancreatology. AST: glutamic-oxaloacetic transaminase. ALT: glutamic-pyruvic transaminase. BUN: blood urea nitrogen. INR: international normalized ratio.

$\chi 2$: Chi-square analysis was used for the comparison between bacteremia and non-bacteremia group. *t*: t-test was used for comparison between bacteremia and non-bacteremia group. U: Mann-Whitney U test was used for comparison between bacteremia and non-bacteremia group.

50×10^9 /L < platelet count $\leq 100 \times 10^9$ /L and those with platelet count $\leq 50 \times 10^9$ /L was significantly higher in bacteremia.

Predictive value of platelet count and plateletcrit for bacteremia in acute cholangitis

ROC curve analysis was applied to assess the predictive value of platelet count and plateletcrit for bacteremia in patients with acute cholangitis (Figure 4a). The results of the ROC curve analysis showed that the platelet count cutoff value was 95.5 × 10^9, the sensitivity was 77.6%, and the specificity was 55.1% (AUC = 0.649), and plateletcrit cutoff value was 0.115, the sensitivity was 76.9%, and the specificity was 54.3% (AUC = 0.655). It can be seen that a certain predictive value of platelet count and plateletcrit for the occurrence of bacteremia in patients with acute cholangitis. Furthermore, ROC curve analysis was used to assess the predictive value of platelet count and plateletcrit for Mix bacteria-Bacteremia, gram-negative bacilli-Bacteremia, gram-positive coccus-Bacteremia in acute cholangitis similarly (Figure 4b,c,d). ROC

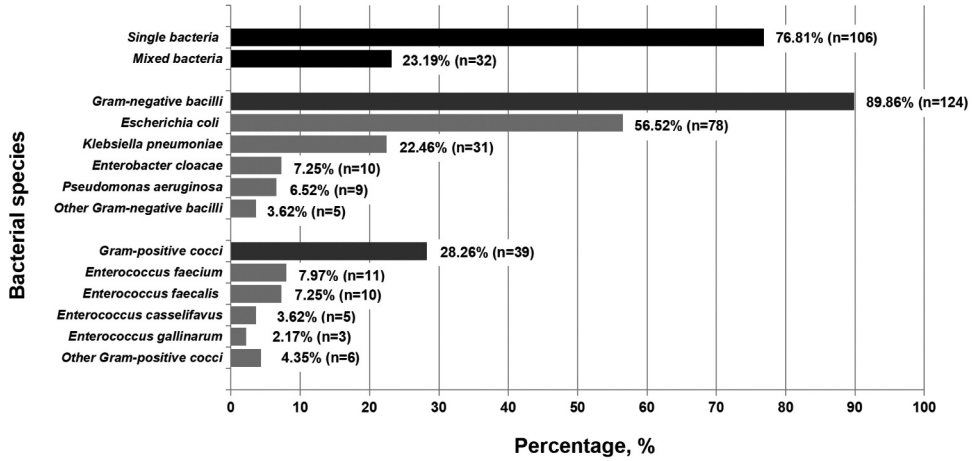


Figure 2. Microbiological distribution of bacteremia in acute cholangitis. Bacterial species were identified by blood culture in 138 patients with bacteremia and classified as gram-negative bacilli and gram-positive cocci. One patient identified only one type of bacteria was defined as Single bacterial, and more than one types of bacteria were defined as Mixed bacteria.

Table II. Comparison of platelet index between bacteremia and non-bacteremia group in acute cholangitis.

Variables	Total (n = 285)	Bacteremia group (n = 138)	NO-Bacteremia group (n = 147)	*P*
Thrombocytopenia, n(%)	111(38.95%)	76(55.07%)	35(23.81%)	<0.001 $^{\chi 2}$
Platelet count, ×10^9 /L	201.50(125.00, 70.00)	84.50(60.00, 180.00)	162.00(102.00,225.00)	<0.001 ^{U}
Mean platelet volume, fi	11.47 ± 1.29	11.43 ± 1.35	11.51 ± 1.23	0.585 ^{t}
Platelet distribution width(SD), fi	14.50(12.45, 17.10)	14.70(12.20, 17.50)	14.50(12.60,16.90)	0.734 ^{U}
Plateletcrit, %	0.15 (0.08, 0.23)	0.10(0.07, 0.21)	0.18(0.12, 0.25)	<0.001 ^{U}
Platelet count to Plateletcrit ratio	865.21 (800.00, 944.01)	858.57(800.00, 938.13)	872.00(805.12, 952.94)	0.434 ^{U}
Platelet large cell ratio, %	36.34 ± 9.79	36.10 ± 9.80	36.56 ± 9.81	0.690 ^{t}

t: t-test was used for comparison between bacteremia and non-bacteremia group.
U: Mann-Whitney U test was used for comparison between bacteremia and non-bacteremia group.
$\chi 2$: Chi-square analysis was used for the comparison between bacteremia and non-bacteremia group.

Table III. Risk factors of bacteremia in acute cholangitis.

Factors	Exp(B)	95% CI	B	*P*
Thrombocytopenia	5.077	1.921–13.416	1.652	0.001
Platelet count	1.019	1.002–1.036	0.019	0.027
Plateletcrit	0.000	0.000–0.895	−14.98	0.048
Platelet count to Plateletcrit ratio	1.000	0.999–1.000	0.000	0.193
Neutrophil percentage	0.972	0.883–1.071	−0.028	0.572
Absolute lymphocyte count	0.856	0.344–2.131	−0.156	0.738
Lymphocyte percentage	0.955	0.824–1.108	−0.046	0.546
Procalcitonin	1.012	1.002–1.021	0.011	0.020
APACHE II score	0.985	0.932–1.042	−0.015	0.606

APACHE II Score: Acute Physiology and Chronic Health Evaluation II Score.

analysis mirrored a strong clinical predictive power of platelet count and plateletcrit to Mix bacteria-Bacteremia. The platelet count cutoff value was 82.5 × 10^9/L, the sensitivity was 71.5%, and the specificity was 68.9% (AUC = 0.709), and plateletcrit cutoff value was 0.115, the sensitivity was 66.0%, and the specificity was 71.9% (AUC = 0.705).

Discussion

In this retrospective observational study, we completed an investigation of the association between bacteremia and platelet index in 285 patients with acute cholangitis. The results showed that the incidence of bacteremia in acute cholangitis is high, especially in grade III patients, which can reach half the proportion. And Platelet count and plateletcrit have a certain value for early prediction of bacteremia in patients with acute cholangitis. Currently, there have been few reports of platelet index predicted bacteremia in patients with acute cholangitis. The current study provides clinical evidence for platelets could predict bacteremia. In cholangitis, a sustained increase in bile duct pressure causes bacteria to enter the bloodstream and lead to bacteremia or sepsis. In our investigation, the incidence of bacteremia in patients with acute cholangitis was 48.42%, which is similar to the results reported in patients with

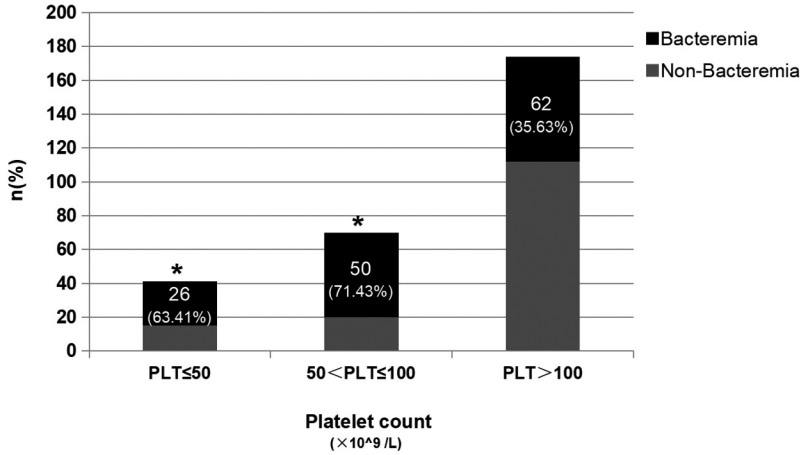


Figure 3. The incidence of bacteremia in acute cholangitis with different platelet count stratification. Patients with acute cholangitis were classified according to platelet count. Using chi-square test to compare the incidence of bacteremia in patients with platelet count $< 50 \times 10^9$ /L, $50 \times 10^9 <$ platelet count$\leq 100 \times 10^9$ /L, and platelet count$> 100 \times 10^9$ /L, respectively. PLT: Platelet count. * there is a diference compared with the patients with platelet count$> 100 \times 10^9$ /L.

acute cholangitis in which the positive rate of blood culture was between 21% and 71% [13]. All of the above results suggest that the incidence of bacteremia in acute cholangitis is extremely high. In our study, the patients in bacteremia group had a higher APACHE II score than that in non-bacteremia group, the rate of bacteremia in grade III (severe) patients was as high as 51.45%, and the mortality rate was as high as 12.32%. This shows that the appearance of bacteremia significantly increases the severity and mortality of acute cholangitis, Therefore, there are important clinical implications for early identification of bacteremia.

Enterobacter is the most common pathogen of acute cholangitis. Enterococcus is another important pathogen which should be to consider in patients with acute cholangitis [14]. Our previous study investigated the distribution characteristics of pathogenic bacteria in patients with acute cholangitis [15], and this study focused on investigating the distribution of pathogenic bacteria in the blood of patients with bacteremia in acute cholangitis. The survey results showed that bacteremia of the patients in acute cholangitis were dominated by a single bacterial infection. Gram-negative bacilli was identified in 89.86%, which dominated by Escherichia coli, and Gram-positive cocci was identified in 28.26%, which dominated by Enterococcus faecium and Enterococcus faecalis. The distribution of pathogenic bacteria in blood was similar to that in bile. It was relatively rare that bacteremia caused by other bacteria, except for Enterobacteriaceae and Enterococcus. Studies have shown that there were 1.1% to 3.1% Pseudomonas aeruginosa, less than 1% Staphylococcus aureus, and 1.1% bacteroides fragilis among blood culture isolates [16]. Similarly, the results of this study also support this view.

To the best of our knowledge, this is the first study to assess the predictive value of platelets for bacteremia in patients with acute cholangitis.

Severe cholangitis is often complicated by DIC (reduced platelet count) [4]. Thrombocytopenia occurred in 38.95% of patients with bacteremia in acute cholangitis and severe thrombocytopenia in 14.39% of them in our study. Platelet parameters were analyzed as prognostic markers in sepsis in most studies, and only few studies have demonstrated MPV/platelet count as a diagnostic marker for bacteremia [12,17,18].

Infection is an important factor causing thrombocytopenia, but the mechanism is still unclear, it may be that patients with bacteremia induce platelet activation and aggregation in vivo [5–8]. There are still a large number of infected patients whose platelets are not reduced. The pathophysiological mechanism of biliary tract infection is different from that of other systemic infections, involving factors such as biliary tract, liver, and intestine. The mechanism of thrombocytopenia in patients with cholangitis is different from that of other systemic infections. However, there is no relevant research on the mechanism of cholangitis and thrombocytopenia.

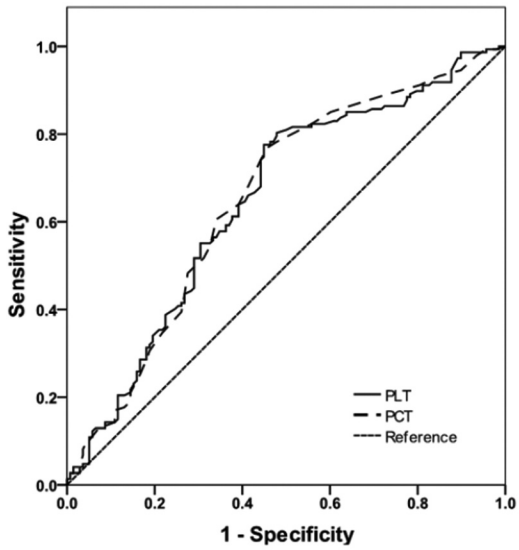
Our study also analyzed the predictive value of platelet count and plateletcrit for Mix bacteria-Bacteremia, gram-negative bacilli-Bacteremia, gram-positive coccus-Bacteremia in patients with acute cholangitis. The findings revealed platelet count and plateletcrit had the strongest prediction ability for Mix bacteria-Bacteremia, the AUC was 0.709 and 0.705, respectively. However, there was no difference in the predictive value of platelet count and plateletcrit for gram-negative bacilli-Bacteremia and gram-positive coccus-Bacteremia. The effect of different types of pathogens on platelets may be various. It has been verified that platelets have a strong protective effect on Gram-negative bacteremia including Escherichia coli, Klebsiella pneumoniae, and Bacillus [19]. Escherichia coli lipopolysaccharide can bind to platelet TLR4 receptor [20]. Many bacterias isolated from patients with gram-positive bacteremia can induce the activation and aggregation of platelet and neutrophils, and platelet-neutrophil complex formation. Peptidoglycan, a major component of Gram-positive bacterial cell walls, has been proved that could induce mitochondrial depolarization and caspase 3 activation, and lead to platelet apoptosis [21]. Johansson added Gram-positive bacterial isolates from 38 patients with bacterial infections into the blood of the same patient, and found that Staphylococcus aureus, Streptococcus hemolyticus, and Enterococcus faecalis all induced platelet aggregation in the host, while pneumococcus did not [22]. Thrombocytopenia is associated with poor prognosis in patients with Staphylococcus aureus bacteremia [23]. Our study admittedly has certain limitations. This is a single-center retrospective observational study, and we excluded patients who did not conducted blood cultures on admission, which may cause a certain degree of selective bias. Additionally, we just analyzed platelet indices at admission, and no dynamic follow-up was performed. Due to this, it is necessary to design a prospective study and to monitor the platelet indices dynamically to validate the findings.

Conclusions

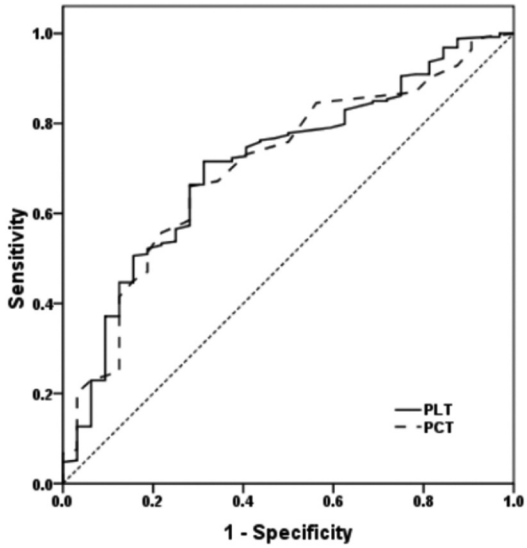
The results of this study suggest that bacteremia has a high morbidity in patients with acute cholangitis. Platelet count and plateletcrit have a certain value for early prediction of bacteremia in patients with acute cholangitis.

Authorship

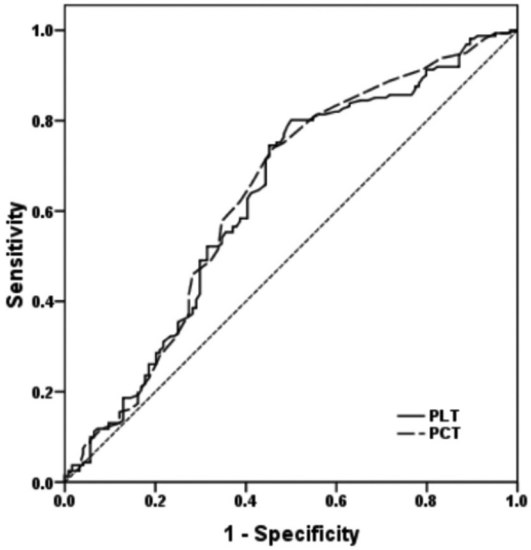
XiaoYing Chen contributed to the conception of the study, performed the data analysis, and wrote the manuscript. Shijing TIAN



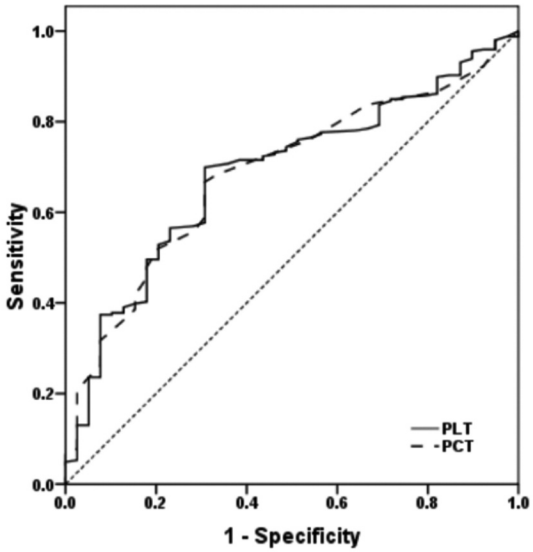
a. ROC curve of Bacteremia



b. ROC curve of Mix bacteria-Bacteremia



c. ROC curve of G- bacilli-Bacteremia



d. ROC curve of G+ coccus-Bacteremia

		AUC	95% CI	Cut-off	p
a. Bacteremia	PLT	0.649	0.585-0.713	95.5	<0.001
	PCT	0.655	0.590-0.719	0.115	<0.001
b. Mix bacteria—Bacteremia	PLT	0.709	0.617-0.801	82.5	<0.001
	PCT	0.705	0.614-0.796	0.115	<0.001
c. G- bacilli—Bacteremia	PLT	0.628	0.561-0.695	82.5	<0.001
	PCT	0.637	0.570-0.703	0.115	<0.001
d. G+ coccus—Bacteremia	PLT	0.628	0.561-0.695	82.5	<0.001
	PCT	0.637	0.570-0.703	0.115	<0.001

Figure 4. ROC curve analysis of platelet count and plateletcrit for bacteremia in acute cholangitis patients. a. ROC analysis for all bacteremia in acute cholangitis. b. Mix bacteria-Bacteremia was defined as more than one types of bacteria in blood. c. Gram negative bacilli-Bacteremia was defined as patients with Gram negative bacilli in blood. d. Gram positive coccus-Bacteremia was defined as patients with Gram positive coccus in blood. ROC: Receiver Operating Characteristic. AUC: area under the curve. CI: Confidence Interval. PLT: Platelet count. PCT: Plateletcrit. G- bacilli: gram negative bacilli. G+ coccus: gram positive coccus.

performed data collection. Fu WEI wrote the manuscript. Dan ZHANG and Shijing TIAN contributed significantly to analysis and manuscript preparation. Dan ZHANG helped perform the analysis with constructive discussions. All authors read and approved the final manuscript.

Availability of data and materials

The clinical data for all patients were collected by the authors and are truly available.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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Informed consent

The Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University approved our study (No. 2022-K132). As this was a retrospective study, the informed consent was waived by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University

Ethical approval and human rights statement

The observational study was approved by an hospital ethical committees and there were no human rights violations.

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