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Original Article

The relationship between platelet parameters and bacterial types in patients with bacteremia: A retrospective observational study

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Abstract

Objective: To analyze the relationship between platelet parameters and bacterial types in patients with bacteremia.
Methodology: Data from 265 patients with positive blood bacterial cultures were collected. Clinical parameters and procalcitonin (PCT) were recorded.
Results: In 265 patients with bacteremia, gram-negative (G-) bacteria accounted for 56% of cases, and gram-positive (G +) bacteria accounted for 44% of cases. In patients with bacteremia, white blood cell counts (WBC), neutrophil counts (NEUT), the percentage of neutrophils (NEUT%), and PCT were increased, and lymphocyte counts (LYM) and the percentage of lymphocytes (LYM%) were decreased. The differences in plateletcrit values, NEUT%, LYM%, and PCT between the G- and the G + bacteria group were significantly different. The cutoff values of PCT, platelet, plateletcrit, and NEUT% were 1.31 ng/mL, 211 × 10^9/L, 0.205%, and 87.41%, respectively. The incidence of thrombocytopenia was 12%. There was no significant difference in WBC, NEUT%, PCT, platelet, platelet nadir, and days of thrombocytopenia between the G- and the G + bacteria among patients with thrombocytopenia.
Conclusions: Platelet, plateletcrit, NEUT%, and PCT are helpful for the early identification of G- and G + bacteria. The combination of PCT and hemogram parameters is more conducive to the early differential diagnosis of bacterial classification.

Key words: bacteremia; platelets; platelet parameters; types of bacteria.

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Introduction

Bloodstream infection (BSI) constitutes a main cause of in-hospital morbidity and mortality [1], with an overall incidence in adult hospitalized patients of approximately 6.5‰ (93.1% of the cases were bacteremia and 6.9% were fungemia) [2]. Without timely and effective treatment, BSI is likely to develop into sepsis, with a mortality rate of up to 30% [3].

Bacterial culture is the gold standard for the diagnosis of bacteremia, but it takes at least 48-72 hours for traditional bacterial culture methods to provide final species identification [4]. Once blood is collected for culture, empirical and broad-spectrum antimicrobial therapy is initiated in patients suspected of having BSI and is continued until the etiological pathogen is identified. As a result, up to 40% of patients with BSI receive inappropriate or even incorrect therapy during the empirical treatment period [5], leading to drug toxicity, antibiotic resistance, and increased healthcare costs [6]. Therefore, it has been a clinical challenge to rapidly identify bloodstream pathogens and administer appropriate antibiotics based on sensitivity tests as early as possible to improve the outcome of patients with BSI.

Clinically, inflammatory indicators, such as procalcitonin (PCT) and white blood cell counts (WBC), are commonly used to determine the presence of a bacterial infection. PCT is considered a biomarker of the host response to bacterial infection and is correlated with the severity of infection [7]. High levels of C-reactive protein (CRP) have also been reported to aid in the detection of severe bacterial infection and

latent bacteremia [8]. WBCs are part of the innate immune response and are one of the fastest cells in the body to respond to infection and inflammation. Platelets are identified as first-line indicators in detecting and acting on diverse pathogens and responding to damage [9]. The interaction between platelets and bacteria not only plays an important role in the pathophysiological response caused by bacterial infection but also affects platelets and platelet-related parameters, such as platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit, and platelet-large cell ratio (P-LCR). MPV and PDW are morphometric indexes that reflect the size distribution of the peripheral platelet population and are surrogate markers of platelet activation [10]. Plateletcrit is the ratio of total platelets in the blood (plateletcrit = PLT × MPV). P-LCR is an indicator of the percentage of platelets larger than 12 fl in the circulating pool and is a good monitoring tool for platelet activity [11].

To date, most reports of thrombocytopenia due to infection are focused on severe infections or sepsis, but the relationship between platelets or platelet parameters and bacterial type in patients with bacteremia has rarely been reported. These hematological parameters are commonly used, timely, convenient, and easily available in clinical practice. Thus, we sought to systematically investigate the relationship between platelets or even platelet-related parameters (MPV, PDW, plateletcrit, and P-LCR) and bacterial type in patients with bacteremia in this retrospective observational study, which is expected to aid in the initial clinical identification of bacterial species and treatment in the early stage of infection.

Methodology

Study design

In this retrospective study, we collected data from 479 patients with positive blood bacterial cultures from January 2020 to November 2020 at Sun Yat-sen Memorial Hospital of Sun Yat-sen University (Guangzhou, China). According to the following exclusion criteria, 265 patients with bacteremia were screened in this study.

The exclusion criteria were as follows: (1) confirmed diagnosis of blood disorders, including leukemia, myelodysplastic syndromes, primary thrombocythemia, and immune thrombocytopenia; (2) confirmed diagnosis of autoimmune disorders, such as systemic lupus erythematosus or rheumatoid arthritis; (3) decompensated cirrhosis; (4) bone marrow suppression after radiotherapy or chemotherapy for tumors or without bone marrow suppression after recent radiotherapy or chemotherapy; (5) severe bleeding during infection; (6) age less than 18 years; (7) incomplete clinical information, such as platelet-related parameters; (8) clinical conditions, such as hepatic or renal failure or disseminated intravascular coagulation (DIC), at the same time as the blood culture testing; (9) patients (considered contaminated) with blood culture results of coagulase-negative staphylococci but without elevation of leukocytes, PCT, CRP and other indicators of inflammation; (10) recent use of platelet-affecting drugs, such as anticoagulants, antiplatelet drugs, linezolid, depakine and quinine; (11) multiple blood cultures infected with different kinds of pathogen; (12) patients with combined viral infections, such as the COVID-19.

This retrospective study was approved by the Institutional Review Board/Independent Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and informed consent was not required since all data were anonymous. Patient privacy and data confidentiality were maintained in accordance with the Declaration of Helsinki.

Data collection

Data included age, sex, underlying disease, diagnosis, days of hospitalization, blood culture results, site of infection, complete blood counts (including PLT count, plateletcrit, MPV, PDW, P-LCR, WBC count, NEUT, neutrophil% (NEUT%), lymphocyte count (LYM), and lymphocyte% (LYM%)), CRP, PCT, serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), serum ferritin (SF), interleukin (IL)2 receptor, IL6, IL8, IL10, IL1β, tumor necrosis factor α (TNF-α), coagulation indicators (prothrombin time, fibrinogen, and D-dimer), and liver and kidney function parameters (total bilirubin and creatinine). All of the above blood tests were drawn at the same time as the patient's fever was greater than 38 degrees Celsius, but only a small percentage of these patients had blood drawn at the same time as their fever to check for "interleukin (IL)2 receptor, IL6, IL8, IL10, IL1β, tumor necrosis factor alpha (TNF-α)", which was done to help further understand the patient's inflammation. Blood tests were taken before antibiotics were administered.

Definition

(1) Bacteremia was defined as the presence of a positive result (isolation of a single microorganism) from a culture from the peripheral blood [12].

(2) Thrombocytopenia was defined as a platelet count $< 100 \times 10^9$/L.

Table 1. Laboratory characteristics of 479 patients with bacteremia.

Variable	Bacteremia (number)			Overall average	G-	G+	*p*	normal range
	Total	G -	G +					
PCT (ng/mL)	424	233	191	1.9 (0.3, 10.1)	3.2 (0.4, 21.4)	0.7 (0.2, 5.6)	< 0.001	0-0.1
CRP (mg/L)	271	157	114	67.5 (14.5, 140.6)	76.6 (22.8, 144.5)	50.1 (9.3, 140.4)	0.053	0-5
SAA (mg/L)	167	99	68	214.7 (81.6, 311.0)	237.3 (98.1, 315.2)	207.0 (45.8, 306.1)	0.301	0-10
ESR (mm/h)	35	20	15	75.6 ± 41.3	75.8 ± 41.9	75.4 ± 41.9	0.981	0-20
SF (ng/L)	81	53	28	548.9 (357.2, 1165.5)	548.9 (347.9, 1173.7)	525.7 (380.9, 1133.6)	0.736	20-300
IL-2R (U/mL)	48	28	20	1152.0 (611.8, 2384.3)	1132.0 (766.3, 2868.3)	1566.2 ± 1416.8	0.660	223-710
IL6 (pg/mL)	48	28	20	48.4 (17.1, 365.8)	41.9 (16.8, 295.3)	99.1 (17.1, 387.8)	0.503	0-5.9
IL8 (pg/mL)	48	28	20	144.5 (51.8, 304.3)	147.0 (60.8, 200.8)	127.0 (37.4, 700.8)	0.933	0-62
IL10 (pg/mL)	48	28	20	12.0 (5.7, 53.3)	12.4 (6.2, 53.3)	12.0 (5.5, 88.2)	0.761	0-9.1
IL1β (pg/mL)	48	28	20	6.5 (5.0, 8.4)	6.9 (5.0, 8.7)	5.0 (5.0, 8.0)	0.204	0-5
TNF-α (pg/mL)	48	28	20	22.5 (10.9, 29.0)	22.55 (10.9, 29.0)	21.0 (10.4, 28.3)	0.802	0-8.1

p: Comparison of differences between G - bacteria and G + bacteria.

(3) DIC is a syndrome characterized by the systemic activation of blood coagulation, which generates intravascular thrombin and fibrin, resulting in the thrombosis of small- to medium-sized vessels and ultimately organ dysfunction and severe bleeding [13]. According to the ISTH Diagnostic Scoring System for overt DIC, overt DIC can be diagnosed with a total score ≥ 5 [14].

(4) Liver dysfunction was defined as S-bilirubin > 45 μmol/L in patients without liver disease, acute cholecystitis, or cholangitis [15].

(5) Renal dysfunction was defined as an S-creatinine increase > 45 μmol/L in patients without chronic renal disease [15].

(6) Major bleeding was defined as any overt bleeding with a decrease in hemoglobin concentration by more than 20 g/L [16].

(7) In this study, *Staphylococcus epidermis*, *Staphylococcus capitis*, *Staphylococcus hominis*, and *Staphylococcus hemolyticus* were collectively referred to as coagulase-negative staphylococcus.

Statistical analyses

Statistical analyses were performed using SPSS version 25. Continuous variables with a normal distribution are expressed as the mean ± standard deviation and were compared using Student's t test or analysis of variance. Continuous variables with abnormal distributions are expressed as interquartile ranges (25th, 75th percentile) and were compared with the Mann–Whitney U test. Categorical variables are expressed as percentages and were compared with chi-squared tests. Binary logistic regression analysis was conducted to determine the strength of the association between observation indicators (there were significant differences between the Gram-negative (G-) bacteria and Gram-positive (G +) bacteria groups) and bacterial species. Moreover, receiver operating characteristic (ROC) curves were constructed to further analyze the diagnostic efficacy and determine the early predictive value. A p value < 0.05 was considered to indicate statistical significance. A p value of $0.05 < p < 0.1$ was considered marginally significant [17,18].

Results

Patients' demographic and clinical characteristics

Laboratory characteristics of the 265 patients as shown in Table 1. In the 265 cases of bacteremia, G- bacteria accounted for 56% (N = 149) of the cases, and G + bacteria accounted for 44% (N = 116) of the cases. The average age of the 265 patients with bacteremia was 62 years old. A total of 42.26% of patients were < 60 years old, and 57.74% of patients were ≥ 60 years old. There were 153 males (57.74%) and 112 females (42.26%). There was no difference in age or sex between the G- BSI and G + BSI groups. In terms of the categories of strains detected from blood cultures, the G- BSI were predominantly *Escherichia coli* (68, 45.6%) and *Klebsiella pneumoniae* (31, 20.8%); the G + BSI were predominantly *Staphylococcus epidermidis* (19, 16.4%), *Staphylococcus aureus* (18, 15.5%) and *Staphylococcus capitis* (18, 15.5%).

Table 2. Demographic and clinical characteristics of 265 patients.

Variable	Total (N = 265)	G - (N = 149)	G + (N = 116)	*p*
Age (years)	62	62 (52,71)	64 (50,73)	0.869
Sex, male, *N* (%)	153	85 (57%)	68 (58.6%)	0.797
Organism, *N* (%)		*Escherichia coli,* 68 (45.6%)	*Staphylococcus epidermidis,* 19 (16.4%)	
		Klebsiella pneumoniae, 31 (20.8%)	*Staphylococcus aureus,* 18 (15.5%)	
		Pseudomonas aeruginosa, 7 (4.7%)	*Staphylococcus capitis,* 18 (15.5%)	
		Enterobacter cloacae, 6 (4.0%)	*staphylococcus hominis*, 14 (12.1%)	
		Acinetobacter baumannii, 5 (3.4%)	*Staphylococcus haemolyticus,* 10 (8.6%)	
		bacteroides fragilis, 4 (2.7%)	*Enterococcus faecalis,* 8 (6.9%)	

Table 3. Laboratory characteristics of 265 patients with bacteremia.

Characteristic	Bacteremia	G -	G +	*p*	normal range
WBC (10^9/L)	11.83 (7.96, 16.85)	11.62 (8.07, 17.03)	12.26 (7.69, 16.28)	0.839	3.5-9.5
NEUTs (10^9/L)	10.39 (6.73, 14.77)	—	—	—	1.8-6.3
NEUT%	88.12% (80.9%, 92.24%)	88.83% (83.80%, 93.18%)	86.04% (79.49%, 90.49%)	0.002	40-75
LYM (10^9/L)	0.75 (0.45, 1.14)	—	—	—	1.1-3.2
LYM%	6.45% (3.79%, 10.48%)	5.96% (3.03%, 9.79%)	7.27% (4.26%, 11.69%)	0.042	20%-50%
PLT (10^9/L)	202 (140, 294)	185 (132, 278)	225 (146, 306)	0.053	125-350
Plateletcrit (%)	0.22 (0.15, 0.30)	0.19 (0.14, 0.28)	0.23 (0.16, 0.33)	0.010	0.16-0.4
MPV (fL)	10.6 (9.8, 11.5)	10.6 (9.8, 11.4)	10.7 (9.7, 11.6)	0.461	6-13
PDW (fL)	12.0 (10.3, 13.9)	12.0 (10.3, 13.8)	11.9 (10.2, 14.1)	0.954	9.8-16
P-LCR (%)	22.2 (29.4, 36.8)	29.2 (22.2, 36.9)	29.6 (22.1, 37.5)	0.560	13-43
PCT (ng/mL)	1.85 (0.23, 9.09)	2.65 (0.33, 20.11)	0.70 (0.16, 4.49)	0.010	0-0.1

Patients' laboratory characteristics

As shown in Table 2, the values of WBC count, NEUT, NEUT%, and PCT were higher than the normal values of the respective index, while the values of LYM and LYM% were decreased. The PLT, plateletcrit, and LYM% values were marginally significantly or significantly lower in the G- BSI group than in the G + BSI group (p = 0.053; p = 0.010; p = 0.042, respectively). The NEUT% and PCT values were significantly higher in the G- BSI group than in the G + BSI group (p = 0.002; p = 0.01, respectively).

Analysis of factors associated with G- BSI

Binary logistic regression analysis was used to identify predictors for early recognition of G-BSI (Table 3). Logistic regression of the variables with marginal or significant differences in the binary logistic regression analysis revealed that the independent predictors of G-BSI were NEUT%, PLT, plateletcrit, and PCT.

Laboratory parameters to predict G- BSI

To further explore the predictive role of these indicators (NEUT%, PLT, plateletcrit, and PCT) in G- or G + BSI, we constructed ROC curves (see Table 4). When the cutoff value of NEUT% was 87.41%, that of platelet count was 211 × 10^9/L, that of plateletcrit was 0.205%, and that of PCT was 1.31 ng/mL, NEUT%, PLT, plateletcrit, and PCT showed moderate ability to distinguish between patients with G- BSI, with PCT having the highest area under the curve (AUC) (0.624), sensitivity (0.631), and specificity (0.595). To further improve the diagnostic efficiency for early G-BSI, we constructed multifactor ROC curves. The highest AUC (0.656), sensitivity (0.539), and specificity (0.748) were achieved when the four indicators (NEUT%, PLT, plateletcrit, and PCT) simultaneously exceeded the cutoff level (Table 4).

Laboratory examination of common bacterial species

The most common species of bacteria were *Escherichia coli*, *CNS,* and *Klebsiella pneumoniae*. Among the groups of the common bacterial species, WBC, NEUT%, LYM%, plateletcrit, MPV, P-LCR, and PCT values were significantly different ($p < 0.05$). Moreover, CRP was marginally significantly different between the G + and G- groups. In terms of the categories of the strains detected from blood cultures,

Table 4. Explore predictors for early discrimination of G- BSI by binary logistic regression analysis.

Characteristic	*p*	OR	95%CI
NEUT%	0.053	1.024	(1, 1.05)
LYM%	0.526	1.009	(0.98, 1.04)
PLT (10^9/L)	0.059	1.002	(1, 1.004)
Plateletcrit (%)	0.022	9.700	(1.39, 67.98)
PCT (ng/mL)	0.059	1.010	(1, 1.021)

Table 5. Receiver operating characteristic (ROC) curve for predicting G- BSI.

Parameters	AUC	*p*	Sensitivity	Specificity	Cut-off
NEUT%	0.608	0.002	0.624	0.595	87.41%
PLT	0.569	0.053	0.560	0.604	211
Plateletcrit	0.592	0.010	0.621	0.557	0.21
PCT	0.624	0.001	0.631	0.595	1.31
NEUT% + PLT	0.608	< 0.001	0.577	0.612	—
NEUT% + Plateletcrit	0.623	< 0.001	0.638	0.595	—
NEUT% + PCT	0.634	< 0.001	0.703	0.560	—
PLT + Plateletcrit	0.613	< 0.001	0.591	0.603	—
PLT + PCT	0.603	< 0.001	0.333	0.865	—
Plateletcrit + PCT	0.617	< 0.001	0.574	0.649	
NEUT% + PLT + Plateletcrit	0.646	< 0.001	0.631	0.621	—
NEUT% + PLT + PCT	0.625	< 0.001	0.603	0.631	—
NEUT% + Plateletcrit + PCT	0.636	< 0.001	0.525	0.739	—
PLT + Plateletcrit + PCT	0.637	< 0.001	0.560	0.649	—
NEUT% + PLT+ Plateletcrit + PCT	0.656	< 0.001	0.539	0.748	—

Table 6. Demographic and laboratory characteristics of patients with different pathogens positive blood cultures.

Parameters	The most common species of bacteria			G+	p^*	p^{**}	p^{***}
	***E. coli* (N = 68)**	**CNS (N = 61)**	***K. pneumoniae* (N = 31)**	***S. aureus* (N = 18)**			
WBC (10^9/L)	15.01 ± 7.06	10.92 (7.43, 14.8)	11.38 ± 6.15	11.92 ± 4.82	0.008	0.015	0.775
NEUT%	90.40% (86.10%, 92.90%)	84.50% (78.83%, 89.71%)	88.70% (86.59%, 94.02%)	85.86% ± 6.02%	0.000	0.994	0.229
LYM%	5.61% (3.60%, 8.10%)	8.02% (4.85%, 13.52%)	6.46% (3.16%, 8.62%)	7.10% (4.10%, 8.50%)	0.017	0.608	0.224
PLT (10^9/L)	210 ± 113	254 ± 157	194 ± 92	246 ± 109	0.058	0.515	0.849
Plateletcrit (%)	0.20 (0.14, 0.28)	0.23 (0.18, 0.35)	0.19 (0.12, 0.26)	0.25 ± 0.11	0.030	0.667	0.774
MPV (fL)	10.5 ± 1.1	11.1 ± 1.3	11.0 ± 1.4	10.3 ± 1.3	0.014	0.059	0.021
PDW (fL)	11.9 (10.1, 13.8)	12.3 (10.8, 14.8)	12.3 (10.5, 13.9)	11.3 (9.5, 12.5)	0.359	0.497	0.057
P-LCR (%)	28.7 ± 8.8	33.1 ± 10.1	32.5 ± 11.7	24.1 (19.2, 32.0)	0.031	0.077	0.022
PCT (ng/mL)	2.92 (0.38, 14.45)	0.57 (0.16, 4.22)	3.71 (0.71, 28.72)	0.70 (0.09, 2.77)	0.008	0.471	0.410

p*: Comparison of differences among *E. coli*, CNS, and *K. pneumoniae;* p**: Comparison of differences between *E. coli* and *K. pneumoniae;* p***: Comparison of differences between CNS and *S. aureus.*

the G-BSIs were predominantly *Escherichia coli* and *Klebsiella pneumoniae*. In the comparison of the two groups (*Escherichia coli* and *Klebsiella pneumoniae*), the WBC count was significantly higher in the *Escherichia coli* group ($p = 0.015$). The G + BSI were predominantly CNS and *Staphylococcus aureus*. MPV and P-LCR were significantly different between the CNS and *Staphylococcus aureus* groups (Table 5).

Incidence of thrombocytopenia in different bacterial types

The incidence of thrombocytopenia in the 265 patients with bacteremia was 12% (N = 31), with 13.4% in the G- BSI group and 9.5% in the G + BSI group. The development of thrombocytopenia in the G- BSI group predominantly occurred in patients infected with *Escherichia coli* (11.8%) and *Klebsiella pneumoniae* (19.4%), while the development of thrombocytopenia in the G + BSI group predominantly occurred in patients infected with *CNS* (9.8%) and *Staphylococcus aureus* (5.6%). In addition, there was no significant difference in the incidence of thrombocytopenia among the bacterial species groups ($p > 0.05$). The characteristics of 31 patients with bacteremia with thrombocytopenia are summarized in Table 6.

Laboratory parameters between the groups with or without thrombocytopenia

Compared to the normal values, the values of WBC, NEU%, and PCT were increased in patients with BSI with thrombocytopenia. Compared to patients with BSI without thrombocytopenia, patients with BSI with thrombocytopenia had higher values of PCT and PCT↑↑% (PCT > 0.3 ng/mL) ($p < 0.05$). The WBC, NEUT%, and PCT were not different between the G- bacteria and G + bacteria groups in patients with BSI with thrombocytopenia ($p > 0.05$) (Table 7).

The analysis of the degree of thrombocytopenia and bacterial type is shown in Table 8. There was no significant difference in PLT count, platelet nadir, or days of thrombocytopenia between the G- BSI with thrombocytopenia group and the G + BSI with thrombocytopenia group ($p > 0.05$).

Discussion

BSI is an acute systemic infection caused by the growth and multiplication of pathogenic bacteria in the blood circulation, producing toxins and other metabolites. It remains one of the most important causes of mortality. Worldwide, the rate of bloodstream infection is currently increasing [19]. In this study, we

Table 7. Clinical Characteristics of 31 patients with bacteremia with thrombocytopenia.

Parameters	Number (rate)	Antibiotic use before blood sampling
Age		
< 60 years old	11 (35.48%)	—
≥ 60 years old	20 (64.52%)	—
Gender		
Male	24 (77.42%)	—
Female	7 (22.58%)	
Basic Diseases		
Respiratory System	4 (12.90%)	0
Septic pleural effusion	1 (3.23%)	0
Lung infection	1 (3.23%)	0
Oral infections	2 (6.45%)	0
Circulation System	3 (9.68%)	0
Infective endocarditis	1 (3.23%)	0
Heart Valve Diseases	1 (3.23%)	0
Aortic arch aneurysm	1 (3.23%)	0
Digestive System	15 (48.39%)	4
Liver abscess	1 (3.23%)	1 (Use of tigecycline)
Liver Cancer	3 (9.68%)	2 (Use of tigecycline)
Acute obstructive pyogenic cholangitis	2 (6.45%)	0
Biliary tract infection	1 (3.23%)	0
Cholangitis	2 (6.45%)	0
Bile Duct Stones	2 (6.45%)	0
Bile Duct Cancer	3 (9.68%)	1 (Use of cephalosporins)
Biliary fistula after bile duct surgery	1 (3.23%)	0
Urinary System	4 (12.90%)	0
Ureteral calculus	1 (3.23%)	0
Urinary tract infections	3 (9.68%)	0
Nervous System	5 (16.13%)	1
Cranial Trauma	2 (6.45%)	1 (Use of cephalosporins)
Subarachnoid hemorrhage	1 (3.23%)	0
Intraspinal abscess	1 (3.23%)	0
Cerebral hemorrhage	1 (3.23%)	0

Table 8. Laboratory characteristics of 31 patients with bacteremia with thrombocytopenia.

Parameters	With thrombocytopenia (N = 31)	Without thrombocytopenia (N = 234)	G- (N = 20)	G+ (N = 11)	p^*	p^{**}	normal range
WBC (10^9/L)	10.95 ± 6.84	11.98 (9.10, 16.80)	10.17 ± 7.28	12.37 ± 6.01	0.064	0.402	3.5-9.5
NEUT%	88.33 (84.50, 93.07)	88.11 (80.37, 92.12)	88.70 (84.94, 93.44)	87.10 ± 5.33	0.482	0.536	40-75
PCT (ng/mL)	23.06 (2.65, 55.96)	1.18 (0.21, 7)	23.54 (1.52, 53.92)	12.52 (2.72, 94.04)	0.000	0.606	0-0.1
PCT↑ (%) (> 0.1 ng/mL)	30 (96.8%)	199 (85%)	20 (100%)	10 (91%)	0.093	0.355	—
PCT↑↑ (%) (> 0.3 ng/mL)	29 (93.5%)	150 (67.9%)	—	—	0.003	—	—

*p**: Comparison of differences between BSI with thrombocytopenia and BSI without thrombocytopenia; *p***: Comparison of differences between G- BSI with thrombocytopenia and G+ BSI with thrombocytopenia.

analyzed the bacterial distribution of patients with BSI in our hospital in 2020. The most common bacteria were *Escherichia coli, Klebsiella pneumoniae, Staphylococcus epidermidis, Staphylococcus aureus,* and *Staphylococcus hominis*, which is consistent with the results reported by the Chinese Bacterial Drug Resistance Surveillance Network in 2020. In addition, similar findings were reported in the Aljouf region of Saudi Arabia in 2019 [19]. In terms of the categories of strains detected from blood cultures, the G- bacteria dominated BSI and were predominantly *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. The G + bacteria were predominantly Staphylococcus (including *Staphylococcus aureus* and CNS) and Enterococcus (including *Enterococcus faecalis* and *Enterococcus faecium).* These findings are similar to those of a previous study [20]. In clinical practice, hematological parameters and indicators of inflammation are commonly used for the early evaluation of infectious diseases. The change in the total number of white blood cells is mainly affected by the number of neutrophil and lymphocyte cells, which usually manifest as neutrophilia and lymphocytopenia [21]. NEUTs may directly phagocytose bacteria [22] or kill bacteria in cases of organismal infection [22,23]. Therefore, neutrophilia could enhance the defense system of the body against pathogenic bacteria during acute infections. In line with previous reports, the WBC, NEUT, and NEUT% levels in patients with bacteremia were significantly higher than normal in our study; thus, they may serve as reliable indicators of bacterial infection. In this study, the absolute values of LYM and LYM% of bacteremia patients were decreased, and these decreases were mainly related to lymphocyte redistribution and accelerated regulated cell death apoptosis [24,25]. Lymphocytopenia was also a predictor of emergency bacteremia [26]. The values of other hematological parameters, such as platelet counts, plateletcrit, MPV, PDW, and P-LCR, were all within the normal range. PCT is a precursor of calcitonin produced by C cells of the thyroid gland, and it was first proposed as a marker of bacterial infection in 1993 [27]. Consistent with the literature [28], the PCT levels of the patients with bacteremia based on blood culture in this study were higher than normal during the same period, with the highest PCT level being 200 ng/mL. CRP and SAA are present only in small amounts in the blood of healthy individuals but are elevated in patients with bacterial infections [29]. In this study, the CRP and SAA levels of the patients with bacteremia were higher than normal during the same period when a blood culture was sent for testing. However, this was measured only at the time of the blood culture draw, without follow-up observation of the disease progression, which may not well reflect their value. ESR and SF are affected by many factors, but most studies suggest that they are also evaluation indicators of inflammation, especially infection of special sites. In this study, the sample sizes of these two indicators were small (35 cases and 81 cases) and were not further analyzed. Interleukins are representative cytokines and inflammatory factors that regulate the immune balance of the body. The levels of IL2R, IL6, IL8, IL10, IL1β, and TNF-α in the patients with bacteremia in this study were higher than the normal values, which was consistent with previous reports. However, the number of cases detected was small (retrospective, random), so these results may not fully reflect the overall situation of bacteremia. Due to the limitation of the sample size, no statistical analysis was carried out between the indicators and the follow-up process.

Next, we compared the hematological parameters and inflammatory indicators of the G- BSI and G + BSI group. In line with Peduzzi *et al.* [30], NEUT% was higher in the G- group in this study. Our further diagnostic test analysis suggested that the best diagnostic efficacy, sensitivity, and specificity were achieved when NEUT% was 87.41%, confirming the status of NEUT% in the determination of G- or G + bacterial infection. In this study, the platelet count was not reduced in bacteremia patients, which is inconsistent with the report by Guida *et al.* [31]. However, there was a marginally significant difference in platelet count between the G- and G + bacteria groups ($p = 0.053$), and the platelet count was lower in the G-

bacteria group than in the G + bacteria group. Further diagnostic tests showed that when the platelet threshold was 211 × 10^9/L, the diagnostic efficiency, sensitivity, and specificity of G- or G + bacteria were 56.9%, 56%, and 60.4%, respectively. At present, there are few studies on platelet parameters, especially plateletcrit. Plateletcrit is directly affected by platelet count and MPV. Jack *et al.* reported that sepsis is often associated with decreased platelet counts and increased MPV [31]. Our study found that the plateletcrit value significantly differed between the G- and G + bacteria groups, and it had certain differential diagnostic values. The plateletcrit value was lower in the G- bacteria group, which emphasizes the role of platelet parameters in the judgment of infection. The above results of this study provide evidence for the clinical use of simple routine blood tests to preliminarily identify G- or G + bacterial infections. Regarding the relationship between bacterial types and inflammatory indicators, PCT is an inflammatory indicator that has been studied and used more frequently in the clinic. In this study, there was a significant difference in PCT between the G- and G + bacteremia groups, and the level of PCT in the G- bacteria group was higher. The optimal cutoff value for identifying G- or G + bacterial infections was 1.31 ng/mL, which was lower than that of 10 ng/mL reported by Thomas-Ruddel *et al.* [32]. The reasons that need consideration may be that the patients in Thomas-Ruddel's study had confirmed or suspected infection in the ICU ward and at least one infection-related organ dysfunction. All patients in our study had bacteremia in our hospital, and patients with liver and kidney failure or DIC during the same period of the blood culture examination were excluded. Therefore, the subjects in this study were considered to have relatively mild disease in terms of the case-collection criteria (only 47 patients (17.8%) were diagnosed with sepsis on the day of the blood culture examination). From another point of view, it also shows that the PCT level can reflect the severity of the disease. In addition, this study also found that the combination of NEUT%, platelet count, plateletcrit and PCT could improve the diagnostic value of distinguishing G- from G + bacterial infections to a certain extent. When the four indicators simultaneously exceeded the threshold value, the diagnostic efficiency reached 65.6%.

The other inflammatory indicators in this study (SF, SAA, ESR, IL2R, IL6, IL8, IL10, IL1β, and TNF-α) showed no significant difference between the G- and G + bacteria groups, and they were not further analyzed due to the small sample size and uneven disease distribution. On the basis of expanding the sample size, the use of these inflammatory indicators or the combination of them with blood cell parameters to explore their relationship with bacterial types may help to identify the pathogenic species of bacteremia early. This study is the first systematic retrospective observational study of platelet count, thrombocytopenia, platelet-related parameters, WBC, NEUT, LYM and inflammatory indexes among the top two categories of G- organisms, the top two categories of G + organisms and the three most common strains of bacteremia in our hospital. Some of the results are reported for the first time and thus may be useful in the clinic.

Thrombocytopenia is common in patients with invasive bacterial infections [15], and its incidence can reach 47.6% in patients with sepsis or septic shock [16]. Infection-induced thrombocytopenia is multifactorial and may include decreased platelet production, hemodilution, increased platelet consumption, increased platelet retention in the microvasculature, and immune-mediated reduction in platelets [33]. The incidence of thrombocytopenia in the 265 patients with bacteremia in this study was only approximately 12% (31 cases), which is lower (20%-29%) than that reported above [15]. The above study analyzed the association between three specific bacteremic infections (*S. aureus, E. coli* and *S. pneumonia*) and thrombocytopenia. However, considering the same analysis of inflammatory indicators, the exclusion criteria for the collected cases were strict (patients with factors affecting platelet factors were excluded). None of the patients were given any medications that clearly caused thrombocytopenia before the blood sampling. Regarding antibiotic use, two patients were on cephalosporins, and three patients were on tigecycline. However, none of their course records mentioned antibiotic-induced thrombocytopenia, which was considered due to possible exacerbation of the infection. No patient was on linezolid or other antibiotics that may cause thrombocytopenia. Therefore, another perspective suggests that thrombocytopenia itself may also be an indicator of the severity of the infection. Next, we compared other markers, such as WBC, NEUT% and PCT, between the thrombocytopenia and non-thrombocytopenia groups. There were statistically significant differences in PCT between the bacteremia with thrombocytopenia and bacteremia without thrombocytopenia groups, but there were no statistically significant differences in the distribution of WBC and NEUT%. One study reported a cutoff value of 0.3 ng/mL for PCT to identify serious and invasive bacterial infections [34]. In our study,

when the PCT threshold was set at 0.3 ng/mL, there was a statistically significant difference in the percentage of PCT > 0.3 ng/mL between the patients with thrombocytopenic bacteremia and the patients without thrombocytopenic bacteremia. The PCT level was higher in the thrombocytopenic bacteremia group, which also indicates that thrombocytopenia is one of the indicators of the severity of infection.

Regarding the interaction between platelets and bacteria, G- bacteria and G + bacteria are similar in that they bind with platelet membrane glycoproteins. This induces platelet aggregation and activation, causing platelet consumption and then thrombocytopenia [35]. Cordero *et al.* reported chronic thrombocytopenia as a feature of *Klebsiella pneumoniae* infection [36]; Khashu *et al.* found that thrombocytopenia was associated with persistent coagulase-negative sepsis [37]. Johansson *et al.* [15] found that the incidence of thrombocytopenia was 29% in *Staphylococcus aureus* bacteremia, 28% in *Escherichia coli* bacteremia, and 20% in *Streptococcus pneumoniae* bacteremia across bacterial species, but there was no significant difference between the three specific bacterial species and thrombocytopenia. It has also been reported [12] that the incidence of thrombocytopenia among sepsis patients with G- and G + strains was not significantly different. In line with the literature, our study found no statistically significant differences in the incidence of thrombocytopenia between the bacterial types (between the G- and G + groups, between the common G- bacteria, and between the common G + bacteria). However, there was a trend toward a slightly higher incidence of thrombocytopenia in the G- bacteremia group (13.4%) than in the G +-induced thrombocytopenia group (9.5%). It was also found that among the common G- bacteria group, those with *Klebsiella pneumoniae* had the highest incidence of thrombocytopenia (19.4%) and the lowest platelet count levels. There are multiple reasons for this. (1) Different strains of *Klebsiella pneumoniae* carry different virulence factors, all of which may cause thrombocytopenia in patients. *Klebsiella pneumoniae* can cause hyperadhesiveness and significantly reduces platelet counts by inducing megakaryocyte aggregation and apoptosis and inhibiting megakaryocyte maturation [38]. (2) *Klebsiella pneumoniae* enhances platelet aggregation through the release of lipopolysaccharide-mediated TLR4/MyD88 and cGMP/PKG-dependent pathways [39,40] or induces apoptosis through the TLR4/NF-kB and JNK/MAPK pathways [41,42], thereby inducing the development of thrombocytopenia. (3) *Klebsiella pneumoniae* can also secrete iron carriers, which are small and high-affinity iron-chelating molecules that chelate and transport iron to bacteria to aid proliferation and alter host cell homeostasis [43], thereby affecting platelet counts. In conclusion, *Klebsiella pneumoniae* can induce thrombocytopenia through multiple pathways, thus explaining the clinical situation in this study where *Klebsiella pneumoniae*, a common G- organism, caused the lowest platelet levels and the highest incidence of thrombocytopenia.

Our present study has several limitations. This was a single-center clinical retrospective study, and thus, the study results may not be suitable for patients with different demographic characteristics. Additionally, the process of collecting cases was not rigorous enough. Second, in addition to PCT, the sample size of the bacteremia patients who received other inflammatory indicators (CRP, SF, SAA, ESR, IL2R, IL6, IL8, IL10, IL1β, TNF-α) at the same time as the blood culture examination was insufficient, and no follow-up was conducted.

Conclusions

In summary, bacteremia in our hospital was mainly due to G- bacterial infections, and the WBC, NEUT, NEUT%, and PCT levels of patients with bacteremia increased, while the LYM and LYM% decreased. According to the diagnostic efficiency, platelet count, plateletcrit, NEUT%, and PCT are helpful for the early identification of G- BSI and G + BSI. The incidence of thrombocytopenia was 12%, and compared with that of the G + bacteria group, the platelet level of the G- bacteria group tended to be lower in the patients with bacteremia. Moreover, the *Klebsiella pneumoniae* group had the highest rate of thrombocytopenia and the lowest platelet level.

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Authors' contributions

Xiaoyan Liu provided constructive advice and critically revised the manuscript. Guanqun Yi wrote the manuscript and created the tables. Guoyang Zhang, Hongyun Liu, Ziyang Liang and Danian Nie provided constructive advice and edited the manuscript. Liping Ma took overall responsibility for the research performed in this study and for data integrity. All authors have read and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Conflict of interests
No conflict of interests is declared.

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