



## RESEARCH ARTICLE

# Combined procalcitonin and hemogram parameters contribute to early differential diagnosis of Gram-negative/Gram-positive bloodstream infections

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**Abstract**

**Background:** Hemogram parameters and procalcitonin (PCT) play auxiliary roles in the diagnosis and outcome of sepsis. However, it is not clear whether these indicators can quickly distinguish bacterial classification or guide the choice of empirical antibiotics.

**Methods:** We retrospectively enrolled 381 patients with bloodstream infections (BSI), divided into Gram-positive bloodstream infections (GP-BSI) and Gram-negative bloodstream infections (GN-BSI). Demographic parameters, hemogram parameters, and PCT were recorded and compared between the two groups.

**Results:** The mean platelet volume (MPV), platelet distribution width (PDW), and PCT in the GN-BSI group were significantly higher than those in the GP-BSI group, while the platelet count (PLT), plateletcrit, platelet count-to-white blood cell count ratio (PWR), platelet count-to-neutrophil count ratio (PNR), platelet count-to-PCT ratio (PLT/PCT), and mean platelet volume-to-PCT ratio (MPV/PCT) were significantly lower in the GN-BSI group. Multivariate stepwise logistic regression analysis revealed that the independent predictors of GN-BSI were MPV, PWR, and PCT. The areas under the curve (AUC) for this prediction model was 0.79, with sensitivity =0.75 and specificity =0.71.

**Conclusions:** There were significant differences in terms of PCT, platelet parameters, and platelet-related index-PCT ratio between GN-BSI and GP-BSI. Combined PCT and hemogram parameters are more conducive to the early differential diagnosis of bacterial classification of BSI.

**KEYWORDS**

Gram-negative bloodstream infection, mean platelet volume, platelet-related index, predictive significance, procalcitonin, sepsis

Gao and Li are Co-First authors

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## 1 | INTRODUCTION

Bloodstream infection (BSI) is still a common infectious disease with high mortality worldwide,<sup>1</sup> which easily develops into sepsis, septic shock, and even death. The incidence and mortality rates of sepsis have declined over the last three decades; nevertheless, the mortality rate remains above 15%.<sup>2-4</sup> One of the most common clinical phenomena of sepsis is thrombocytopenia. According to relevant studies, the probability of experiencing thrombocytopenia in patients with sepsis can reach more than 50%, and thrombocytopenia is closely related to poor prognosis and high mortality.<sup>5,6</sup>

Platelets play an essential role in pathophysiological processes, including hemostasis, thrombosis, inflammation, and antimicrobial host defense.<sup>7</sup> It is believed that the occurrence of thrombocytopenia in patients with sepsis is mainly related to the increase in platelet loss and destruction caused by platelet activation stimulated by bacteria or their toxins.<sup>8</sup> Activated platelets interact with white blood cells (WBCs) such as lymphocytes, monocytes, and macrophages to exert anti-inflammatory activity.<sup>9</sup> Platelet and platelet-associated parameters, such as platelet count (PLT), mean platelet volume (MPV), plateletcrit, platelet distribution width (PDW), and platelet-large cell ratio (P-LCR), measured in readily available blood routine tests have been increasingly recognized for their role in managing inflammatory diseases. Platelet and MPV are useful markers for evaluating inflammatory activity and the therapeutic response of infectious diseases.<sup>10</sup> MPV is a surrogate marker of platelet activation and has been associated with infectious diseases, such as hepatic hydatid cysts,<sup>11</sup> tuberculosis,<sup>12</sup> and chronic prostatitis.<sup>13</sup> Moreover, it is also related to inflammatory conditions, such as nasal polyposis,<sup>14</sup> rheumatoid arthritis,<sup>15</sup> obesity,<sup>16</sup> coronary artery disease,<sup>17</sup> type 2 diabetes mellitus,<sup>18</sup> and irritable bowel disease.<sup>19</sup> Similarly, PDW was suggested to be associated with irritable bowel syndrome,<sup>20</sup> diabetes mellitus,<sup>21</sup> coronary artery disease,<sup>22</sup> and tuberculosis.<sup>12</sup> The mean platelet volume-to-platelet count ratio (MPV/PLT) has been reported to be increased in type 2 diabetes mellitus,<sup>23</sup> severe sepsis,<sup>24</sup> and influenza A infection.<sup>25</sup>

The effectiveness of initial treatment is essential to improving the prognosis and reducing mortality in patients with severe sepsis.<sup>26,27</sup> However, blood culture results usually require 2-3 days or even longer to obtain conclusive results and are limited by false-negative results. It is a challenge for many clinicians to administer antibiotics empirically, and they rely on personal clinical experience in the absence of definitive evidence of pathogens. The use of broad-spectrum antibiotics or combinations of antimicrobials has many disadvantages, such as increasing health care costs, adverse drug reactions, and the incidence of drug-resistant bacteria. There is a significant difference in antimicrobial use against Gram-negative and Gram-positive bacteria, and early prediction of the pathogens of sepsis facilitates early and precise treatment. Routine blood tests, as well as C-reactive protein (CRP) and procalcitonin (PCT), are simple and rapidly available, which

help to effectively distinguish bloodstream infections from non-bloodstream infections. Although it has been reported that PCT or platelet-related parameters can be used to predict Gram-negative bacteria infection, there are still some defects in the current results, which do not allow achieving better sensitivity and specificity simultaneously. Therefore, this study aimed to provide clinical data to support the early assessment of pathogen classification in sepsis and studies related to platelet-assisted anti-inflammatory therapy in infectious diseases.

## 2 | METHODS

### 2.1 | Subjects

In this retrospective study, we recorded data from consecutive adult inpatients with infectious fever and positive blood cultures between January 2013 and December 2018 at the Nanfang Hospital of Southern Medical University (Guangzhou, China). Inclusion criteria were as follows: 1) age over 18 years; 2) fever ( $\geq 38^{\circ}\text{C}$ ) or low temperature ( $\leq 36^{\circ}\text{C}$ ), chills, and other infection symptoms; 3) "Two bottles of bilateral" blood cultures tests and the corresponding pathogenic bacteria had been cultured; "Double-bottle bilateral" refers to the collection of 2-3 sets of blood culture specimens (each containing one aerobic bottle and one anaerobic bottle) within a short time or interval. 4) All patients met the criteria for Sepsis-3.<sup>28</sup>

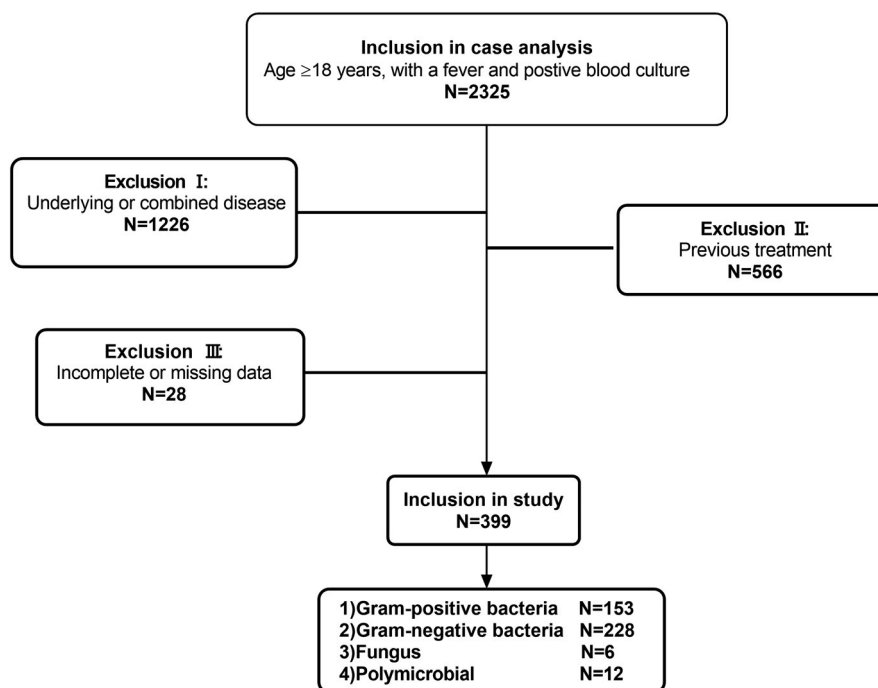
Exclusion criteria were as follows: 1) confirmed diagnosis of blood disorders, including leukemia, thalassemia, immune thrombocytopenia, and multiple myeloma; 2) confirmed diagnosis of tumors such as liver cancer, lung cancer, ovarian cancer, gastric cancer, or lymphoma; 3) confirmed diagnosis of autoimmune diseases such as vasculitis, systemic lupus erythematosus, or ankylosing spondylitis; 4) confirmed diagnosis of fatty liver, cirrhosis, hypersplenism, or other related diseases; 5) treatment with antibiotics within 3 days prior to undergoing peripheral blood culture; and 6) treatment with anticoagulants, antiplatelet agents, hemostatic agents, granulocyte boosters, or clinical transfusion therapy (eg, platelets, red blood cells, or plasma) within 7 days before obtaining a culture. The flow chart of the study protocol is shown in Figure 1. After excluding 18 patients with multiple bacterial or fungal infections, we eventually enrolled 381 patients. This retrospective study was approved by the Institutional Review Board/ Independent Ethics Committee of Nanfang Hospital of Southern Medical University, and the need for informed consent was waived since all data were anonymous. Patient privacy and confidentiality of data were maintained in accordance with the Declaration of Helsinki.

### 2.2 | Data collection

Data included sex, age, underlying disease, diagnosis, days of hospitalization, blood culture results, site of infection, complete blood

**FIGURE 1** Patient flow chart.

Exclusion I: Patients confirmed diagnosis of blood disorders ( $N = 718$ ), tumors ( $N = 376$ ), autoimmune disease ( $N = 64$ ) or fatty liver, cirrhosis, hypersplenism, and other related diseases ( $N = 68$ ).  
 Exclusion II: Patients received antibiotics within 3 days before blood-cultured, or who received anticoagulants, antiplatelet agents, hemostatic agents, granulocyte boosters, or clinical transfusion therapy within 7 days before blood-cultured.  
 Exclusion criteria III: Patients with incomplete or missing data

**TABLE 1** Demographic and clinical characteristics of all patients

Variable	Total ( $N = 381$ )	GP-BSI group ( $N = 153$ )	GN-BSI group ( $N = 228$ )	$p$ value
Age (years)	$53.8 \pm 16.9$	$51.9 \pm 17.5$	$55.1 \pm 16.5$	0.072
Sex, male, $N$ , (%)	227 (59.6)	100 (65.4)	127 (55.7)	0.06
Duration of hospital stay (days)	17 (12, 26)	18 (12, 28)	17 (12, 25)	0.477
Source of infection, $N$ , (%)				
Urinary system	71 (18.6)	19 (12.4)	52 (22.8)	0.011
Biliary system	58 (15.2)	15 (9.8)	43 (18.9)	0.016
Venous catheter-related	47 (12.3)	24 (15.7)	23 (10.1)	0.103
Respiratory system	37 (9.7)	17 (11.1)	20 (8.8)	0.45
Others or unexplained sources	168 (44.1)	78 (51)	90 (39.5)	-
Comorbidity, $N$ , (%)				
Hypertension	108 (28.3)	42 (27.5)	66 (28.9)	0.751
Diabetes	92 (24.1)	28 (18.3)	64 (28.1)	0.029
Kidney disease	72 (18.9)	40 (26.1)	32 (14)	0.003
Organism, $N$ , (%)				
		<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	
		46 (30.1)	98 (43)	
		<i>Staphylococcus epidermidis</i>	<i>Klebsiella pneumoniae</i>	
		20 (13.1)	50 (21.9)	
		<i>Enterococcus faecalis</i>	<i>Pseudomonas aeruginosa</i>	
		15 (9.8)	13 (5.7)	
		<i>Staphylococcus haemolyticus</i>	<i>Enterobacter cloacae</i>	
		7 (4.6)	10 (4.4)	
		<i>Streptococcus pharyngitis</i>	<i>Acinetobacter baumannii</i>	
		7 (4.6)	5 (2.2)	

Abbreviations: GN-BSI, gram-negative bloodstream infections; GP-BSI, gram-positive bloodstream infections.

counts (including WBC count, neutrophil count, lymphocyte count, monocyte count, PLT, MPV, plateletcrit, PDW, P-LCR), CRP, and PCT. Calculation of platelet parameter ratios were as follows: platelet count-to-lymphocyte count ratio (PLR), platelet count-to-WBC count ratio (PWR), platelet count-to-neutrophil count ratio (PNR), mean platelet volume-to-platelet count ratio (MPV/PLT, calculated by  $MPV/PLT \times 100$ ), and platelet distribution width-to-platelet count ratio (PDW/PLT, calculated by  $PDW/PLT \times 100$ ). We stratified cases according to the magnitude of the  $PLT^5$  and  $PCT^{29}$  as follows: 1)  $PLT \geq 150 \times 10^9/L$ ,  $100 \times 10^9/L \leq PLT < 150 \times 10^9/L$ , and  $PLT < 100 \times 10^9/L$ ; 2)  $PCT < 0.5 \text{ ng/ml}$ ,  $0.5 \text{ ng/ml} \leq PCT < 2 \text{ ng/ml}$ ,  $2 \text{ ng/ml} \leq PCT < 10 \text{ ng/ml}$ , and  $PCT \geq 10 \text{ ng/ml}$ .

### 2.3 | Statistical analyses

Statistical analysis was performed using SPSS version 26.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation or median and interquartile range (25th, 75th percentile), which were compared with Student's *t* test or the Mann-Whitney *U* test. The categorical variables were expressed as frequency and percentage and were compared with the chi-squared tests or Fisher's exact test. The Spearman rho test of correlation was performed for platelets and platelet parameters. Relevant variables were subjected to receiver operating characteristic (ROC) curve analysis to determine the early predictive value for Gram-negative (GN)-BSI. Optimal cut-off values were determined using the Youden index. Univariate and multivariate logistic (forward stepwise) regression analyses were performed to explore predictors associated with GN-BSI. All tests were two-sided and a *p*-value  $< 0.05$  was considered statistically significant.

## 3 | RESULTS

### 3.1 | Demographic and clinical characteristics of all patients

Data from the 381 patients are presented in Table 1. There was no difference in age or sex between the Gram-negative (GN)-BSI and Gram-positive (GP)-BSI groups. The source of initial infection in the GN-BSI group was predominantly the urinary or biliary system ( $p = 0.011$ ;  $p = 0.016$ ; respectively), and it was venous catheter-related in the GP-BSI group ( $p = 0.103$ ). The GN-BSI group had a significantly higher proportion of patients with diabetes than the GP-BSI group ( $p = 0.029$ ), but had a lower proportion of patients with kidney disease ( $p = 0.003$ ). In terms of the categories of strains detected from blood cultures, Gram-negative bacteria were predominantly *Escherichia coli* (98, 43%) and *Klebsiella pneumoniae* (50, 21.9%); Gram-positive bacteria were predominantly *Staphylococcus aureus* (40, 26.1%) and *Staphylococcus epidermidis* (20, 13.1%).

TABLE 2 Laboratory characteristics of GP-BSI group and GN-BSI group

Variable	GP-BSI group (N = 153)	GN-BSI group (N = 228)	<i>p</i> value
WBC ( $\times 10^9/L$ )	12.5 $\pm$ 6.1	13.3 $\pm$ 6.3	0.198
Lymphocyte ( $\times 10^9/L$ )	1.1 (0.7, 1.4)	0.9 (0.5, 1.3)	0.012
Neutrophil ( $\times 10^9/L$ )	10.4 $\pm$ 5.8	11.5 $\pm$ 6.1	0.082
Monocyte ( $\times 10^9/L$ )	0.7 (0.5, 0.9)	0.6 (0.4, 1.0)	0.147
PLT ( $\times 10^9/L$ )	221.3 $\pm$ 97.1	187.8 $\pm$ 108.1	0.002
Plateletcrit (ml/L)	2.3 $\pm$ 0.9	2.0 $\pm$ 1.0	0.003
MPV (fL)	10.1 (9.5, 11.0)	10.7 (9.9, 11.6)	$< 0.001$
PDW (fl)	11.2 (9.9, 12.9)	12.3 (10.9, 14.3)	$< 0.001$
P-LCR (%)	25.2 (20.3, 32.6)	30.1 (23.6, 37.2)	$< 0.001$
CRP (mg/L)	82.2 (45.5, 145.7)	109.6 (59.5, 186.8)	0.015
PCT (ng/ml)	0.9 (0.3, 4.1)	5.8 (1.2, 24.4)	$< 0.001$
PLR	201.9 (145.3, 304.5)	181.3 (116.9, 317.8)	0.315
PWR	18.2 (12.7, 25.4)	14.0 (8.8, 22.0)	$< 0.001$
PNR	21.7 (15.2, 32.0)	16.3 (10.2, 26.7)	$< 0.001$
MPV/PLT	4.8 (3.7, 7.5)	6.3 (4.0, 10.5)	$< 0.001$
PDW/PLT	5.4 (4.0, 8.4)	7.1 (4.4, 12.7)	$< 0.001$
PLT/PCT	227.9 (41.2, 709.4)	26.1 (5.9, 150.1)	$< 0.001$
MPV/PCT	12.2 (2.6, 38.8)	1.81 (0.5, 9.1)	$< 0.001$
PDW/PCT	14.5 (2.8, 43.5)	2.0 (0.5, 10.4)	$< 0.001$

Abbreviations: CRP, C-reactive protein; GN-BSI, gram-negative bloodstream infections; GP-BSI, gram-positive bloodstream infections; MPV, mean platelet volume; PCT, procalcitonin; PDW, platelet distribution width; P-LCR, platelet-large cell ratio; PLR, platelet count-to-lymphocyte ratio; PLT, platelet; PNR, platelet count-to-neutrophil count ratio; PWR, platelet count-to-white blood cell count ratio; WBC, white blood cell.

### 3.2 | Laboratory characteristics between groups of patients with sepsis

In the comparison of the two groups in Table 2, the lymphocyte count was significantly higher in the GP-BSI group ( $p = 0.012$ ), while the CRP and PCT were significantly higher in the GN-BSI group than in the GP-BSI group ( $p = 0.015$ ;  $p < 0.001$ ; respectively). In terms of platelets and their parameters, MPV, PDW, and P-LCR were also significantly higher in the GN-BSI group (all  $p < 0.001$ ); however, PLT and PCT were significantly lower ( $p = 0.002$ ;  $p = 0.003$ ; respectively). The MPV/PLT and PDW/PLT were significantly higher in the GN-BSI group (both  $p < 0.001$ ), while PNR, PWR, PLT/PCT, MPV/

PCT, and PDW/PCT were significantly higher in the GP-BSI group (all  $p < 0.001$ ).

### 3.3 | Correlation between PLT and platelet-related parameters

In the correlation comparison of platelet-related parameters (Table S1), the PLT was positively correlated with the plateletcrit ( $r = 0.955$ ,  $p < 0.001$ ) and negatively correlated with PDW, MPV, and P-LCR ( $r = -0.473$ ,  $p < 0.001$ ;  $r = -0.521$ ,  $p < 0.001$ ;  $r = -0.547$ ,  $p < 0.001$ ; respectively).

### 3.4 | Multivariate analysis of factors associated with GN-BSI

Binary logistic regression analysis was performed to identify predictors for early discrimination of GN-BSI (Table 3). We set  $PLT \geq 150 \times 10^9/L$  and  $PCT < 0.5 \text{ ng/ml}$  as dummy variables. Multivariate stepwise logistic regression of variables with significant differences in univariate logistic regression analysis revealed that independent predictors of GN-BSI were MPV (odds ratio [OR]: 1.7, 95% CI: 1.147–2.52,  $p = 0.008$ ), PWR (OR: 0.966, 95% CI: 0.938–0.994,  $p = 0.018$ ), and PCT ( $0.5 \text{ ng/ml} \leq PCT < 2 \text{ ng/ml}$ , OR: 2.436, 95% CI: 1.011–5.868,  $p = 0.047$ ;  $2 \text{ ng/ml} \leq PCT < 10 \text{ ng/ml}$ , OR: 2.503, 95% CI: 1.027–6.098,  $p = 0.0431$ ;  $PCT \geq 10 \text{ ng/ml}$ , OR: 8.128, 95% CI: 2.999–22.031,  $p < 0.001$ ). The predictive equation was  $(P) = -5.423 + 0.53 \times MPV$

$-0.035 \times PWR + 0.89 \times PCT(0.5-2 \text{ ng/ml}) + 0.917 \times PCT(2-10 \text{ ng/ml}) + 2.095 \times PCT(\geq 10 \text{ ng/ml})$ . The goodness-of-fit of the multivariable model was determined using Hosmer-Lemeshow test (Chi-square = 10.471,  $p = 0.233$ ).

### 3.5 | Comparison of ROC curves of related indicators and model as markers of GN-BSI

To further explore the predictive role of these indicators, their ratios to PCT, and the predictive equation model in early GN-BSI, we constructed ROC curves. As shown in Figure 2 and Table 4, the MPV, PCT, PWR, MPV/PCT, and PLT/PCT showed moderate ability to distinguish between patients within GN-BSI, with PLT/PCT having the highest areas under the curve (AUC) (0.73, 95% CI: 0.67–0.77), sensitivity = 0.80, specificity = 0.55. It should be noted that when PWR, PLT/PCT, and MPV/PCT were less than or equal to cut-off values, these indicators suggested a greater likelihood of GN-BSI. Based on the predictive equation model, the following were calculated: the AUC = 0.79 (95% CI: 0.73–0.85), sensitivity = 0.75, specificity = 0.71.

## 4 | DISCUSSION

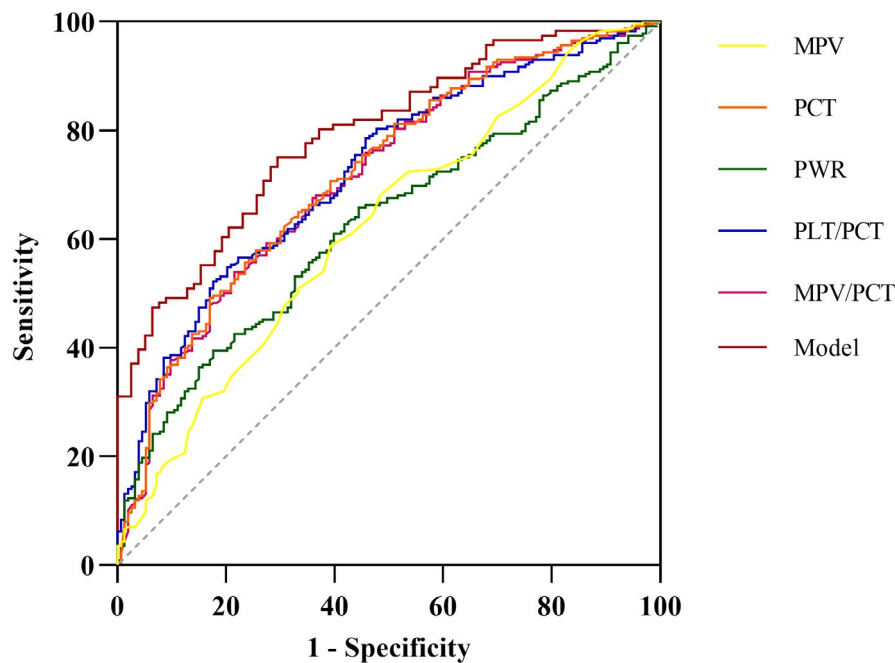
The results of this study demonstrated that PCT, platelet parameters, and the platelet-related index-PCT ratio were significantly different between GP-BSI and GN-BSI groups. PCT, MPV, PWR, PLT/PCT, and MPV/PCT values obtained from routine blood tests can be

TABLE 3 Explore predictors for early discrimination of GN-BSI by binary logistic regression analysis

Variable	Univariate				Multivariate			
	B	OR	95% CI	p value	B	OR	95% CI	p value
MPV	0.38	1.462	1.212–1.764	<0.001	0.53	1.7	1.147–2.52	0.008
PDW	0.146	1.157	1.068–1.253	<0.001				
PWR	-0.021	0.979	0.964–0.994	0.007	-0.035	0.966	0.938–0.994	0.018
PNR	-0.013	0.987	0.977–0.998	0.018				
MPV/PLT	0.071	1.074	1.028–1.122	0.001				
MPV/PCT	-0.024	0.976	0.967–0.986	<0.001				
PLT ( $\times 10^9/L$ )				<0.001				
$\geq 150$	Reference							
100–150	0.42	1.522	0.902–2.567	0.115				
<100	1.389	4.013	1.993–8.081	<0.001				
PCT (ng/ml)				<0.001				0.001
<0.5	Reference							
0.5–2	0.884	2.421	1.055–5.554	0.037	0.89	2.436	1.011–5.868	0.047
2–10	1.085	2.961	1.28–6.846	0.011	0.917	2.503	1.027–6.098	0.043
$\geq 10$	2.451	11.605	4.573–29.454	<0.001	2.095	8.128	2.999–22.031	<0.001
Constant					-5.423	0.004		0.014

Note:  $PLT \geq 150 \times 10^9/L$  and  $PCT < 0.5 \text{ ng/ml}$  were set as dummy variables.

Abbreviations: GN-BSI, gram-negative bloodstream infections; MPV, mean platelet volume; PCT, procalcitonin; PDW, platelet distribution width; PLT, platelet; PNR, platelet count-to-neutrophil count ratio; PWR, platelet count-to-white blood cell count ratio.



**FIGURE 2** Receiver operating characteristic curve of related indicators and model for differential diagnosis of GN-BSI. GN-BSI, gram-negative bloodstream infections; MPV, mean platelet volume; PCT, procalcitonin; PWR, platelet count-to-white blood cell count ratio (PLT/WBC)

Parameters	AUC	95% CI	<i>p</i> value	Cut-off	Sensitivity	Specificity
MPV	0.62	0.56–0.68	<0.001	10.15	0.68	0.52
PCT	0.72	0.67–0.77	<0.001	3.70	0.58	0.75
PWR <sup>a</sup>	0.63	0.57–0.68	<0.001	10.89	0.82	0.40
PLT/PCT <sup>a</sup>	0.73	0.67–0.77	<0.001	28.87	0.80	0.55
MPV/PCT <sup>a</sup>	0.72	0.66–0.77	<0.001	2.17	0.78	0.54
Model	0.79	0.73–0.85	<0.001	0.55	0.75	0.71

**TABLE 4** Receiver operating characteristic (ROC) curve for predicting GN-BSI

Abbreviations: GN-BSI, gram-negative bloodstream infections; MPV, mean platelet volume; PCT, procalcitonin; PWR, platelet count-to-white blood cell count ratio.

<sup>a</sup>Represents a positive prediction when the parameters are less than or equal to the cut-off value.

used to discriminate Gram-negative bloodstream infections among bloodstream infections to some extent. The combination of MPV, PWR, and PCT is helpful for the clinical diagnosis of GN-BSI, with more effective sensitivity and specificity. This would substantially benefit a wide range of clinical workers and patients, particularly in economically compromised developing countries.

Sepsis still is a common life-threatening medical emergency. Previous studies have shown a higher incidence of severe sepsis or septic shock in GN-BSI relative to GP-BSI.<sup>30,31</sup> Early differential diagnosis of GN-BSI and initiation of targeted antibiotic therapy are extremely important. After ruling out factors that may affect platelet parameters, we found that MPV, PDW, and P-LCR levels were significantly higher in the GN-BSI group, while PLT and plateletcrit were lower. However, the diagnostic value of these platelet parameters was not particularly high, and the highest AUC for MPV was only 0.62, and the specificity is relatively low. Catal et al. found that both PLT and MPV were significantly higher in the Gram-negative bacteria infection group in patients with upper urinary tract infection.<sup>32</sup> In another study involving very low birth weight newborns,

PLT levels were lower in the Gram-negative bacteria infection group, but MPV showed no significant differences.<sup>33</sup> Conversely, Manzoni et al. proposed that platelets were not an organism-specific marker of sepsis.<sup>34</sup> Our study also found that the MPV/PLT ratio was significantly higher in the GN-BSI group, which was similar to findings by Djordjevic et al.<sup>35</sup> Interestingly, we did not observe any significant differences in PLR in the groups; however, Djordjevic et al. found a higher PLR in patients with trauma and peritonitis whose blood culture grew Gram-negative bacteria ( $p = 0.01$ ).<sup>35</sup> The reason for this difference may be that the underlying diseases of the included patients were different in the two studies.

The increase in MPV, PDW, and P-LCR values reflected the size and morphology of platelets and indicated the degree of activation of platelet function and a higher degree of aggregation and inflammatory response. Platelet count and platelet activity, size, or volume are often negatively correlated. This was confirmed by our results. GN-BSI induce a stronger inflammatory response in the organism with higher concentrations of inflammatory factors than GP-BSI.<sup>30,36</sup> Some studies have reported that Gram-positive

bacteria are associated with more pronounced platelet activation, and platelet hyperreactivity compared with common Gram-negative bacteria.<sup>37</sup> This different degree of thrombocytopenia and platelet activation may lead to changes in platelet parameters, which can reflect changes in platelet volume, aggregation, and volume variation. However, differences in hematological levels of these non-specific biomarkers still need to be further clarified at the molecular level of different pathogenic mechanisms.

In this study, we found that lymphocytes, CRP, and PCT showed different levels of expression in GP-BSI and GN-BSI groups, and PCT helped to distinguish GN-BSI from GP-BSI, with an AUC of 0.72 and a specificity of 0.75, but a low sensitivity of 0.58. Several studies have shown significantly higher levels of PCT in patients with GN-BSI than in those with GP-BSI,<sup>38–40</sup> which is consistent with the findings of our study. Both Bassetti et al. and Liu et al. showed that there were no differences in CRP levels between the two groups.<sup>39,40</sup> Similarly, a meta-analysis also concluded that PCT is superior to CRP in the diagnosis of Gram-negative bacterial infections.<sup>41</sup> The different levels of PCT may be related to the inflammatory response and the different degrees of the systemic inflammatory response induced by the two bacteria classes through the induction and activation of different signal transduction pathways.<sup>31,36</sup> Differences in PCT may also be related to the fact that endotoxins on the cell wall of Gram-negative bacteria can directly induce PCT stimulation. Nevertheless, the value of early identification of sepsis or GN-BSI using PCT alone to assess infection remains debatable,<sup>42</sup> and we often need to interpret these findings in the context of clinical conditions. Thomas-Ruddel et al. and Yu et al. concluded that PCT serum concentrations were also influenced by the different sites of infection, and its differential diagnosis value for GN-BSI was limited.<sup>43,44</sup>

In different bacterial bloodstream infections, platelet and PCT concentrations in the blood circulation are variable, and the ratio between these indicators may better reflect the degree of systemic inflammatory response. In the present study, our results suggested that the PWR, PLT/PCT, and MPV/PCT values may be useful markers for the differential diagnosis of GN-BSI, with a high sensitivity of up to 0.82. PWR, obtained from the complete blood count, is a hematological marker of the systemic inflammatory response. Previous studies have shown that low PWR is associated with a poor prognosis of hepatitis B virus-associated decompensated cirrhosis and acute-on-chronic liver failure.<sup>45,46</sup> Further, PWR has been shown to not only predict the risk of infectious complications in patients with renal malignancies receiving radical nephrectomy,<sup>47</sup> but can also distinguish infections and normal response after splenectomy.<sup>48</sup> However, there are no other reference data on the early differential diagnosis of these indicators in BSI or sepsis.

Our study found that the diagnostic value of PLT/PCT and MPV/PCT was superior to either MPV or PCT individually. Compared with PCT, the sensitivity of these ratios was increased by more than 20%. The multivariate stepwise logistic regression analysis results indicated that MPV, PWR, and PCT were useful independent predictors of the early differential diagnosis of GN-BSI. Therefore, we

developed an equation model for early differential diagnosis of GN-BSI, having a good predictive value in the cohort of 381 patients with BSI in this study. The combination of MPV, PWR, and PCT may improve the sensitivity and specificity of the differential diagnosis of GN-BSI, compensating for the low sensitivity or low specificity of one indicator alone. The model with the combined indexes showed an 18% increase in sensitivity compared with PCT and a 31% increase in specificity compared with PWR.

Our present study has several limitations. It was a single-center retrospective study, and the results may be susceptible to selection bias. There are currently very few similar studies elsewhere that can be used as references, and multi-center prospective studies are needed to verify our findings. In the next step, we will conduct prospective trials to validate this model in a larger patient population.

## 5 | CONCLUSIONS

Leukocyte parameters, platelet parameters, and the platelet-related index-PCT ratio were significantly different between GP-BSI and GN-BSI groups. PCT, MPV, PWR, PLT/PCT, and MPV/PCT values were useful in the differential diagnosis of Gram-negative from Gram-positive bloodstream infections. The equation model consisting of MPV, PWR, and PCT is helpful for the clinical diagnosis of GN-BSI, which can effectively improve the sensitivity and specificity.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## DATA AVAILABILITY STATEMENT

Authors can confirm all relevant data are included in the article and materials are available on request from the authors.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.