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ORIGINAL RESEARCH

Epidemiology and Risk Factors of Community-Associated Bloodstream Infections in Zhejiang Province, China, 2017–2020

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Purpose: Community-associated bloodstream infection (CA-BSI) is increasing in many community settings. However, the clinical significance and epidemiology of CA-BSI present in hospital admissions in China are not well established. In this work, we identified the risk factors in outpatients presenting with CA-BSI, and investigate the role of procalcitonin (PCT) and hypersensitive C-reactive protein (CRP) in diagnosing different types of the pathogen in patients with acute CA-BSI.

Methods: A retrospective study enrolling 219 outpatients with CA-BSI from The Zhejiang People's Hospital from January 2017 to December 2020 was performed. Susceptibility of the isolates obtained from these patients was examined. Subjecting receiver operating characteristic curves (ROC) were constructed to analyze the specificity and sensitivity of PCT, CRP, and WBC in determining infections caused by different bacterial genera. Risk factors for CA-BSI in the emergency setting were analyzed using essential information and simple identification of other pathogenic bacterial species through rapidly tested biomarkers.

Results: A total of 219 patients were included in the selection criteria, of which 103 were infected with Gram-positive bacteria (G+) and 116 with Gram-negative bacteria (G-). The PCT was significantly higher in the GN-BSI group than in the GP-BSI group, while no significant difference was observed between the two groups for CRP. Subjecting ROC curves were constructed to analyze WBC, CRP, and PCT, and the area under the curve (AUC) of the PCT in this model was 0.6661, with sensitivity = 0.798 and specificity = 0.489.

Conclusion: The PCT between the GP-BSI group and the GN-BSI group was significantly different. By combining the knowledge of clinicians and the clinical signs of patients, PCT should be utilized as a supplementary approach to initially determine pathogens and direct medication in the early stages of clinical practice.

Keywords: community-associated bloodstream infections, PCT, gram-negative, gram-positive, diagnostic predictions

Introduction

Bloodstream infection (BSI) is usually caused by an endogenous or exogenous pathogen invading the host's bloodstream system, stimulating a systemic inflammatory response, and causing bloodstream infection. A local inflammatory response can lead to further infection and cause systemic inflammatory response syndrome (SIRS), sepsis, septic shock and even death. Community acquired bloodstream infection (CA-BSI) is a type of bloodstream infection that is acquired within 48 hours of the patient's admission from the community. Typical diseases acquired in the community are pneumonia, abdominal infection, urinary tract infection, meningitis, infective endocarditis and skin and soft tissue infection. Although the mortality rate from sepsis has improved in the last decade, it is still higher than 15%.[1–3] The emergency department (ED), as the primary department in the hospital receiving patients with acute and critical illnesses, needs to quickly identify and first precisely treat patients presenting with acute fever and suspected BSIs.[4,5] It is also necessary to rapidly assess the condition through several laboratory tests or scoring scales and to make clinical decisions.[6] In the past,

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much attention has been paid to the focal issues of timely diagnosis, risk assessment and prognostic evaluation of sepsis. Various relevant disease scores are also used to assess or predict mortality in patients with sepsis in EDs and acute intensive care units.

When a patient presents to the ED with an acute fever, there is usually an inflammatory response. In contrast, infection or sepsis can occur when patients present with severe infections. In previous guidelines for the management of sepsis, it has been suggested that some nonspecific biomarkers may be necessary to establish sepsis's prognosis.[7] Usually, blood culture is the gold standard for diagnosing bloodstream infections. Although blood cultures take time to grow and test in the clinic, they are still the best way to identify bacteria in the blood, as they are less likely to be contaminated or produce false positives.[8] Therefore, it does not provide quick guidance in treating fever or severe infections in patients who present to the ED.[9,10]

Leukocytes (WBC) and their sorting cells, as traditional anti-inflammatory cells involved in the inflammatory response, have long been used to assess a patient's infection status. Procalcitonin (PCT), a precursor of calcitonin, has likewise been shown to be an important reference marker for infection.[11] Hypersensitive C-reactive protein (CRP) is an acute-phase reactive protein that rapidly reflects the severity of inflammation. In previous studies, CRP and PCT concentrations have been correlated with the prognosis of patients with sepsis.[12] In a mate analysis, PCT was found to be more effective in diagnosing bacterial infection than CRP and IL-6.[13] These indicators can be monitored to treat the patient's infection properly.

We noticed that there were a few studies have demonstrated the epidemiology and risk factors of CA-BSI in China.[14–17] We therefore retrospectively evaluated the risk factors among ED patients in 2017–2020 at Zhejiang Provincial People's Hospital. Our work provides a simple prediction of the pathogenic genus of patients with suspected CA-BSI by using some simple tests in EDs so that the appropriate antibiotics can be selected for rapid and accurate treatment of the patient in the EDs.

Methods

Case Definition and Enrollment

In this retrospective clinical study, we recorded data on all patients with emergency fever and blood cultures through the Department of Emergency Medicine, Zhejiang Provincial People's Hospital from January 2017 to December 2020. Inclusion criteria: 1. age > 16 years; 2. fever ≥ 37.3°C; 3. blood cultures on both sides; 4. meeting diagnostic criteria for sepsis. Exclusion criteria: 1. previous haematological disorders, autoimmune diseases, or tumour-related diseases; 2. treatment on anti-infective drugs before emergency admission; 3. emergency transfer patients. The research flow chart of this study is shown in Figure 1.

The study was approved by the Institutional Review Board/Independent Ethics Committee of Zhejiang Provincial People's Hospital, and all data are anonymized without the need to sign informed consent. Patient privacy and data confidentiality are maintained following the Declaration of Helsinki.

Data Collection

The data included in this item are age, gender, underlying illness, days in the hospital, days with fever, season of stay, blood culture results, WBC count, CRP, and PCT. The blood culture results are those taken at the first emergency visit of the emergency patient; the complete blood count, CRP, and PCT results are those taken before the first visit of the emergency patient without antibiotics and those taken on the second and third day after the emergency hospitalization.

Statistical Analyses

Statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean (standard deviation) or median (interquartile range) expressions and analyzed comparatively by *t*-test or Wilcoxon test. Categorical variables were expressed as frequencies and percentages and analysed using the chi-square test or Fisher's exact test. The Loess method was utilized to create a fitting curve, which illustrated the varying pattern of inflammatory indicators. Relevant variables were subjected to subject operating characteristic curve analysis to determine

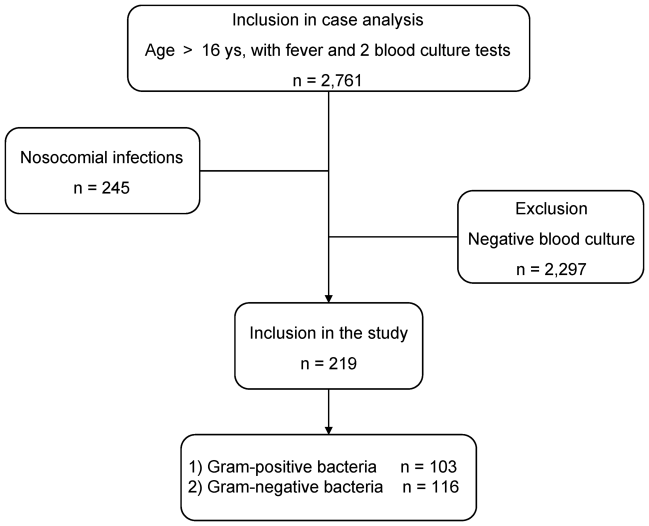

Figure 1 The flow chart for the selection of data for the study is as follows.

the early predictive value of Gram-negative bloodstream infections; all tests had both conditions, and $p < 0.05$ was considered statistically significant. A statistical comparison of AUCs was conducted using DeLong's test.

Patient and Public Involvement

Patients or the public were not involved in our research's design, conduct, reporting, or dissemination plans.

Results

The Basic Profile of All Febrile Patients and Positive Blood Cultures

The data from this study on positive blood cultures for CA-BSI are listed in Table 1. A total of 219 patients with positive blood cultures were enrolled, including 103 patients with Gram-positive bloodstream infections and 116 patients with Gram-negative bloodstream infections. As can be observed in Table 1, there was no statistical difference between the age and gender of the patients infected with Gram-negative and Gram-positive bacteria. The mean age of onset for all

Table 1 Basic Profile and Prognosis of Patients with Emergency Fever

Features	Total	GP-BSI	GN-BSI	*P*
N	219	103	116	
Age mean (SD)	67.05 (18.23)	65.67 (18.81)	68.28 (17.69)	0.292
Hospitalization days median (IQR)	12 (8.16)	12 (8.14)	11 (8.18)	<0.001
Number of fever days median (IQR)	1 (1.3)	1 (1.3)	1 (1.3)	0.860
Sex				0.652
Male	123 (56.16)	60 (58.25)	63 (54.31)	
Female	96 (43.84)	43 (41.75)	53 (45.69)	
Hospitalization season				0.070
Spring	39 (17.81)	20 (19.42)	19 (16.38)	
Summer	69 (31.51)	38 (36.89)	31 (26.72)	
Autumn	73 (33.33)	34 (33.01)	39 (33.62)	
Winter	38 (17.35)	11 (10.68)	27 (23.28)	
Basic diseases				
Hypertension	97 (44.29)	49 (47.57)	48 (41.38)	0.433
Diabetes	65 (29.68)	33 (32.04)	32 (27.59)	0.568

(*Continued*)

Table 1 (Continued).

Features	Total	GP-BSI	GN-BSI	*P*
Anemia	33 (15.07)	19 (18.45)	14 (12.07)	0.260
Tumor	48 (21.92)	27 (26.21)	21 (18.10)	0.199
Kidney disease	108 (49.32)	49 (47.57)	59 (50.86)	0.726
Liver disease	78 (35.62)	33 (32.04)	45 (38.79)	0.368
Sources of Infection				
Urinary tract infections	24 (10.96)	6 (5.83)	18 (15.52)	0.038
Uremia	18 (8.22)	15 (14.56)	3 (2.59)	0.003
Cholecystitis	51 (23.29)	21 (20.39)	30 (25.86)	0.426
Cholangitis	25 (11.42)	6 (5.83)	19 (16.38)	0.025
Lung disease	86 (39.27)	47 (45.63)	39 (33.62)	0.093

Notes: Categorical variables: chi-square test; continuous variables (non-normality): Wilcoxon rank sum test.
Abbreviations: GP-BSI, Gram-positive bloodstream infection; GN-BSI, Gram-negative bloodstream infection.

patients with bloodstream infections was 67.05 years. For CA-BSI, there were no statistically significant differences between seasons, but the distribution of patients was observed to be more frequent in summer and autumn. The mean number of hospital days for all patients was 12 days, with shorter hospital days for GN-BSI compared to the GP-BSI group ($p < 0.001$), which was statistically significant. The short duration of the fever may be related to the prompt anti-infective and antipyretic treatment after emergency consultation. The number of GN-BSI and GP-BSI was similar in patients with bloodstream infection combined with hypertension and diabetes and was not statistically significant.

The proportion of patients with combined liver disease and renal disease in the GN-BSI group was not statistically different from that in the GP-BSI group ($p = 0.368$; $p = 0.726$; respectively); meanwhile, bloodstream infections leading to shock accounted for 22.37% of patients, with GN-BSI causing significantly more shock than GP-BSI, but not statistically significant. Initial infections in the GN-BSI group were primarily found in urinary tract infections and biliary tract infections ($p = 0.038$; $p = 0.025$; respectively.) The GP-BSI group mainly was associated with pulmonary infections and inflammatory gallbladder disease, but there was no statistically significant difference between the two groups (divided into $p = 0.093$; $p = 0.426$;). A total of 18 patients developed bloodstream infections in uremia, 15 in the GP-BSI group and 3 in the GN-BSI group, with a statistically significant comparison between the two groups ($p = 0.003$).

Pathogenic Distribution and Characteristics

Table 2 and Figure 2 show that a total of 219 patients with positive blood cultures were counted in this study, of which 116 were of negative genera, accounting for 52.97% of all positive blood culture patients, and 103 were of positive genera, accounting for 47.03% of all positive blood culture patients. Among the Gram-negative genera, *Escherichia coli*

Table 2 Distribution and Composition Ratio of Pathogenic Bacteria in Blood Cultures (n = 219)

Pathogenic Bacteria	Number of Strains	Composition Ratio (%)
Gram-negative bacteria	116	52.97
Escherichia coli	57	49.14
Klebsiella pneumoniae	31	26.72
Pseudomonas aeruginosa	6	5.17
Proteus mirabilis	3	2.59
Aeromonas hydrophila	3	2.59
Enterobacter cloacae	3	2.59
Acinetobacter baumannii	2	1.72
Klebsiella acidophilus	2	1.72

(*Continued*)

Table 2 (Continued).

Pathogenic Bacteria	Number of Strains	Composition Ratio (%)
Bacteroides fragilis	2	1.72
Morganella morganii	2	1.72
Paratyphoid A	1	0.86
Raoultella ornithinolytica	1	0.86
Salmonella group D	1	0.86
Burkholderia cepacia	1	0.86
Gram-positive bacteria	103	47.03
Staphylococcus aureus	29	28.15
Staphylococcus epidermidis	24	23.30
Staphylococcus humanus subspecies	17	16.50
Enterococcus faecalis	5	4.85
Streptococcus dysgalactiae (group C)	5	4.85
Staphylococcus haemolyticus	4	3.88
Candida albicans	2	1.94
Streptococcus pneumoniae	2	1.94
Streptococcus constellatus	2	1.94
Streptococcus haematobium	2	1.94
Staphylococcus saprophyticus	1	0.97
Streptococcus gordonii	1	0.97
Streptococcus gallateolyticus	1	0.97
Candida subsmoothis	1	0.97
Enterococcus oryzae	1	0.97
Staphylococcus goatus	1	0.97
Enterococcus faecalis	1	0.97
Clostridium perfringens	1	0.97
Staphylococcus cephalicus	1	0.97
Corynebacterium striatum	1	0.97
Streptococcus pharyngeus	1	0.97

(57, 49.14%) and *Klebsiella pneumoniae* (31, 26.72%) were predominant. Gram-positive bacteria were dominated by *Staphylococcus aureus* (25, 24.27%) and *Staphylococcus epidermidis* (24, 23.30%). Figure 3 suggests that *Enterobacter* spp. infections accounted for a high proportion of all blood culture-positive patients (90, 41%), followed by coagulase-negative *Staphylococcus* and other genera (52, 24%). Gram-negative *Enterobacter* spp. had a high susceptibility to imipenem (94.03%) and some resistance to quinolones, second and third-generation cephalosporins (19.12–22.86%). Coagulase-negative staphylococci were more common among the gram-positive bacteria, with high susceptibility to vancomycin, linezolid, quinupristin/da, and high resistance to penicillin, oxacillin, erythromycin, ciprofloxacin and levofloxacin (46–93.33%). The next most susceptible genus, *S. aureus*, had high susceptibility to vancomycin, linezolid, and quinupristin/da while having high resistance to penicillin G and second- and third-generation cephalosporins (Table 3).

Laboratory Characteristics of Patients with CA-BSI

Table 4 and Table 5 show that in all patients with positive blood cultures and a CRP test taken on the first day, for the GN-BSI group, the CRP values were significantly higher than for the GP-BSI group but not statistically different (p=0.095). In contrast, there was no difference between the GN-BSI group and the GP-BSI group for patients with a WBC test left on the first day (p = 0.097). After these patients were admitted to the emergency department, they were empirically treated with anti-infective therapy, and a total of 122 CRP values were counted on the second day. CRP values were similar between the two groups of patients in this group and were not statistically significantly different (p = 0.814). After the patients were admitted, both groups had identical peak CRP values and were not statistically significant.

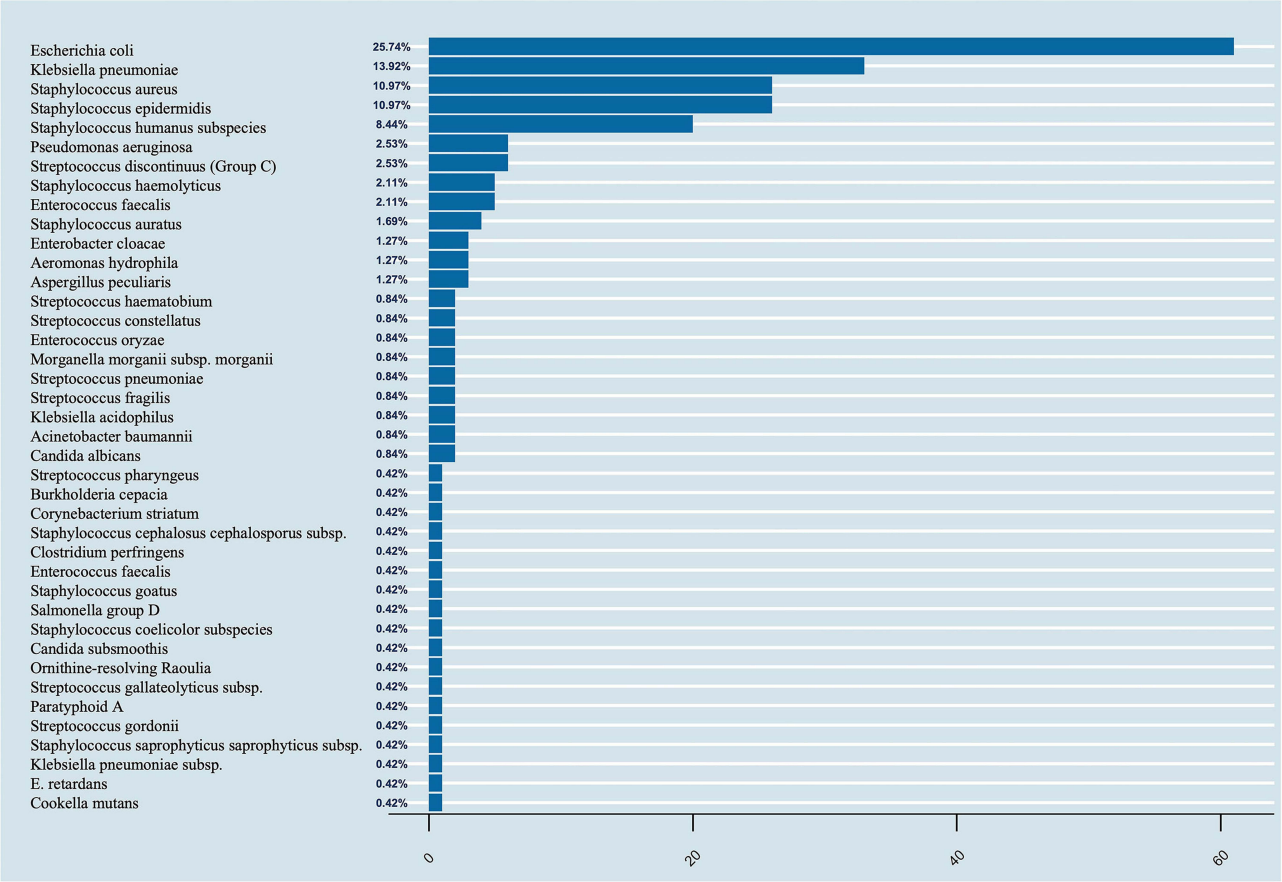

Figure 2 Blood culture distribution of pathogenic bacteria by species.

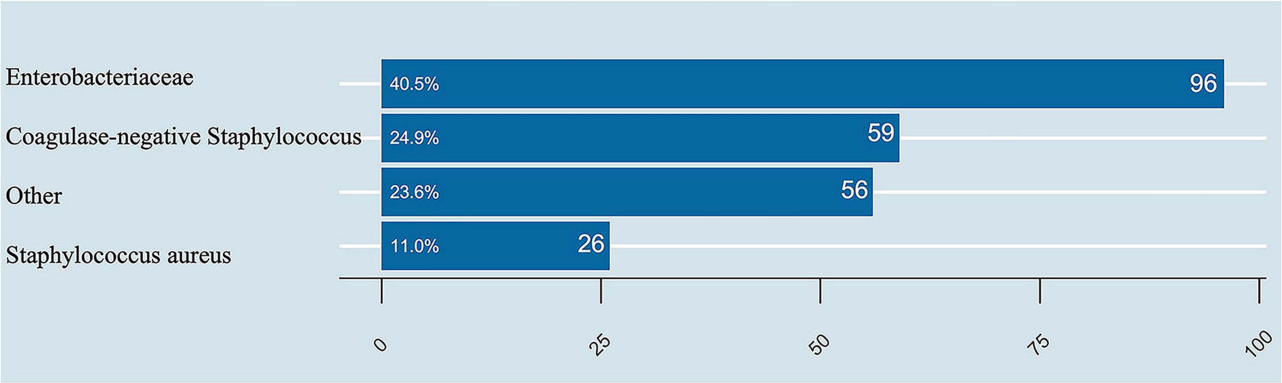

Figure 3 Blood culture distribution of Enterobacteriaceae, coagulase-negative *Staphylococcus, Staphylococcus aureus*, and other pathogens.

A total of 166 patients had positive blood cultures, and PCT tests were left on the first day, with the GN-BIS group being significantly higher than patients in the GP-BIS group (p = 0.001). However, in the 77 patients who left for PCT testing on the second day, the results were similar in the GN-BIS and GP-BIS groups and were not statistically significant (p = 0.680). As seen in Figure 4, the inflammatory markers in patients with CA-BSI, whether CRP or PCT, peaked on the second day and gradually decreased on the empirical administration of antibiotics following admission.

Table 3 Resistance of Coagulase-Negative Staphylococci/Enterobacteriaceae to Commonly Used Antimicrobials

Antibiotics	Coagulase-Negative Staphylococci (n =52)			Enterobacteriaceae (n = 90)			*Staphylococcus aureus* (n = 25)		
	No. of Strains	No. of Resistant Strains	Resistance Rate (%)	No. of Strains	No. of Resistant Strains	Resistance Rate (%)	No. of Strains	No. of Resistant Strains	Resistance Rate (%)
Ciprofloxacin	50	25	50.00	70	16	22.86	25	6	24.00
Levofloxacin	50	27	54.00	68	13	19.12	25	6	24.00
Cotrimoxazole	50	23	46.00	70	21	30.00	25	2	8.00
Gentamicin	50	7	14.00	68	16	23.53	25	5	20.00
Tigecycline	-	-	-	-	-	-	20	1	5.00
Minocycline	-	-	-	25	3	12.00	-	-	-
Vancomycin	50	0	0.00	-	-	-	20	0	0.00
Erythromycin	50	34	68.00	-	-	-	20	9	45.00
Linezolid	50	0	0.00	-	-	-	20	0	0.00
Moxifloxacin	49	16	32.65	-	-	-	24	5	20.83
Quinupristin/da	49	0	0.00	-	-	-	20	0	0.00
Rifampicin	49	4	8.16	-	-	-	-	-	-
Benzocillin	50	34	68.00	-	-	-	24	6	25.00
Penicillin G	45	42	93.33	-	-	-	24	24	100.0
Clindamycin	41	25	60.98	-	-	-	20	9	45.00
Tetracycline	42	4	9.52	-	-	-	20	7	35.00
Ceftazidime	-	-	-	87	18	20.69	1	1	100.0
Imipenem	-	-	-	67	4	5.97	-	-	-
Cefoxitin	-	-	-	39	5	12.82	4	3	75.00

Table 4 Comparison of Gram-Negative and Gram-Positive Bacteria CRP and WBC

	CRP (mg/L)†	CRP Peak (mg/L)	CRP (mg/L)*	WBC (*10^9/L)
n	212	150	122	219
GN-BSI	124 (203.8)	170.5 (157.95)	171 (131.7)	11.58 (9.9)
GP-BSI	90.95 (153.75)	166 (148.57)	180 (167)	12.07 (10.23)
Total	106 (191)	169.1 (158.8)	175.5 (133.68)	11.75 (10.02)
p	0.095	0.499	0.814	0.097

Notes: Median (interquartile spacing); †patient's CRP value on day 1; *patient's CRP value on day 2.
Abbreviations: CRP, C-reactive protein; WBC, white blood cells.

Multi-Factor Regression Analysis

A multifactorial regression equation was constructed combining gender, age, days in the hospital and inflammatory factors (Table 6). The results showed that men were at a higher risk of developing infections compared to women. While older age was associated with a higher risk of developing bloodstream infections, statistical significance did not emerge. Although gender, days in hospital and age were not statistically significant in the predictiveness of GN-BSI, this may be related to the small sample size of subjects included in this project. In contrast, for inflammatory indicators, the higher the WBC, the higher the risk of Gram-negative bloodstream infection, which was statistically significant (OR = 0.956,

Table 5 An Analysis of the PCT Value of Gram-Negative and Gram-Positive Bacteria

	PCT (ng/mL)†	PCT Peak (ng/mL)	PCT (ng/mL)*
n	166	125	77
GN-BSI	10.8 (32.05)	22.68 (40.66)	24.02 (39.3)
GP-BSI	3.17 (12.96)	17.46 (56.54)	28.32 (93.68)
Total	5.2 (24.05)	21.05 (46.91)	24.75 (59.19)
p	0.001	0.389	0.680

Notes: Median (interquartile spacing); †the PCT value of the patient on the initial day. *The PCT value of the patient on the second day.
Abbreviation: PCT, calcitoninogen.

95% CI 0.915–0.998, $p < 0.05$). The higher the calcitoninogen, the higher the risk of Gram-negative bloodstream infection, which was statistically significant (OR = 1.020, 95% CI 1.006–1.035, $p < 0.05$). An increased WBC count is not only an indication of Gram-positive bacteria, it could also be a sign of Gram-negative bacteria. It is proposed that a higher PCT value is more indicative of a negative bacterial presence.

ROC Curves of Relevant Indicators and Models as Markers of GN-BSI

The corresponding ROC curves were constructed to further confirm the predictive value of the indicators we explored. As shown in Figure 5 and Table 7, PCT showed a higher ability to identify different pathogen types than CRP and WBC.

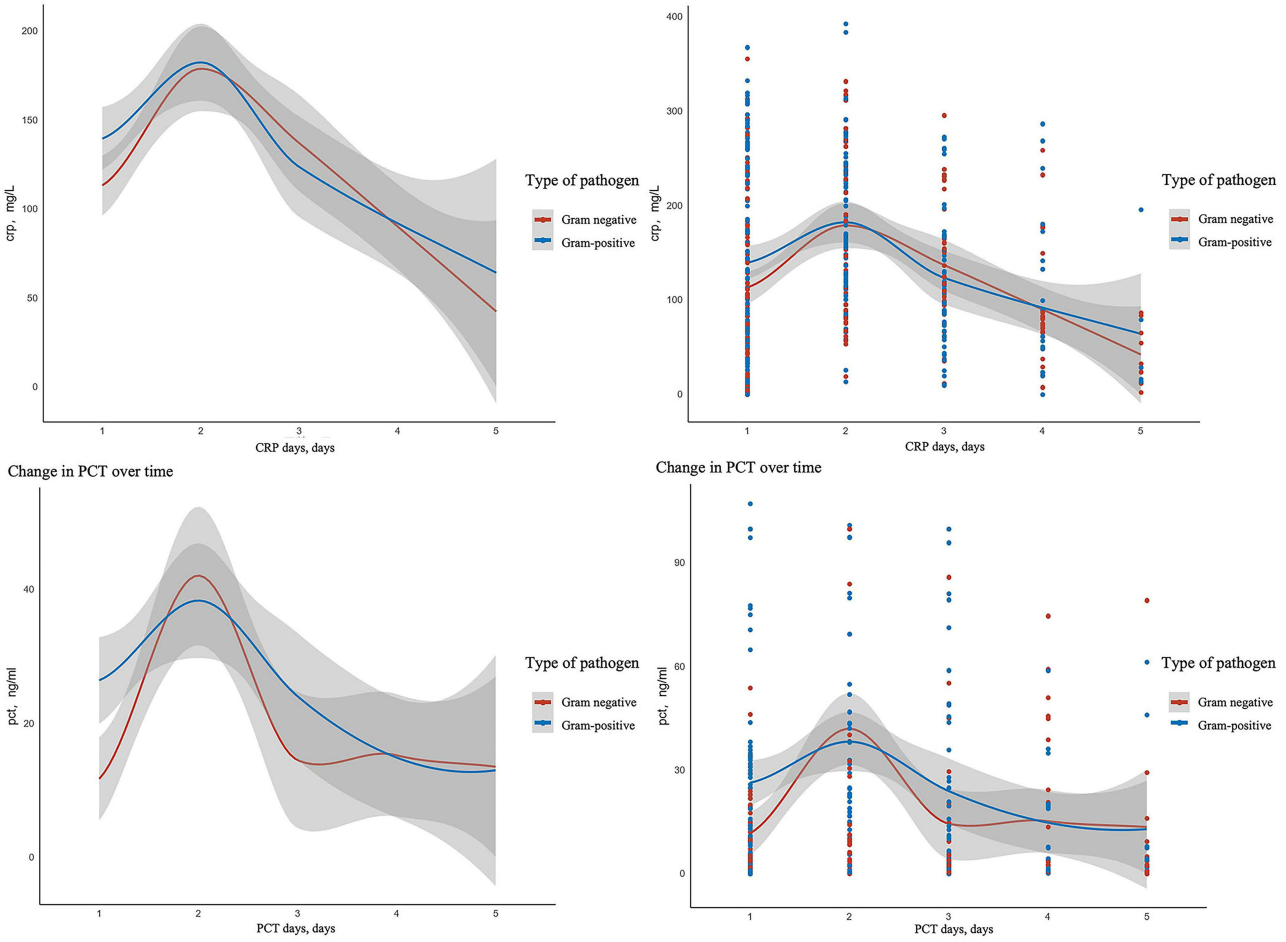

Figure 4 The variation of PCT and CRP over time.

Table 6 Multi-Factor Regression Analysis Exploring Predictors of Early Identification of GN-BSI

Variables	Subgroup	b-Value	b-Value Standard Error	Wald Chi-Squared	*P*-value	OR-Value	95% CI of OR-Value
Gender	Male*						
	Female	−0.183	0.342	0.287	0.592	0.833	0.462–1.268
Days in hospital		−0.001	0.017	0.003	0.959	0.999	0.966–1.034
Age		0.015	0.009	2.800	0.094	1.016	0.997–1.034
WBC		−0.045	0.022	4.199	0.040	0.956	0.915–0.998
CRP		0.001	0.002	0.447	0.504	1.001	0.998–1.005
PCT		0.020	0.007	7.631	0.006	1.020	1.006–1.035

Note: *Control group.

The PCT had a higher area under the curve (AUC) (0.6661, 95% CI: 0.593–0.739), sensitivity = 0.798 and specificity = 0.489, with $p < 0.0001$ being statistically significant.

Discussion

Sepsis is still one of the diseases with a high mortality rate worldwide. Previous studies have also suggested that bloodstream infections caused by Gram-negative bacteria are more prone to more severe sepsis or even septic shock than Gram-positive bacteria,[18–20] which also leads to a higher mortality rate. Therefore, it is important to quickly identify the source of infection in patients with CA-BSI, determine the type of pathogen, making early diagnosis and early treatment, and thus reduce patient mortality.[21]

WBC, CRP and PCT are all readily available blood tests, and PCT has good sensitivity for identifying Gram-negative bloodstream infections to some extent. This is an excellent diagnostic and therapeutic aid for patients and clinicians who present to the ED with suspected CA-BSI. Blood cultures are not a quick guide to the condition of patients with bloodstream infections, or sepsis is seen in the ED, but WBC, CRP and PCT can be performed quickly and accurately in the ED to reflect the patient's inflammatory status.

Our study found that most CA-BSI comes from primary infections in the bloodstream from the lungs, urinary system and gallbladder, where Gram-negative bacteria also predominate. However, most patients with uremic syndrome complicated by bloodstream infections had predominantly positive organisms. These patients are primarily dialysis-related catheter-associated infections, the same as most of the national and international researchers who have mainly studied.[22] Most patients with pulmonary diseases associated with bloodstream infections are triggered by the pulmonary route of infection into the bloodstream. Most patients are considered to have predominantly community-acquired pneumonia as their first disease, with *K. pneumoniae* and *Staphylococcus* predominating. Most of the patients with CA-BSI had one or even

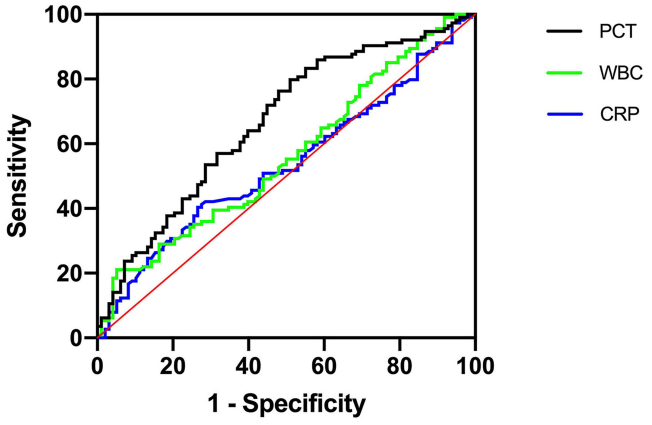

Figure 5 The predicted ROC curve for GN-BSI.

Table 7 Predicted ROC Value for GN-BSI

	AUC	95% CI	*p*	Cut-Off	Sensitivity	Specificity
PCT	0.6661	0.593–0.739	<0.0001	1.74	0.798	0.489
CRP	0.5370	0.459–0.615	0.3537	4.485	0.404	0.735
WBC	0.5604	0.483–0.638	0.1299	173.5	0.211	0.949

more co-morbidities. Preliminary statistical analysis shows that the average age of patients with CA-BSI is around 67 years, with a predominance of male patients over female patients. Statistically, CA-BSI did not significantly correlate with the season but occurred more often in summer and autumn. Therefore, older men with more previous illnesses are at a higher risk of CA-BSI.

In the EDs, CRP and PCT are the more readily available tests. In this study, we found that CRP showed varying degrees of elevation in both the GN-BSI and GP-BSI groups, while mostly peaking on the second day. However, the comparison between the two groups was not statistically significant due to the small volume of patients and the lack of second-day CRP results in some patients. However, in our study, we found that CRP, either on the first day or at the peak, did not show statistically significant differences between the GN-BSI and GP-BSI groups, which is consistent with the study by Bassetti and Liu HH et al[23,24] Additionally, the construction of working characteristic curves for the subjects showed that CRP and WBC did not show significant sensitivity and specificity ($p > 0.05$). The curves of inflammatory indicators over time could also indicate that the decrease in inflammatory indicators was more pronounced in the patients after they were treated by emergency consultation and prompt selection of the appropriate anti-infective treatment, most of them based on the empirical selection of carbapenem antibiotics that are more sensitive to Gram-negative bacteria.

PCT is used as an important biomarker for infectious diseases and even sepsis, which can be obtained quickly in an emergency and guide treatment. It is also used as an important indicator for the rapid diagnosis of sepsis and even septic shock.[25] PCT was first identified in thyroid tumour cell cultures and is a peptide hormone. And in earlier reports, it was also suggested that PCT is altered to varying degrees in infectious and non-infectious diseases.[26] The level of PCT in the blood is proportional to the severity of the infection.[27] Therefore, PCT is also used as a common test to determine the infectious disease. The value of PCT in the diagnosis of nosocomial GNBSI has long been demonstrated in previous clinical studies of nosocomial bloodstream infections. The use of PCT for the rapid diagnosis of CA-BSI, where the common causative organisms are different from those of nosocomial infections, was also part of this project. The results of this study showed that PCT was diagnostic for GN-BSI in 219 patients collected, with the first day of PCT results in all emergency admissions indicating significantly higher negative bacterial infections compared to positive bacterial infections ($p = 0.001$), and the construction of subject working characteristic curves indicated an AUC of 0.6661 (95% CI 0.593 to 0.739) with a sensitivity of 0.798 and specificity of 0.489 ($p < 0.0001$). And it was also shown in some studies that the GN-BSI group had a higher level of PCT than the GP-BSI group, which is consistent with our findings.[11,23,24] Gram-negative bacteria stimulate the body to produce an inflammatory response through their endotoxins, which can also induce stimulation of different concentrations of PCT, so that PCT can identify different bacterial types of infection.[28] However, the value of PCT as a biomarker for the diagnosis of sepsis or even septic shock alone is still being investigated and remains controversial in some studies.[29,30] In certain individuals with impaired liver function, the production of CRP may be disrupted, thus making PCT a more reliable measure for the diagnosis of all-inflammatory infections.[31] In sepsis 3.0, PCT is also recommended only as a biomarker for the prognosis of sepsis, not for diagnosis. And in this study, although PCT proved to be of high diagnostic significance in Gram-negative *spp*., it could not be used as one of the only indicators for the diagnosis of CA-BSI or sepsis and should be considered in conjunction with the patient's clinical presentation and other scores.

It has also been shown in previous studies that indicators such as platelets and mean platelet volume in routine blood tests can also identify bloodstream infections caused by different pathogenic bacteria. However, Manzoni et al suggested that platelets are not used as a marker for the specific diagnosis of bloodstream infections.[32] However, studies in recent years have shown that a stronger inflammatory response can inhibit platelet production and stimulate varying degrees of

platelet activation and increased reactivity, thereby causing changes in platelet parameters. In one study, it was shown that the identification of different bacterial types by changes in indicators such as platelets may have some sensitivity and specificity.[18] This also provides the theoretical basis for the Centre's subsequent research.

This is a single-center retrospective study and the results are subject to varying degrees of bias, including data volume, and may require a multi-center, multi-sample prospective study for further confirmation and statistical discovery of additional and more sensitive indicators for the rapid identification of patients with CA-BSI to guide clinical management.

Conclusions

Owing to the limited sample size and single-center nature of this study, the results must be interpreted with caution. PCT, WBC and CRP were significantly altered in all patients with bloodstream infections; PCT was significantly different between the GP-BSI and GN-BSI groups. PCT can be used for early differential diagnosis of community-associated Gram-negative and Gram-positive bloodstream infections with good sensitivity. PCT is an accurate indicator for CA-BSI, yet it is not specific. PCT should be employed as a supplementary tool in clinical practice, in conjunction with the expertise of clinicians and the clinical signs of patients, to make an initial assessment of the pathogenic bacteria and direct the use of medications in the early stages of treatment. Once complete blood culture and drug sensitivity results have been obtained, the treatment plan can be adjusted accordingly.

Ethics Approval

This project is a retrospective study and does not involve the privacy of the subjects. The Ethics Committee of Zhejiang Provincial People's Hospital has approved this project under the Ethics Approval No. 2021QT369.

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Disclosure

The authors report no conflicts of interest in this work.

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