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Original Article

Predictive Value of IL-6, PCT, NLR, and CRP in differentiating gram-negative bacterial bloodstream infections from gram-positive bacterial and fungal bloodstream infections in febrile patients

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Abstract: Identification of bloodstream infections (BSI) in patients with fevers is crucial for the timely implementation of specific and acute therapies, including early administration of antibiotics and source control. Many studies have evaluated the roles of biomarkers in diagnosing initial BSIs, distinguishing between BSIs caused by different sources and species of bacteria. The aim of the current study was to evaluate the diagnostic ability of interleukin-6 (IL-6), procalcitonin (PCT), neutrophil/lymphocyte ratio (NLR), and C reactive protein (CRP) in discriminating gram-negative (GN) bacterial infections from gram-positive (GP) bacterial and fungal infections in febrile patients with BSIs. This retrospective study was conducted for a total of 567 patients with fevers at the Fever Clinic of the Chinese PLA General Hospital, between November 2015 and December 2017. Serum levels of IL-6, PCT, and CRP, as well as the NLR, were obtained from electronic medical records and compared between the GN-BSI group (n=188), GP-BSI group (n=168), Fungal-BSI group (n=38), and culture negative group (n=173). Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), Youden index, and areas under the ROC curve (AUC) were determined, analyzing the diagnostic abilities of these biomarkers in discriminating between bloodstream infections caused by different pathogens. Results showed that IL-6 was useful in discriminating GN-BSI from GP-BSI and fungal-BSI. NLR was valuable in discriminating Fungal-BSI from GP-BSI in febrile patients. Utilization of these biomarkers to predict bloodstream infections caused by different pathogens requires further assessment, however, in future studies.

Keywords: IL-6, neutrophil/lymphocyte ratio (NLR), gram-negative, gram-positive, fungal, bloodstream infection, febrile

Introduction

Regarding outpatients attending the Fever Clinic, fevers are the most common symptom, along with other clinical manifestations, including headaches, diarrhea, abdominal pain, and vomiting [1]. Many primary infections, including respiratory, traumatic skin and tissue, urinary tract, and gastro-intestinal infections, often lead to BSI and may generate fevers [2]. In febrile outpatients, nonspecific clinical signs and symptoms, as well as delayed blood culture reports, prevent the doctor from making accurate diagnoses [3]. Without convincing laboratory evidence, patients are treated empirically. Broad-spectrum antibiotics are prescribed arbitrarily, leading to wrong diagnoses, poor prognosis, and the promotion of antibiotic resistance [4, 5]. Therefore, a rapid, efficient, and accurate laboratory method of determining BSI in febrile patients is urgently needed for appropriate initial antimicrobial treatment.

Blood culturing has long been considered the gold standard of detecting BSI. However, this routinely used method is time-consuming (3-5 days) and does not always yield conclusive results. Contamination of specimens and the overuse of broad spectrum antibiotics may lead to false positives and false negatives, respec-

tively [6]. Therefore, identification of useful and applicable biomarkers to predict bacteremia is a promising and effective strategy.

Currently, biomarkers used to detect infection, such as CRP and leukocyte counts, are not sufficiently specific in differentiating bacterial infections from SIRS in febrile patients [7, 8]. PCT, the precursor of the hormone calcitonin, has been increasingly used as a promising biomarker in diagnosing bacterial infections. PCT levels rise dramatically during bacterial infections, while low levels of PCT have been detected during viral infections or in noninfectious febrile conditions [9-12]. Furthermore, some researchers have begun to investigate PCT levels upon infection with different bacterial species, evaluating the value of PCT in distinguishing between gram-negative, gram-positive, and fungal bloodstream infections [13]. A proinflammatory factor, IL-6 increases dramatically in the serum in the early stages of bacterial infections, stimulating the activation of monocytes/macrophages and inducing expression and the release of CRP and PCT [14-17]. The value of the NLR has been evaluated in patients with lung cancer, colorectal cancer, and primary hepatocellular carcinoma, correlating well with overall and cancer-specific survival rates [18-21]. At present, interest in the NLR as an independent predictor of bacteremia is increasing. Goodman and colleagues initially studied the use of the NLR in patients with suspected appendicitis. They reported that the NLR was a more sensitive parameter than raised WBC counts [22]. Cornelis PC de Jager et al. explored the ability of the NLR, compared with traditional parameters, in predicting bacteremia in an Emergency Care Unit. They reached the conclusion that the NLR has an even higher value in predicting bacteremia than CRP and lymphocyte counts [23].

Therefore, detection of IL-6, PCT, NLR, and CRP may be a feasible method of identifying early bloodstream infections in febrile patients at the Fever Clinic. Once a useful diagnosis is obtained, objective and useful advice may be given for the rational use of antibiotics. The current study retrospectively compared diagnostic properties and assessed the predictive value of IL-6, PCT, NLR, and CRP in differentiating gram-negative bloodstream infections from gram-positive and fungal bloodstream infections in febrile patients at the Fever Clinic.

Patients and methods

Study design and patients

The current retrospective study of febrile patients at the Fever Clinic at the General Hospital of Chinese PLA, between November 2015 and December 2017, was performed. The aim of the current study was to evaluate the diagnostic ability of IL-6, PCT, NLR, and CRP in discriminating between bloodstream infections caused by different pathogenic bacteria. All adult outpatients with an axillary temperature ≥38°C were enrolled. Another important inclusion criterion was serological indicators, including IL-6, PCT, NLR, CRP, and blood culturing, which were concurrently ordered and analyzed. Exclusion criteria included the lack of a serological test, temperature <38.0°C, pregnancies, autoimmune diseases, tumors, or a discharge diagnosis for a fever of unknown origin.

Clinical data and laboratory records

Medical and laboratory records of all enrolled patients with an axillary temperature ≥38°C that had blood cultures taken were retrieved and analyzed. Demographic information, including age, sex, signs and symptoms, routine laboratory reports, final diagnosis, and clinical treatment process, were noted. Serum levels of IL-6, PCT, and CRP within 12 hours after patients were presented to the Fever Clinic were obtained. Moreover, the NLR was calculated based on routine blood indexes.

Group classification

According to blood culture results from the Clinical Microbiology Laboratory, the patients were divided into four groups, including gram-negative bloodstream infection (GN-BSI), gram-positive bloodstream infection (GP-BSI), fungal bloodstream infection (Fungal-BSI), and culture negative groups. Coagulase-negative *Staphylococcus, Corynebacterium spp., Bacillus, Micrococcus, Citrobacter,* and other skin commensals were considered contaminants when they were isolated from only one set of BCs in the absence of clinical and/or laboratory data suggesting their pathogenic role.

Table 1. Clinical features of patients with BSI

Characteristic	
Age (yr) (mean ± SD)	40.25 ± 21.75
Sex	
Male	236 (60%)
Female	158 (40%)
Presenting signs and symptoms	
Fever	394 (100%)
Headache	359 (91.1%)
Cough	201 (51.0%)
Chills	192 (48.7%)
Malaise	187 (47.5%)
Diarrhea	143 (36.3%)
Abnormal chest findings	126 (31.2%)
Skin lesions	65 (16.5%)
Hepatomegaly	62 (15.7%)
Splenomegaly	40 (10.2%)
Lymphadenopathy	29 (7.4%)

Statistical analysis

Statistical Product and Service Solutions (SPSS) 22.0 statistical software package (SPSS, Chicago) was used for all statistical analyses. First, the normality of data was tested. Data with a normal distribution are presented as mean ± SEMs. They were analyzed using one-way analysis of variance (ANOVA) and SNK-*q* tests. Abnormally-distributed data are described using medians (interquartile range, IQR) and were analyzed using nonparametric tests. *P* values <0.05 indicate statistical significance. All graphs were made using GraphPad Prism 7.0 software. ROC curve analysis was performed, the area under the curve (AUC) was determined, and sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and Youden indexes were obtained, assessing and comparing differential diagnostic abilities of involved biomarkers in discriminating between bloodstream infections caused by different pathogens.

Results

Group classification

Blood samples from a total of 5,092 patients with fevers were sent for culturing during the study period. Of these, a single pathogen was isolated from 394/5,092 samples. Another 75 positive cultures with mixed infections and 58 with contaminants were excluded from the study. According to results, 394 patients (236 male vs 158 female, 40.25 ± 21.75 years) were divided into three groups, including 188 (122 male vs 66 female, 41.50 ± 19.25 years) with GN-BSI, 168 (92 male vs 76 female, 40.25 ± 20.50 years) with GP-BSI, and 38 (23 male vs 15 female, 39.75 ± 21.75 years) with Fungal-BSI. A total of 173 patients (102 male vs 71 female, 40.50 ± 21.35 years) randomly selected from 4,565 patients with negative results were classified as the negative culture group.

Clinical features of patients with BSIs

Clinical features of patients with BSIs (n=394) are shown in **Table 1**. Common clinical symptoms included fevers (394/394, 100%), headaches (359/394, 91.1%), coughing (201/394, 51.0%), chills (192/394, 48.7%), malaise (187/394, 47.5%), and diarrhea (143/394, 36.3%). Final diagnoses of enrolled patients (n=567) are shown in **Table 2**. In positive culture cases, the most common diagnosis was bacterial pneumonia (172/394, 43.7%). In negative culture cases, the most common diagnosis was viral respiratory tract infections (61/173, 35.3%).

Etiological agents of the BSIs

Escherichia coli was the most common bacteria, isolated from 93/394 (23.6%) cultures. It was followed by *Staphylococcus hominis* in 52/394 (13.2%) cultures, *Klebsiella pneumoniae* in 47/394 (11.9%) cultures, and *Staphylococcus aureus* in 41/394 (10.4%) cultures. Four types of fungi were isolated from 38 patients with fevers, including *Candida albicans, Candida tropicalis, Candida parapsilosis,* and *Candida glabrata*. Etiological agents of the BSIs in these patients are summarized in **Table 3**.

Levels of IL-6, PCT, and CRP, along with the NLR, in the four groups

Levels of IL-6, PCT, and CRP, along with the NLR, in the four groups are shown in **Table 4**. Significance levels of differences between the four indexes of any two groups are summarized in **Table 5**. There was a significant (P<0.05) difference in levels of IL-6, PCT, CRP, and the NLR among the four groups. In this study, levels of IL-6, PCT, CRP, and the NLR in the GN-BSI group

Table 2. Final diagnosis of enrolled patients (n=567) with fevers

Culture Positive groups		Culture Negative group	
Diagnosis	No.	Diagnosis	No.
Bacterial pneumonia	172	Viral respiratory tract infection	61
Urinary tract infection	78	Viral pneumonia	42
Bacterial gastroenteritis	53	Acute gastroenteritis	19
Pyogenic Cholecystitis	22	Adult Still's disease	13
Bacterial respiratory tract infection	17	Viral meningitis	9
Severe acute pancreatitis	15	Alcoholic pancreatitis	8
Endocarditis	8	Kidney stone	6
Bacterial peritonitis	6	Arthritis	5
Nephrotic syndrome	6	pleural effusion	3
Liver abscess	5	Mononucleosis	3
Tuberculosis	4	Acute cholangitis	2
Bacterial meningitis	3	Acute promyelocytic leukemia	2
Acute lymphadenitis	2		
Thermoplegia	2		
Soft tissue contusion	1		
Total	394		173

were all significantly higher than those in the GP-BSI group and culture negative group (P<0.05). Levels of IL-6 in the GP-BSI group were higher than those in the culture negative group (P=0.007), but there was no significant differences in the NLR and levels of PCT and CRP between these two groups (P>0.05). In the Fungal-BSI group, the NLR and levels of IL-6 and PCT were higher than those in culture negative patients (P<0.05). However, differences in CRP levels were not obvious (P>0.05) (**Table 5**).

ROC analysis

To further identify and diagnose different types of bloodstream infections, ROC analysis was carried out (**Figures 1-3**). Median IL-6 and PCT levels in the GN-BSI group (358.60 pg/mL, interquartile range (IQR): 78.56-1543.50 and 3.28 ng/mL, IQR: 0.83-12.07, respectively) were significantly higher than those in the GP-BSI group (81.27 pg/mL, IQR: 36.92-149.23 and 0.42 ng/mL, IQR: 0.19-1.02, respectively) or the Fungal-BSI group (99.36 pg/mL, IQR: 32.89-265.05 and 0.53 ng/mL, IQR: 0.18-1.60, respectively) (P<0.05). At a best cut-off value of 232.5 pg/mL, IL-6 exhibited a larger area under the curve (AUC) (0.767, 95% CI: 0.725-0.805, P<0.001) than PCT (0.751, 95% CI: 0.708-0.796, P<0.001) at a cut-off value of 0.767 ng/mL when discriminating GN-BSI from GP-BSI. There was a specificity of 84.5% and a Youden index of 44.1% (**Table 6**). When discriminating GNBSI from Fungal-BSI, the AUC for IL-6 (0.695, 95% CI: 0.651-0.747, P<0.001) at a cut-off value of 464.3 pg/mL was also larger than the AUC for PCT (0.630, 95% CI: 0.585-0.688, P<0.001) at a cut-off value of 0.68 ng/mL (**Table 7**). Additionally, ROC analysis showed an AUC for the NLR of 0.685 (95% CI: 0.646-0.727, P<0.001) when discriminating Fungal-BSI from GP-BSI at a best cut-off value of 9.03. This value was larger than the AUCs for IL-6, PCT, or CRP (**Table 8**).

Discussion

Present results suggest that IL-6 is useful in discriminating GN-BSI from GP-BSI and Fungal-BSI in febrile patients at the Fever Clinic. IL-6 exhibited a greater predictive value than PCT and other biomarkers, including NLR and CRP. The NLR was valuable in discriminating Fungal-BSI from GP-BSI in febrile patients at the Fever Clinic.

Identification of BSIs in patients with fevers is crucial for the timely implementation of specific and acute therapies, including early administration of antibiotics and source control. Many studies have evaluated the roles of biomarkers in diagnosing initial BSIs and distinguishing between BSIs caused by different sources and species of bacteria. The current study retrospectively compared diagnostic properties of IL-6, PCT, NLR, and CRP in differentiating gram-negative bloodstream infections from gram-positive and fungal bloodstream infections in febrile patients at the Fever Clinic. The aim was to discover promising diagnostic markers and provide useful advice for selection of optimized antimicrobial therapies when blood culture results are not available.

A systemic inflammatory marker, CRP, synthesized in the liver in response to the stimulation of IL-6, is an established biomarker of infec-

Table 3. Bacterial pathogens isolated from enrolled febrile patients

Pathogen		
Gram negative bacteria		
Escherichia coli	93	23.6%
Klebsiella pneumoniae	47	11.9%
Pseudomonas aeruginosa	9	2.3%
Enterobacter cloacae	7	1.8%
Enterobacter aerogenes	6	1.5%
Acinetobacter baumannii	5	1.3%
Aeromonas hydrophila	5	1.3%
Klebsiella oxytoca	4	1.0%
Salmonella Typhi	3	0.8%
Pseudomonas putida	2	0.5%
Morganella morganii	2	0.5%
Leuconostoc mesenteroides	2	0.5%
Proteus mirabilis	1	0.3%
Serratia marcescens	1	0.3%
Burkholderia cepacia	1	0.3%
Gram positive bacteria		
Staphylococcus hominis	52	13.2%
Staphylococcus aureus	41	10.4%
Staphylococcus epidermidis	34	8.6%
Streptococcus viridans	27	6.8%
Staphylococcus capitis	5	1.3%
Enterococcus faecium	4	1.0%
Staphylococcus haemolyticus	2	0.5%
Streptococcus constellatus	1	0.3%
Veillonella parvula	1	0.3%
Streptococcus gordonii	1	0.3%
Fungi		
Candida albicans	15	3.5%
Candida tropicalis	13	3.3%
Candida parapsilosis	7	1.8%
Candida glabrata	3	0.8%
Total	394	100%

tions and inflammation [24]. However, levels of CRP do not reach their peak for 48 hours. CRP levels are elevated in many noninfectious conditions [25]. Therefore, CRP demonstrates poor sensitivity and specificity in the early diagnosis of bacterial infections [26-28]. In patients with fevers, CRP levels within 12 hours were obviously elevated in the GN-BSI group ($P<0.001$), but there were no significant differences in CRP levels in patients in the GP-BSI and Fungal-BSI groups, compared with patients in the culture negative group ($P>0.05$). ROC analysis also showed the poor value of CRP as an early predictor in distinguishing between GN-BSI, GP-BSI and Fungal-BSI (**Tables 6**-**8**). Results are in accord with studies [29-31].

PCT has been recommended as a useful biomarker for bacterial infections, guiding the administration of antibiotics [32, 33]. Nakajima A et al. [34] and Marková M et al. [35] reported that serum PCT levels differed in patients with bacterial or fungal infections and were significantly elevated in patients with gram-negative bacteremia, compared to levels in control patients. According to current data, levels of PCT in the GN-BSI group were higher than those in the Fungal-BSI group ($P=0.027$). Previous studies have reported that PCT levels could be used to distinguish gram-negative bacterial sepsis from gram-positive bacterial and fungal sepsis, showing promising predictive ability [36-38]. However, in the current study, when differentiating GN-BSI from GP-BSI and GN-BSI from Fungal-BSI, the AUC for IL-6 was larger than the AUC for PCT (0.767 vs 0.751 and 0.695 vs 0.630, respectively) for both comparisons (**Tables 6**, **7**). When GP-BSI was differentiated from Fungal-BSI, the AUC for the NLR was larger than the AUC for PCT (0.685 vs 0.644) (**Table 8**).

IL-6 is an important pro-inflammatory factor secreted by T-cells and macrophages. Normal IL-6 levels are very low. However, when bacterial infections occur, a large amount of IL-6 is released into the blood circulation, causing damage to organs [39, 40]. Persistent infections lead to a rapid increase of IL-6 [41, 42]. Gram-negative bacteremia induces a greater inflammatory response than gram-positive bacteremia. This may explain the higher IL-6 and PCT levels measured in gram-negative bacteremia than in gram-positive bacteremia. The major membrane component in gram-negative bacteria is lipopolysaccharide (LPS) (the major component of endotoxin), while that in gram-positive bacteria is peptidoglycan (PGN). LPS is a ligand of Toll-like receptor 4 (TLR4), and PGN is a ligand of TLR2. Gram-negative bacteria and gram-positive bacteria activate different TLR signaling pathways, resulting in the production of distinct proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and IL-6, that stimulate PCT expression and release [16, 17, 43, 44]. Hence, the rise in IL-6 levels in GN-BSI is earlier than the rise in PCT levels. The time interval to reach peak concentrations is shorter

Table 4. Demographic and laboratory characteristics of enrolled patients (n=567) with fevers

Parameters	GN-BSI	GP-BSI	Fungi	Culture Negative
Number	188	168	38	173
Sex (male vs female)	122 vs 66	92 vs 76	23 vs 15	102 vs 71
Age (yr) (Mean ± SD)	41.50 ± 19.25	40.25 ± 20.50	39.75 ± 21.75	40.50 ± 21.35
IL-6 (pg/ml) Median (IQR)	358.60 (78.56-1543.50)	81.27 (36.92-149.23)	99.36 (32.89-265.05)	33.98 (12.94-75.09)
PCT (ng/ml) Median (IQR)	3.28 (0.83-12.07)	0.42 (0.19-1.02)	0.53 (0.18-1.60)	0.27 (0.08-0.76)
NLR Median (IQR)	12.46 (6.77-21.44)	7.65 (4.15-14.20)	14.16 (6.27-29.92)	7.45 (3.91-12.82)
CRP (mg/l) Median (IQR)	90.5 (41.0-140.8)	54.7 (23.7-108.8)	74.0 (44.8-127.3)	53.1 (16.9-106.0)

Table 5. Significance of differences (*P* value) in the four indexes levels between any two groups

	P value			
	IL-6	PCT	NLR	CRP
Gram Negative VS Gram Positive	<0.001	<0.001	<0.001	0.005
Gram Negative VS Fungi	0.018	0.027	1.000	1.000
Gram Negative VS Culture Negative	<0.001	<0.001	<0.001	<0.001
Gram Positive VS Fungi	0.169	0.080	0.002	0.558
Gram Positive VS Culture Negative	0.007	0.092	1.000	1.000
Fungi VS Culture Negative	0.002	0.039	<0.001	0.139

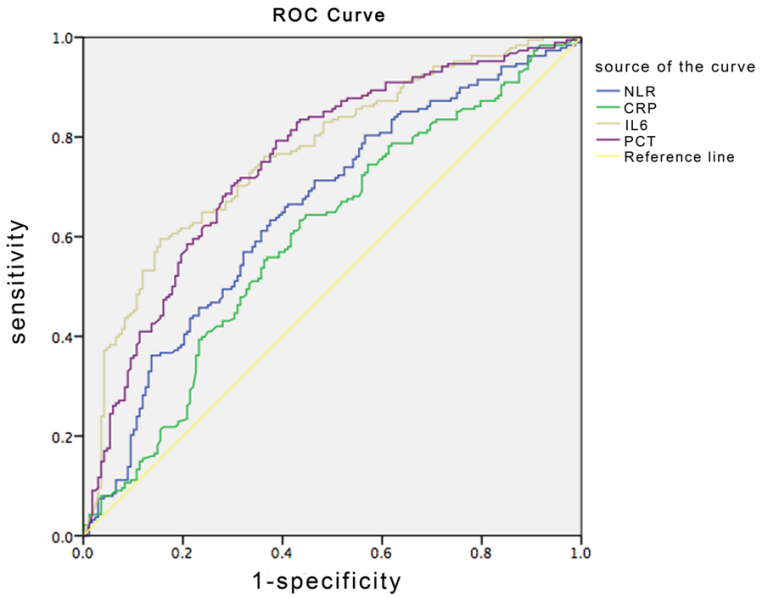

Figure 1. ROC curve analysis showing the differential diagnosis performance of IL-6, PCT, NLR, and CRP in discriminating GN-BSI from GP-BSI in febrile patients at the Fever Clinic. The AUCs of IL-6, PCT, NLR, and CRP were 0.767, 0.751, 0.654, and 0.600, respectively.

(within 6 hours). In the current study, serum levels of IL-6 and PCT were measured within 12 hours after patients were presented to the Fever Clinic. Therefore, in the early stages of GN-BSI, IL-6 levels increased more dramatically. This may explain why IL-6 is better able to differentiate early GN-BSI from GP-BSI and Fungal-BSI, compared to PCT.

The NLR has gained increasing attention as an independent and helpful predictor of bacteremia in recent years. Zahorec et al. documented the NLR as an easily measurable parameter, evaluating the severity of systemic inflammation and sepsis in 90 oncology patients [45]. Wyllie DH et al. researched the relationship between lymphopenia and bacteremia in adults with medical emergencies. They found that neutrophilia is usually accompanied by lymphocytopenia, suggesting it as a valuable predictor of bacteremia [46]. This notion was supported by a study of changes in lymphocyte subpopulations in sepsis conducted by Holub M, et al. [47]. Cornelis PC de Jager et al. also reported that the NLR predicted bacteremia better than conventional infection markers in emergency settings [23]. However, there is a lack of information concerning the potential use of the NLR to discriminate GN-BSI from GP-BSI and Fungi-BSI in febrile patients at the Fever Clinic. In the current study, ROC analysis showed that the predictive value of the NLR in discriminating GN-BSI from GP-BSI and in discriminating GN-BSI from Fungi-BSI in febrile patients was inferior to the predictive value of

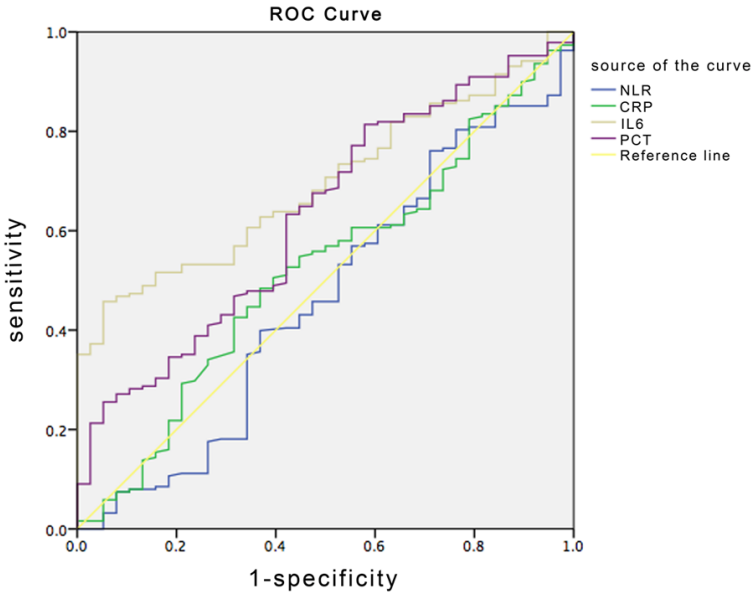

Figure 2. ROC curve analysis showing the differential diagnosis performance of IL-6, PCT, NLR, and CRP in discriminating GN-BSI from Fungal-BSI in febrile patients at the Fever Clinic. The AUCs of IL-6, PCT, NLR, and CRP were 0.695, 0.630, 0.461, and 0.519, respectively.

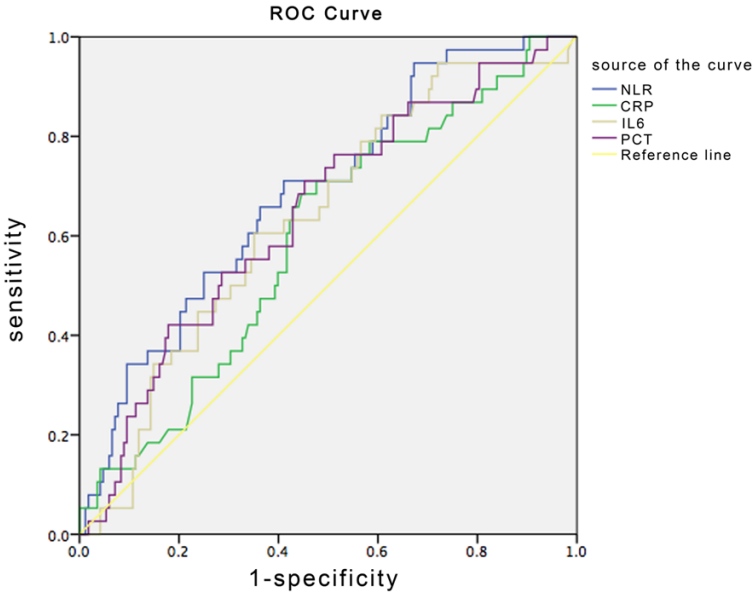

Figure 3. ROC curve analysis showing the differential diagnosis performance of IL-6, PCT, NLR, and CRP in discriminating Fungal-BSI from GP-BSI in febrile patients at the Fever Clinic. The AUCs of IL-6, PCT, NLR, and CRP were 0.635, 0.644, 0.685, and 0.594, respectively.

IL-6 and PCT. However, when discriminating Fungal-BSI from GP-BSI, the NLR exhibited an AUC of 0.685 (95% CI: 0.646-0.727, $P<0.001$) with a best cut-off value of 9.03. This was superior to those of IL-6, PCT, and CRP. There were no significant differences in levels of IL-6, PCT, and CRP in Fungal-BSI and GP-BSI groups (P=0.169, P=0.080, and P=0.558, respectively). Present results and the involved mechanisms, however, require further verification and exploration.

There were several limitations to the current study. First, this study was retrospective. A low number (n=38) of febrile patients with fungal infections were enrolled, reflecting the low prevalence of fungal BSI. Second, it was difficult to distinguish between CoNS (contaminants or infections unknown) and real infections. In this study, 13 blood culture results indicating CoNS, together with samples from patients infected with 39 other contaminants, were excluded. This may have generated selection bias. More rigorous inclusion and exclusion criteria should be established in future studies, eliminating the impact of contaminants as much as possible. Third, the predictive efficacy of each single indicator was assessed. However, the value of combinations of two or more factors was not evaluated. This should be addressed in future studies. The utility of these biomarkers in predicting bloodstream infections caused by different pathogens needs to be assessed in the future.

Disclosure of conflict of interest

None.

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Table 6. AUCs of the ROC for IL-6, PCT, NLR, and CRP and the best cut-off values in discriminating GN-BSI from GP-BSI in febrile patients

	GN-BSI vs GP-BSI						
	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index (%)
IL-6 (pg/ml)	232.5	0.767	59.6	84.5	79.4	67.7	44.1
PCT (ng/ml)	0.767	0.751	79.3	61.3	67.2	74.8	40.6
NLR	9.65	0.654	63.3	62.5	62.8	63.0	25.8
CRP (mg/l)	59.7	0.600	64.4	55.4	59.1	60.9	19.8

Table 7. AUCs of the ROC for IL-6, PCT, NLR, and CRP and the best cut-off values in discriminating GN-BSI from Fungal-BSI in febrile patients

	GN-BSI vs Fungal-BSI						
	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index (%)
IL-6 (pg/ml)	464.3	0.695	45.7	94.7	89.6	63.6	40.4
PCT (ng/ml)	0.68	0.630	81.4	42.1	58.4	69.4	23.5
NLR	6.58	0.461	76.1	28.9	51.7	54.7	5.0
CRP (mg/l)	92.5	0.519	48.4	63.2	56.8	55.1	11.6

Table 8. AUCs of the ROC for IL-6, PCT, NLR, and CRP and the best cut-off values in discriminating Fungal-BSI from GP-BSI in febrile patients

	Fungal-BSI vs GP-BSI						
	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index (%)
IL-6 (pg/ml)	79.59	0.635	60.5	64.9	63.3	62.2	25.4
PCT (ng/ml)	0.46	0.644	71.1	54.8	61.1	65.5	25.9
NLR	9.03	0.685	71.1	58.9	63.4	67.1	30.0
CRP (mg/l)	59.8	0.594	68.4	55.4	60.5	63.7	23.8

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