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Accuracy of blood heparin-binding protein (HBP) for diagnosis bacteremia in patients with sepsis

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Blood heparin-binding protein (HBP) for diagnosing bacteremia in patients with sepsis has not been fully investigated. This study aims to explore the diagnostic value of blood HBP in predicting bacteremia in patients with sepsis compared with procalcitonin (PCT), Interleukin 6 (IL-6), C-reactive protein (CRP), white blood count (WBC), and neutrophil. In this observational study, we enrolled consecutive 146 patients, who were divided into two groups as the bacteremia group ($n = 57$) and the control group ($n = 89$). HBP, PCT, IL-6, CRP, WBC, and neutrophil were measured. The Chi-squared test and Student's t-test were used to compare the baseline characteristics. The area under the receiver operating characteristic curve (AUC) was calculated to describe the diagnostic accuracy of the biomarkers for predicting bacteremia in patients with sepsis. Spearman's correlation was used to analyze associations between the biomarkers. The concentration of HBP (204.13 ± 87.30 ng/mL) in the bacteremia group was significantly higher than that in the control group (81.43 ± 61.53). HBP achieved the largest AUC for predicting bacteremia, with a value of 0.88 (95% confidence interval [CI], 0.82–0.94). This value was higher than those of the other biomarkers: 0.78 (95% CI 0.69–0.86) for PCT, 0.59 (95% CI 0.48–0.70) for IL-6, 0.56 (95% CI 0.45–0.67) for WBC, 0.73 (95% CI 0.64–0.83) for CRP, and 0.64 (95% CI 0.53–0.74) for neutrophil. The best cut-off value of blood HBP for identifying bacteremia was 95.69 ng/mL, with a sensitivity of 88.64%, a specificity of 68.06%, a positive predictive value of 64.1%, and a negative predictive value of 89.71%. A significant association was found between HBP and CRP (Spearman's rho = 0.528, $p < 0.01$). However, the correlations among PCT, IL-6, WBC, and neutrophil (Spearman's rho < 0.5, $p < 0.01$) were relatively weak. Blood HBP may be a useful auxiliary diagnostic marker that is preferable over PCT, IL-6, CRP, WBC, and neutrophil in identifying bacteremia in patients with sepsis.

Keywords Blood heparin-binding protein, Bacteremia, Sepsis, Infection, Biomarker

Abbreviations
HBP Heparin-binding protein
PCT Procalcitonin
IL-6 Interleukin 6
CRP C-reactive protein
WBC White blood counts
BNP Brain natriuretic peptide (NT-pro)
AST Aspartate aminotransferase
ALT Alanine aminotransferase
ICU Intensive care medicine

Sepsis is an ongoing and substantial challenge in global healthcare, and it significantly contributes to morbidity and mortality rates associated with hospitalization[1]. Sepsis and septic shock are significant global healthcare challenges, which affect millions of individuals annually[2,3]. Sepsis can develop in any individual who is infected, and its incidence among hospitalized patients is estimated to be as high as 1–2%[4]. Sepsis is characterized as

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a critical condition where organ dysfunction arises due to an imbalanced host response to infection, which poses a life-threatening situation[5]. The pathophysiological process of sepsis involves an intricate disruption of the delicate equilibrium between pro- and anti-inflammatory responses[6]. The activation of immune cells by invading microorganisms or damaged tissue elements can trigger the release of proinflammatory cytokines, reactive oxygen species, and enzymes[7]. The widespread use of antibiotics in recent years has resulted in a rise in antibiotic resistance, which significantly impacts the effectiveness of treatment outcomes[5,8]. Long-term sepsis leads to immunosuppression, which is characterized by increased release of anti-inflammatory cytokines, immunocyte death, decreased HLA-DR expression, increased expression of negative costimulatory molecules, and expansion of immunomodulatory cells[5]. Research indicates that sepsis leads to substantial reductions in CD4 and CD8 T cells, which significantly impair immune responses and diminish the ability of the host to combat microbial threats[9]. Early detection and timely intervention in the critical hours following the onset of sepsis greatly enhance prognosis and overall patient outcomes[10,11]. Therefore, discovering new biomarkers that can enable the early, precise, and effective identification of pathogens is crucial. Newer markers such as heparin-binding protein (HBP) are being increasingly explored for sepsis diagnosis to address the aforementioned challenges[7,12].

HBP, which is also known as the cationic antimicrobial protein of 37 kDa (CAP37) or azurocidin, is a protein found in neutrophil granules; it was first discovered and identified in 1984 by Shafer et al.[13]. HBP is swiftly released from activated neutrophils during the initial stages of inflammation, as a response to infections[14]. This characteristic positions HBP as a promising biomarker with increasing relevance in the diagnosis of infectious diseases[15,16]. The protein has demonstrated its superior performance to procalcitonin (PCT), Interleukin 6 (IL-6), and C-reactive protein (CRP) in early detection of infections[17–19]. Similarly, HBP has exhibited a more potent diagnostic capacity for sepsis[20–22]. To date, blood culture, which is the current important indicator for sepsis diagnosis and management, has inherent limitations. It requires several days to produce conclusive results and can yield false negatives due to pre-emptive antibiotic administration. However, existing evidence on the accuracy of HBP to predict positive blood bacterial cultures in septic patients is still lacking. This research aims to assess the value of blood HBP in identifying bacteremia in patients with sepsis.

Methods

Study design and patient population

This retrospective observational study was conducted at the Chinese PLA General Hospital between December 2021 and August 2023. Eligible subjects who were older than 18 years of age and met the SEPSIS-3 criteria were enrolled in the study[23]. Exclusion criteria were subjects who had undergone operation and experienced trauma within the past 24 h, which may be affect the expression of HBP, those receiving immunosuppressive therapy (e.g., organ transplants, rheumatological, and autoimmune diseases), pregnant individuals, and those younger than 18 years. Patients who had already received empiric antibiotic therapy prior to sampling were not excluded from the study. The project protocol was approved by the ethics committee of the Chinese PLA General Hospital and was conducted in accordance with the relevant guidelines/recommendations. Patient informed consent was waived given the retrospective nature of this study. Demographic data of the patients, including age, sex, laboratory test findings, duration of intensive care unit (ICU) stay, clinical outcomes, and causes of ICU admission, were obtained from their medical records. Based on the clinical manifestations and blood culture results, the patients were categorized into two groups: the bacteremia group and the control group.

Blood sample collection and analysis

Blood samples were collected from patients when patients were diagnosed with sepsis during 24 h. If sepsis is diagnosed upon admission to the ICU, a blood sample will be collected at that time. Our department has been using standardized blood culture collection methods to prevent contamination during the blood culture process. In order to prevent blood culture contamination from affecting the accuracy of results, infections of unknown origin have been excluded from this study. Blood samples were collected from the patients for HBP, PCT, IL-6, CRP, WBC, neutrophil, and culture analyses. The blood samples were collected in 5 ml sodium citrate anticoagulation tubes and centrifuged at 3,000 rpm for 10 min immediately. The HBP level was measured using a commercially available immunofluorescence dry quantitation method assay kit (Joinstar Biomedical Technology Co., Ltd., Hangzhou, China). The assay kit had a detection range for HBP of 5.9–300 ng/mL. The detection methods for PCT, IL-6, and CRP were electrochemiluminescence, chemiluminescence, and nephelometry, respectively.

Statistical analysis

Baseline characteristics were compared using the Chi-squared test, while group comparisons and subgroup analyses were conducted using the Student's t-test. The diagnostic accuracy of blood biomarkers was assessed by calculating the area under the receiver operating characteristic curve (AUC). Considering the positive correlations observed in previous studies among HBP, PCT, WBC, IL-6, CRP, and neutrophil, Spearman's correlation analysis was conducted to examine the associations among these biomarkers. The analysis involved controlling the effect of one biomarker while assessing the correlation between the two others. Statistical significance was defined as a p-value less than 0.05. All statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software (https://www.graphpad.com), USA) and SPSS version 29.0 (IBM Corporation, USA).

Results

Baseline characteristics

Blood samples were collected from 171 patients who were diagnosed with sepsis and underwent blood culture. However, 25 patients were ultimately excluded due to surgeries or trauma within the past 24 h, which could potentially affect the expression of HBP[24,25]. A total of 146 samples were analyzed, including 57 samples from the bacteremia group and 89 samples from the control group. Table 1 presents a comprehensive summary of the baseline characteristics for 146 patients. No statistically significant differences were observed in the demographic characteristics and medical conditions between the two groups, and no statistically significant differences were found in the proportion of causes of ICU admission between the two groups. The liver function, kidney function, brain natriuretic peptide, and ICU days showed no significant differences between the two groups.

Variable	Bacteria($n = 57$)	Control($n = 89$)	P value
Sex (n, % male)	43(75.44)	54(60.67%)	0.07
Age (year)	63.6 ± 17.02	63.18 ± 17.46	0.8
Causes of ICU admission (n)			
Postoperative surgery	24	23	0.05
Multiple injuries	7	13	0.81
Respiratory disease	4	12	0.28
Digestive system disease	3	10	0.08
Heatstroke	3	5	0.99
Central nervous system disease	2	4	0.99
Cardiovascular disease	2	3	0.99
Other disease	12	16	0.67
Main comorbidities (n)			
MODS	22	35	0.99
respiratory failure	6	11	0.80
renal failure	3	6	0.99
cardiac insufficiency	1	2	0.99
pulmonary infection	3	6	0.99
perforation of the digestive tract	1	4	0.65
ileus	1	2	0.99
Other comorbidities	20	23	0.26
HBP (ng/mL)	204.13 ± 87.30	81.43 ± 61.53	$p < 0.001$
PCT (ng/mL)	15.00 ± 40.35	3.89 ± 12.12	$p < 0.01$
IL-6 (pg/ml)	462.7 ± 995.58	202.8 ± 319.14	$p < 0.05$
WBC (10^9/L)	13.48 ± 7.95	11.14 ± 5.49	$p < 0.05$
CRP (mg/dl)	10.48 ± 7.27	5.816 ± 5.05	$p < 0.001$
Neutrophil	0.87 ± 0.08	0.83 ± 0.13	0.057
BNP (pg/ml)	6651.27 ± 10420.44	4693.95 ± 9458.49	0.26
AST	93.12 ± 320.366	78.98 ± 220.46	0.76
ALT	77.61 ± 243.24	66.82 ± 113.06	0.73
Creatinine	129.9 ± 154.32	113 ± 127.58	0.49
Lactate	1.685 ± 1.47	1.689 ± 1.67	0.98
Glucose	8.285 ± 3.10	7.931 ± 2.63	0.48
ICU days	20(2 ~ 374)	20(1 ~ 406)	0.58
ICU mortality (n, %)	13(22.4)	18(20.2)	0.84
CRRT	17(29.82)	24(26.97)	0.71
Mechanical ventilation	52(91.23)	72(80.90)	0.1
SOFA	9.79 ± 4.78	10.36 ± 4.23	0.46
APACHE II	19.21 ± 6.94	20.93 + 6.80	0.15

Table 1. General characteristics of the study subjects. Notes *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *BNP* brain natriuretic peptide (NT-pro), *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICU* Intensive care medicine, *CRRT* continuous renal replacement therapy, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation (APACHE) II, *MODS* Multiple organ dysfunction syndrome.

Bacteria of positive blood cultures

As summarized in Tables 2 and 57 patients were tested positive for bacterial growth in their blood cultures, which resulted in 64 instances of blood culture-positive bacteria. Gram-positive and Gram-negative mixed infections were found in 7 of the patients who tested positive in blood culture. Other patients showed a positive culture only from a single Gram-positive or Gram-negative bacterium. Among these bacteria, the most prevalent Gram-positive bacterium was *Staphylococcus*, which accounted for 43.8%. The main sources of coagulase - negative staphylococci include pneumonia(10, 35.72%), gastrointestinal tract(5, 17.86%), urinary tract infection (5, 17.86%), central venous catheters (2, 7.14%), and other foci of infections (6, 21.43%). The most prevalent Gram-negative bacterium was *Klebsiella pneumoniae*, which accounted for 17.2%. Other bacteria recorded included *Acinetobacter baumannii*, *Escherichia coli*, *Enterococcus*, *Pseudomonas aeruginosa*, *Clostridium septicum*, *Enterobacter aerogenes*, *Eliza meningosepticum*, *Clostridium perfringens*, *Klebsiella oxytoca*, *Serratia marcescens*, and *Proteus mirabilis*.

Value of blood HBP for predicting bacteremia in patients with sepsis

We found that blood parameters (HBP, PCT, IL-6, CRP, and WBC) universally increased in the bacteremia group compared with the control group (Fig. 1). The concentration of HBP (204.13 ± 87.30 ng/mL) in the bacteremia group was significantly higher than that in the control group (81.43 ± 61.53 ng/mL). The receiver operating characteristic (ROC) curve for the discrimination of bacteremia and blood culture negative showed that blood HBP achieved the largest AUC of 0.88 (95% confidence interval [CI], 0.82–0.94), which was higher than those of the other biomarkers: 0.78 (95% CI 0.69–0.86) for PCT, 0.59 (95% CI 0.48–0.70) for IL-6, 0.73 (95% CI 0.64–0.83) for CRP, 0.56 for WBC (95% CI 0.45–0.67), and 0.64 (95% CI 0.53–0.74) for neutrophil (Fig. 2). The best cut-off value of blood HBP for identifying bacteremia was 95.69 ng/mL, with a sensitivity of 88.64%, a specificity of 68.06%, a positive predictive value of 64.1%, and a negative predictive value of 89.71% (Table 3). The sensitivity and specificity of PCT for distinguishing bacteremia and blood culture negative were found to be 95.45 and 51.39%, respectively. Those of IL-6, CRP, WBC, and neutrophil were found to be 34.09 and 84.72, 68.2 and 70.8, 33.33 and 83.34%, and 52.3 and 76.4%, respectively (Table 3).

Correlation between blood biomarkers

A strong association existed between HBP and CRP (Spearman's rho = 0.528, $p < 0.001$). However, the correlations among PCT, IL-6, WBC, and neutrophil (Spearman's rho < 0.5, $p < 0.001$/ $p < 0.05$) were relatively weak (Table 4; Fig. 3).

Diagnostic accuracy of blood HBP in patients who received empiric antibiotics in ICU

A total of 102 patients were documented to have received empiric antimicrobial therapy prior to sampling in ICU. No statistical significance was found in the concentrations of blood HBP, PCT, IL-6, CRP, WBC, and neutrophil between the patients who received empiric antibacterial therapy ($n = 102$) and those who did not in ICU ($n = 44$) (Figure S1).

Diagnostic accuracy of blood HBP in identifying Gram-positive and Gram-negative bacteria

There was no significant difference in the levels of HBP, PCT, IL-6, CRP, WBC and neutrophil between the Gram-positive group and Gram-negative group (Figure S2). We then further evaluated the diagnostic efficiency of these parameters using ROC analysis. The receiver operating ROC curve analysis was conducted to evaluate

Bacteria	Classification	N (%)
Staphylococcus	Gram-positive	28(43.8)
staphylococcus epidermidis		*11(39.3)*
staphylococcus hominis		*8(28.6)*
staphylococcus capitis		*5(17.9)*
staphylococcus aureus		*3(10.7)*
staphylococcus warneri		*1(3.6)*
Klebsiella pneumoniae	Gram-negative	11(17.2)
Acinetobacter baumannii	Gram-negative	6(9.4)
Escherichia coli	Gram-negative	4(6.3)
Enterococcus	Gram-positive	3(4.7)
Pseudomonas aeruginosa	Gram-negative	3(4.7)
Clostridium septicum	Gram-positive	2(3.1)
Enterobacter aerogenes	Gram-negative	2(3.1)
Eliza meningosepticum	Gram-negative	1(1.6)
Clostridium perfringens	Gram-positive	1(1.6)
Klebsiella oxytoca	Gram-negative	1(1.6)
Serratia marcescens	Gram-negative	1(1.6)
Proteus mirabilis	Gram-negative	1(1.6)

Table 2. Bacteria of positive blood cultures.
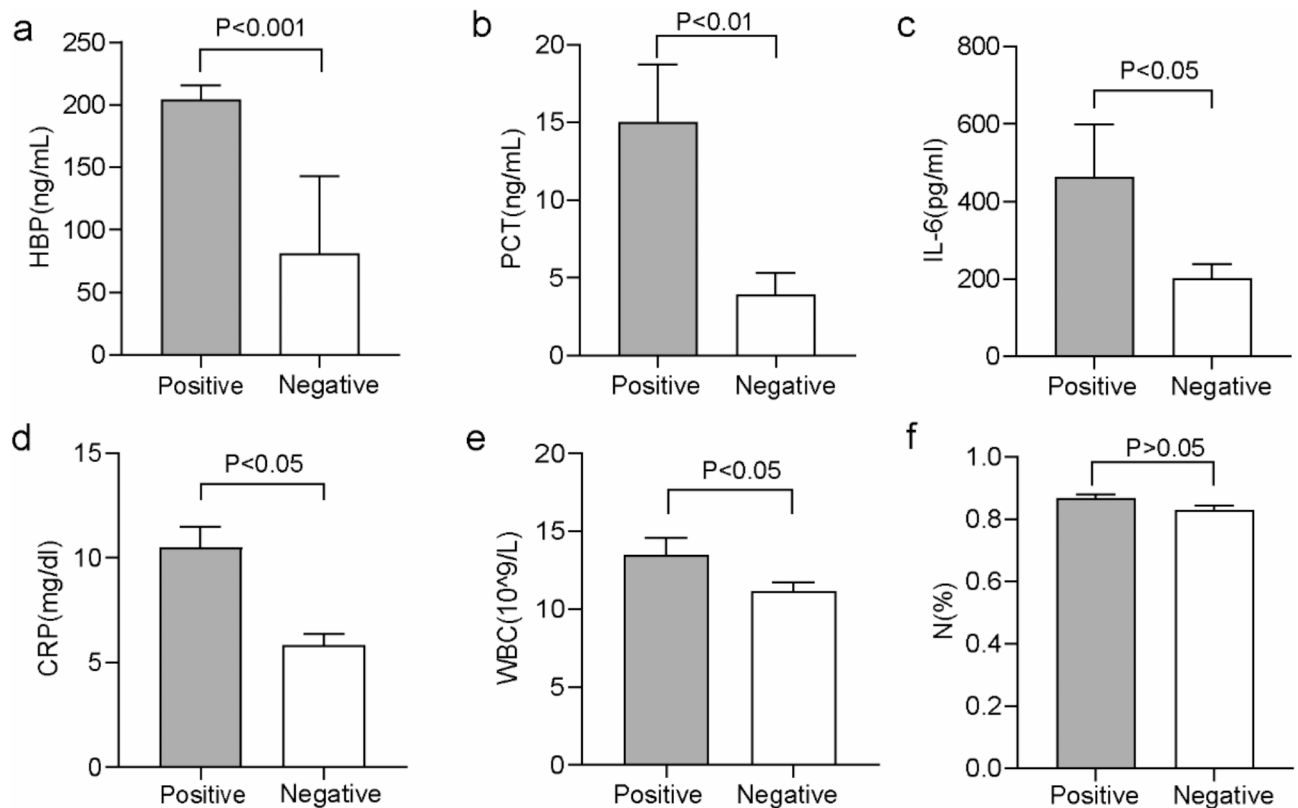
Fig. 1. Levels of HBP, PCT, CRP, IL-6, WBC and neutrophil in blood. (**A**)HBP; (**B**)PCT; (**C**)IL-6; (**D**) CRP; (**E**) WBC; (**F**) neutrophil. *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *N* neutrophil.

the ability of various parameters (HBP, PCT, IL-6, CRP, WBC, and neutrophil) to discriminate between Gram-positive and Gram-negative bacterial infections. However, the areas under the curves of HBP, PCT, IL-6, CRP, WBC and neutrophil were 0.535, 0.583, 0.422, 0.538, 0.424 and 0.436 respectively. The results indicated that none of these parameters showed discriminatory power in distinguishing between Gram-positive and Gram-negative bacterial infections (Figure S3).

Discussion

We found that HBP achieved the largest AUC as a diagnostic marker compared with PCT, IL-6, CRP, WBC, and neutrophil for diagnosing bacteremia in patients with sepsis. The concentrations of HBP, PCT, IL-6, CRP, WBC, and neutrophil were significantly higher in the bacteremia patients than in the blood culture negative patients. In addition, the subgroup analysis failed to ascertain the ability of blood HBP in identifying Gram-positive and Gram-negative bacterial infection and the influence on HBP levels of empiric antibiotics.

Our data confirmed previous research suggesting that the concentration of HBP was significantly increased in bacterial sepsis patients compared with those with non-bacterial infection[26,27]. However, plasma HBP levels appeared to be the most reliable parameter for distinguishing between severe sepsis and mild infection[7]. At a cut-off level of 15 ng/ml, the sensitivity for HBP in diagnosing severe sepsis was 87%, and the specificity was 95%[28]. Another previous study showed the best cut-off value of concentration of HBP for identifying sepsis and non-sepsis patients was 30 ng/mL[29]. By contrast, a cut-off value of HBP ≥ 95.69 ng/mL gave a sensitivity of 88.64% and a specificity of 68.06% in diagnosing bacteremia in patients with sepsis in the present study. In differentiating sepsis patients with positive blood culture results, HBP displayed enhanced diagnostic ability compared with PCT, IL-6, CRP, WBC, and neutrophil counts. This insight is helpful for rapid treatment decision making by clinicians.

HBP is a granular protein that is generated during the maturation process in the bone marrow and later released by neutrophils at the site of inflammation, and bacteria can induce the synthesis and secretion of HBP by neutrophils[7]. In healthy individuals, blood levels of HBP are exceedingly low. Upon the onset of an infection, certain pathogens can infiltrate the bloodstream and stimulate neutrophils to secrete HBP, which results in an elevation of HBP levels in the blood. The production and release of HBP have been documented in various bacterial infections[30]. Previous studies have shown that blood HBP could have a significant clinical potential for early identification of patients with sepsis[28]. Clinicians should exercise caution when dealing with sepsis patients who present increased blood HBP levels. In such cases, the presence of bacterial infections should be considered until a negative blood culture is obtained. Despite the numerous advancements in technology, obtaining a blood
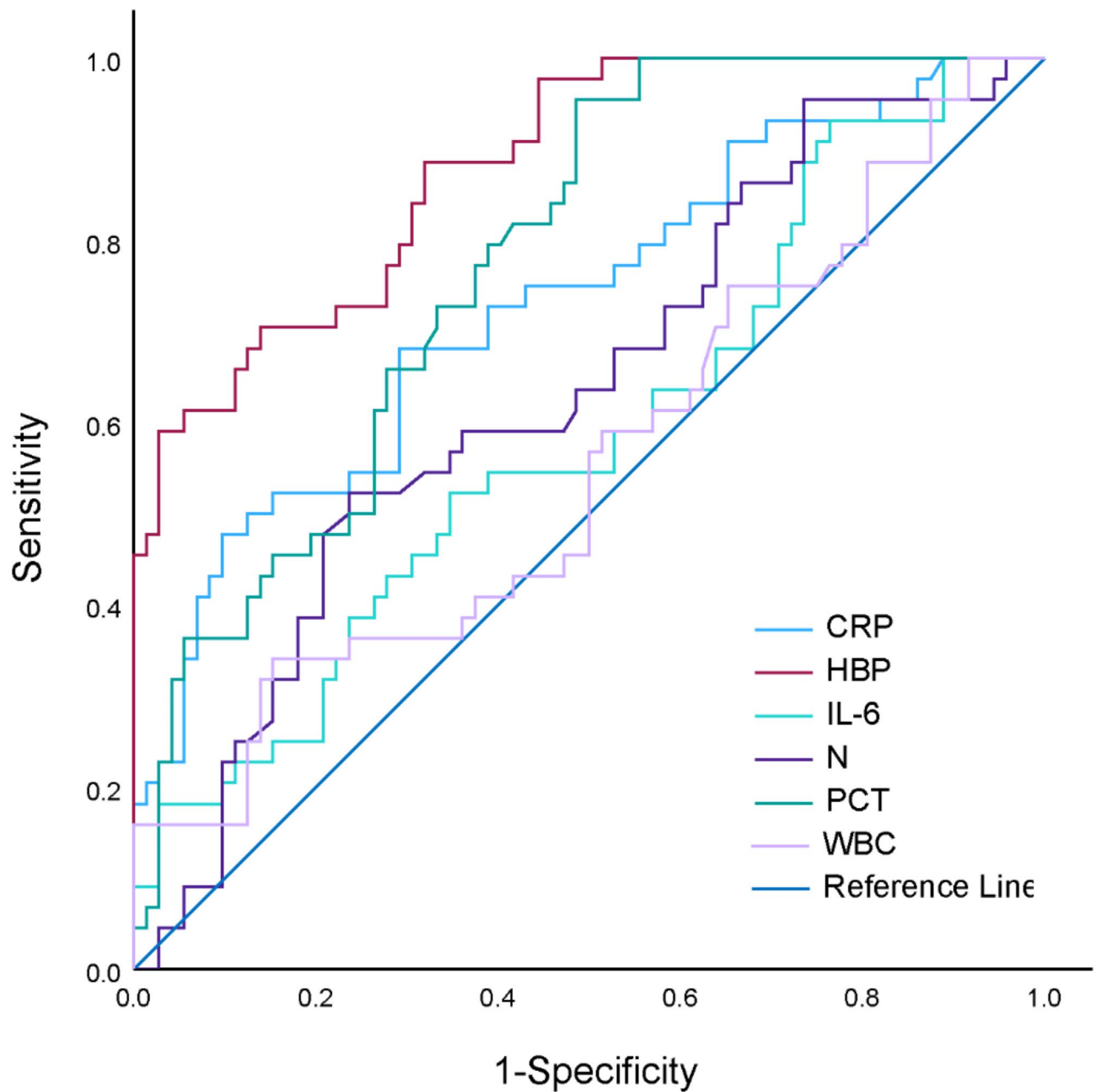
Fig. 2. ROC curves of blood biomarkers for diagnosing bacteremia in patients with sepsis. *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *N* neutrophil.

Parameters	HBP (ng/mL)	PCT (ng/mL)	IL-6(pg/ml)	CRP (mg/dl)	WBC (10^9/L)	N (%)
Area	0.88	0.78	0.59	0.73	0.56	0.64
p values (comparison of AUCs of other biomarkers versus HBP)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Cutoff level	95.69	0.4255	16.84	7.17	16.05	0.91
Sensitivity (%)	88.64	95.45	34.09	68.2	33.33	52.3
Specificity (%)	68.06	51.39	84.72	70.8	83.34	76.4
Positive predictive value (%)	64.1	54.46	60.6	60	55.89	58.82
Negative predictive value (%)	89.71	95.56	67.26	77.78	66.07	71.58

Table 3. Diagnostic efficiency of blood biomarkers. Notes *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *N* neutrophil.

Biomarkers	Spearman's correlation coefficients	P Value
HBP-PCT	0.43	p < 0.001
HBP-CRP	0.528	p < 0.001
HBP-IL-6	0.304	p < 0.001
HBP-WBC	0.208	p < 0.05
HBP-N	0.213	p < 0.05

Table 4. Spearman's correlation coefficients. Notes *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *N* neutrophil.
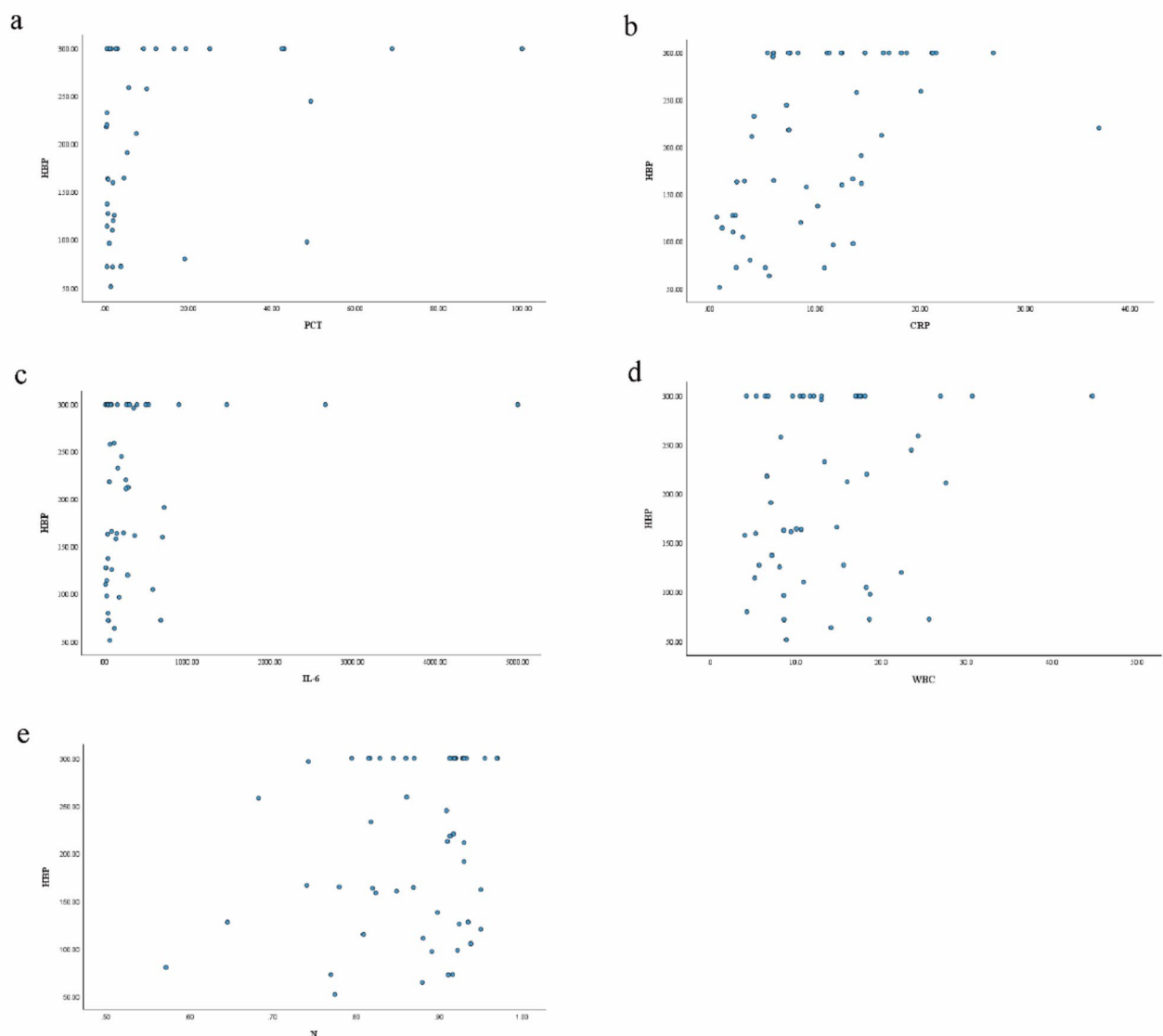
Fig. 3. Correlation between HBP and other blood biomarkers. (**A**)HBP and PCT; (**B**) HBP and CRP; (**C**) HBP and IL-6; (**D**) HBP and WBC; (**E**) HBP and neutrophil. *HBP* heparin-binding protein, *PCT* procalcitonin, *IL-6* Interleukin 6, *CRP* C-reactive protein, *WBC* white blood counts, *N* neutrophil.

culture result still typically takes at least 24 h to 48 h. As a result, the subsequent delays in diagnosing and treating infections can have detrimental effects on patient care within the ICU. Therefore, HBP could serve as a useful additional tool for stratifying patients with possible bacteremia in sepsis, but it cannot substitute for blood culture results.

The correlation between HBP and PCT, IL-6, WBC, and neutrophil was weak in our study, although a previous study showed that plasma HBP was positively correlated with serum PCT, WBC, and neutrophil in

patients[31]. However, in keeping with another previous study[32], our study demonstrated significant correlation between HBP and CRP. This finding aligns with the conclusion drawn in a previous study, which indicated that plasma HBP levels serve as significant biomarkers for assessing inflammatory response in patients with sepsis[33].

Unexpectedly, our results indicated that patients with sepsis who received empirical antimicrobial therapy did not exhibit a significant difference in HBP levels compared with those who did not. Our results are consistent with the findings of a previous study[34]. Blood HBP could serve as a valuable marker in resolving diagnostic dilemmas encountered in these patients. In our study, we also evaluated the diagnostic accuracy of blood HBP in identifying Gram-positive and Gram-negative bacteria. However, no statistical significance was found in blood HBP levels for identifying Gram-positive and Gram-negative bacteria.

The novelty of our study is that we demonstrated the efficacy of blood HBP in predicting bacteremia in patients with sepsis. Furthermore, our study included patients who received antibiotic therapy prior to blood culture, which aligns more closely with real-world clinical scenarios. By contrast, previous studies predominantly excluded these patients.

Our study has some limitations. First, we only recruited patients with bacterial infection and did not include those with infection of other microbes, such as fungi and viruses. Second, the numbers of cases in positive blood culture were small. Third, the majority of our patients had complications that could potentially impact the levels of biomarkers. For instance, patients with cardiovascular diseases tend to exhibit higher expression of HBP. These factors should be considered when interpreting the biomarker results for accurate assessment and treatment decisions in prospective studies. Finally, Due to the diverse sources of patients in our department, such as those after surgical operations, from the emergency department, and transferred from other hospitals, etc., many patients are very likely to have been treated with antibiotics before they are admitted to the ICU. Nevertheless, we are unable to obtain the data of each patient prior to their admission to the ICU. Therefore, the actual proportion of empirical antibiotic application may far exceed the data we presented. This is also one of the possible reasons for the insignificant difference in the expression levels of HBP between the empirical antibiotic application and the no empirical antibiotic application in our study. In the future, strict prospective studies may be able to improve this result.

Conclusions
Blood HBP may serve as a useful auxiliary diagnostic marker, which is preferable over PCT, IL-6, CRP, WBC, and neutrophil in identifying bacteremia in patients with sepsis. However, blood culture still plays a very important role in the diagnosis of sepsis. Strict prospective studies may be needed in the future to evaluate the diagnostic role of HBP for bacteremia in the ICU setting.

Data availability
All data generated or analyzed during this study are included in this published article. WSY should be contacted for data requests related to this study.

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Author contributions

ZM conceived and designed this study. MMY and Jie Gao collected data. JWZ designed and performed the statistical analyses. WSY wrote the first draft of the manuscript. FHZ, HJK and HL reviewed and modified the final manuscript. All authors approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The project protocol was approved by the ethics committee of the Chinese PLA General Hospital.

Additional information

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