

Heparin-binding protein as a biomarker of severe sepsis in the pediatric intensive care unit: A multicenter, prospective study

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Research Article

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Abstract

Background: Heparin-binding protein (HBP) is a promising candidate as a biomarker for sepsis. However, there is limited study on the use of HBP among children with sepsis in pediatric intensive care unit (PICU). The aim of this study is to assess HBP as a diagnostic and prognostic biomarker of severe sepsis in the PICU.

Methods: A multicenter, prospective study was conducted among children with sepsis and severe sepsis in nine different PICUs in China from October 2019 to June 2021. Plasma levels of HBP, procalcitonin (PCT), C-reactive protein (CRP), lactate, and white blood cell (WBC) count were determined at enrollment and 72 hours after enrollment. Receiver operating characteristic curve (ROC) analysis was used to evaluate the ability of biomarkers in diagnosing severe sepsis. Multivariate logistical analysis was performed to assess the association between biomarkers and in-hospital mortality. Spearman's correlation was used to identify the relationship between HBP and other biomarkers.

Results: Of 355 included patients, 132 patients were diagnosed with non-severe sepsis (referred to as sepsis), 223 patients had severe sepsis. Patients with severe sepsis had significantly elevated levels of HBP compared with sepsis (median 170.5 vs. 74.1 ng/mL, $P < 0.001$). Adding HBP to a diagnostic model with PCT and lactate could significantly improve the diagnostic capability for severe sepsis (area under the curve (AUC) 0.702 vs. 0.628, $p < 0.001$). The plasma levels of HBP correlated positively with the number of dysfunctional organs. After adjusting for confounding factors, the HBP levels at enrollment could not predict in-hospital mortality. However, declined levels of HBP at 72 hours had a significant association with decreased in-hospital mortality (adjusted odds ratio (aOR) 0.242, $P < 0.001$). The levels of HBP showed weak positive correlations with PCT, CRP, WBC, and no correlation to lactate.

Conclusions: HBP at enrollment can be an independent indicator for severe sepsis and the dynamic changes at 72 hours can be a predictor for in-hospital mortality in PICU.

Background

Sepsis is a major contributor to morbidity and mortality in children globally.¹ In 2017, an estimated 48.9 million (95% CI, 38.9–62.9) incident cases of sepsis were recorded worldwide and 11.0 million (95% CI, 10.1–12.0) sepsis-related deaths were reported, representing 19.7% (95% CI, 18.2–21.4) of all global death. The percentage of sepsis-related deaths was highest in early childhood among all age groups. There were an estimated 2.9 million (95% CI, 2.6–3.2) deaths related to sepsis worldwide among children younger than 5 years.² Severe sepsis is a life-threatening condition commonly treated in pediatric intensive care unit (PICU) worldwide. A meta-analysis based on 94 studies including 7561 children showed that the mortality rate in pediatric severe sepsis and septic shock was 31.7% (95% CI, 27.3%–36.4%) in developing countries, and 19.3% (95% CI, 16.4%–22.7%) in developed countries.³ Considering the high mortality of severe sepsis early recognition and risk-stratification could assist clinicians to manage the care of these patients more effectively and to improve outcome.⁴

Laboratory tools to identify patients with severe sepsis early and to stratify the severity are in high demand. Although a multitude of biomarkers have been proposed in the field of sepsis, so far none is considered adequate for routine clinical use.⁵ Heparin binding protein (HBP), also known as azurocidin or CAP37, is an antimicrobial protein stored in the secretory vesicles and azurophilic granules of neutrophils and is released when neutrophils are activated.⁶ The release of HBP has been demonstrated in various infectious diseases such as meningitis, pneumonia and urinary tract infection.⁷⁻¹⁰ HBP also has been shown to be the link in neutrophil-derived induction of vascular leakage.¹¹ These characteristics make HBP a promising candidate as a biomarker for sepsis. Previous studies have successfully evaluated plasma HBP for prognosticating infection-induced organ dysfunction (OD) in sepsis and disease severity.¹²⁻¹⁵ Most of published results regarding the powerful diagnostic and prognostic capability of HBP in adult patients with sepsis. However, the clinical value of HBP in pediatric patients has not been comprehensively assessed.

Therefore, in this study, a multicenter prospective study was performed to investigate the plasma levels of HBP among children with sepsis in PICU, aiming to 1) assess the clinical validity of HBP for diagnosing severe sepsis, and predicting in-hospital mortality, and 2) to compare the properties of HBP to other sepsis biomarkers currently in use, including lactate, procalcitonin (PCT), C-reactive protein (CRP) and white blood cell (WBC).

Methods

Study design and participants

This was a prospective, multicenter study of PICU patients with sepsis, conducted at nine children's hospitals in China from October 2019 through June 2021. This study was approved by the institutional ethics committees of the participating hospitals.

Patients < 18 years of age admitted to PICUs with sepsis were recruited. Sepsis and severe sepsis were defined according to the 2005 International Pediatric Sepsis Consensus Conference. Sepsis was defined as confirmed or suspected invasive infection with two or more systemic inflammatory response syndrome criteria; severe sepsis was defined as sepsis in addition to one of the following: cardiovascular dysfunction, acute respiratory distress syndrome, or two or more other organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic).¹⁶ Patients with neutropenia due to hematological malignancies were excluded. The final diagnosis was made by the attending physicians who were unaware of the research results.

Sample and laboratory analysis

Blood samples were collected in BD sodium citrate vacuum tubes (1.8ml) from patients at the time of inclusion (at enrollment) and again 72 hours after the initial sample (72 hours).

Samples were processed locally at each site, centrifuged at 1000 g for 10 minutes. HBP, PCT, and CRP were measured in plasma by a fluorescence dry quantitative immunoassay using the Jet-iStar 3000 analyzer (Join-Star, Hangzhou, China) according to the manufacturer's recommendations. In addition, laboratory tests including WBC count and lactate were performed as part of clinical routine at each site.

HBP levels ≤ 5.9 ng/ mL or ≥ 300 ng/mL were considered as 5.9 ng/mL and 300 ng/mL, respectively. PCT levels ≤ 0.1 ng/mL or ≥ 100 ng/ mL were considered as 0.1 ng/mL and 100 ng/mL, respectively. CRP levels ≤ 0.5 mg/L or ≥ 200 mg/L were considered as 0.5 mg/L and 200 mg/L, respectively.

Clinical data collection

All clinical data of enrolled patients were obtained from medical records, including demographics, comorbidities, medication usage, underlying infections, organ dysfunction and outcomes.

Statistical analysis

Categorical variables were expressed as numbers (%) and compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as medians (interquartile range, IQR) and were analyzed with using Mann Whitney U test.

Receiver operator characteristics (ROC) curves were drawn and the areas under the curve (AUC) were calculated to assess the diagnostic power of biomarkers and different diagnostic models. To assess the value of HBP on diagnosing severe sepsis beyond other conventional biomarkers, we established 2 diagnostic models. Model 1 was a conventional diagnostic model including PCT and lactate. These biomarkers were chosen based on ROC analyses for each biomarker in the study. Model 2 was a novel model which additionally add HBP to the model 1. The diagnostic models were based on the predicted probabilities of a multivariate logistic regression model. The AUCs for these were compared using the DeLong's test. Youden's index was used to choose the best cut-off points for assessment of sensitivity and specificity.

Jonckheere-Tepstra trend test was used to verify whether the levels of HBP increased with the number of dysfunctional organs.

Multivariate logistic regression analysis was done to evaluate the association of HBP and other biomarkers (levels at enrollment; dynamic changes at 72 hours) with in-hospital mortality among children with sepsis. We adjusted for age, sex and the presence of comorbidity. The results were described as the adjusted odds ratio (aOR) and 95% confidence interval (CI).

Spearman non-parametric correlation was used for calculating the correlations between HBP and other biomarkers.

All of the tests were two tailed, and a value of $P < 0.05$ represented statistical significance. Statistical analyses were conducted in SPSS version 26.0 software (IBM, New York, USA) or MedCalc version 20.1 software (MedCalc, Mariakerke, Belgium).

Results

Characteristics of the patients

Table 1 displays the baseline clinical characteristics of the patients included in the study. A total of 355 PICU patients with sepsis were enrolled in the study. According to the 2005 International Pediatric Sepsis Consensus, the research subjects were divided into non-severe sepsis group (referred to as sepsis group) (n=132) and severe sepsis group (n=223). The overall median age was 15 months (IRQ 5 to 55) and 58.6% were male. Patients with severe sepsis were older than patients with sepsis.

One hundred fifty-one (42.5%) patients had at least one comorbidity. The most common comorbidity was immunological diseases (11.8%), followed by cardiovascular diseases (8.2%), gastrointestinal diseases (5.4%) and metabolic diseases (3.7%). There was no significant difference in the proportion of comorbidities among groups. The respiratory tract infection was the predominant source of infection in all groups, followed by gastrointestinal tract, central nervous system and genitourinary infections. Respiratory tract infections had a higher prevalence in the severe sepsis group. Of all patients, 290 (81.7%) had at least one organ dysfunction with respiratory (59.2%) and cardiovascular (40.0%) dysfunctions the most common.

The in-hospital mortality of the entire cohort was 20.3%, while the median length of PICU stay were 9 days (IRQ 6 to 15). Mortality among patients in severe sepsis group was significantly higher compared to sepsis group. There was no significant difference in the length of PICU stay between groups.

Higher HBP levels in patients with severe sepsis

At the time of inclusion, the concentration of HBP in the severe sepsis group (median 170.5 ng/mL, IQR 46.1-300) was significantly greater than that in the sepsis group (median 74.1 ng/mL, IQR 24.5-175.5). PCT and lactate levels were also significantly higher ($P<0.01$) but there was no significant difference in CRP ($P=0.892$) or WBC levels ($P=0.088$) in the severe sepsis group compared to sepsis group (Figure 1).

HBP significantly improves diagnostic value

ROC analyses were performed for HBP and other biomarkers to discriminate between severe sepsis and sepsis. The AUC for HBP, PCT and lactate was 0.640 (95% CI: 0.582-0.698), 0.623 (95% CI: 0.564-0.683), and 0.589 (95% CI: 0.526-0.652), respectively (Table 2). The optimal cutoff level was 193.6 ng/ml for HBP, with sensitivity of 0.48 and specificity of 0.81. Although the AUC for HBP was higher than PCT and lactate, there was no significant difference when using DeLong's test (Table 2) (Figure 2A).

We next explored whether inclusion of HBP could improve and allow better recognition of patients with severe sepsis. The diagnostic value was assessed using 2 models (Model 1: PCT and lactate; model 2: model 1 + HBP). The AUC for model 2 was 0.702 (95% CI: 0.647-0.752), which was significantly higher than model 1 (AUC: 0.628; 95% CI: 0.571-0.682) (Table 2) (Figure 2B). Thus, the inclusion of HBP to the model with PCT and lactate levels significantly improved the diagnostic value for severe sepsis.

HBP levels are related to the severity of the disease

The severity of the sepsis was stratified based on number of dysfunctional organs. Median HBP level at the inclusion significantly increased along with the number of dysfunctional organs with a monotonic trend, as demonstrated with a Jonckheere–Terpstra test (Figure 3A). Statistically significant increasing trends were also observed in the level of PCT and Lactate (Figure 3B, C), while the level of WBC decreased as the number of dysfunctional organs increased (Figure 3D). There was no significant association between CRP level and the number of dysfunctional organs (Figure 3E).

Dynamics of HBP is associated with in-hospital mortality

In total, 72 out of 355 patients (20.3%) died during the study. The results of multivariate logistic regression indicated that the declined level of HBP at 72 hours (compare with levels at enrollment) had a statistically significant association with decreased patient mortality (aOR: 0.242; 95% CI [0.116–0.507]; $P < 0.001$) (Figure 4). However, no significant association was found between HBP levels at enrollment and mortality (Figure 4). A decrease in PCT levels at 72 hours was also associated with decreased mortality (aOR: 0.368; 95% CI [0.172–0.789]; $P = 0.010$) (Figure 4). Higher lactate levels (aOR: 0.368; 95% CI [0.172–0.789]; $P = 0.010$) and lower CRP levels (aOR: 0.368; 95% CI [0.172–0.789]; $P = 0.010$) at enrollment were associated with increased mortality (Figure 4).

Correlations of HBP with other biomarkers

The levels of HBP showed weak positive correlations with PCT ($r = 0.184$; $P < 0.001$), CRP ($r = 0.130$; $P < 0.015$), WBC ($r = 0.108$; $P = 0.043$) and no correlation to lactate (Figure 5).

Discussion

Early diagnosis and evaluation of severe sepsis are crucial for physician to modify treatments and associated with decreased in-hospital mortality.¹⁷ In this multicenter prospective study, the utility of HBP was assessed among children with sepsis in PICUs. We found HBP to be a promising biomarker that distinguished severe sepsis from sepsis and combination of HBP with PCT and lactate could significantly improve the diagnostic value for severe sepsis. Moreover, the dynamic changes of HBP at 72 hours after enrollment could predict in-hospital mortality among children with sepsis in PICU.

HBP acts as an amplifier of inflammatory responses and induces capillary leakage, both of which are highly dysregulated in severe sepsis.⁶ As expected, we observed that the levels of HBP at enrollment were significantly higher in severe sepsis group (median 170.5 ng/mL) compared with sepsis group (median 74.1 ng/mL). Our results are consistent with previous researches in adult patients. Linder et al. reported that HBP levels were significantly higher in the severe sepsis group (median 28 ng/mL) as compared to the patients with non-septic critical condition (median 14.5 ng/mL) in ICU.¹⁴ Similar results were also obtained among adult patients with sepsis under Sepsis-3 criteria (sepsis defined as organ dysfunction caused by infection).^{18–20} In addition, our study showed that the HBP levels at enrollment significantly

increased along with the number of dysfunctional organs, implying that HBP is a marker of disease severity. This is in keeping with a study conducted in adult Emergency Department.¹³ Taken together, those results further prove the key role of HBP in the pathophysiology of organ dysfunction in sepsis, not only in adults but also in children. Of note, the median values of HBP in children with severe sepsis were significantly higher than in adults reported in previous studies.^{14, 19–21} One plausible explanation for these differences is that the activation of peripheral blood neutrophils might be varied among children and adults. Differences in baseline characteristics such as the presence of comorbidity or receipt of steroids, may also explain such differences. Larger cohort studies are needed to further verify those results.

The diagnostic capability of HBP as a biomarker in severe sepsis has been evaluated in previous cohort studies among adults. Linder et al. reported that a cut-off level for HBP of ≥ 15 ng/mL showed a sensitivity of 87.1% and a specificity of 95.1% in diagnosing severe sepsis from control group (sepsis, infection without SIRS, and SIRS without infection).²¹ Zhou et al. revealed that a cut-off value for HBP of ≥ 28.1 ng/mL gave a sensitivity of 84.9% and a specificity of 78.3% in diagnosing sepsis (sepsis-3 criteria) from infected people.²⁰ The diagnostic capability of HBP was higher than other tested biomarkers (e.g. PCT, CRP and lactate) in both studies. In the present study, the results of the ROC curve analysis also showed that HBP had the highest AUC, followed by PCT and lactate. However, there was no significant difference of AUC between HBP and PCT or lactate when using Delong's test, which means the diagnostic capability of HBP was not significantly superior to PCT and lactate in distinguishing severe sepsis from sepsis. Whereas, the diagnostic capability was significantly improved when adding HBP to the diagnostic model with PCT and lactate (AUC 0.702 vs. 0.628, $P < 0.001$). We also found that there was little correlation of HBP with other biomarkers, indicating that HBP provides separate information as a biomarker. These observations suggested that HBP levels were associated with severe sepsis independent of PCT and lactate levels, and the combination of HBP, PCT and lactate to diagnose children with severe sepsis was considered as a superior approach in clinical practice.

We found that initial plasma HBP at enrollment was not associated with in-hospital mortality after adjusting for age, sex and the presence of comorbidity. The results were concordant with prior studies of HBP in sepsis, which showed that HBP could not predict 28-day mortality in the emergency department and the plasma levels of HBP did not correlate with survival in non-septic and septic patients with shock.^{19, 22} However, an important new finding in our study was that the declined level of HBP at 72 hours had a significant association with decreased in-hospital mortality and the prognostic value of HBP dynamic changes was better than the other biomarkers. These findings suggested that serial plasma HBP measurements provided useful prognostic information in children with sepsis and the dynamic of HBP could potentially be used to inform medical decision to improve patient outcomes in PICU.

Our study had several strengths. First, this was the first large prospective, multicenter study evaluating the role of HBP as a biomarker in the diagnosis and prognosis of severe sepsis in children. Second, the patients included in this study involve a broad range of diagnoses and comorbidities in nine PICUs in

China, which provided more applicable results for children with sepsis in PICU. Third, the plasma levels of HBP, PCT and CRP were simultaneously detected in the same plasma sample, which made the results more comparable. Fourth, with all patients reviewed by at least two PICU physicians according to the 2005 International Pediatric Sepsis Consensus, the diagnosis of sepsis was accurately determined.

The study also had some limitations. First, this study included only pediatric patients who were diagnosed with sepsis and critically ill in PICU. Thus, the results may not be generalizable to patients with sepsis in emerging department or general ward. Second, there were a lot of HBP levels exceeding the detection limit (300 ng/mL), especially in the severe sepsis group, which might decrease the statistical power. Third, critically ill patients without sepsis were not enrolled as control in this study. Chew et al. found elevated HBP levels in some patients with noninfectious shock.²² Further investigations are needed to better address to what extent HBP is specifically associated with sepsis in children.

Conclusions

Our study reveals that the initial plasma HBP level at enrollment could be a useful biomarker to diagnose severe sepsis and was related to the severity of disease in PICU. The declined level of HBP at 72 hours had a statistically significant association with decreased patient mortality. The levels of HBP showed weak positive correlations with PCT, CRP, WBC, and no correlation to lactate. Further studies are needed to validate these findings in patients with sepsis in PICU.

Abbreviations

PICU: pediatric intensive care unit; HBP: Heparin binding protein; OD: organ dysfunction; PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell; IQR: interquartile range; ROC: Receiver operator characteristics; AUC: areas under the curve; aOR: adjusted odds ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committees of the participating hospitals. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Declaration of Competing Interest

None

Availability of data and materials

Additional data are available from the first author and corresponding author upon reasonable request.

Competing interests

The authors declared no competing interests.

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Authors' contributions

PL, JX, SS, LM and WQ conceived and designed the experiments; PL, DC, JL, CH, YZ, CW, HW, GY, ZZ, FG, LG, GL, LM, and SD performed the experiments and collected the clinical information; JX, DC, JL and CH interpreted the data. PL wrote the manuscript. JX revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of the study population

	Overall (n=355)	Sepsis (n=132)	Severe sepsis (n=223)	<i>P</i> value*
Demographics				
Age, median (IQR), m	15 (5-55)	13 (4-37)	16 (6-72)	0.032
Male, n (%)	208 (58.6)	78 (59.1)	130 (58.3)	0.883
Comorbidity, n (%)				
Immunological	42 (11.8)	16 (12.1)	26 (11.7)	0.896
Cardiovascular	29 (8.2)	9 (6.8)	20 (9.0)	0.475
Gastrointestinal	19 (5.4)	7 (5.3)	12 (5.4)	0.975
Metabolic	13 (3.7)	2 (1.5)	11 (4.9)	0.172
Malignancy (blood)	11 (3.1)	3 (2.3)	8 (3.6)	0.708
Malignancy (solid)	11 (3.1)	5 (3.8)	6 (2.7)	0.795
Other congenital defect	9 (2.5)	5 (3.8)	4 (1.8)	0.420
Neuromuscular	7 (2.0)	2 (1.5)	5 (2.2)	0.935
Renal and urological	7 (2.0)	1 (0.8)	6 (2.7)	0.384
postoperative	4 (1.1)	1 (0.8)	3 (1.3)	1.000
Respiratory	1 (0.3)	1 (0.8)	0 (0.0)	0.372
No comorbidities	204 (57.5)	80 (60.6)	124 (55.6)	0.359
Source of infection, n (%)				
Respiratory	201 (56.6)	61 (46.2)	140 (62.8)	0.002
Gastrointestinal	105 (29.6)	36 (27.3)	69 (30.9)	0.464
Central nervous system	68 (19.2)	30 (22.7)	38 (17.0)	0.188
Genitourinary	22 (6.2)	9 (6.8)	13 (5.8)	0.709
Other	12 (3.4)	7 (5.3)	5 (2.2)	0.216
unknown	22 (6.2)	9 (6.8)	13 (5.8)	0.709
Organ dysfunction, n (%)				
Respiratory	210	40 (30.3)	210 (76.2)	<0.001

	(59.2)			
Cardiovascular	142 (40.0)	0 (0.0)	142 (63.7)	<0.001
Hepatic	111 (31.3)	16 (12.1)	95(42.6)	<0.001
Hematologic	85 (23.9)	6 (4.5)	79 (35.4)	<0.001
Neurologic	61 (17.2)	5 (3.8)	56 (25.1)	<0.001
Renal	33 (9.3)	0 (0.0)	33 (14.8)	<0.001
None	65 (18.3)	65 (49.2)	0 (0.0)	<0.001
Treatment with antibiotics (before inclusion), n (%)	318 (89.6)	115 (87.1)	203 (91.0)	0.244
Outcome				
In-hospital mortality, n (%)	72 (20.3)	7 (5.3)	65 (29.1)	<0.001
Length of PICU stay, median (IQR), d	9 (6-15)	9 (6-14)	10 (6-16)	0.731

* Comparison between sepsis group and severe sepsis group. Abbreviations: IQR, interquartile range; m, months; d, days.

Table 2. Performance of biomarkers and models to discriminate severe sepsis from sepsis.

	AUC (95% CI)	Cut off value	Sensitivity (%)	Specificity (%)	<i>P</i> value	<i>P</i> value (versus HBP)*	<i>P</i> value (versus model 1)*
Biomarkers							
HBP	0.640 (0.582-0.698)	193.55	47.95	81.06	<0.001	-	-
PCT	0.623 (0.564-0.683)	11.5	48.62	71.54	<0.001	0.726	-
Lactate	0.589 (0.526-0.652)	3.3	23.9	95.37	0.010	0.192	-
WBC	0.554 (0.493-0.615)	8.82	42.15	69.70	0.083	0.052	-
CRP	0.504 (0.451-0.558)	6.93	14.61	92.42	0.890	0.003	-
Models							
Model 1	0.628 (0.571-0.682)	-	37.31	87.85	<0.001	-	-
Model 2	0.702 (0.647-0.752)	-	57.71	78.5	<0.001	-	0.0101

*Discrimination of the different biomarkers and models was assessed by comparing the AUC using the DeLong's test. Model 1: PCT + Lactate; Model 2: model 1 + HBP.

Abbreviations: AUC, area under the curve; CI, confidence interval; HBP, heparin binding protein; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein.

Figures

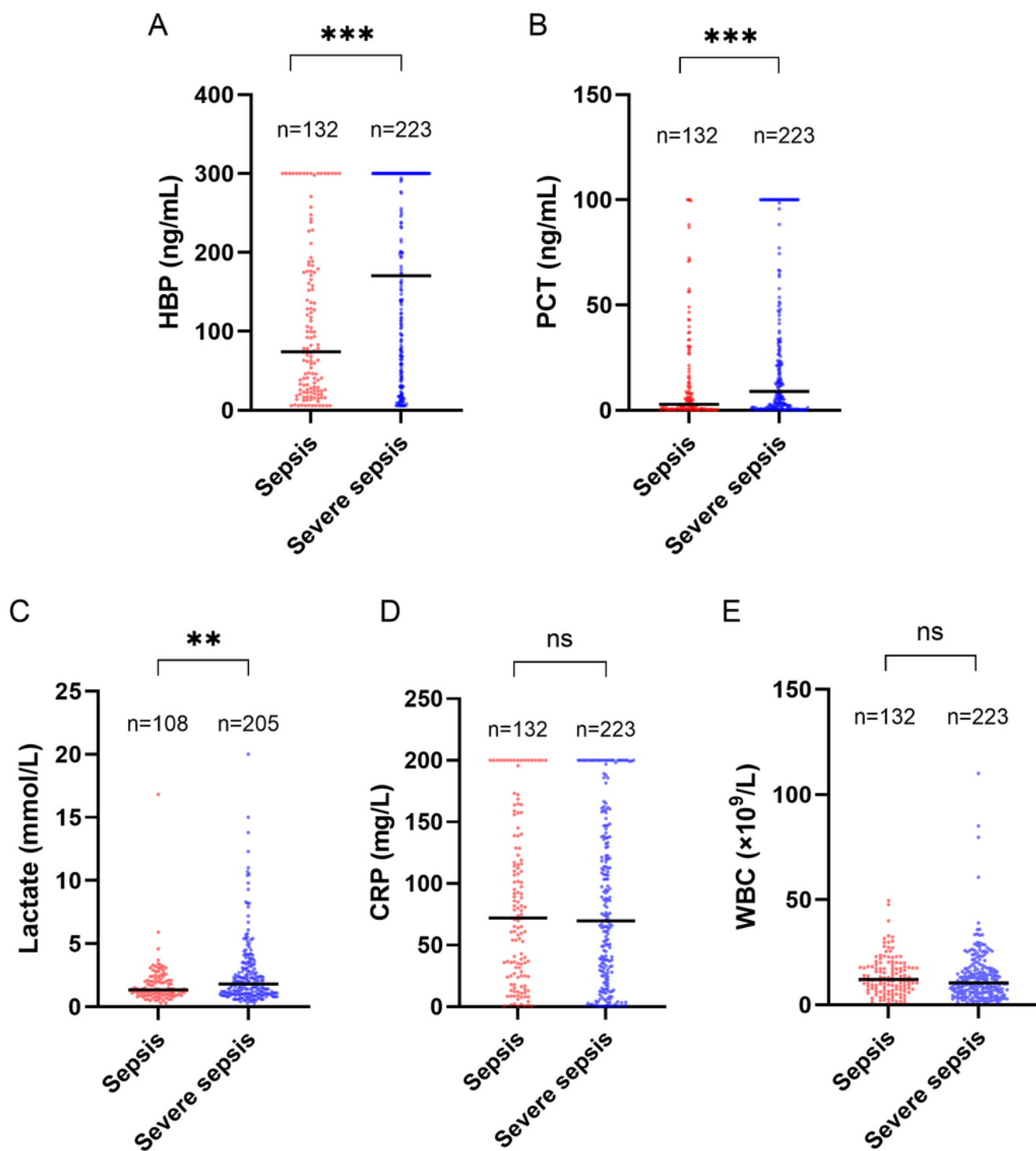


Figure 1

levels of HBP (A), PCT (B), Lactate (C), CRP (D) and WBC (E) measured at the time of inclusion in patients with sepsis and severe sepsis. Each dot represents the concentration in an individual plasma sample at enrollment. Statistical evaluations were made with Mann-Whitney test. **: significant level at P value < 0.01 ; ***: significant level at P value < 0.001 ; ns: not significant. HBP, heparin-binding protein; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell.

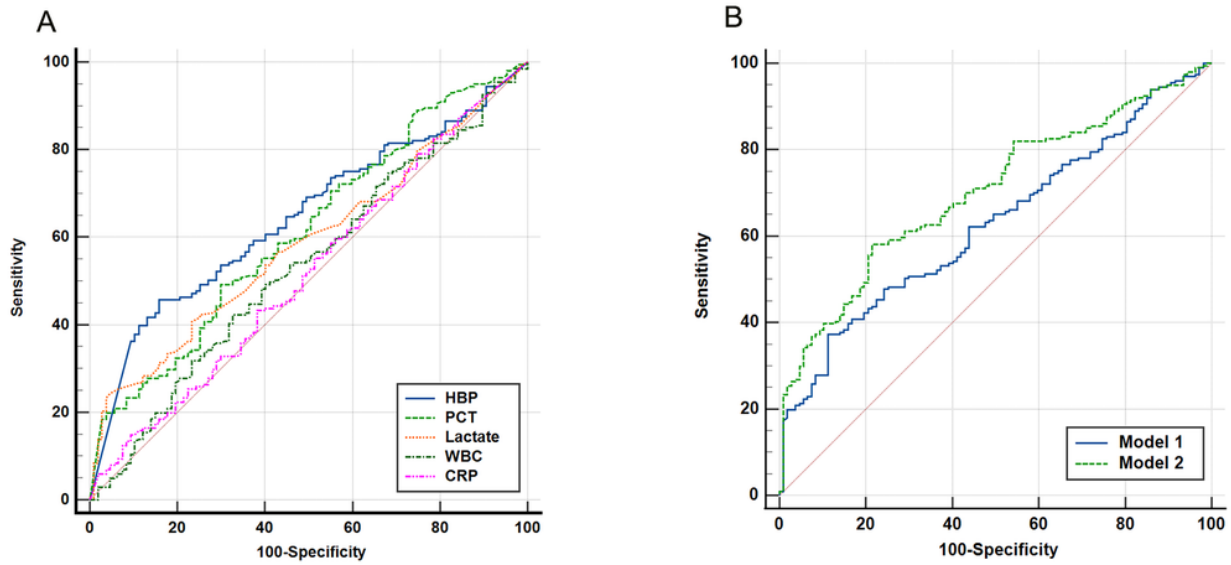


Figure 2

ROC curves for biomarkers and models in distinguishing severe sepsis from sepsis. (A) ROC curves are shown comparing the diagnostic value of HBP, PCT, lactate, WBC, and CRP. (B) ROC curves are shown comparing the diagnostic value of model 1 and model 2. Model 1: PCT + lactate; Model 2: Model 1 + HBP. Abbreviations: ROC, receiver operator characteristics; HBP, heparin binding protein; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein.

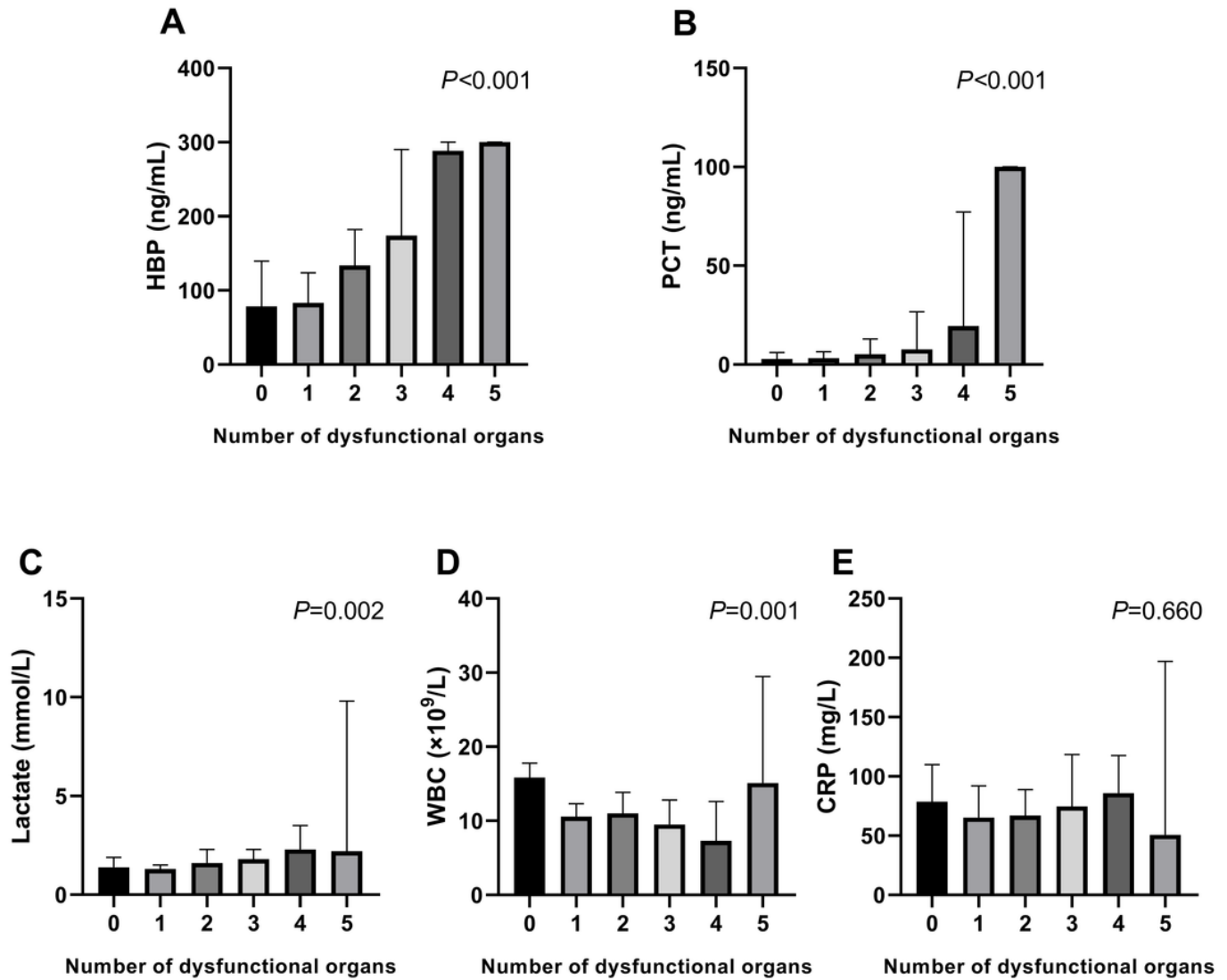


Figure 3

Trends of HBP and other biomarkers by the number of dysfunctional organs. The levels of HBP (A), PCT (B), and lactate (C) increased with the number of dysfunctional organs. The level of WBC (D) decreased with increasing number of dysfunctional organs. The level of CRP (E) has no significant association with the number of dysfunctional organs. The trends of biomarkers were assessed using Jonckheere – Terpstra test. Bar graph show median values and 95% confidence intervals. HBP, heparin binding protein; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein.

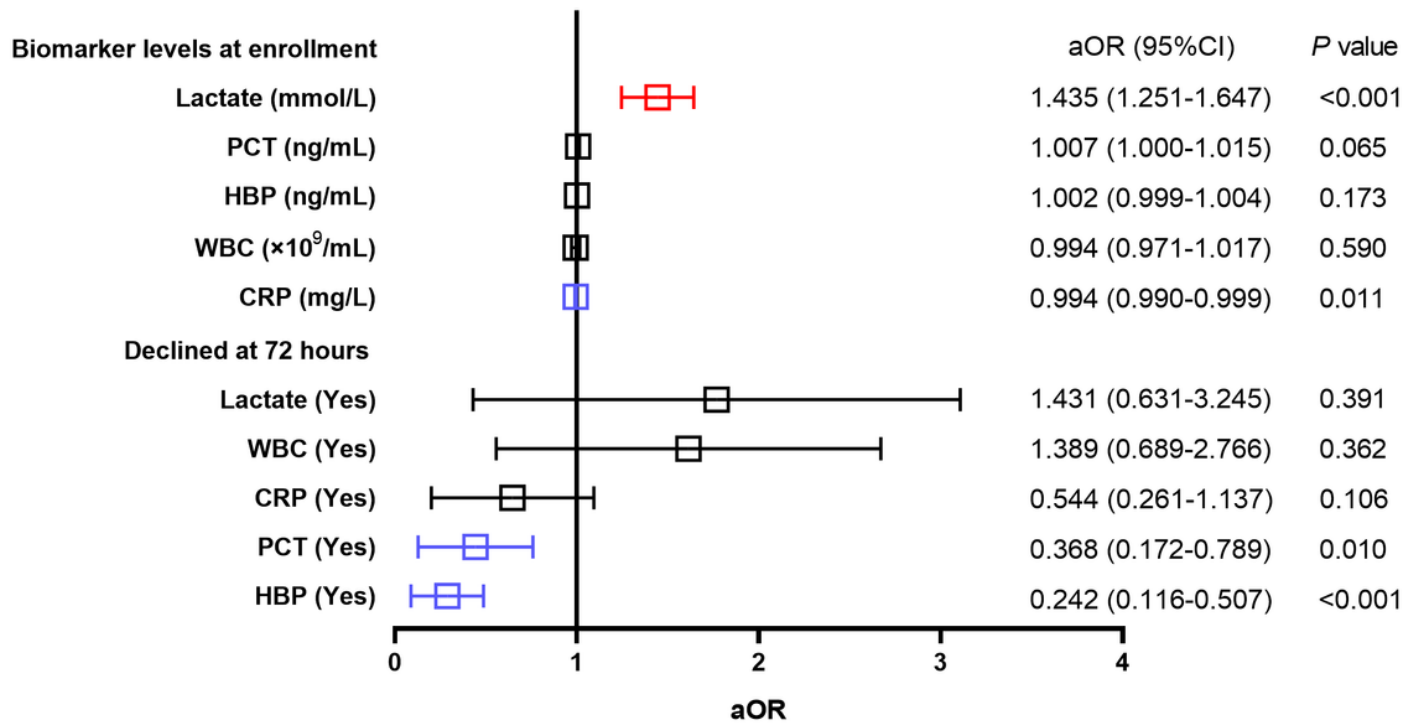


Figure 4

Multivariable logistic regression analysis evaluating the association between biomarkers and in-hospital mortality among patients with sepsis. Confounding factors including age, sex and the presence of comorbidity were adjusted in the model. aOR CIs significantly associated with mortality ($P < 0.05$) are shown in red when aOR > 1 and in blue when aOR < 1 . aOR, adjusted odds ratio; CI, confidence interval; HBP, heparin binding protein; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein.

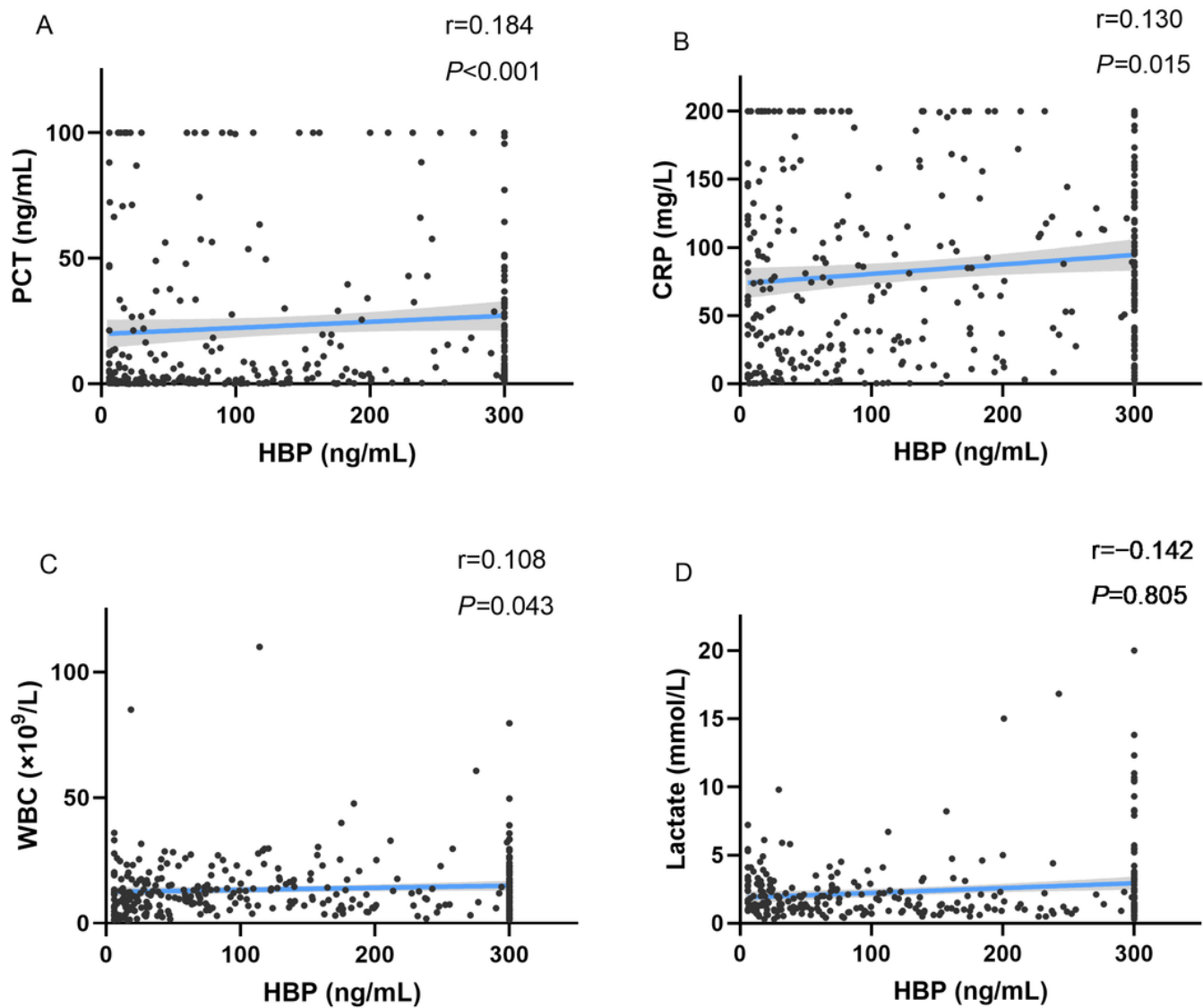


Figure 5

The correlations of HBP with PCT (A), CRP (B), WBC (C) and lactate (D). Concentrations of biomarkers were measured at enrollment. HBP, heparin binding protein; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein.