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Diagnostic and prognostic value of serum osteopontin in pediatric sepsis: a prospective cohort study compared with procalcitonin and C-reactive protein

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Abstract

Background

Sepsis remains a leading cause of morbidity and mortality in children. Early and accurate diagnosis is critical for improving outcomes, yet current biomarkers like procalcitonin (PCT) and C-reactive protein (CRP) lack sufficient specificity. Osteopontin (OPN), a glycoprotein involved in inflammation and immune response, has shown promise as a biomarker in adult sepsis, but its value in the pediatric population remains unclear.

Methods

In this prospective cohort study, we measured serum OPN, PCT, and CRP levels in 108 children with sepsis, 77 children with common infections, and 65 healthy controls. The primary objective was to evaluate the diagnostic and prognostic performance of OPN for pediatric sepsis.

Results

Serum OPN levels were significantly elevated in children with sepsis compared to both common infection and healthy control groups ($P < 0.001$). Notably, OPN levels did not differ significantly between the common infection and healthy groups, highlighting its specificity for sepsis-related organ dysfunction. The area under the receiver operating characteristic curve (AUC) for OPN in diagnosing sepsis was 0.94 (95% CI: 0.91–0.98), which was superior to that of PCT (0.83) and CRP (0.76). At a cutoff of 132.8 ng/mL, OPN demonstrated a sensitivity of 85.2% and a remarkable specificity of 98.7%. While a single admission OPN measurement did not significantly predict 28-day mortality, longitudinal monitoring in a subgroup revealed that persistently elevated or rising OPN levels were associated with non-survival.

Conclusions

Serum OPN is a highly specific and sensitive biomarker for diagnosing pediatric sepsis, outperforming conventional markers. While a single measurement may not predict prognosis, dynamic monitoring of OPN levels shows potential for identifying patients at risk of adverse outcomes.

BACKGROUND

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host immune response to infection, poses a significant global health burden, particularly for children[1]. Despite advances in critical care, pediatric sepsis is associated with high morbidity and mortality, with an estimated death rate of 8 ~ 10%[2]. The cornerstone of sepsis management is the timely administration of appropriate antimicrobial therapy and supportive care; delays of even one hour are associated with a significant increase in mortality[3]. Therefore, the development of reliable tools for the early and accurate diagnosis of sepsis is paramount.

Diagnosing sepsis in children is notoriously challenging due to the nonspecific nature of clinical signs, which often overlap with those of less severe infections. While biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) are widely used, their utility is limited by suboptimal specificity, as their levels can be elevated in various inflammatory and infectious conditions without organ dysfunction[4–7]. This underscores the urgent need for novel biomarkers that can more accurately distinguish sepsis from uncomplicated infections in the pediatric population.

Osteopontin (OPN), also known as secreted phosphoprotein 1, is a pleiotropic glycoprotein expressed by various immune cells, including macrophages and T lymphocytes, as well as endothelial cells[8]. It plays a crucial role in mediating inflammation, cell migration, and vascular permeability—key pathophysiological processes in sepsis[9–13]. In adult studies, elevated plasma OPN levels have been strongly associated with the severity of sepsis, organ failure, and mortality[14–16]. Similarly, high OPN levels have been linked to adverse outcomes in other critical inflammatory conditions like severe COVID-19[17]. Although one study identified increased OPN expression in the myocardial tissue of children who died from sepsis[18], clinical evidence regarding the diagnostic and prognostic value of circulating OPN levels in pediatric sepsis is lacking.

This study aims to bridge this knowledge gap by evaluating the performance of serum OPN as a diagnostic and prognostic biomarker in a prospective cohort of children with sepsis, comparing its efficacy directly with the conventional biomarkers PCT and CRP.

METHODS

Study subjects

This prospective cohort study was conducted at the Children's Hospital of Chongqing Medical University, China, between July 1, 2021, and March 31, 2023. The study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Fig. 1).

We enrolled children (< 18 years old) diagnosed with sepsis based on the International Pediatric Sepsis Consensus Conference criteria, which required a confirmed or suspected infection and a pediatric sequential organ failure assessment (pSOFA) score ≥ 2[19–20]. Septic shock was defined as sepsis with cardiovascular dysfunction requiring vasoactive support. Key exclusion criteria included known immunodeficiency, current use of immunosuppressants, and age < 28 days.Sepsis management in the hospital unit was based on the Surviving Sepsis Campaign recommendations[21–22].

Two control groups were recruited for comparison: (1) a 'common infection' group, consisting of children with localized infections but no evidence of organ dysfunction (pSOFA score < 2), and (2) a 'healthy control' group of children undergoing routine physical examinations with no signs of acute illness.

The study protocol was approved by the Institutional Review Board of the Children's Hospital of Chongqing Medical University (No. 2021325-1), and written informed consent was obtained from the parents or guardians of all participants.This research was registered in the National Health Security Information Platform (No. MR-50-24-001771).

Data extraction

Demographic data (age, gender), clinical characteristics, infection source, and outcomes were collected from electronic medical records. Laboratory parameters, including complete blood count (CBC), CRP, and PCT, were recorded upon admission to the pediatric intensive care unit (PICU). The pSOFA score was calculated for all sepsis patients at the time of PICU admission.

Determination of serum OPN concentration

Venous blood samples were collected from sepsis patients on days 1, 3, and 7 of their PICU stay. For both control groups, a single sample was collected upon enrollment. Serum was isolated and stored at − 80℃until analysis. Serum OPN concentrations were measured using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (FineTest, Palm Coast, FL, USA; batch no. EH0248), according to the manufacturer's instructions. The assay's detection range was 0.156 ~ 10 ng/mL, with a sensitivity of 0.094 ng/mL.

Statistical analysis

Sample size was calculated using PASS15 software (NCSS, Kaysville, UT, USA). To achieve a pre-experimental area under the receiver operating characteristic (ROC) curve (AUC) > 0.9, with an ineffective hypothesis of 0.8, a ratio of healthy to diseased individuals of 0.7 in the target population, a two-sided α of 0.05, and a power of 0.90, the PASS15 software (NCSS) predicted that at least 90 and 63 complete medical records were needed for the sepsis group and the common infection group, respectively. Cases with missing key outcome data were excluded from the specific analysis involving those variables. No imputation was performed due to the low rate of missingness (< 5%).

Categorical variables were expressed as percentages. Normally distributed or approximately normally distributed continuous variables were presented as the mean ± standard deviation. Non-normally distributed continuous variables were presented as the median with interquartile range. The chi-square test was used in the analysis of categorical variables. The independent sample t-test was used to compare two groups for normally distributed or approximately normally distributed continuous variables. The non-parametric Mann-Whitney U test was used in the analysis of non-normally distributed continuous variables. The above statistical methods were used for the preliminary screening of diagnostic and prognostic risk factors for pediatric sepsis. A P-value < 0.05 was considered as a measure of statistical significance.

Variables with a P < 0.05 in univariate analysis, along with potential confounding factors including age, gender, presence of underlying comorbidities, and pSOFA score, were included in the multivariate binary logistic regression model to determine independent predictive factors for pediatric sepsis. ROC curve analysis was performed to determine the AUC for each indicator, calculate the optimal cutoff point, and compare sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value. GraphPad Prism 9.5, SPSS 26.0, and R Studio were used to perform the statistical analyses and generate graphs.

RESULTS

Baseline characteristics of the study population

A total of 250 children were enrolled: 108 with sepsis, 77 with common infections, and 65 healthy controls (Fig. 1). The baseline characteristics are detailed in Table 1. The sepsis and common infection groups were comparable in terms of age, gender, and prevalence of underlying comorbidities. The 28-day mortality rate among the patients with sepsis was 24.1%(26/108). Sepsis patients who had an unfavorable prognosis (death) had significantly higher pSOFA scores upon admission to the PICU than those who had a favorable prognosis(12.5 vs 6.57, $P < 0.001$).

Table 1
Demographic and clinical characteristics of patients with sepsis and control subjects

	All patients(n = 184)	**Septic group(n = 108)**	**Common infection group(n = 77)**	**P value**
Clinical parameters				
Male, N(%)	94(50.8%)	5(46.3%)	44(57.1%)	0.057
Age (months), N(%)	24.0(8.5–69.6)	23.0(8.4–85.0)	24.0(10.1–57.0)	0.494
Bacteria-infected,N(%)	76(41.1%)	46(42.6%)	30(39.0%)	0.652
Virus-infected,N(%)	61(33.0%)	26(24.1%)	35(45.5%)	0.003*
Other pathogen - infection,N(%)	10(5.4%)	4(3.7%)	6(7.8%)	0.324
Mixed-infection,N(%)	38(20.5%)	32(29.6%)	6(7.8%)	<0.001*
respiratory infection,N(%)	129(69.7%)	56(51.9%)	73(94.8%)	<0.001*
Other system infection,N(%)	56(30.3%)	52(48.1%)	4(5.2%)	<0.001*
Combined underlying disease,N(%)	44(23.8%)	27(25%)	17(22.1%)	0.727
Laboratory data	Laboratory data			
WBC(10^9/L)	10.5(6.3–16.1)	11.2(5.7–19.2)	10.1(7.0-13.2)	0.211
NE(10^9/L)	5.4(2.8–10.4)	7.3(3.5–14.3)	4.1(2.3–6.3)	<0.001*
LYM(10^9/L)	2.5(1.2–4.5)	2.0(0.9–3.9)	3.4(1.6–5.2)	0.003*
PLT(10^9/L)	266.5(153.5-384.5)	210.0(66.0-327.0)	324.0(242.0-430.5)	<0.001*
TBIL(μmol/L)	7.4(4.2–13.5)	10.4(6.2–23.0)	5.0(3.5–7.5)	<0.001*
Cr(μmol/L)	29.0(22.0-45.8)	32.5(20.0-66.5)	26.0(23.0–32.0)	0.020*
CRP(mg/L)	18.0(6.9–64.6)	41.0(8.6-109.8)	7.0(1.5–25.8)	<0.001*
PCT(ng/ml)	0.4(0.1–3.4)	2.1(0.4–26.8)	0.10(0.08–0.25)	<0.001*
OPN(ng/ml)	132.8(54.5-511.4)	440.3(222.9-653.1)	53.9(33.8–76.7)	<0.001*
Score	Score			
Psofa	1.0(0.0–1.0)	7.0(4.0–11.0)	0.0(0.0–0.0)	<0.001*

* and bold indicate P < 0.05, and the difference was statistically significant

A univariate analysis of clinical and laboratory data revealed that a higher proportion of patients in the sepsis group had mixed infections than in the common infection group (29.6% vs 7.8%, $P < 0.001$); in accordance, fewer infections in the sepsis group were caused by a single virus (24.1% vs 45.5%, $P = 0.003$). We next evaluated the source of infection and found that the proportion of patients with non-respiratory infections was significantly higher in the sepsis group than in the common infection group (48.1% vs 5.2%, $P < 0.001$). There were no significant differences between the two groups in terms of age, gender ratio, proportion of patients with single bacterial infections or other types of infections, and underlying comorbidities.

In terms of laboratory data, sepsis patients had significantly higher neutrophil counts and plasma levels of bilirubin, creatinine, procalcitonin (PCT), C-reactive protein (CRP), and OPN than individuals in the common infection group ($P < 0.05$); by contrast, lymphocyte and platelet counts were significantly lower ($P < 0.05$) in the sepsis group than in the common infection group, while the white blood cell count was not significantly different between the groups ($P = 0.163$).

Notably, the median pSOFA score of the sepsis patients was significantly higher than that of the common infection group (7.0 and 0.0, respectively) (Table 1), suggesting that patients with sepsis had severe organ dysfunction.

Serum OPN levels are significantly elevated in pediatric sepsis

The serum OPN levels of sepsis patients were significantly higher than those of the healthy group and the common infection group (Fig. 1). Furthermore, patients with septic shock had significantly higher serum OPN levels than those without septic shock (635.3 ± 531.6 vs 436.6 ± 355.6 ng/ml, $P < 0.01$) (Fig. 2); meanwhile there was no statistical difference between the serum OPN concentrations of the healthy and common infection groups (59.93 ± 33.44 vs 58.33 ± 34.04 ng/ml, $P = 0.999$) (Fig. 2).

Among the patients with sepsis, 27 had identifiable non-infectious underlying diseases, including airway developmental abnormalities, cardiovascular developmental abnormalities, and genitourinary system malformations; however, there was no significant difference in the serum OPN concentrations of patients with and those without underlying comorbidities (Supplementary Fig. 1A).

Among the patients with sepsis, 42.6% (46/108) had bacterial infections, 24.1% (26/108) had viral infections, 3.7% (4/108) had other pathogenic infections (e.g., fungi, mycoplasma, and *Mycobacterium tuberculosis*), and 29.6% (32/108) had mixed infections involving multiple types of microorganisms. We found no significant difference in the serum OPN concentrations among these four groups (Supplementary Fig. 1B), indicating that OPN elevation is driven by the septic host response itself, rather than being confounded by specific underlying comorbidities or pathogen types.

Serum OPN levels correlate with inflammatory marker expression and pSOFA score

A total of 29 patients with sepsis underwent testing for interleukin (IL)-6 and IL-10 on the day of PICU admission. Linear correlation analysis was performed to assess the relationship between the IL-6/10 and OPN

levels in the 29 patients. These 29 children were not specially selected, but only received blood samples for the determination of inflammatory factors. Furthermore, we conducted a linear correlation analysis between serum OPN levels and several other laboratory parameters, as well as pSOFA score, in all sepsis patients, including those with and those without septic shock (n = 108). The results revealed a positive correlation between serum OPN levels and IL-10 ($r = 0.5$, $P < 0.01$) (Fig. 3A), as well as PCT ($r = 0.2$, $P < 0.05$) (Fig. 3B), creatinine ($r = 0.3$, $P < 0.001$) (Fig. 3C), and pSOFA score ($r = 0.3$, $P < 0.001$) (Fig. 3D).

Conversely, a negative correlation was observed between OPN levels and platelet count ($r=-0.2$, $P < 0.05$). No linear correlation was found between OPN levels and IL-6 concentration (Supplementary Fig. 2).

Kinetics of serum OPN levels during early treatment in the PICU

Although the serum OPN levels of septic patients with a poor prognosis (death) were higher than those of septic patients with a good prognosis (survival) on the day of admission to the PICU, this difference did not reach statistical significance ($P > 0.05$). Due to several clinical (withdrawal or death) and financial reasons, only 25 cases were monitored continuously for three days. 25 sepsis patients (20 survivors and five non-survivors) underwent serum OPN concentration monitoring on days 1, 3, and 7 of hospitalization. Comparison of the survivor and non-survivor groups showed no significant difference in their OPN serum concentrations ($P > 0.05$); however, the non-survivor group had a higher average OPN level than the survivor group. Additionally, the OPN levels of the survivor group decreased with the duration of hospital stay, while those of the non-survivor group increased (Fig. 4). These results indicate that monitoring changes in serum OPN levels over time would be more useful for predicting the 28-day mortality rate of patients with sepsis than solely comparing the OPN levels on the day of PICU admission.

Serum OPN is an independent predictive factor for pediatric sepsis

We next selected the laboratory parameters which differed significantly between the patients in the sepsis group and those in the common infection group (i.e., lymphocyte count, neutrophil count, platelet count, bilirubin, creatinine, CRP, PCT, OPN) for inclusion in a binary logistic regression analysis. After adjusting for potential confounders such as age, gender, pSOFA score, and presence of underlying comorbidities, multivariate logistic regression analysis showed that OPN (OR = 1.028, 95% CI: 1.014–1.041, $P < 0.001$) remained an independent predictive factor for sepsis (Table 2).

Table 2
Summary of multivariate logistic regression model parameters for predicting sepsis outcomes, adjusted for age, gender, comorbidities, and pSOFA score

OPN(ng/ml)	OR	95% CI	P value	B	Standard error	Wald	Degree of freedom
	1.028	**1.015–1.041**	**<0.001***	**0.027**	**0.007**	**17.488**	**1**
LYM(10^9/L)	0.906	0.768–1.069	0.243	-0.098	0.084	1.360	1
NE(10^9/L)	1.107	0.986–1.243	0.085	0.102	0.059	2.962	1
PLT(10^9/L)	1.000	0.996–1.005	0.919	<0.001	0.002	0.010	1
TBIL(μmol/L)	1.038	0.984–1.094	0.173	0.037	0.027	1.856	1
Cr(μmol/L)	0.988	0.935–1.044	0.670	-0.012	0.028	0.182	1
CRP(mg/L)	0.987	0.966–1.009	0.238	-0.013	0.011	1.392	1
PCT(ng/ml)	1.301	0.946–1.790	0.106	0.263	0.163	2.611	1
OR, odds ratio; CI, confidence interval							
*P < 0.05, and the difference was statistically significant							

To further determine the efficacy of OPN in the diagnosis of sepsis, ROC curve analysis was performed to compare the diagnostic value of OPN with that of commonly used clinical indicators (e.g., white blood cell count, neutrophil count, lymphocyte count, CRP, and PCT). Furthermore, we calculated the positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value. The results showed that at a serum OPN level ≥ 132.8 ng/ml, the sensitivity for diagnosing sepsis was 85.2%, the specificity was 98.70%, the positive likelihood ratio was 65.54, the negative likelihood ratio was 0.15, the positive predictive value was 98.92%, and the negative predictive value was 82.61%. Sensitivity analysis excluding the top 1% of OPN outliers showed consistent diagnostic accuracy, with the AUC slightly changing from 0.944 to 0.938.

Ultimately, serum OPN level had the best diagnostic value for sepsis among all the biomarkers evaluated, in terms of specificity, positive predictive value, and negative predictive value (Table 3).

Table 3
Summary of AUC analysis results for various sepsis biomarkers

OPN	Cut off	Specificity	Sensitivity	+LR	-LR	PPV	NPV	AUC	AUC(95%CI)
	132.8	**98.70%**	**85.20%**	**65.54**	**0.15**	**98.92%**	**82.61%**	**0.944**	**0.911–0.977**
PCT	1.03	96.10%	63.00%	16.15	0.39	95.77%	64.91%	0.832	0.773–0.892
CRP	38.43	51.90%	88.30%	4.44	0.54	86.15%	56.67%	0.758	0.689–0.827
WBC	14.24	39.80%	83.10%	2.36	0.72	76.79%	49.61%	0.554	0.471–0.637
NE	6.80	54.60%	79.20%	1.77	0.36	79.70%	55.50%	0.652	0.573–0.731
LYM	16.11	07.40%	100.0%	-	0.926	100.0%	43.50%	0.372	0.292–0.452

Note: +LR, positive likelihood ratio; -LR, negative likelihood ratio ; PPV, positive predictive value;

NPV, negative predictive value ; AUC, Area Under Curve ; CI, confidence interval

Value of serum OPN level on day of PICU admission for predicting 28-day mortality

For the univariate analysis, the 108 pediatric patients with sepsis were divided into the survivor (82 patients) and non-survivor (26 patients) groups. The mean arterial pressure($P < 0.001$), white blood cell count($P = 0.007$), neutrophil count($P < 0.0044$), and platelet count($P < 0.041$) upon admission to the PICU were lower in the non-survivor than in the survivor group. On the other hand, bilirubin($P < 0.020$), creatinine($P < 0.043$), PCT($P < 0.024$), and pSOFA score($P < 0.001$) were higher in the non-survivor than in the survivor group(Table 4). Of note, although the serum OPN level on the first day of PICU admission was higher in the non-survivor than in the survivor group, this difference did not reach statistical significance ($P = 0.203$) (Table 4).

Table 4
Univariate analysis of 28-day outcomes in children with sepsis

	All patients(n = 108)	Survivor group(n = 82;75.9%)	Non-survivor group(n = 26;24.1%)	P value
Clinical parameters				
Male, N(%)	50(46.3%)	36(43.9%)	14(53.8%)	0.48
Age (months), N(%)	50.7(40.6–60.7)	56.0(44.6–68.2)	33.5(17.9–51.0)	0.054
Combined underlying disease,N(%)	27(25.0%)	19(23.2%)	8(30.7%)	0.64
MAP(mmHg)	64.6(62.0-67.3)	67.8(65.2–70.5)	54.5(48.4–60.5)	<0.001*
PaO2/FiO2	249.9(231.0-268.8)	260.6(239.3-281.9)	216.1(176.2-256.1)	0.052
Laboratory data				
WBC(10^9/L)	11.2(5.7–19.2)	13.4(7.2–20.1)	6.1(2.8–13.0)	0.007*
NE(10^9/L)	9.4(7.9–10.9)	10.3(8.6–11.9)	6.7(3.5–9.8)	0.044*
LYM(10^9/L)	2.0(0.9–3.8)	2.1(1.1–3.9)	1.5(0.5-4.0)	0.202
PLT(10^9/L)	215.0(66.2-326.5)	232.0(96.5–332.0)	90.5(35.8–328.0)	0.041*
TBIL(μmol/l)	29.0(8.4–91.1)	16.4(12.0-20.8)	69.0(25.7-112.3)	0.020*
Cr(μmol/L)	32.5(20.0-66.5)	30.5(20.0-56.3)	63.0(23.5–96.8)	0.043*
CRP(mg/L)	41.0(8.6-109.8)	38.0(8.9-113.3)	69.2(7.0-103.8)	0.832
PCT(ng/ml)	21.4(14.4–28.3)	15.9(9.1–22.7)	38.8(20.1–57.4)	0.024*
OPN(ng/ml)	440.3(222.9-653.1)	413.9(162.3-641.3)	487.5(256.6-764.4)	0.203
Scores				
pSOFA	7.0(4.0–11.0)	6.57(5.84–7.31)	12.5(8.3–17.0)	<0.001*

*P < 0.05, and the difference was statistically significant. The 108 children with sepsis were divided into survival group (82 cases) and death group (26 cases) for univariate analysis. The mean arterial pressure, white blood cell count, neutrophil count and platelet count of the children with sepsis death were lower than those with sepsis survival, and the scores of bilirubin, creatinine, PCT and pSOFA were higher than those of the children with sepsis survival. The serum OPN level of sepsis dying children on the first day of ICU was higher than that of sepsis surviving children, but there was no statistical difference (P > 0.05).

DISCUSSION

This prospective cohort study demonstrates that serum OPN is a highly accurate biomarker for diagnosing pediatric sepsis. Our key finding is that OPN not only distinguishes sepsis from health but, more importantly, from common infections with exceptional specificity (98.7%), outperforming the widely used biomarkers PCT and CRP.

The pathophysiology of sepsis involves a complex and dysregulated host response. OPN, as a key mediator of inflammation and immune cell trafficking, is logically implicated in this process[9–13]. Our results align with previous studies in adults, which have shown elevated OPN levels in sepsis and a correlation with disease severity[14–15]. Interestingly, the median OPN level in our pediatric sepsis cohort (527.2 ng/mL) was substantially higher than that reported in a study of adults in an emergency department setting (225.2 ng/mL) [15]. This discrepancy may be attributed to several factors. First, our cohort consisted of critically ill children admitted to the PICU, who likely had a more severe systemic inflammatory response compared to a general adult emergency department population. Second, it may reflect inherent differences in the immune response between children and adults, with children potentially mounting a more robust, albeit dysregulated, inflammatory reaction.In accordance, we found that patients with septic shock had higher serum OPN levels than those who did not have this complication.

There was no significant difference between the serum OPN levels of the healthy control group and those of the common infection group, indicating that normal infection does not increase OPN levels. Instead, we found that OPN levels only increased significantly when infection was complicated by organ dysfunction. The latest diagnostic criteria for adult sepsis[1] and the pSOFA score published in 2017 in *JAMA Pediatrics*[19] both emphasize that sepsis is a state of life-threatening organ dysfunction caused by a dysregulated host immune response. The results of this study demonstrate that serum OPN level could assist the diagnosis of pediatric sepsis with a high degree of specificity. However, we found no difference in serum OPN levels among patients with different pathogenic infections, indicating that this parameter cannot differentiate between infection types.

The superior diagnostic performance of OPN observed in our study aligns with recent insights into the role of endothelial dysfunction in sepsis pathogenesis. Emerging evidence suggests that OPN is a critical regulator of vascular permeability and endothelial activation, acting as a bridge between inflammation and coagulopathy[23–24]. Unlike PCT or CRP, which reflect general inflammation, the sharp rise in OPN in our sepsis cohort likely mirrors the specific endothelial injury and glycocalyx shedding that drive organ dysfunction. Persistent elevation of OPN is associated with impaired vascular barrier recovery, suggesting that OPN is not merely a byproduct of inflammation but an active driver of the microcirculatory failure characteristic of pediatric septic shock.

The univariate and multivariate regression analyses of 108 children with sepsis and 77 children with common infections revealed that serum OPN levels could serve as an independent predictive factor for sepsis. Further ROC curve analysis showed that the AUC of OPN reached 0.94. At present, PCT and CRP are the most commonly used biomarkers for the diagnosis of sepsis; however, their diagnostic efficacy is often inadequate[4–5]. Although the serum concentrations of PCT and CRP are correlated with the severity of infection and organ failure, accumulating evidence indicates that PCT and CRP levels are raised even in infected patients without organ failure[6] or those with non-infectious diseases[7]. Taking 132.8 ng/ml as the cut-off serum OPN concentration, permitted the diagnosis of pediatric sepsis with a sensitivity of 85.2%, the specificity of 98.70%, a positive likelihood ratio of 65.54, a negative likelihood ratio of 0.15, a positive predictive value of 98.92%, and a negative predictive value of 82.61%. Our results are consistent with those of previous studies of adult sepsis, which found that the AUC of serum OPN for diagnosing adult sepsis was 0.878 (95% CI 0.798–0.935), with a cut-off value of 112.8 ng/ml, a sensitivity of 80.4%, and a specificity of 88.9% [15].

There is controversy regarding whether serum OPN levels can predict adverse outcomes in sepsis. A 2019 Italian study showed that serum OPN levels upon admission could not predict the 30-day mortality rate in septic patients[15]. However, a 2020 multicenter study demonstrated that serum OPN levels upon admission were independent predictors of the 28-day and 90-day mortality rates of septic patients[16]. In the present study, the 28-day mortality rate of pediatric patients with sepsis was 24.1%, which is slightly higher than the mortality rate reported in previous study[3]. Our univariate analysis of 82 sepsis survivors and 26 non-survivors found no significant difference in their serum OPN levels on the first day of PICU admission, suggesting that OPN levels on the first day of ICU admission cannot predict adverse outcomes in children with sepsis.

Based on these results, we concluded that although a single measurement of serum OPN level upon admission to the PICU may not be sufficient to predict adverse outcomes, continuous monitoring of OPN levels may be beneficial in predicting poor prognosis in sepsis. However, the ability of changes in OPN levels to predict adverse outcomes in patients with sepsis, such as sepsis-related mortality, remains limited and may require larger-scale studies of continuous OPN concentration monitoring.

This study had several limitations. Firstly, it is a single-center study, the results of which will need to be validated in multi-center studies to improve their generalization. Secondly, the study primarily focused on the serum levels of OPN on the first day of PICU admission, which may not represent the early stages of sepsis, especially as some children were admitted after receiving treatment in other hospital departments or at other hospitals. Thirdly, only a small subset of patients had longitudinal OPN measurements. While this limits the statistical power to draw definitive conclusions on OPN dynamics over time, the observed trends provide valuable preliminary data that warrant validation in future larger-scale longitudinal studies. Finally, we did not evaluate the mechanism underlying the relationship between serum OPN concentration and poor outcomes in sepsis. Future work will focus on increasing the sample size, expanding the number of participating centers, and evaluating the underlying mechanism to clarify the clinical value of OPN in the diagnosis and prognosis of sepsis.

CONCLUSIONS

In conclusion, serum OPN is a highly sensitive and specific biomarker for the diagnosis of pediatric sepsis, demonstrating superior diagnostic accuracy compared to PCT and CRP. Its ability to distinguish sepsis from common infections makes it a promising tool for early clinical decision-making. While a single admission value may not predict mortality, the dynamic trend of OPN levels shows potential for prognostic stratification. Future multi-center studies with larger cohorts are needed to validate these findings and further elucidate the role of OPN in the pathogenesis and management of pediatric sepsis.

Declarations

Supplementary material and data availability

Supplementary material is available on journal website; questions or comments relating to this material should be addressed to the corresponding author.

Ethics approval and consent to participate

The original study protocol was reviewed and approved by the Children's Hospital of Chongqing Medical University Institutional Review Board prior to patient enrollment (Chongqing, China; IRB No.2021-325-1). All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Informed consent was obtained from all the patients' guardians prior to their enrollment in the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, in compliance with patient privacy regulations.

Competing interests

The authors do not have a commercial or other association that might pose a conflict of interest.

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Author contributions

Conceptualization: Lingxiao Li, Dandan Pi, Jing Li, and Qin Luo. Methodology: Lingxiao Li, Dandan Pi, Changxue Xiao, and Jing Li. Investigation: Lingxiao Li, Dandan Pi, Shaojun Li, Qian Wang, and Changxue Xiao. Formal Analysis: Lingxiao Li, Dandan Pi, Shaojun Li, Changxue Xiao, Qin Luo, and Feng Xu. Writing-original draft: Lingxiao Li, Dandan Pi, Zhixin Song, and Jing Li. Writing-review&editing: All authors. Supervision: Zhixin Song, Jing Li, and Feng Xu. Project Administration: Zhixin Song, Jing Li, and Feng Xu. All authors read and approved the final manuscript.

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References

1. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775–87. 10.1001/jama.2016.0289.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200–11.

10.1016/S0140-6736(19)32989-7.

3. Ko BS, Choi SH, Kang GH, et al. Time to Antibiotics and the Outcome of Patients with Septic Shock: A Propensity Score Analysis. Am J Med. 2020;133(4):485–e4914. 10.1016/j.amjmed.2019.09.012.
4. Bhattacharya S, Munshi C. Biological significance of C-reactive protein, the ancient acute phase functionary. Front Immunol. 2023;14:1238411. 10.3389/fimmu.2023.1238411. Published 2023 Oct 4.
5. Sager R, Wirz Y, Amin D, et al. Are admission procalcitonin levels universal mortality predictors across different medical emergency patient populations? Results from the multi-national, prospective, observational TRIAGE study. Clin Chem Lab Med. 2017;55(12):1873–80. 10.1515/cclm-2017-0144.
6. Castelli GP, Pognani C, Meisner M, et al. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care. 2004;8(4):R234–42. 10.1186/cc2877.
7. Dornbusch HJ, Strenger V, Sovinz P, et al. Non-infectious causes of elevated procalcitonin and C-reactive protein serum levels in pediatric patients with hematologic and oncologic disorders. Support Care Cancer. 2008;16(9):1035–40. 10.1007/s00520-007-0381-1.
8. Subraman V, Thiyagarajan M, Malathi N, et al. OPN -Revisited. J Clin Diagn Res. 2015;9(6):ZE10–3. 10.7860/JCDR/2015/12872.6111.
9. Lang F, Li Y, Yao R et al. Osteopontin in Chronic Inflammatory Diseases: Mechanisms, Biomarker Potential, and Therapeutic Strategies. Biology (Basel). 2025;14(4):428. Published 2025 Apr 16. 10.3390/biology14040428
10. Balmos IA, Horváth E, Brinzaniuc K et al. Inflammation, Microcalcification, and Increased Expression of Osteopontin Are Histological Hallmarks of Plaque Vulnerability in Patients with Advanced Carotid Artery Stenosis. Biomedicines. 2023;11(3):881. Published 2023 Mar 13. 10.3390/biomedicines11030881
11. Zhang J, Yang G, Zhu Y, et al. Relationship of Cx43 regulation of vascular permeability to osteopontin-tight junction protein pathway after sepsis in rats. Am J Physiol Regul Integr Comp Physiol. 2018;314(1):R1–11. 10.1152/ajpregu.00443.2016.
12. Hirano Y, Aziz M, Yang WL et al. Neutralization of osteopontin attenuates neutrophil migration in sepsis-induced acute lung injury. Crit Care. 2015;19(1):53. Published 2015 Feb 26. 10.1186/s13054-015-0782-3
13. Fortis S, Khadaroo RG, Haitsma JJ, et al. Osteopontin is associated with inflammation and mortality in a mouse model of polymicrobial sepsis. Acta Anaesthesiol Scand. 2015;59(2):170–5. 10.1111/aas.12422.
14. Vaschetto R, Nicola S, Olivieri C, et al. Serum levels of osteopontin are increased in SIRS and sepsis. Intensive Care Med. 2008;34(12):2176–84. 10.1007/s00134-008-1268-4.
15. Castello LM, Baldrighi M, Molinari L, et al. The Role of Osteopontin as a Diagnostic and Prognostic Biomarker in Sepsis and Septic Shock. Cells. 2019;8(2):174. 10.3390/cells8020174. Published 2019 Feb 18.
16. Carbone F, Bonaventura A, Vecchiè A, et al. Early osteopontin levels predict mortality in patients with septic shock. Eur J Intern Med. 2020;78:113–20. 10.1016/j.ejim.2020.04.035.
17. Hayek SS, Roderburg C, Blakely P et al. Circulating Osteopontin Levels and Outcomes in Patients Hospitalized for COVID-19. J Clin Med. 2021;10(17):3907. Published 2021 Aug 30. 10.3390/jcm10173907
18. Irion CI, Parrish K, John-Williams K, et al. Osteopontin Expression in Cardiomyocytes Is increased in Pediatric Patients With Sepsis or Pneumonia. Front Physiol. 2018;9:1779. 10.3389/fphys.2018.01779. Published 2018 Dec 10.

19. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr. 2017;171(10):e172352. 10.1001/jamapediatrics.2017.2352.
20. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2–8. 10.1097/01.PCC.0000149131.72248.E6
21. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486–552. 10.1097/CCM.0000000000002255.
22. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med. 2020;21(2):e52–106. 10.1097/PCC.0000000000002198.
23. Zhang J, Yang G, Zhu Y, et al. Relationship of Cx43 regulation of vascular permeability to osteopontin-tight junction protein pathway after sepsis in rats. Am J Physiol Regul Integr Comp Physiol. 2018;314(1):R1–11. 10.1152/ajpregu.00443.2016.
24. Nie X, Fan J, Qin Y et al. Osteopontin promoted cardiac inflammation through increased interleukin-12 in acute myocarditis. Mol Biomed. 2025;6(1):85. Published 2025 Oct 24. 10.1186/s43556-025-00333-z

Figures

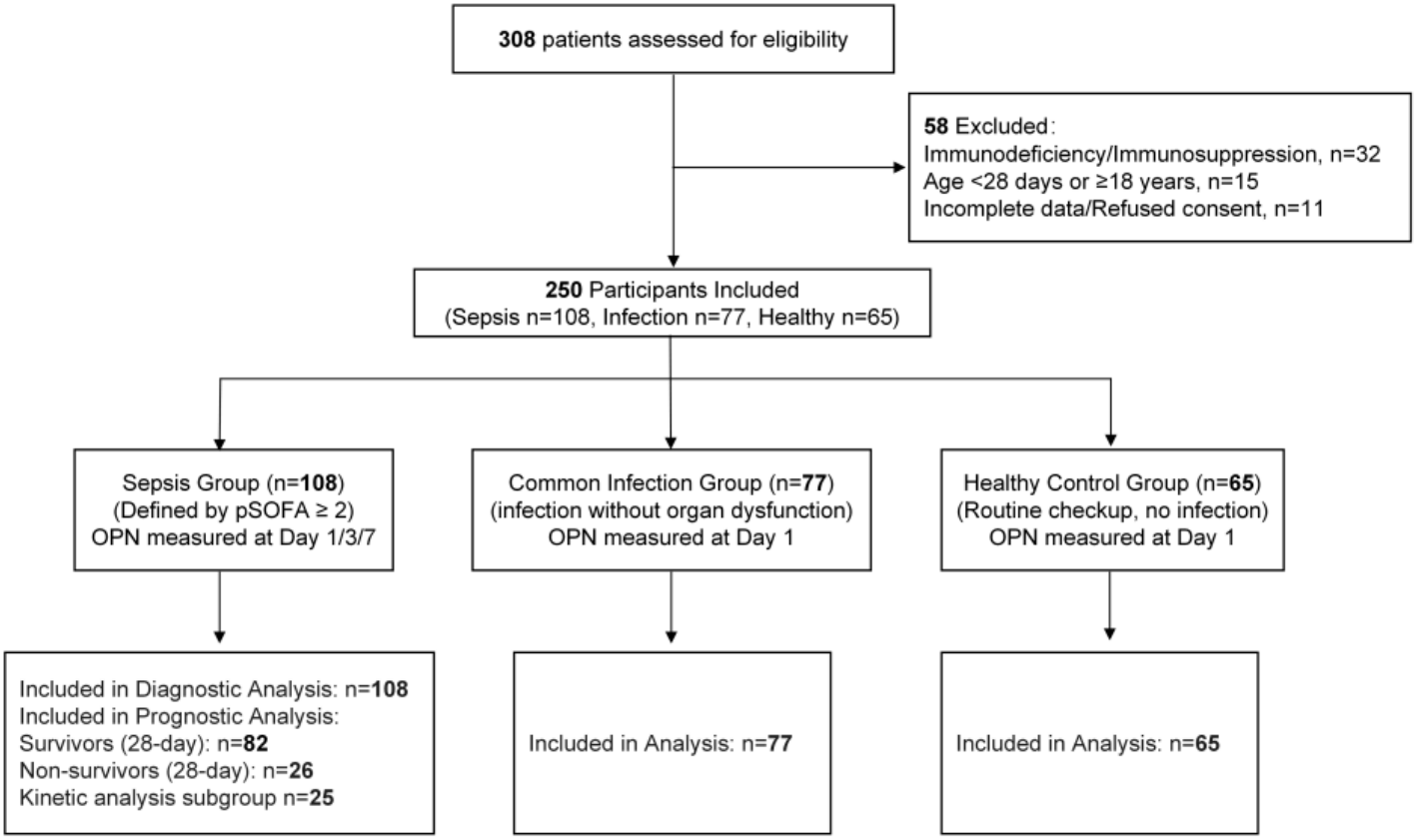


Figure 1

STROBE flow diagram

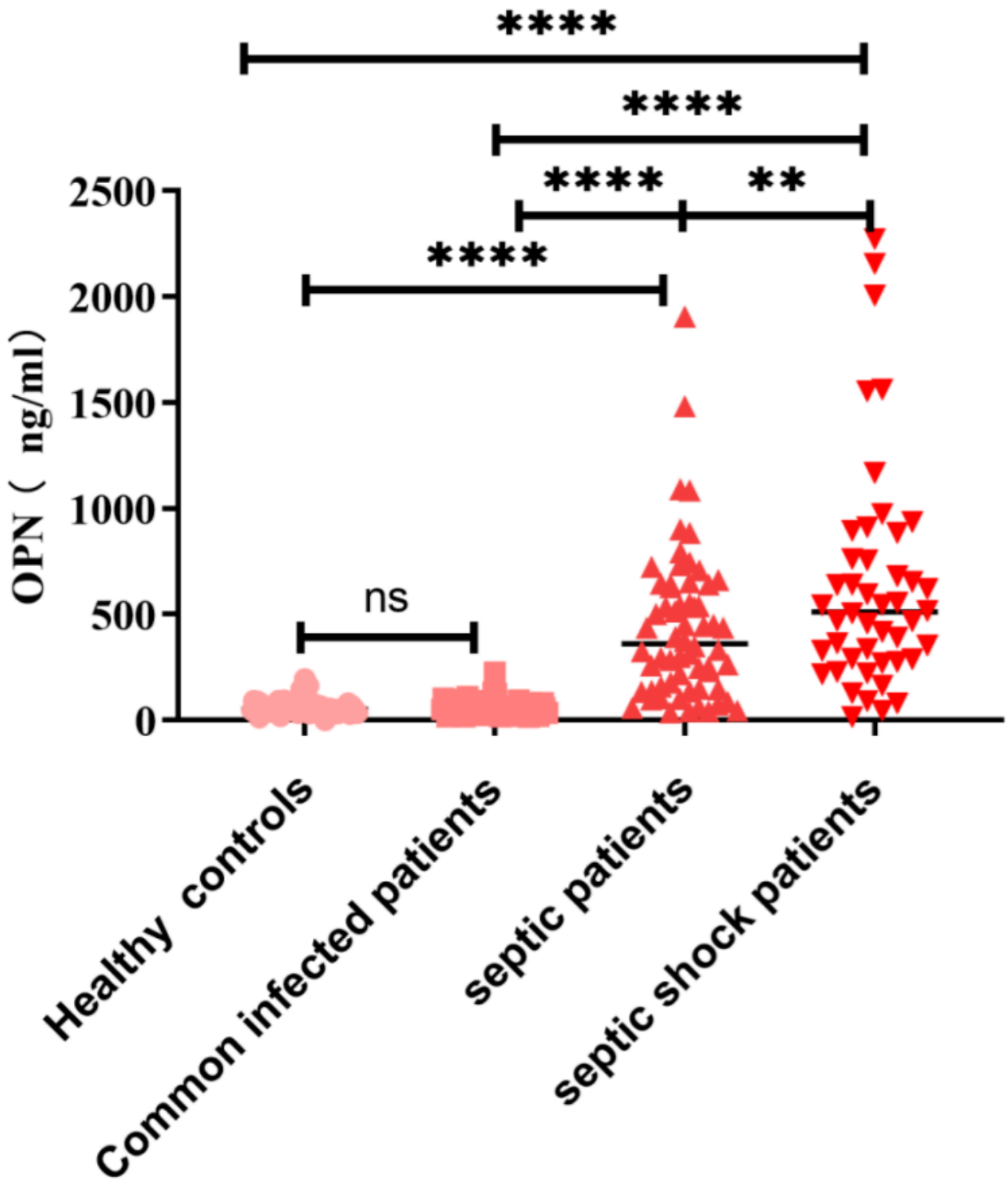


Figure 2

Serum Osteopontin(OPN) levels at admission are elevated in patients with sepsis. OPN concentrations were measured in serum samples collected from 62 patients with sepsis, 46 patients with sepsis shock, 77 patients with common infections, and 32 healthy control subjects.

The nonparametric Mann-Whitney U test or Kruskal-Wallis test followed by the Dunn multiple comparisons post-test were used to compare groups. ****P<0.0001;**P<0.01;*P<0.05; ns, non-significant.

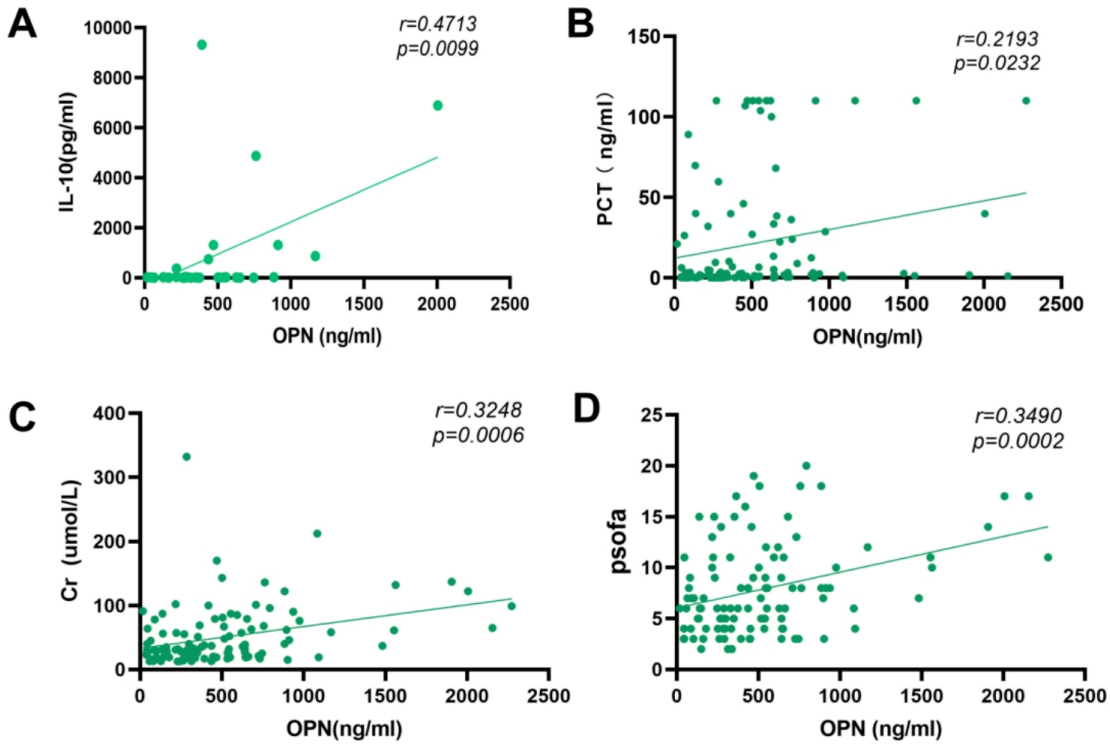


Figure 3

Linear correlation analysis between serum OPN levels and other laboratory test parameters. (A) Correlation between OPN and IL-10 (A), PCT (B), creatinine (C) levels of patients with sepsis on PICU admission. (D) Correlation between OPN levels and the pSOFA scores of patients with sepsis on PICU admission.

The Spearman correlation coefficient was used to evaluate the significance of correlations between OPN concentrations and PCT levels, creatinine levels, IL-10 levels, or pSOFA scores.

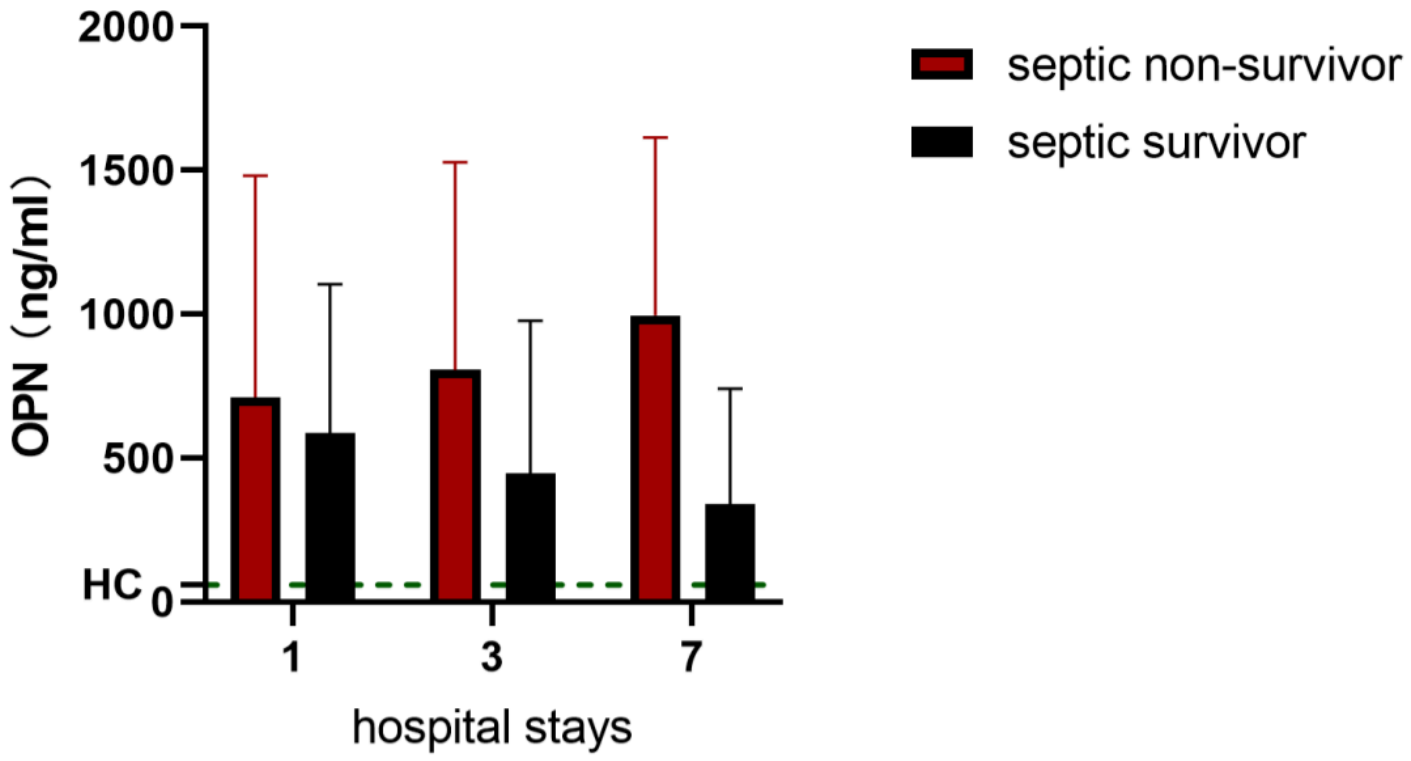


Figure 4

Comparison of serum OPN levels on days 1, 3, and 7 of hospitalization in the sepsis survivor and non-survivor groups. A group of 25 patients with sepsis for whom serum OPN concentration monitoring was performed on days 1, 3, and 7 of hospitalization were divided into the survivor (n=20) and non-survivor (n=5) groups. The OPN levels in these subgroups were compared to those of healthy controls (n=65).

The nonparametric U test was used to compare between the sepsis survivor and non-survivor groups. The data are presented as the mean +/- standard deviation.

Supplementary Files

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- Supplementarymaterial20260721.docx