



# Is Presepsin a Reliable Marker of Sepsis Diagnosis in Pediatric Intensive Care Unit?

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## Abstract

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**BACKGROUND:** Sepsis is a major challenge in emergency departments and intensive care units (ICUs). Sepsis also mimics or interacts with many other disorders causing high mortality and morbidity. There is no accurate biomarker or test to diagnose or predict sepsis. The treatment of sepsis is often based on the clinician's experience.

**AIM:** We conducted this study to analyze the serum level of presepsin in pediatric critical patients with SIRS, sepsis, severe sepsis, and septic shock.

**METHODS:** The study included 58 children, 32 septic pediatric patients admitted to the Pediatric ICU (PICU) of Cairo University Teaching Hospital and 26 healthy children who served as a control group. The aim was to estimate the diagnostic accuracy of presepsin in predicting sepsis in PICU. We classified the patients into systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock according to the international consensus conference criteria.

**RESULTS:** In our study, we detected a positive correlation between C-reactive protein and presepsin levels at day 1 and day 3 of admission and a negative correlation between hemoglobin and presepsin levels at day 1. However, we found no difference in the serum presepsin between the children who had sepsis and the healthy ones (at day 1 [p = 0.430] and at day 3 [p = 0.845]). We also found that serum levels of presepsin were not significantly increased with the increasing severity of sepsis despite the higher median values with increasing sepsis severity.

**CONCLUSIONS:** It was noted that presepsin levels increased in anemic critical patients, whereas presepsin had no role in differentiating the septic critical patients from healthy children. However, its level increased with increasing severity of sepsis grade.

## Introduction

Sepsis is a type of systemic inflammatory response syndrome (SIRS) caused by the invasion of pathogens or conditional pathogenic bacteria into the blood circulation. It can develop into severe sepsis, septic shock, and multiple organ failure [1].

Sepsis is the most common cause of death in infants and children worldwide. Lack of reporting and the fact that sepsis mimics or interacts with many other disorders make estimating the burden of sepsis difficult. However, in industrialized countries, the overall mortality rate of children with severe sepsis and septic shock is estimated between 2 and 10%, whereas mortality in developing countries is reported as high as 50% [2].

The majority of sepsis cases and deaths are estimated to occur in low and middle-income countries [3]. In 2017, there were an estimated 23.7 million (20.1–28.8) incident sepsis cases among adults 20 years and older [4].

Early diagnosis and timely intervention are essential to improve the prognosis of septic patients. Bacterial culture is generally regarded as the gold standard for the diagnosis of sepsis, but it

is time-consuming, frequently yields false-negative results, and microbial contamination can greatly affect its diagnostic value. Thus, the treatment of sepsis is often based on the clinician's experience, which risks an increase in antibiotic resistance and the cost of medical care. It is, therefore, necessary and urgent to develop a rapid and accurate method for the diagnosis of sepsis [5]. Anti-microbial resistance may be a major driver of the global burden of both community and hospital-acquired sepsis. More than 700,000 deaths/year may be attributable to anti-microbial resistance infections globally [3]. About 76% of the patients who were admitted to Indian Pediatric Intensive Care Units (PICU) received more than two antibiotics simultaneously. The antibiotic policy may aid in the development of anti-microbial resistance [6]. A study from Kazakhstan reporting high prevalence of antibiotic resistance in the intensive care units (ICU) [7].

Various biomarkers have been reported useful in sepsis diagnosis such as pro-calcitonin and C-reactive protein (CRP). However, these biomarkers may also be elevated in non-septic conditions such as trauma, burns, and post-operative settings and some are slow to rise after the onset of sepsis. It, thus, remains necessary to find reliable biomarkers to replace or improve those that are currently available [5].

Recent systematic reviews reported that presepsin had high sensitivity and specificity in predicting sepsis in neonates [8], [9], [10]. It was reported that presepsin levels peak at 3h after the onset of infection. Serum presepsin can be measured easily and rapidly [11]. Therefore, presepsin could be a useful biomarker for the early diagnosis of sepsis [12]. Pediatrics studies about presepsin are few. We conducted this study to analyze the serum level of presepsin in pediatric critical patients with SIRS, sepsis, severe sepsis, and septic shock.

## Patients and Methods

### Settings

This study was carried out in the PICU of the main children hospital of Cairo University, Egypt, in the period between April 2016 and December 2017.

### Patients

Fifty-eight children were enrolled in this study and were divided them into two groups: Group I: 32 septic critical pediatric patients and Group II: 26 healthy children who served as a control group from the outpatient clinic coming for elective surgical procedures who were age- and sex-matched. Inclusion criteria were the presence of sepsis, severe sepsis, or septic shock according to the international consensus conference criteria and three post-operative patients with suspected SIRS according to the international consensus conference criteria [13]. Exclusion criteria were those suffering from renal impairment. All the patients in this study received the ethical committee approval and informed consent was taken from the parents.

### Data collection

The data collection was sequential organ failure assessment score [14], Glasgow coma scale, complete blood picture, liver and kidney function tests, coagulation profile, CRP, blood culture, and blood gases.

### Sampling

Five milliliters of venous blood were withdrawn from each subject under complete aseptic conditions. Presepsin concentration was measured using a commercially available ELISA kit supplied by Bioneovan Co., China. Assay range was 65 pg/ml–3000 pg/ml.

### Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the

Social Sciences) version 23. Data were summarized using median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal–Wallis and Mann–Whitney tests [15]. Correlations between quantitative variables were done using Spearman correlation coefficient [16].  $p < 0.05$  was considered as statistically significant.

## Results

Patients were divided into two groups: Group I: 32 septic pediatric patients, Group II: 26 healthy children, 17 (53.1%) males and 15 (46.9%) females, their age ranged from 2 months to 12 years. As regards the sepsis classification, 3 patients (9.4%) had SIRS, 10 (31.2%) had sepsis, 12 (37.5%) had severe sepsis, and 7 (21.9%) had septic shock. The most common cause of ICU admission was a respiratory failure (31.3%) followed by septic shock (21.9%). About 21% of the patients were mechanically ventilated (Table 1).

**Table 1: The clinical characteristics of studied patients**

Clinical data of the study group	Frequency and % (1.5 years) 2 months–11 years No. (%)
Age median and range	
Sex	
Males	17 (53.1)
Females	15 (46.9)
Diagnosis	
Respiratory failure	10 (31.3)
Septic shock (blood born)	7 (21.9)
Central nervous system infection	4 (12.5)
Post-operative (intestinal obstruction)	4 (12.5)
Other*	3 (9.4)
Gastroenteritis	2 (6.2)
Heart failure	2(6.2)
Grades of sepsis	
SIRS*	3 (9.4)
Sepsis	10 (31.2)
Severe sepsis	12 (37.5)
Septic shock	7 (21.9)
GCS*(median and range)	12(3–15)
SOFA score**	5 (0–14)
Mechanical ventilation no and %	
n	28.1%
Laboratory characteristics	Median (Min-Max)
Hb (g/dL)**	10.3 (7.6–15.7)
CRP (mg/L)**	48 (28–184)
PT (s)**	15.95 (10.70–37.90)
ALT (U/L)**	46.50 (14–972)
Creatinine (mg/dL)	0.50 (0.20–3.20)

\*Others (toxin ingestion and infected hematoma in a hemophilia patient); \*\*SOFA: Sequential organ failure assessment, Hb: Hemoglobin, CRP: C-reactive protein, PT: Prothrombin time, ALT: Alanine aminotransferase.

Presepsin levels at day 1 and day 3 of admission were not different between critical septic and healthy children (Table 2).

**Table 2: Comparison of presepsin levels between septic patients and healthy children at day 1 and day 3 of admission**

Presepsin at day 1 and 3	Patients Median (Min-Max)	Controls Median (Min-Max)	P value
Presepsin (pg/ml) at day 1	364.90 (149.40–2640)	376.85 (228.20–2479.70)	0.430
Presepsin (pg/ml) at day 3	384.10 (75.90–2263.60)	376.85 (228.20–2479.70)	0.845

Presepsin levels were correlated with the grade of sepsis ( $r = 0.346$ ,  $p = 0.04$ ). Critical patients were further subdivided children into two groups, the sepsis only group ( $n = 10$ ) and the severe sepsis and septic shock group ( $n = 19$ ). We observed that the median level of presepsin had a progressive increase in the severe sepsis, septic shock group at day 3, but we did not observe a similar increase in the sepsis only group. This increase, however, did not reach a statistical significance (Table 3).

**Table 3: Comparison of presepsin levels at day 1 and day 3 between two groups of patients (patients with only sepsis and patients with severe sepsis and septic shock as a second group)**

Subgroup	Presepsin at day 1		Presepsin at day 3		p value
	Median (Min-Max)		Median (Min-Max)		
Sepsis (n=10)	355.70 (169.80–428.90)		345.70 (190.60–465.30)		0.188
Severe sepsis and septic shock (n=19)	394.50 (149.40–2640)		500.60 (75.90–2263.60)		0.084

There was a significant statistical difference between the CRP level and hemoglobin level of patients and the presepsin level at day 1 but not at day 3 (Table 4).

**Table 4: Comparison between presepsin at day 1 and day 3 and clinical and laboratory parameters of patients**

Clinical and laboratory data	Presepsin at day 1		Presepsin at day 3	
	Correlation coefficient	p value	Correlation coefficient	p value
SOFA score	0.128	0.483	0.038	0.838
Grade of sepsis	0.365	0.040	0.325	0.07
PH	-0.160	0.383	0.196	0.281
HCO <sub>3</sub>	0.212	0.243	0.243	0.180
Hemoglobin	-0.369	0.038	-0.183	0.317
WBC count	0.001	0.998	-0.294	0.102
Platelet count	-0.029	0.877	0.164	0.370
CRP	0.576	0.001	0.598	0.001

There was a non-significant difference between the presepsin level at day 1 and day 3 and the type of organism causing infection but it was noticed that the median level of the marker at day 1 and day 3 was highest at the Gram-negative cultures and lowest with the fungal infections (Table 5).

**Table 5: Comparison between the presepsin at day 1 and day 3 and the results of the cultures**

Organism	Presepsin at day 1		Presepsin at day 3	
	Median (Min-Max)	p value	Median (Max-Min)	p value
Fungal infection	154.30 (154.30–154.30)	0.298	140 (140–140)	0.072
Gram-negative bacteria	395 (149.40–2640)		451.30 (202.90–2263.60)	
Gram-positive bacteria	380.10 (302.90–1575.40)		345.20 (75.90–839.10)	

## Discussion

Early recognition of sepsis, severe sepsis and septic shock, and speed and appropriateness of therapy in the initial hours after presentation considerably influence the outcomes of septic patients [17]. Blood culture usually requires several days for results to be known [18] and false-negative results may delay the

antibiotic administration and consequently lead to increased mortality [19]; hence, the importance of early diagnostic markers of sepsis and proper follow up of the response to the therapy.

Our study showed that presepsin levels could not differentiate between the critically ill septic patients (median = 365 pg/ml) and the healthy children (median = 376 pg/ml) neither at day 1 nor day 3. This was similar to a study conducted on a cohort of pediatric critical patients and suggested that the presepsin could not differentiate between septic critical patients and healthy controls and thus raising doubt on its value as an inflammatory marker in pediatric critical illness [20].

Age-related variations in the cutoff value were reported. In the adult study, a cutoff value of 317 pg/ml was used in diagnosing sepsis [21], while in preterm neonates, it was 885 ng/l [22]. In a recent study, presepsin levels were found to be lower in neonates with more advanced gestational age [23]. This may explain why the median values of presepsin levels in our children were lower than neonatal studies.

A recent systematic review and meta-analysis in children indicated the high sensitivity and diagnostic accuracy of presepsin in detecting sepsis, but lower specificity, than procalcitonin (PCT) or CRP [12]. This analysis included four studies, of which three included pediatric hemato-oncological patients; some of them had chemotherapy-induced neutropenic fever.

Controversies in adult studies excited, some suggested that its use is associated with a relatively high rate of miss diagnosis and misdiagnosis and should instead be used in conjunction with more conventional tests, such as PCT, rather than replace it [24]. Others described it to have a moderate diagnostic capacity for the detection of sepsis [1], [25]. On the contrary, others suggested the differentiating value of presepsin between cases and controls [26], [27].

Neonatal studies suggested the high sensitivity of presepsin for the detection of sepsis in neonates [27], [28], [29]. Similarly, Poggi *et al.* detected the possible use for monitoring antibiotic response in septic neonate [22].

We detected a positive correlation between the grade of sepsis and presepsin level. Carpio *et al.* mentioned that presepsin levels were elevated at an early stage of sepsis and increased with its progression [30].

We observed that there was a significant statistical difference between the presepsin levels at day 1 in anemic versus non-anemic patients. In accordance with our results, Malgorzata *et al.* and Motoi *et al.* found that there was a significant inverse correlation between presepsin concentrations in septic newborns and hemoglobin, hematocrit value, and platelet counts [31], [32].

There was a significant association between the CRP level of the septic patients and presepsin

level at day 1 and day 3. This result was in agreement with a study on septic newborns which concluded that there was a positive correlation between presepsin concentrations and CRP in septic newborns [23]. Moreover, Chenevier-Gobeaux *et al.* and Motoi *et al.* reached similar results in a study conducted on adults [11], [32].

We noticed that the median levels of the marker at day 1 and day 3 were highest in the Gram-negative cultures and lowest with the fungal infections with a p-value only approaching statistical significance. Studies concluded that presepsin showed the highest sensitivity in predicting Gram-negative bacteria [33], [34], [35]. On the contrary, Topcuoglu *et al.* stated that there were no differences between the initial presepsin levels of patients in the late-onset sepsis and the type of growth in blood culture [21]. This result was agreed by two studies which were conducted on adults [32], [36].

## Conclusions

This study demonstrated that presepsin is not a reliable marker for discrimination between the critically sick septic children and healthy children. However, its serum levels increased congruently with the severity of sepsis in critically sick children. Our small sample size is a limiting factor and further studies with larger sample sizes, with each group of sepsis severity, are needed.

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