

Is There a Role of Presepsin as a Novel Biomarker in Pediatric Sepsis?

Daisy Khera¹, Nisha Toteja², Surjit Singh³, Simranjeet Singh⁴, Prawin Kumar⁵, Praveen Sharma⁶, Kuldeep Singh⁷

ABSTRACT

Background: Sepsis in children is a conundrum of diagnostic and therapeutic challenges. There is an exigent need for a novel biomarker that can serve as a clear distinguisher of sepsis from other non-septic inflammatory conditions. The role of presepsin as a biomarker of sepsis in children is still a matter of scientific inquiry.

Aim and objectives: To evaluate the diagnostic accuracy of presepsin for the prediction of septic shock, in children aged 1 month to 18 years.

Materials and methods: This prospective cohort study was conducted in the pediatric emergency, ward, and intensive care unit of a tertiary care hospital. We enrolled all consecutive admissions aged 1 month to 18 years with a diagnosis of sepsis and compared the presepsin, procalcitonin, and C-reactive protein (CRP) levels on admission (day 1) and 72 hours later (day 4) with the clinical outcomes.

Results: The mean (\pm SD) presepsin values in blood culture-proven sepsis patients at admission and 72 hours later were 609.77 ± 417.30 and 839 ± 748.07 , respectively. The procalcitonin and presepsin levels at 72 hours in sepsis patients with shock were significantly elevated (38.2 ± 45.55 and 1129.1 ± 1133.80 , respectively) as compared to those without shock (10.7 ± 25.42 and 472.5 ± 507.81 , respectively), $p < 0.05$. The receiver operating characteristic (ROC) curve analysis of presepsin at 72 hours had an area under curve (AUC) of 0.730, suggesting a fair diagnostic accuracy.

Conclusion: Elevated presepsin levels may indicate greater severity of sepsis, particularly in those with shock. However, it lacks diagnostic ability early in the disease and has limited prognostic potential in predicting mortality.

Keywords: Biomarkers, Presepsin, Sepsis.

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INTRODUCTION

Sepsis in children is a multifaceted disorder with protean manifestations. Early identification and goal-directed therapy are the cornerstones of management, and any delay can potentially result in devastating consequences. However, the proof of infection is seldom encountered in practice, especially in pediatric sepsis, as the confirmatory microbial culture yield can be as low as 25–30%.¹ Hence, clinicians often depend on commonly available biomarkers such as C-reactive Protein (CRP) and procalcitonin (PCT) for diagnosing infection and monitoring response to treatment. Even though helpful, these markers are fraught with errors and limitations.² Hence, there is an unmet need for a biomarker that can help accurately predict or diagnose infection in children.

One such promising candidate is presepsin (sCD14-ST). It is the fragmented form of a glycoprotein found on macrophages' surface, which is released upon activation of inflammatory cascade triggered by bacterial lipopolysaccharides.³ Several studies in the adult population have supported its favorable diagnostic as well as prognostic capability in sepsis.⁴ However, literature on the role of presepsin in pediatric sepsis, in particular, is still evolving. Hence, we aimed to elucidate its utility in pediatric sepsis in comparison to the conventional biomarkers.

MATERIALS AND METHODS

We conducted this prospective cohort study over 12 months from October, 2018, to September, 2019, in a tertiary care hospital in Western India. Consecutive patients aged 1 month to 18 years

^{1,4,5,7}Department of Pediatrics, AIIMS, Jodhpur, Rajasthan, India

²Department of Pediatrics, AIIMS, Gorakhpur, Uttar Pradesh, India

³Department of Pharmacology, AIIMS, Jodhpur, Rajasthan, India

⁶Department of Biochemistry, AIIMS, Jodhpur, Rajasthan, India

Corresponding Author: Nisha Toteja, Department of Pediatrics, AIIMS, Gorakhpur, Uttar Pradesh, India, Phone: + 91 9873245575, e-mail: nishatoteja2000@yahoo.co.in

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admitted in the pediatric emergency, ward or PICU with a diagnosis of sepsis were enrolled after written informed parental consent. Exclusion criteria included failure to obtain blood samples within the first hour of admission and lack of consent. The study was commenced after approval from the Institution Ethics Committee (IEC No. 2017/959) and conducted in accordance with ICH-GCP and ICMR guidelines.

Sepsis was defined as per sepsis-3 definition as an acute rise in the pediatric sequential organ failure assessment score (pSOFA) of two points or more, from 48 hours before the infection to 24 hours after the infection.⁵ Similarly, septic shock was defined as the requirement of vasoactive drugs and a serum lactate level higher than 2 mmol/L (18 mg/dL) in a patient diagnosed with sepsis.⁶ A complete sepsis panel which included CRP, complete blood cell

counts (CBC), procalcitonin, and presepsin, was assayed for each of the enrolled patients on day 1 (within 1 hour of admission) and at 72 hours (day 4). Blood cultures and other relevant body fluid cultures were also obtained. Other labs and radiological investigations were evaluated as clinically indicated. The clinical correlates were documented along with the final outcome of the enrolled patients.

Once enrolled, 2–3 mL of venous blood was withdrawn within the first hour of admission on day 1 and distributed into three separate vials each of EDTA, plain, and heparin-coated, in addition to blood cultures. The complete blood count was estimated from the EDTA vial on Sysmex 1000, Gumbly, Germany. Plain vial sample was allowed to clot and processed for high sensitivity CRP (reference range <1 mg/L) using the immunoturbidimetry method and procalcitonin quantified (reference range <0.1 ng/mL) using ADVIA Centaur third-generation chemiluminometry. Presepsin assay was performed on 0.1 mL of heparinized blood by a point of care (POC) test instrument (PATHFAST, Mitsubishi Chemical Europe), based on the principle of noncompetitive chemiluminescence enzyme immunoassay. Reference values (95th percentile) for presepsin were taken as 320 pg/mL.⁷ Daily pSOFA score was also noted. The same samples were repeated at 72 hours of admission (day 4). The children were followed up till death or discharge and their outcomes recorded. The primary outcome was to assess the diagnostic accuracy of blood levels of presepsin for predicting septic shock in patients with sepsis as defined by the sepsis-3 criteria. The secondary outcome was to evaluate the prognostic accuracy (mortality) of presepsin compared to currently available infection biomarkers.

Statistical Analysis

The Chi-square test or Fischer's Exact test was used for the analysis of categorical variables. Numerical data between two groups were compared using the student *t*-test. Receiver operating characteristic (ROC) curves of presepsin and procalcitonin were constructed, and the area under ROC curve was calculated. Diagnostic accuracy parameters of presepsin and procalcitonin for the diagnosis of septic shock were calculated using MEDCALC software (Available from: https://www.medcalc.org/calc/diagnostic_test.php). All data were reported along with 95% confidence intervals (CI). *p*-value <0.05 was considered for statistical significance. All analysis was done using the SPSS (IBM SPSS, Version 23.0. Armonk, New York: IBM Corp).

The sample size was calculated based on the study done by Ghazy et al.⁸ Considering the sensitivity of presepsin in predicting mortality in septic patients on day 3 of admission as 86% with a precision of 10%, the estimated sample size was 46 children.

RESULTS

We enrolled 54 children with a diagnosis of sepsis according to sepsis-3 criteria. Eighteen children (33%) developed septic shock, and six (11.6%) children died. The baseline characteristics of participants with and without sepsis shock are detailed in Table 1. The most common focus of infection was identified as pneumonia (51.8%), followed by neuro-infections (12.9%). Others included empyema (3.7%), urinary tract infections (3.7%), skin and subcutaneous infections (3.7%), and intra-abdominal infections (5.5%), whereas no clear source could be identified in nine cases (16.6%). Two-thirds (68.5%) of the study cohort comprised infants and young children below 5 years of age. No children with

Table 1: Baseline characteristics of the two groups

Baseline characteristics	Sepsis (n = 36)	Septic shock (n = 18)	<i>p</i> value (two sided)
Age (months), Mean ± SD	44.55 ± 48.89	54.28 ± 77.60	0.576
Male/Female, <i>n</i> (% of males)	24/12 (66.7)	11/7 (61.1)	0.456
Weight (kg), Mean ± SD	10.7 ± 8.11	11.6 ± 9.40	0.093
Height/length (cm), Mean (±SD)	107 ± 8.11	116 ± 8.11	0.873
Fever (<i>n</i>) (%)	35 (97.2)	15 (83.3)	0.103
Respiratory distress (<i>n</i>)	24 (66.6)	16 (88.8)	0.73
Antibiotic usage in last 10 days (<i>n</i>) (%)	17 (47.2)	10 (55.6)	0.387
Immunocompromised (<i>n</i>) (%)	0 (0)	4 (22.2)	0.10
Severe acute malnutrition (<i>n</i>) (%)	4 (11.1)	5 (27.8)	0.124
Pulse (/minute), Mean (±SD)	112.23 ± 6.82	120.72 ± 5.85	0.710
Systolic BP (mm Hg), Mean (±SD)	95.86 ± 13.24	96.74 ± 14.18	0.766
Diastolic BP (mm Hg), Mean (±SD)	58.14 ± 7.7	51.03 ± 17.48	0.326

underlying primary immunodeficiency were enrolled. However, four (7.4%) children in the study had secondary immunosuppression due to chemotherapy. Thirteen children in the study had various co-morbidities. These included hematological conditions (*n* = 2), solid organ cancer (*n* = 2), type I diabetes (*n* = 1), cystic fibrosis (*n* = 1), chronic kidney disease (*n* = 3), acyanotic heart disease (*n* = 2), and cerebral palsy (*n* = 2).

Causative organisms were identified in 17 children, among which blood culture-positive sepsis was seen in 10 children (18.5%), bronchioalveolar lavage grew organism in 5 children (9.2%), and 2 children had candiduria (3.7%). Amongst the blood culture-positive infections, nine were due to gram-negative bacteria, and the remaining one had gram-positive-MSSA. All five positive bronchoalveolar fluid cultures had gram-negative bacterial growth.

The mean presepsin values in the blood culture-proven sepsis patients at admission (0 hours) and 72 hours were 609.77 ± 417.30 and 839 ± 748.07, respectively. The presepsin, procalcitonin, and CRP levels in blood culture positive and negative patients and those with and without septic shock at 0 and 72 hours are detailed in Tables 2 and 3. The baseline procalcitonin and presepsin levels at the time of admission before antibiotics administration in patients with and without septic shock were comparable. However, at 72 hours, both procalcitonin and presepsin levels in sepsis patients with shock were significantly elevated (38.2 ± 45.55 and 1129.1 ± 1133.80, respectively) compared to those without shock (10.7 ± 25.42 and 472.5 ± 507.81, respectively), *p* = 0.006 and 0.005, respectively. The serum lactate at admission and the worst pSOFA score also differed significantly between these two groups (Table 3). The sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, and the diagnostic accuracy of procalcitonin and presepsin at admission and 72 hours for the prediction of septic shock are detailed in Table 4.

The baseline procalcitonin and the serum lactate at admission (day 1) and the worst pSOFA were significantly elevated in the

non-survivors compared to the survivors (Table 3). Though the presepsin levels were also higher in non-survivors, this difference was not statistically significant. The ROC curve of procalcitonin, presepsin, and CRP at admission (0 hours) did not show diagnostic accuracy. However, the ROC curves of procalcitonin (AUC = 0.718) and presepsin (AUC = 0.730) at 72 hours of admission showed fair diagnostic accuracy (Fig. 1). On binary logistic regression, pSOFA score [OR (95% CI) 1.75 (1.30–2.34), $p < 0.001$] was found to have a significant correlation with septic shock.

DISCUSSION

Presepsin or CD (cluster of differentiation)-14 is a cell-surface glycoprotein expressed in macrophages, monocytes, dendritic cells, and neutrophils.⁸ Presepsin levels rise within 2 hours and peak at 3 hours after the onset of infection. The new point of care presepsin assay allows bedside testing with a turn-around time of

2 minutes.⁹ However, the cost of the test is a significant limitation, especially in resource-constrained settings.

Several recently published studies indicate the potential role of presepsin as a biomarker for the early diagnosis of sepsis. A recent systematic review concluded that presepsin had high sensitivity and specificity in predicting neonatal sepsis.¹⁰ Another pediatric meta-analysis comprising four studies concluded that presepsin has higher sensitivity and diagnostic accuracy but lower specificity than procalcitonin or CRP in detecting sepsis in children.¹¹ Nevertheless, the scientific query into the utility and role of presepsin in pediatric sepsis warrants further research.

Fundamentally, most existing biomarkers are acute phase reactants, and their levels exhibit a proportionate rise in response to the presence and degree of the inflammatory process. However, existing acute phase reactants do not discriminate well between various etiologies of inflammation. Furthermore, whether the level of biomarkers can help distinguish sepsis caused by specific microorganisms is also uncertain. A previous study had observed a similar trend in presepsin levels within the groups of microorganisms; the median presepsin value was 1668 pg/mL (range:

Table 2: Mean values of procalcitonin, presepsin, C-reactive protein, serum lactate, and worst pSOFA scores in blood culture-positive and blood culture-negative sepsis

Parameters Mean ± SD	Blood culture positive sepsis (n = 10) Mean ± SD	Blood culture negative sepsis (n = 44) Mean ± SD	p value (two-sided)
	Procalcitonin at 0 hours (ng/mL)	10.03 ± 8.613	
Procalcitonin at 72 hours (ng/mL)	40.37 ± 47.83	15.74 ± 31.67	0.057
Presepsin at 0 hours (pg/mL)	609.77 ± 417.30	865.81 ± 661.78	0.448
Presepsin at 72 hours (pg/mL)	839.22 ± 748.06	980.09 ± 843.96	0.561
hs-CRP at 0 hours (mg/L)	63.73 ± 80.06	69.25 ± 68.85	0.832
hs-CRP at 72 hours (mg/L)	72.0 ± 61.64	47.38 ± 59.76	0.267
Serum lactate (mmol/L)	2.91 ± 1.37	2.30 ± 1.19	0.180
Worst *pSOFA score	15.67 ± 4.56	12.36 ± 5.08	0.076

*pSOFA, pediatric sequential organ failure assessment

Table 4: Diagnostic accuracy of procalcitonin and presepsin at 72 hours for diagnosing septic shock in sepsis patients

Diagnostic criteria	Procalcitonin at 72 hours (n = 54)	Presepsin at 72 hours (n = 54)
Test positive/test negative in septic shock	13/5	14/4
Test positive/test negative in no septic shock	16/20	15/21
Sensitivity	72.2% (46.52–90.31)	77.8% (52.36–93.59)
Specificity	55.6% (38.10–72.06)	58.3% (40.76–74.49)
PPV	44.79% (33.78–56.34)	48.24% (37.1–59.58)
NPV	80.0% (64.28–89.92)	84.0% (67.97–92.87)
LR+	1.62 (1.02–2.58)	1.87 (1.18–2.95)
LR–	0.50 (0.22–1.11)	0.38 (0.15–0.94)
Diagnostic accuracy	61.1% (46.87–74.08)	64.8% (50.62–77.31)

PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR–, likelihood ratio negative

Table 3: Mean values of procalcitonin, presepsin, CRP, serum lactate, and worst pSOFA scores in septic shock and sepsis patients and deaths and survivors

Parameters Mean ± SD	Septic shock (n = 18) Mean ± SD	Sepsis (n = 36) Mean ± SD	p value (two-sided)	Deaths (n = 6)	Survivors (n = 48)	p value (two-sided)
	Procalcitonin at 0 hours (ng/mL)	14 ± 26.75				
Procalcitonin at 72 hours (ng/mL)	38.17 ± 45.55	10.67 ± 25.42	0.006	12.19 ± 24.54	11.07 ± 32.81	0.106
Presepsin at 0 hours (pg/mL)	837 ± 810.07	816.2 ± 970.85	0.938	723.67 ± 537.1	643.24 ± 651.25	0.575
Presepsin at 72 hours (pg/mL)	1129.11 ± 1133.8	472.47 ± 507.8	0.005	848.07 ± 950.2	564.32 ± 831.24	0.201
#CRP at 0 hours (mg/L)	43.39 ± 53.25	80.79 ± 74.65	0.064	89.39 ± 48.15	65.70 ± 68.10	0.440
#CRP at 72 hours (mg/L)	44.95 ± 42.33	54.75 ± 67.71	0.578	65.69 ± 68.10	46.94 ± 57.59	0.117
Serum lactate (mmol/L)	3.58 ± 1.2	1.8 ± 0.691	<0.001	3.91 ± 0.99	2.21 ± 1.12	0.001
Worst *pSOFA score	18.11 ± 2.49	10.30 ± 3.95	<0.001	20 ± 1.7	12.02 ± 4.67	0.000

#CRP, C-reactive protein; *pSOFA, pediatric sequential organ failure assessment

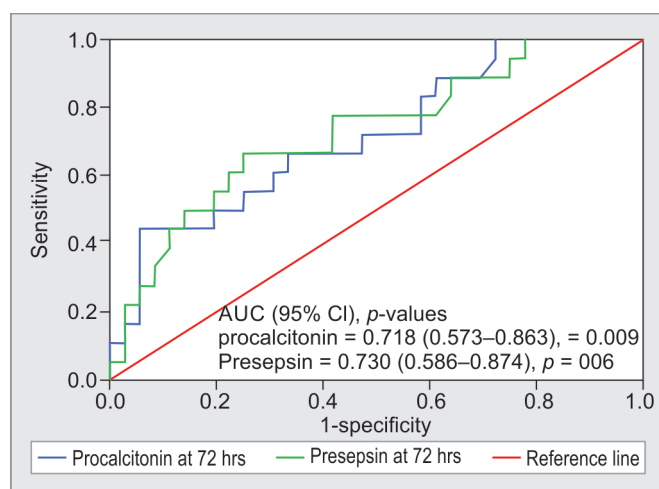


Fig. 1: Receiver operating characteristic curve of presepsin and procalcitonin at 72 hours

1048–2935) for gram-positive bacteremia patients, 1756 pg/mL (range: 1,103–2,033) for gram-negative bacteremia patients, and 1406 pg/mL (range: 1,348–1,566) for candidemia patients.¹² Another study observed that the mean log value of presepsin was 2.47 (SD 0.13) (pg/mL) for gram-positive bacteremia patients and 2.64 (SD 0.29) (pg/mL) for gram-negative bacteremia patients with no statistical difference ($p = 0.237$).¹³ However, we could not conduct subgroup analysis as our study cohort was comprised almost entirely of gram-negative bacteria as the prevailing isolate.

We enrolled 54 cases of sepsis in children as defined by sepsis-3 criteria and evaluated the performance of presepsin with that of conventional biological markers such as CRP and procalcitonin. We did not find presepsin levels at admission to be diagnostic for predicting septic shock in septic children. However, we cannot predict the diagnostic accuracy for sepsis as we did not have healthy children as controls in the present study. In terms of diagnostic threshold and accuracy, Ghazy et al. reported that on day 1 with a threshold point of 983 ng/L, AUC = 0.58, presepsin had 57% specificity and 71% sensitivity, while on day 3, with a threshold point of 1300 ng/L, AUC = 0.82, presepsin had 73% specificity and 86% sensitivity as a predictor for 30-day mortality in pediatric sepsis patients.¹⁴ Olad et al. studied presepsin levels in children with malignancies with chemotherapy-induced severe neutropenia and found that although it was not sensitive for detection of bacteraemia, it was significantly higher in blood culture-positive cases where there was no clinically detectable source of infection.¹⁵ Baraka et al. found that presepsin had high sensitivity (100%) and high specificity (85.7%) in detecting bacteraemia in pediatric patients with hematological malignancies who had febrile neutropenia.¹⁶ Basaranoglu et al. in their study found that presepsin levels were significantly higher in catheter-related bloodstream infections in pediatric patients compared with healthy controls with an area under the curve of 0.98 (95% CI 0.97–1), and the best cut off value was 990 pg/mL.¹² Urbonas et al. did not find any significant difference in presepsin levels between bacteremia/sepsis group and fever of unknown origin group in pediatric oncology patients with febrile neutropenia.¹⁷ Plesko et al. studied the role of presepsin in pediatric haemato-oncological patients and found that presepsin had good sensitivity (84%) and specificity (58%) for predicting clinical signs of sepsis but poor specificity (27%) and positive predictive value (24%) for detecting

bacteraemia.¹³ According to our analysis, presepsin at 72 hours after admission had a diagnostic accuracy of 64.8%, a sensitivity of 77.8%, and specificity of 58.3%, which was higher than that of procalcitonin and CRP. Also, even though elevated presepsin levels were observed in those with greater disease severity, it did not help in predicting mortality. These observations resonate well with the previous work by Algebaly et al.¹⁸ They reported that presepsin did not discriminate well the critically septic patients from healthy children both early and later in the course of infection. However, elevations in the presepsin levels were in accord with the increasing severity of sepsis. Shozushima et al. concluded that cutoff levels of presepsin were significantly higher in those with sepsis and commensurated with the degree of severity of sepsis.¹⁹ They found presepsin values of 721 pg/mL in local infections, 817.9 pg/mL in sepsis, and 1992.9 pg/mL in severe sepsis compared to 294.2 pg/mL in noninfected patients.

Our study indicated a significant correlation between presepsin levels and the presence of septic shock at 72 hours of admission. In a pediatric study by Ghazy et al., it was found that presepsin levels were significantly higher amongst septic patients versus controls and the incremental rise was proportional to the severity of sepsis, particularly in those with hypoperfusion/shock.¹⁴ Similarly, Romualdo et al., concluded that presepsin has a good ability to differentiate adult septic shock from sepsis at the time of admission.²⁰ Some of the published literature on the adult population has also highlighted these observations.^{7,19,21,22} Similar conclusions were reported by a recent retrospective study conducted on 91 adult patients, defined by sepsis-3 criteria which concluded that presepsin did demonstrate a favorable diagnostic accuracy for discrimination of non-sepsis from sepsis and septic shock when compared against CRP and procalcitonin.²³

Interestingly, while none of the study biomarkers had any predictive ability for mortality at the time of admission, serum lactate and worst pSOFA scores depicted a significant correlation with adverse outcomes such as septic shock and death. We found significantly elevated presepsin levels at 72 hours in those with septic shock; its clinical implications remain uncertain. Even though there was a trend towards higher values in non-survivors in our study, it was not statistically significant. In the study by Ghazy et al., the presepsin levels were significantly higher amongst non-survivors.¹⁴ These conflicting results may be attributable to differences in study design as well as patient selection criteria. Our study defined sepsis by the latest guidance issued by the third International Consensus Definitions for Sepsis and Septic Shock, which incorporates organ dysfunction. To the best of our knowledge, no pediatric study on presepsin incorporating sepsis-3 definitions has yet been published.

This study has some strengths, including the prospective study design, use of the latest sepsis-3 definitions, and comparison of various biomarkers that enabled us to explore previously unanswered scientific queries regarding this novel biomarker in children. However, the number of participants in the study was relatively small. Also, we did not have a control group for comparative analyses, limiting our results' generalizability.

CONCLUSION

Even though the early evidence in specific patient groups suggests diagnostic utility in sepsis, its relevance in children remains uncertain. In light of our findings, we believe that even though presepsin and procalcitonin did demonstrate diagnostic accuracy

for septic shock in our study cohort at 72 hours of admission, it has limited diagnostic and prognostic ability as a tool to guide clinical decision-making in pediatric sepsis. However, further large-scale studies are needed to make definite conclusions on this subject. Nonetheless, our observations should prompt further evaluation of presepsin in different clinical settings along with a suitable control population. Furthermore, combined biomarker strategies for diagnostic and prognostic assessment need to be investigated in extensive prospective clinical studies.

ORCID

Daisy Khara  <https://orcid.org/0000-0002-2963-1370>

Nisha Toteja  <https://orcid.org/0000-0002-3667-5881>

Surjit Singh  <https://orcid.org/0000-0002-8990-3235>

Simranjeet Singh  <https://orcid.org/0000-0002-4012-9736>

Prawin Kumar  <https://orcid.org/0000-0002-2365-8097>

Praveen Sharma  <https://orcid.org/0000-0002-8324-737X>

Kuldeep Singh  <https://orcid.org/0000-0002-9375-3233>

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