Diagnostic Accuracy of Serum Presepsin as Biomarker of Bacterial Sepsis in Paediatric Patients

Maham Shakoor[1], Rehma Dar[2] and Komal Javed[3]

[1]*Department of Chemical Pathology, University of Health Sciences, Lahore, Pakistan*
[2]*Department of Chemical Pathology, Services Institute of Medical Sciences, Lahore, Pakistan*
[3]*Department of Pathology, THQ Hospital Karor Lal Eason, Lahore, Pakistan*

ABSTRACT

Objective: To determine the diagnostic accuracy of serum Presepsin for bacterial sepsis in paediatric patients keeping blood culture as the gold standard test.

Study Design: Cross-sectional study.

Place and Duration of the Study: Department of Chemical Pathology, Paediatric Emergency Department and Intensive Care Unit, King Edward Medical University (KEMU), Mayo Hospital Lahore, from December 2020 to May 2021.

Methodology: A total of 57 patients, aged >4 weeks and ≤12 years with suspicion of sepsis on the basis of Systemic Inflammatory Response Syndrome to be confirmed by blood culture were enrolled in the study after informed consent. Patients with renal dysfunction and congenital anomalies were excluded. Blood samples were taken for blood culture and Presepsin levels. Presepsin levels were measured by enzyme linked immunosorbent assay (ELISA). Data were analysed by SPSS-20. Quantitative variables were presented as median (IQR) or mean ± SD depending on data distribution. Qualitative variables were presented as frequency and percentage. ROC curve was plotted to determine the optimal cut-off value of Presepsin levels to differentiate between sepsis and non-sepsis. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) of Presepsin were calculated.

Results: The median (IQR) age and total leukocyte count, and male: female ratio was not significantly different in patients with and without sepsis. Using 600 pg/ml cut-off value, Sn, Sp, PPV, and NPV for Presepsin were calculated as 72.73, 71.43, 62 and 81%, respectively.

Conclusion: Serum Presepsin level has overall good diagnostic accuracy to diagnose bacterial sepsis.

Key Words: *Presepsin, Systemic Inflammatory Response Syndrome, Bacterial sepsis, Paediatric patients.*

How to cite this article: Shakoor M, Dar R, Javed K. Diagnostic Accuracy of Serum Presepsin as Biomarker of Bacterial Sepsis in Paediatric Patients. *J Coll Physicians Surg Pak* 2023; **33(11)**:1288-1292.

INTRODUCTION

Sepsis is defined as a "life threatening organ dysfunction resulting from the dysregulated host response to infection".[1] It is one of the leading causes of admissions in neonatal, paediatric, and adult intensive care units worldwide. Sepsis has been reported in 17.3% children admitted to the PICU with mortality rate of 24% in Pakistan.[2] The increased mortality associated with sepsis is mainly due to delay in diagnosis and therefore, delay in initiation of targeted therapy. A well-defined criterion has been established to clinically diagnose sepsis in adult patients.[3] But the criteria to diagnose sepsis in paediatric population is still not clearly defined. In children, sepsis is usually diagnosed as Systemic Inflammatory Response Syndrome (SIRS) with suspected or documented infection.[4]

Correspondence to: Dr. Maham Shakoor, Department of Chemical Pathology, University of Health Sciences, Lahore, Pakistan
E-mail: mahamshakoor1@gmail.com
Received: April 05, 2023; Revised: July 17, 2023; Accepted: October 11, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.11.1288

SIRS is the clinical condition resulting from abnormal inflammatory response to infectious and non-infectious causes like autoimmune disorders, trauma, burns, and surgery. It is based on clinical features including respiratory rate, heart rate, body temperature, and a laboratory test called total leukocyte count (TLC).[5]

The gold standard test for the diagnosis of bacterial sepsis is blood culture.[1] It takes almost 48 to 72 hours to obtain culture results. The blood culture results are affected by many factors like unsterile sample collection, inappropriate inoculation volume, and delayed transportation to laboratory.[6] Some biomarkers have been studied to diagnose sepsis, like Procalcitonin (PCT), C-reactive protein (CRP), and Presepsin. CRP is an acute phase protein which increases in response to infection, inflammation, and tissue damage. It lacks specificity as it cannot differentiate between infectious and non-infectious SIRS. Moreover, it is not useful as early marker for diagnosis of sepsis as it becomes detectable about 12 hours after the onset of clinical symptoms.[7] Procalcitonin is another biomarker used for the diagnosis of bacterial sepsis. It is calcitonin precursor protein secreted by hepatocytes and monocytes on exposure to bacterial endotoxins. It rises within 4 hours after pathogen

exposure.[8] Although it is reported to be superior than CRP as it can differentiate between bacterial and non-bacterial infections, it cannot differentiate between infectious and non-infectious SIRS.[9]

Presepsin is an emerging marker of bacterial sepsis. It begins to rise in the first hour of exposure to pathogens and reaches its peak in 2 to 3 hours. It is known to rise in sepsis caused by bacterial infections and remains unchanged in non-infectious SIRS, so helps to differentiate the two.[10] Presepsin is a type of cluster of differentiation 14 (CD14) glycoprotein. CD14 is a part of innate immune response of the body. It identifies and presents the ligands of pathogens like lipopolysaccharides attached with lipopolysaccharide binding proteins (LBP) to Toll like receptors (TLRS). TLRs, in turn, activate immune response through cytokine production resulting in SIRS. CD14 has two forms: membrane CD14 (m CD14) and soluble CD14 (s CD14). m CD14 is present on the surface of macrophages/ monocytes. s CD14 circulates in blood synthesised from shedding of m CD14 by the action of proteases cathepsin D or by secretion from cells. The soluble CD14 subtype is named as Presepsin.[8]

Since Presepsin is known to be more specific and early to rise in septic patients, it can be used as an early biomarker of bacterial sepsis. In this background, this study was conducted to determine the diagnostic accuracy of Presepsin as a biomarker of bacterial sepsis, keeping the blood culture as the gold standard test.

METHODOLOGY

It was a cross sectional study conducted at the Department of Chemical Pathology of King Edward Medical University, Paediatric Emergency Department and Paediatric ICU of Mayo Hospital, Lahore for six months period from 1st December, 2020 to 31st May, 2021. Sample size of 57 patients was estimated by using 95% confidence level. Non-probability convenient sampling was used. Patients of both genders, aged >4 weeks and ≤12 years with suspicion of sepsis on the basis of SIRS that were to be confirmed by blood culture were included in the study after informed consent of the guardian. Patients with renal dysfunction and congenital syndromes/ anomalies were excluded.

The relevant information of each patient was recorded in study proforma and arterial or venous 5-6 ml blood sample was drawn for blood culture and Presepsin levels under aseptic conditions. The blood culture sample was sent to microbiology laboratory. The blood sample for Presepsin levels was collected in yellow top vacutainer labelled with patient's name and ID. The serum was separated through centrifugation at 3000 revolutions per minute (RPM) and stored in eppendorf cups at -70° C till analysis. The sandwich ELISA was performed for quantitative determination of Presepsin levels using kit by Bioassay Technology Laboratory on Diamate 710 ELISA plate reader instrument in 2 batches.

The data were entered and analysed in Statistical Package for Social Sciences (SPSS-20). Quantitative variables like age, body temperature, and TLC were presented as median (IQR). Qualitative variables like gender were presented as frequency and percentage. Normality of variables was examined by applying Shapiro-Wilk test. Mann Whitney U test was applied to compare age, body temperature, and TLC, and Chi-square test was used to compare gender distribution between patients with sepsis and without sepsis. A p-value <0.05 was taken as statistically significant.

ROC curve was plotted in SPSS to calculate the optimal cut-off value of Presepsin levels to differentiate between sepsis and non-sepsis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Presepsin were calculated by appropriate formulae using the 2×2 contingency table.

RESULTS

Blood culture was used as gold standard to classify patients into septic and non-septic groups. Out of 57 patients, 22 blood culture results were positive (sepsis group) while 35 were negative (non-sepsis group) as shown in Table I.

The ROC curve was plotted to derive the optimal cut-off value of 600pg/ml for Presepsin levels to differentiate between sepsis and non-sepsis with area under curve (AUC) = 0.815 at 95% confidence interval (Figure 1).

Sn, Sp, PPV, and NPV of Presepsin in paediatric patients were calculated as 72.73, 71.43, 62 and 81%, respectively (Table II).

Table I: Demographic and clinical characteristics of study subjects.

Variables	Sepsis (n=22)	Non-sepsis (n=35)	p-value
Age, months Median (IQR)	30 (33)	5 (22)	0.064
Gender (M:F)	13(59%): 9(41%)	18(51%): 17(49%)	0.572
Body temperature (°F) Median (IQR)	102 (9)	101 (8.4)	*0.012
Total leukocyte count (cells X 10^6/l) Median (IQR)	16.5 (57.3)	11.8 (36.3)	0.066

*Chi-square test used for gender. Mann Whitney U test used for age, body temperature, and total leukocyte count. *p- value <0.05 was taken as statistically significant. Pneumonia was the most common cause of infection in the patients with sepsis (13; 59%). The other clinical presentations were meningitis (6; 27%) and gastroenteritis (3;14%).*

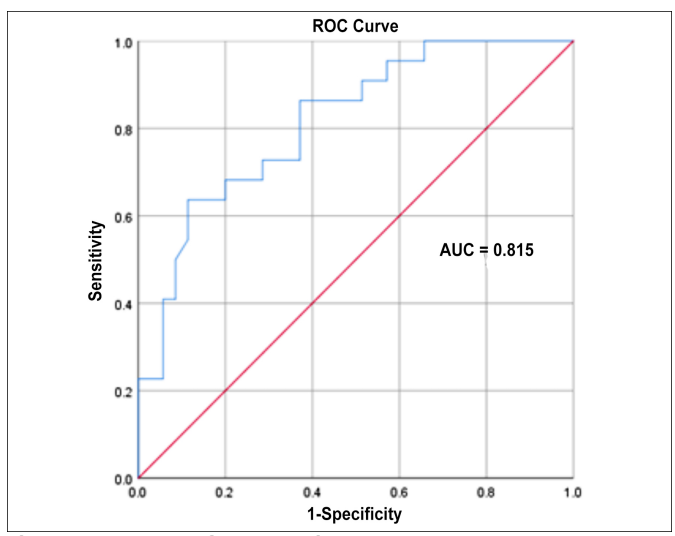

Figure 1: ROC curve for Presepsin.

Table II: 2 × 2 Contingency table according to the calculated cut-off value of Presepsin.

Presepsin (cut-off value= 600pg/ml)	On the basis of blood culture	
	Sepsis	Non-sepsis
Positive	16 (True Positive)	10 (False positive)
Negative	6 (False Negative)	25 (True Negative)

DISCUSSION

Sepsis is one of the leading causes of morbidity and mortality in paediatric population globally.[4] Although blood culture is the gold standard for the diagnosis of bacterial sepsis, delay in results of culture evoke the need of a diagnostic tool that is efficient to detect bacterial sepsis earlier in paediatric patients.[6] Some biomarkers are being studied for the earlier diagnosis of bacterial sepsis like Procalcitonin and CRP having their own pitfalls.[1,4] The diagnostic accuracy of Presepsin, a newly proposed biomarker of bacterial sepsis was determined in this study.

The paediatric patients included in the study with suspected sepsis were 57. Keeping the blood culture as the gold standard, 22 were labelled with sepsis whereas 35 with non-sepsis.

The median (IQR) age and gender distribution were not statistically different among patients with and without sepsis. These findings were in accordance with the studies performed by Sakyi *et al*. and Ghazy *et al*. on paediatric group.[6,11] The median (IQR) TLC also showed no statistically significant difference among patients with and without sepsis. This result was in accordance with that of Leli *et al*.[12] The median (IQR) body temperature was significantly different among patients with and without sepsis in this study (p-value = 0.012). These results were similar to the study by Sakyi *et al*.[6]

The most common clinical presentation was pneumonia (59%) among septic patients in this study. The other clinical presentations were meningitis (27%) and gastroenteritis (14%). This result was in agreement with the findings of study by Ghazy *et al*. in which pneumonia was the most common cause of sepsis followed by gastroenteritis and meningitis.[11] However, these findings differed from the study of Leli *et al*. in which urinary tract infection was the most common cause of sepsis.[12] The difference might be due to different age groups (median age being 73 years) with differences in the frequency of infections.

The optimal cut-off value for Presepsin was calculated as 600 pg/ml from ROC curve to differentiate between sepsis and non-sepsis in the study. The AUC was 0.815 at this cut-off.

Sn, Sp, NPV, and PPV were 72.73, 71.43, 81, and 62%, respectively. The results were in agreement with that of study by Ghazy *et al*. in which the sensitivity and specificity of Presepsin in children were 86 and 73%, respectively, and AUC was 0.820 at cut-off of 1300 pg/ml.[11] The results were also comparable to study by Zhang *et al*. who conducted a meta-analysis and showed that Presepsin had diagnostic sensitivity and specificity of 0.83 and 0.78, respectively, with AUC of 0.88 for bacterial sepsis. The cut-off in this meta-analysis ranged from 317-729 pg/ml.[13]

The cut-off value of 600 pg/ml for Presepsin in this study was similar to that of Endo *et al*. with sensitivity and specificity calculated as 87.8 and 81.4%, respectively.[14] However, the sensitivity and specificity are slightly different from this study. The reason might be due to difference in population characteristics as their study was conducted in Japan. Moreover, the reference value of analytes varies in population.

According to multicentric trials, when the cut-off value of 600 pg/ml was used, Presepsin levels were remarkably high in patients suffering from bacterial infections than in patients with non-bacterial infections.[14] However, some studies reported that cut-off of 600 pg/ml was not able to distinguish between gram-negative and gram-positive bacterial infections. A study by Masson *et al*. showed that Presepsin concentration of more than 946 pg/ml was present in patients with Gram-negative as compared to Gram-positive bacterial sepsis. This is because of its role in the formation of the CD14-LPS-LBP complex.[15]

Several acute phase reactants have been used to diagnose bacterial sepsis in paediatric population like C-reactive protein (CRP), interleukin (IL), Procalcitonin (PCT), and soluble form of triggering receptor expressed on myeloid cells-1 (Strem-1). But, the clinical utility of these biological markers in the diagnosis of sepsis is still controversial.[1] Some studies have compared the diagnostic efficiency of Presepsin with that of PCT and CRP for the diagnosis of sepsis. According to a study by Baraka *et al*., the sensitivity and specificity of Presepsin, PCT, and CRP were 97 and 85%, 97 and 80%, and 76 and 66%, respectively.[16]

Another study by Bellos *et al*. stated that Presepsin had higher diagnostic accuracy for sepsis in terms of AUC than PCT (0.959 *versus* 0.783) and CRP (0.975 *versus* 0.858).[17] On the other hand, some studies showed that Presepsin and PCT were comparable in differentiating bacterial and non-bacterial infections; AUCs for Presepsin and PCT were 0.908 and 0.905, respectively.[14] Whereas, study by Van-Rossum *et al*., showed the AUC of Presepsin was less than PCT (0.70 *versus*. 0.87) for sepsis.[18]

According to a meta-analysis, Presepsin had better diagnostic accuracy as compared to CRP or PCT. The pooled sensitivity of Presepsin was higher than those of PCT and CRP. However, the pooled specificity of Presepsin was less than that of PCT and CRP. The AUC of Presepsin (0.925) was larger than that of PCT (0.830) and CRP (0.715).[4] The underlying reason for low diagnostic accuracies of other biomarkers as compared to Presepsin was that they lacked specificity as they were raised in many inflammatory conditions other than bacterial sepsis like trauma, malignancies, autoimmune diseases, etc. Moreover, they did not rise earlier as compared to Presepsin that rose within the first hour of bacterial invasion.[19]

In a multicentric prospective study, comparison of Presepsin was done with IL-6, PCT and blood culture. The researchers concluded that Presepsin was a better marker than blood culture and other conventional inflammatory markers for the diagnosis of sepsis.[14]

The Presepsin levels are also found to be related to the severity of sepsis. They were remarkably high in patients with sepsis (817.9 pg/ml), and severe sepsis (1,992.9 pg/ml) than in patients with localised infection (721 pg/ml) and those without any infection (294.2 pg/ml).[20] The levels of Presepsin were not found to be significantly different in Gram-positive and Gram-negative bacterial infections.[4]

The so-far-known limitation for the utility of Presepsin for the diagnosis of sepsis is that in addition to sepsis, its levels are raised in end stage renal disease. This is due to the fact that it is filtered and cleared by kidneys.[21] A different cut-off level is needed to use it in patients of renal impairment to diagnose sepsis. Although a study by Nakamura *et al*. showed that Presepsin levels are not affected in patients of early kidney damage, it could be used as a reliable indicator of sepsis in them.[22]

To the best of authors' knowledge, this study was one of the first studies conducted in Pakistan to determine the diagnostic accuracy of Presepsin in bacterial sepsis. Moreover, it was also one of the few studies conducted on paediatric population. However, the study was performed on small scale and the diagnostic accuracy of Presepsin was not compared with other biomarkers of bacterial sepsis due to financial constraints.

CONCLUSION

Serum Presepsin levels have overall good diagnostic accuracy to diagnose bacterial sepsis in paediatric patients, and it has the potential to be used as a biomarker of sepsis in paediatric population.

ETHICAL APPROVAL:

The approval for this study was taken from Advance Study and Review Board of KEMU, Lahore.

PATIENTS' CONSENT:

Informed consent was taken from each participant before the data collection.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

MS: Literature research, collection of data, and statistical analysis.
RD: Conception and design of research topic, and final approval of version to be published.
KJ: Drafting manuscript and critical revision.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Richter DC, Heininger A, Brenner T, Hochreiter M, Bernhard M, Briege J, *et al*. Bacterial sepsis. *Anaesthesist* 2019; **68(1)**:40-62. doi: 10.1007/s00101-017-0396-z.
2. Khan MR, Maheshwari PK, Masood K, Qamar FN, Haque AU. Epidemiology and outcome of sepsis in a tertiary care PICU of Pakistan. *Indian J Pediatr* 2012; **79(11)**:1454-8. doi: 10.1007/s12098-012-0706-z.
3. Venugopalan DP, Pillai G, Krishnan S. Diagnostic value and prognostic use of Presepsin *versus* procalcitonin in sepsis. *Cereus* 2019; **11(7)**:e5151. doi: 10.7759/cureus.5151.
4. Yoon SH, Kim EH, Kim HY, Ahn JG. Presepsin as a diagnostic marker of sepsis in children and adolescents: A systemic review and metanalysis. *BMC Infect Dis* 2019; **19(1)**:1-11. doi: 10.1186/s12879-019-4397-1.
5. Asmaa OA, Shaimaa MS. Presepsin: A new marker for early diagnosis of septicemia. *Med J Cairo Univ* 2018; **86(5)**: 2237-44.
6. Sakyi SA, Enimil A, Adu DK, Ephraim RD, Danquah KO, Fondjo L, *et al*. Individual and combined bioscore model of presepsin, procalcitonin, and high sensitive C-reactive protein as biomarkers for early diagnosis of paediatric sepsis. *Heliyon* 2020; **6(9)**:e04841. doi: 10.1016/j.heliyon.2020.e04841.
7. Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. *J Cell Biochem* 2019; **120(4)**: 5852-9. doi: 10.1002/jcb.27870.
8. Memar MY, Baghi HB. Presepsin: A promising biomarker for the detection of bacterial infections. *Biomed Pharmacother* 2019; **111(1)**:649-56. doi: 10.1016/j.biopha.2018.12.124.
9. Ruan L, Chen GY, Liu Z, Zhao Y, Xu GY, Li SF, *et al*. The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis;a meta-analysis and systematic review. *Crit Care* 2018; **22(1)**:1-9. doi: 10.1186/s13054-018-2236-1.
10. Chenevier C, Bardet V, Poupet H, Poyart C, Borderie D, Claessens YE. Presepsin (sCD14-ST) secretion and kinetics by peripheral blood mononuclear cells and monocytic THP-1 cell lone. *Ann Biol Clin* 2016; **74(1)**:93-37.
11. Ghazy MM, El-Halaby HA, El-Sabbagh AM, Shaltout AA. Diagnostic and prognostic values of soluble CD14 (presepsin) in sepsis in paediatric intensive-care patients. *Alex J Pediatr* 2018; **31(3)**:141-7.
12. Leli C, Ferranti M, Marrano U, Al Dhahab ZS, Bozza S, Cenci E, *et al*. Diagnostic accuracy of Presepsin (sCD14-ST) and procalcitonin for prediction of bacteremia and bacterial DNAaemia in patients with suspected sepsis. *J Med Micrbiol* 2016; **6(8)**:713-9. doi: 10.1099/jmm.0.000278.
13. Zhang J, Hu ZD, Song J, Shao J. Diagnostic value of Presepsin for sepsis: A systematic review and meta-analysis. *Medicine* 2015; **94(47)**:e2158. doi: 10.1097/MD. 0000000000002158.
14. Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A, *et al*. Usefulness of presepsin in the diagnosis of sepsis in a multicentre prospective study. *J Infect Chemother* 2012; **18(6)**:891-7. doi: 10.1007/s10156-012-0435-2.
15. Masson S, Caironi P, Fanizza C, Thomae R, Bernasconi R, Noto A, *et al*. Circulating presepsin (soluble CD14 subtype) as a marker of host response in patients with severe sepsis or septic shock: Data from the multicentre, randomised ALBIOS trial. *Intensive Care Med* 2015; **41(1)**:12-20. doi: 10.1007/s00134-014-3514-2.
16. Baraka A, Zakaria M. Presepsin as a diagnostic marker of bacterial infections in febrile neutropenic paediatric patients with hematological malignancies. *Int J Hematol* 2018; **108(2)**:184-91. doi: 10.1007/s12185-018-2447-x.

17. Bellos I, Fitrou G, Pergialiotis V, Thomakos N, Perrea DN, Daskalakis G. The diagnostic accuracy of presepsin in neonatal sepsis: A meta-analysis. *Eur J Pediatr* 2018; **177(5)**:625-32. doi: 10.1007/s00431-018-3114-1.

18. Van-Rossum AM, Wulkan RW, Oudesluys-Murphy AM. Procalcitonin as an early marker of infection in neonates and children. *Lancet Infect Dis* 2004; **4(10)**:620-30. doi: 10.1016/S1473-3099(04)01146-6.

19. Rogic D, Juros GF, Petrik J, Vrancic AL. Advances and pitfalls in using laboratory biomarkers for the diagnosis and management of sepsis. *J Int Fed Clin Chem* 2017; **28(2)**:114-121.

20. Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S. Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. *J Infect Chemother* 2011; **17(6)**:764-9. doi: 10.1007/s10156-011-0254-x.

21. Piccioni A, Santoro MC, de-Cunzo T, Tullo G, Cicchinelli S, Saviano A, *et al*. Presepsin as early marker of sepsis in emergency department: A narrative review. *Medicina* 2021; **57(8)**:770-81. doi: 10.3390/medicina57080770.

22. Nakamura Y, Ishikura H, Nishida T, Kawano Y, Yuge R, Ichiki R, *et al*. Usefulness of presepsin in the diagnosis of sepsis in patients with or without acute kidney injury. *BMC Anesthesiol* 2014; **14(1)**:1-7. doi: 10.1186/1471-2253-14-88.