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Research Article

INFLAMMATORY MARKERS OF SEPSIS IN PEDIATRICS CASES

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Abstract

Background: Sepsis is currently one of the important problems in medicine due to its complexity from pathophysiologic, clinical and therapeutic perspectives. The study was aimed to assess the levels of inflammatory markers and evaluate their performance in predicting severity and outcome in pediatric sepsis cases. **Methods:** The study included 84 cases admitted to pediatric intensive care unit with suspicion of sepsis based on International Pediatric Sepsis Consensus Criteria for sepsis (2005). Blood sample from cases were assessed for serum presepsin, procalcitonin, C-reactive protein in addition to routine investigations in sepsis including blood culture at the time of admission. **Results**: The study sample comprised 47 cases with sepsis and 37 cases with severe sepsis. The mean values of serum presepsin, procalcitonin and C-reactive protein in severe sepsis were significantly higher in comparison to sepsis cases with p value <0.01. The rise in serum presepsin was six fold in severe sepsis as compared to its rise in sepsis cases. However, increase in C-reactive protein was two folds in severe sepsis cases as compared to sepsis cases. The area under the curve (AUC) of serum presepsin (0.814) was highest followed by C-reactive protein (0.749) and procalcitonin (0.718) in predicting the severity. With serum presepsin value greater than 650 pg. /ml, had 80% positive predictive value and 76% negative predictive value. Serum presepsin showed higher specificity (95 % against 55% and 49%) and positive predictive value (55 % against 17% and 15%) than procalcitonin and C-reactive protein respectively, in predicting mortality. **Interpretation and Conclusion**: Serum presepsin was found to be better inflammatory marker of sepsis than procalcitonin and C-reactive protein in predicting both severity and mortality in these cases.

Keywords: C-reactive protein, inflammatory markers, presepsin, procalcitonin, sepsis.

1. INTRODUCTION

Sepsis is a systemic inflammatory response to severe infection and its clinical manifestations vary with rapid progression [1]. Sepsis lowers patient's living quality and increases the mortality significantly. Sepsis occurs in 1%–2 % of all hospitalized patients and accounts for as much as 25% of ICU cases. The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, circulatory abnormalities, humoral and cellular reactions [2, 3]. During the course of treatment of sepsis, early administration of antibiotics is given priority before comprehensive treatment. However, due to the existence of non-infectious systemic inflammatory response syndrome (SIRS) in many critical patients and to differentiate sepsis from SIRS at the early stage has become challenging. There are numerous biological markers of sepsis including C-reactive protein (CRP), procalcitonin (PCT) [4, 5]. Biomarkers released during pathogenesis of sepsis have potential role in diagnosis and prognosis of sepsis. The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis [6]. Procalcitonin (PCT) has been proposed as a more specific and better prognostic marker than CRP, although its value has also been challenged [7]. Nevertheless, the exact role of biomarkers in the management of septic patients remains undefined. Furthermore, as there is no 'gold standard' for the diagnosis of sepsis, the effectiveness of biomarkers needs to be compared with current methods used to diagnose and monitor sepsis in day to day clinical practice, i.e., by the combination of clinical signs and available laboratory variables

A novel biomarker presepsin (sCD14-ST), formed by cleavage of N-terminal of soluble CD14 (sCD14) which is a member of the Toll-like receptors (TLRs) is postulated to be more specific for diagnosis, risk stratification and therapeutic response monitoring, of sepsis as it is directly implicated in the innate immune pathogenesis of the syndrome [8]. Several studies, in adult patients have explored the utility of serum presepsin in sepsis have reported be a reliable marker [9, 10]. On the other hand, presepsin in pediatric cases with sepsis, especially in Indian population, is not well reported. Thereby the study was undertaken to evaluate the performance of presepsin in sepsis in pediatric cases and relating it with the conventional biomarkers.

2. MATERIALS AND METHODS

The study was conducted at M.S. Ramaiah teaching hospital, Bangalore. A prospective observational study was carried out at hospital pediatric ICU to evaluate the role of serum presepsin in predicting the severity and outcome of sepsis in pediatric cases in association with serum procalcitonin (PCT) and C-reactive protein (CRP). The study was approved by the Institutional Research and Ethics Committee and informed consent was taken from the study population before the collection of the sample.The study population consisted of 84 pediatric cases, admitted to pediatric ICU, aged between 1 month to 17 years with suspicion of sepsis based on the International Pediatric Sepsis Consensus Criteria for sepsis (2005) were recruited for the study. Patients with noninfectious causes of SIRS, pneumonia, on hemodialysis and other conditions which can interfere with the study were excluded. Informed consent was taken from the parents/guardians as applicable. Demographic details, anthropometry, clinical presentation, vitals and examination findings were recorded for the recruited cases for the study. Using aseptic precaution 3 ml of whole blood in EDTA vacationer and 5 ml of venous blood sample in yellow vacutainer were collected at the time of admission to PICU. The sample in yellow vacutainer was allowed to stand for about 15 minutes for clotting and was then centrifuged at 5000 rpm. The serum sample was separated and stored at - 20º Celsius till estimation was done for. Sepsis panel routinely requested in these cases included total leukocyte count, platelet count, blood culture, blood gas analysis including lactate, liver and kidney function tests were estimated. Chest X ray was done and pediatrics Sequential Organ Failure Assessment score (pSOFA) at the time of admission were recorded. Serum presepsin was estimated by Human Enzyme Linked Immunosorbent Assay (ELISA) - Elabscience USA, Serum procalcitonin by ELISA automated kits, ELK Biotechnology and CRP - by Immunoturbidimetric method, VITROS 5600 analyzer.

The study cases were divided into two groups: Group A (Sepsis) and Group B (Severe Sepsis, Septic shock, Multi organ dysfunction syndrome) according to the International Pediatric Sepsis Consensus Criteria for sepsis (2005) [11]. Children from Group A, who worsened during the course of PICU stay were included under group

B for result analysis**.** All the cases were followed up for need for ventilation, inotropic support, length of ICU stays, discharge or death.

2.1 Statistical Methods

The results were expressed as mean ± SD. Significance was assessed at 5% level of significance. Data was analyzed using SPSS 22 version software. Independent t- test was used as test of significance to identify the mean difference between two quantitative variables. ROC curve and optimal cut-off points were chosen for the calculation of sensitivity, specificity, positive and negative predictive values. An area under the ROC curve above 0.8 indicated fairly good prediction. The p value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

3. RESULTS

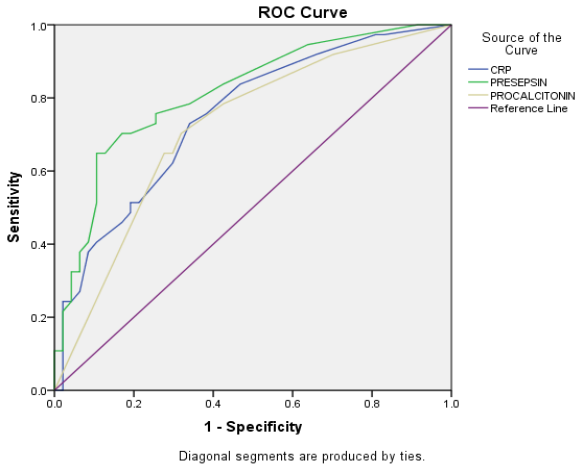
A total of 84 cases were included of which 47 cases were in group A and 37 cases in group B (Fig 1). Among the 84 study subjects, 76 survived and 8 died. Demographic profiles, such as age and gender compared between group A and group B did not show any statistical significance (p value: 0.518 and 0.647 respectively). The indicators of infection were compared between the two group A & B. The mean presepsin, (3440.5 pg/ml), PCT (3.64 ng/ml) and CRP (10.41 mg/dl) were higher in group B with statistical significance (p value <0.05) (Table 1). Further, ROC curve for analysis of biomarkers for predicting severity (Fig 2) showed presepsin to have higher AUC values (0.814, p<0.001), when compared to CRP and PCT (0.749 and 0.718). With the cut off > 650 pg/ml, serum presepsin had higher specificity (87%).

Table 3 summaries the parameters between survivors and non survivors. Among the 84 study subjects, 76 survived and 8 died. The mean presepsin values among survivors were 1331 pg/ml and among non survivors were 6487 pg/ml (p value <0.01). The mean PCT value was 2.64 ng/ml among survivors and 4.5 ng/ml in non-survivor cases which were statistically significant. CRP though higher among the non survivors as compared to survivors, but was not statistically significant. The ROC curve plotted to assess the performance of the biomarkers in predicting mortality showed the AUC of presepsin to be 0.781 similar to that of procalcitonin (Table 4). With the cut off > 4500 pg/ml, presepsin had an Odd's ratio of 15.8 in predicting mortality with the sensitivity of 62.5%, specificity of 96% with positive predictive value of 62.5% and negative predictive value of 96% becoming a better predictor of mortality than other biomarkers (Table 4). Further, revealed presepsin, pSOFA scores and length of PICU stay in sepsis and severe sepsis cases were highly significant, suggesting presepsin as a good indicator of severity of disease.

Table 1: Comparison of clinical and blood parameters between sepsis and severe sepsis.

Parameters	Group A (Sepsis) Mean ± SD	Group B (Severe Sepsis) Mean ± SD	p value
Total Leukocyte count ($x10^3$/cu.mm)	11.38 ± 6.04	15.21 ± 7.53	0.011
Platelet count (10^5/cu.mm)	2.37 ± 0.84	1.82 ± 1.15	0.013
Blood Lactate (mmol /L)	1.6 ±0.95	2.38 ±2.21	0.04
S. Creatinine (mg/dl)	0.38 ± 0.27	0.62 ±0.48	0.006
S. Albumin (g/dl)	3.00 ± 0.68	2.47 ± 0.76	< 0.001
p SOFA score	0.72 ±1.210	4.43 ±4.32	<0.001
S. Presepsin (pg/ml)	549 ± 1119.76	3440.5 ±3755.5	<0.001
S. Procalcitonin (ng/ml)	2.17 ± 2.07	3.64 ± 2.01	<0.001
S. CRP (mg/dl)	5.15 ± 9.53	10.41 ± 8.37	<0.001
Duration of ICU stay (days)	3.00 ±1.12	4.70 ± 1.66	<0.001

Fig 2. Various biomarkers in predicting severity by ROC analysis



Receiver operating characteristic (ROC) curves of presepsin, PCT and CRP for predicting the severity of sepsis. AUC = 0.814 (95% CI: 0.721 to 0.907) for presepsin, AUC = 0.718 (95% CI: 0.608 to 0.829) for PCT and AUC = 0.749 (95% CI: 0.644 to 0.853) for CRP.

Table 2: Sensitivity and Specificity of Biomarkers in predicting severity of sepsis.

Biomarkers	Cut off	AUC	95% CI	Odd's ratio	sensitivity	specificity
Presepsin	>650pg/ml	0.814	0.721-0.907	6.09	70%	87%
Procalcitonin	>2ng/ml	0.718	0.608-0.829	1.84	70%	68%
C-reactive protein	>5.75 mg/dl	0.749	0.644-0.853	2.0	62%	70%

Table 3: Clinical and Blood parameters of sepsis cases (between survivors and non survivors)

Parameters	Survivors (Mean ± SD)	Non survivors (Mean ± SD)	p value
Total leukocyte count (10^3/cumm)	13.07 ± 6.97	12.93 ± 7.36	0.957
Platelet count (10^5/L)	2.22 ±1.02	1.21 ±0.40	0.007
Blood Lactate (mmol /L)	1.8 ±1.11	3.4± 4.13	0.01
S Creatinine (mg/dl)	0.43 ±0.29	0.97 ±0.77	0.00
S. Albumin (g/dl)	2.78± 0.72	2.65 ± 1.10	0.464
p SOFA score	1.63 ± 2.427	9.25 ± 4.833	<0.001
S. Presepsin(pg/ml)	1331.58 ±1792.89	6487.50±6601.18	<0.001
S. Procalcitonin (ng/ml)	2.64 ±2.13	4.50 ±1.75	0.019
S. CRP (mg/dl)	7.38 ± 9.59	8.29 ± 7.33	0.796
Duration of ICU stay (days)	3.61 ± 1.41	5.13 ± 2.75	0.011

Table 4 : **Performance of biomarkers in predicting outcome.**

Biomarkers	Cut off	AUC	95% CI	Odd's ratio	Sensitivity	Specificity
Presepsin	>4500 pg/ml	0.781	0.678 To 0.864	15.8	62.5%	95%
Procalcitonin	>2 ng/ml	0.781	0.678 to 0.864	5	87.5%	55%
C- reactive protein	>3.5 mg/dl	0.628	0.516 to 0.731	5.78	87.5%	48.7

4. DISCUSSION

Sepsis is currently one of the important problems in medicine due to its complexity from pathophysiologic, clinical and therapeutic perspectives. Sepsis is an unusual systemic response, at times to an otherwise ordinary infection. It is moreover an important reason for hospitalization and a major cause of death in the Intensive Care Units (ICUs) worldwide. Biomarkers play a key role in early diagnosis and intervention which, although primarily supportive, can reduce the risk of death. 84 cases of clinically diagnosed sepsis in pediatric age group were recruited for the study. In the study population, at the time of admission presepsin levels were higher in cases with severe sepsis. Of the many proposed markers for sepsis, acute phase proteins have perhaps been the one most widely assessed. C-reactive protein (CRP) is a traditional biomarker which is also elevated in infection and other inflammatory states [12]. However, CRP has low specificity in the diagnosis of sepsis, as the plasma level of CRP is not a reliable indicator for the degree of systemic inflammation.

Accordingly, high early levels of PCT in sepsis have been suggested to be associated with unfavorable prognosis. In comparison with CRP, PCT seems to be a better marker to differentiate sepsis from non-infectious SIRS [13]. The specificity and sensitivity of PCT for the diagnosis of sepsis is relatively low (typically below 90%), regardless of the cut-off value. Although other biomarkers are preferred over serum CRP in terms of sepsis diagnosis, but CRP is commonly used in clinical practice because of its greater availability and cost effectiveness. Albumin also has been identified to have partly anti-inflammatory effects and be beneficial to the patients with sepsis. Decreased levels of albumin were significantly associated with poor prognosis in sepsis [14]. Physiologically, albumin is synthesized in the liver and liver function may be impaired in sepsis, leading to the synthesis deficiency of albumin. At the time of admission, if serum presepsin is estimated, it may possibly play a role in anticipating the severity of sepsis. The rise in serum presepsin levels is sepsis is observed as compared to CRP, PCT and leukocyte counts. This may be because, most of the biomarkers are fundamentally acute phase reactants and their rise in proportion to degree of inflammation while presepsin being a part of Toll like receptors is involved in innate immune system against infections. Ozkan et al. have also found in their study, higher level of presepsin in cases of sepsis and correlated with the degree of severity of sepsis. [15]. In a pediatric study, it was found presepsin levels were significantly higher amongst septic patients and the incremental rise was proportional to the severity of sepsis in pediatric cases [16].

Presepsin was recently identified as a molecule involved in the inflammatory response and represents a promising diagnostic biomarker with high sensitivity and specificity [17]. The study also showed a significant positive correlation between presepsin and pSOFA scores, which is an established severity index of organ failure in critically ill children thus emphasizing the predictive ability of presepsin in sepsis children. This resonates well with the data by Lee et al. [18]. In terms of outcome, with threshold of >4500pg/ml on day 1, presepsin had specificity of 96% and sensitivity of 62.5% in predicting mortality. Studies have showed that on day 1 with a threshold point of 983 ng/L, presepsin had 57% specificity and 71% sensitivity, in predicting 30-day mortality in sepsis in pediatric cases. [16]. He RR et al. also reported, increased 60-day in house mortality in adult patients with values of presepsin > 1000 pg/ml [19]. Generally, PCT increases 4 hours after infection, slowly reaching a plateau at 8–24 hours and peaking one day after infection. Presepsin increases at 2 hours post-infection and peaks at 3 hours as reported in several studies as compared to other inflammatory markers including PCT. Presepsin has potential both as a diagnostic and prognostic sepsis biomarker. Masson et al in ALBIOS study also concluded presepsin to be superior in early risk stratification and mortality [20].

In the study, serum presepsin had significant prognostic value (AUC= 0.784) with high specificity and predictive values compared to PCT and CRP, predicting severity thus strengthening our assumption of serum presepsin being a reliable marker in pediatric sepsis. The study by Yoon et al. also stated presepsin showed higher sensitivity and accuracy but relatively lower specificity for the diagnosis of pediatric sepsis than either PCT or CRP [21]. A similar study in adults have reported, significant prognostic value of presepsin levels in 30 days and 6 months all-cause mortality (range of AUC 0.64 to 0.71) when compared to procalcitonin and other markers [22]. The study has few limitations. First, this study was limited to the single center with limited number of patients. As healthy controls were not part of study, the diagnostic accuracy of presepsin could not be concluded.

5. CONCLUSION

Our study showed Serum presepsin to be better than procalcitonin and C-reactive protein in predicting both severity and mortality in septic children. Serum presepsin had the highest specificity and predictive values among the biomarkers. Hence, presepsin can be used as an early risk stratification for septic children. The results demonstrated that presepsin may be a reliable biomarker for sepsis because of its good overall diagnostic performance. In view of the complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found.

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COMPETING INTERESTS

Authors have declared that no competing interests exist. **Source of funding**: None

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

CONSENT

"All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal."

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