EVALUATE THE ROLE OF PROCALCITONIN AND C-REACTIVE PROTEIN AS A ENCOURAGING BIOMARKERS FOR DIAGNOSING PEDIATRIC SEPSIS

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Abstract:

Diagnosis of Pediatric Sepsis is a challenge because of its nonspecific presentation together with low sensitivity of the time-consuming bacterial cultures. Sepsis markers, like C-reactive protein (CRP), and procalcitonin (PCT), have encouraging results to improve its diagnosis. This study was done to investigate the role of CRP and PCT in promoting the early diagnosis of pediatric sepsis an attempt to decrease morbidity and mortality.

Methods: This prospective study was conducted on 122 children age between 2 days to 10 years suspected with sepsis enrolled in tertiary care hospital of North India. Blood cultures for these patients were done before starting antibiotics. Measurements of CRP using the immunoturbidimetry method, PCT using electrochemiluminescence were done to all enrolled patients. Total leucocytes count (TLC) was performed on Sysmex KX-21 analyzer.

Results: Forty-four children with proved sepsis were found to be positive in blood culture. The most common isolated organisms were *Klebsiella* (54.55%), followed by *E. coli* (13.64%) *CONS* (11.37%), Staph aureus (9.09%), GBS (6.81%) and Citrobacter (4.54%). We detected much significant higher levels of PCT and CRP in the proved sepsis group than the suspected pediatric sepsis cases. TLC, Serum PCT and CRP levels showed the highest sensitivity of 90.9%, 90.9% and 84.1%; specificity of 65.4%, 74.5% and 70.5% respectively. PPV of 59.7%, 66.7% and 61.7%; NPV of 92.7%, 93.5%, and 88.7% respectively.

Conclusion: PCT and CRP along with TLC together has satisfactory characteristics as a good marker for the diagnosis of pediatric sepsis.

Keywords: Procalcitonin, C-reactive protein, TLC, Paediatric sepsis

Introduction:

Sepsis is a generalized systemic inflammatory disease with the high prevalence. There are approximately 20 million people on an average suffering from sepsis per year around the world and this number is still rising each year [1-2]. In routine clinical practice, the rapid and accurate diagnosis of pediatric sepsis is often difficult because the clinical presentation of sepsis may be confused with non-infectious disorder. Improving the accuracy of diagnostic testing may improve outcomes in those with true sepsis and decrease the indiscriminate use of antibiotics in those without sepsis [3]. A recent study in India reported that 28.3% of patients contact sepsis during their ICU stay and have 34% mortality rate [4]. Sepsis is characterized by nonspecific symptoms and clinical diagnosis remains difficult. Delay in empirical treatment for sepsis increase mortality, making treatment recognition of infection and initiation of appropriate therapy an important goal [5]. Although Total White Blood Cells (WBC), Absolute Neutrophil Counts (ANC), platelet counts and blood culture are ordered to screen for suspected sepsis, these values are ineligible as infection markers due to insufficient sensitivity and specificity [6]. Procalcitonin is a 116- amino acids protein, a precursor of calcitonin which is produced by the thyroid. After exposure to bacterial endotoxin, PCT levels within 2- 4 hours rise sharply, within 6 - 8 hours they reach plateau and then they return to normal level after 24 hours [7]. Although numerous papers raised the same issue, this manuscript is one of the few publications about this issue in our locality. Moreover, pediatric sepsis is a challenging problem indeed, and physicians are always in need of methods of prediction and early diagnosis of sepsis to initiate therapy as rapidly as possible to decrease the negative impact on the patient's health and therefore decrease the duration of hospital stay and costs. Therefore, we have carried out our study to search for better markers than CRP for the diagnosis of sepsis. Serum PCT level appears to correlate with the severity of the microbial attack and rapidly decrease after appropriate antibiotic treatment. CRP is a nonspecific and inflammation- related protein that is produced in the liver and regulated by plasma interleukin 6 (IL-6). When infection or body damage occurs, the concentration of CRP will be greatly altered [8]. In a recently published meta-analysis, CRP was found to have a sensitivity ranging from 30% to 80% but a higher specificity 83% to 100% at the onset of symptoms. If done later say 24 hours and 48 hours after the child become symptomatic. There was an increasing trend in sensitivity (after 24 h) and specificity (after 48 h) [9]. Blood culture is the gold standard for the diagnosis of sepsis in children. However, the results are usually available beyond 2-3 days [10]. Meanwhile the early initiation of antibiotic therapy should be done to reduce morbidity and mortality due to sepsis. Due to lack of right diagnosis and children shows nonspecific symptoms and sign, the antibiotic therapy may result in treating up to 30 uninfected neonates for a single one who is probably diagnosed to be infected [11]

Material and Methods:

It is a prospective observational study was conducted in tertiary care hospital in North India. A total of 122 children, fulfilling the predefined inclusive criteria were studied.

Inclusive criteria:

Patients selected as per the international guideline of the sequential organ failure assessment (SOFA) score.
According to the guideline, a sepsis diagnosis requires the presence of infection which can be proven or suspected and 3 or more of the following criteria
A) Temperature > 38º C or <36º C
B) Respiratory rate >20 breath/min
C) Heart rate >90 bpm
D) WBC count >12,000/mm^3 or <4000/mm^3
E) Lactate >2 mmol/L
F) Hypotension (systolic blood pressure <90mmHg or fallen by >40 from baseline, means arterial pressure <70mmHg)

Exclusive criteria:

A) Child with malformation/ congenital anomalies.
B) Received antibiotics already.

Methodology:

Patients less than 10 years of age at the hospital with a suspected infection and a sequential organ failure assessment score more than three points.

Sample Collection:

Samples were taken at the time of admission before starting antibiotics. For C-reactive protein (CRP) and Procalcitonin (PCT) 2-3 ml. of venous blood was collected aseptically. As soon as it was clotted, centrifuged it at 3000 RPM for 15 minutes and serum was separated and did the tests. If tests were not done at same day, stored serum samples at 2-8º C for up to 7 days or keep at -20º C for up to three months.
CRP level: CRP level was measured by Quantitative Turbidimetric Immunoassay detection and performed by using Transasia XL 640 analyzer. The standards and calibrator were provided by the manufacturer and tests were conducted in strict accordance with good instruction.
PCT level: PCT level was measured by Electrochemiluminescence technology, the detection was performed by using Cobas e-411 of Roche.
Blood Culture: One ml of peripheral venous blood was drawn under complete aseptic precautions from each child and inoculated immediately in the pediatric blood culture bottle. Blood culture bottles were incubated at 37º C for 7 days, and subculture was inoculated at 37º C after 24 hours. The isolated bacteria were identified by using standard microbiological techniques [12]

Result:

Among the 122 children, there were 80(65.5%) males and 42(34.5%) females.

Table 1: Distribution of the Participants in Terms of Gender (n = 122)

Gender	Frequency	Percentage
Male	80	65.6%
Female	42	34.4%
Total	122	100.0%

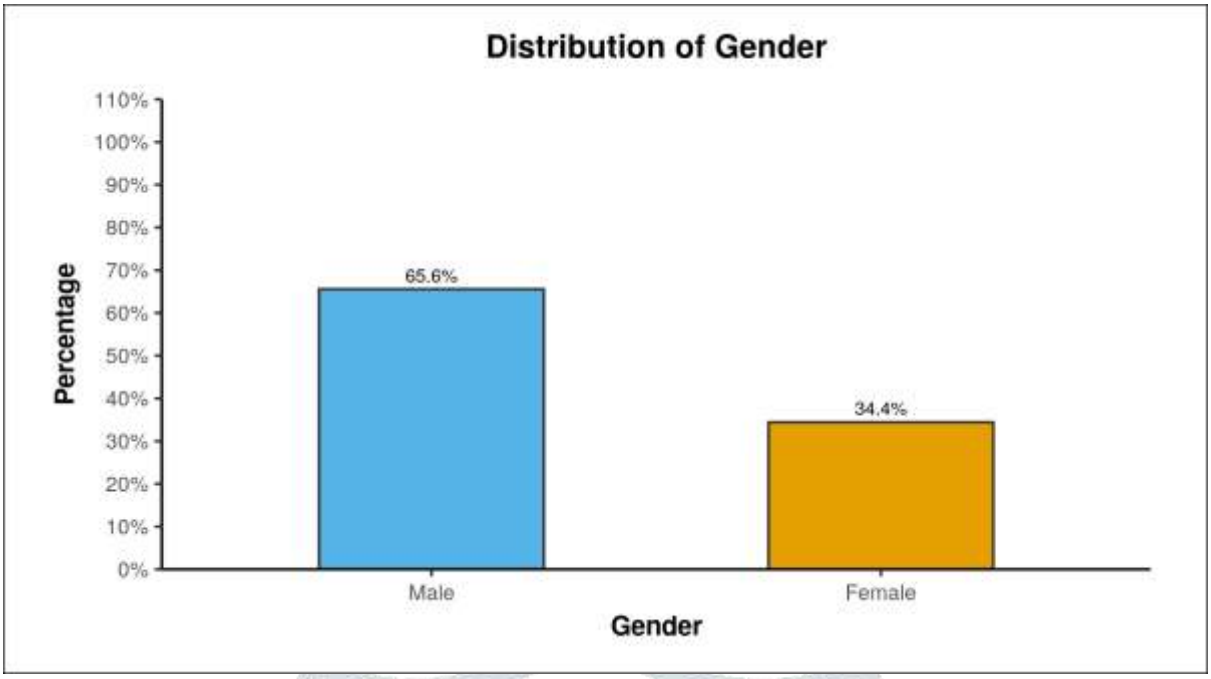

Fig. 1-Distribution of Gender

Table 2: Distribution of the Participants in Terms of Weight (Kg) (n = 122)

Weight (Kg)	
Mean (SD)	9.87 (6.18)
Median (IQR)	9.10 (4.85-14.73)
Range	1.75 - 32.5

The variable Weight (Kg) was not normally distributed (Shapiro-Wilk Test: p = <0.001). The mean (SD) of Weight (Kg) was 9.87 (6.18). The median (IQR) of Weight (Kg) was 9.10 (4.85-14.73). The Weight (Kg) ranged from 1.75 - 32.5.

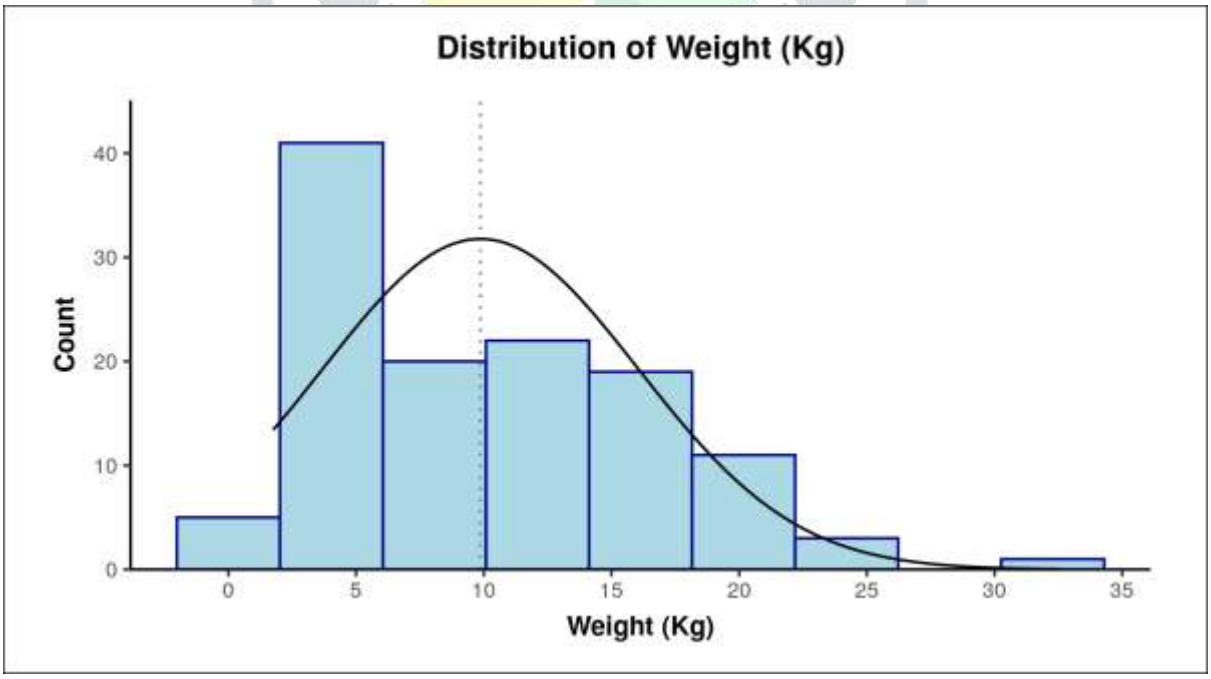

Fig. 2-Distribution of weight

Table 3: Distribution of the Participants in Terms of Blood Culture (n = 122)

Blood Culture	Frequency	Percentage
Positive	44	36.1%
Negative	78	63.9%
Total	122	100.0%

36.1% of the participants had Blood Culture: Positive. 63.9% of the participants had Blood Culture: Negative

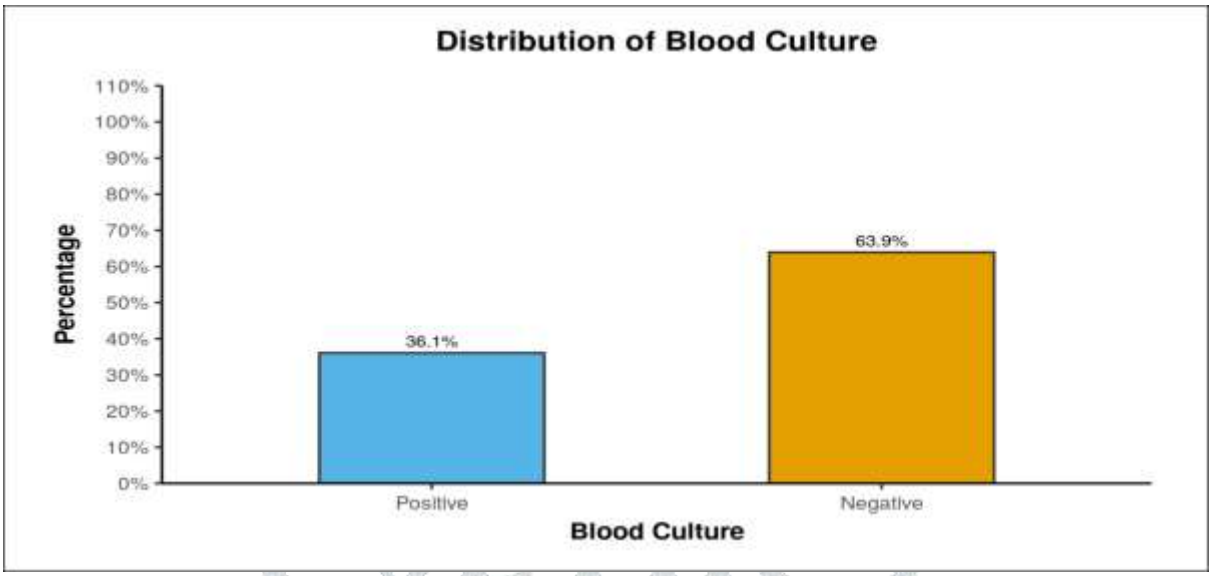

Fig. 3- Distribution of Blood Culture

Table 4: Distribution of the Participants in Terms of Organism Grown (n = 44)

Organism Grown	Frequency	Percentage
Klebseilla	24	54.5%
E.coli	6	13.6%
CONS	5	11.4%
S aureus	4	9.1%
GBS	3	6.8%
Citrobactor	2	4.5%
Total	44	100.0%

54.5% of the participants had Organism Grown: Klebsiella. 13.6% of the participants had Organism Grown: E.coli. 11.4% of the participants had Organism Grown: CONS. 9.1% of the participants had Organism Grown: S aureus. 6.8% of the participants had Organism Grown: GBS. 4.5% of the participants had Organism Grown: Citrobacter.

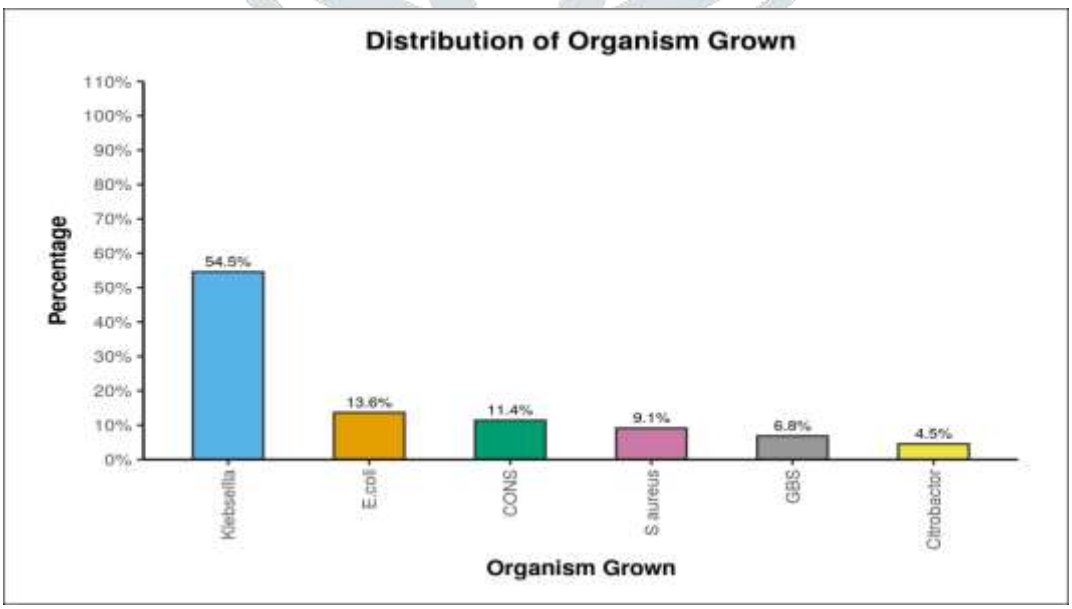

Fig. 4- Distribution of Organism Grown

Table 5: Association between Blood Culture and Gender (n = 122)

Gender	Blood Culture			Chi-Squared Test	
	Positive	Negative	Total	χ2	P Value
Male	35 (79.5%)	45 (57.7%)	80 (65.6%)	5.951	0.015
Female	9 (20.5%)	33 (42.3%)	42 (34.4%)		
Total	44 (100.0%)	78 (100.0%)	122 (100.0%)		

Chi-squared test was used to explore the association between 'Blood Culture' and 'Gender'.
There was a significant difference between the various groups in terms of distribution of Gender ($\chi 2 = 5.951$, $p = 0.015$).
79.5% of the participants in the group [Blood Culture: Positive] had [Gender: Male]. 20.5% of the participants in the group [Blood Culture: Positive] had [Gender: Female]. 57.7% of the participants in the group [Blood Culture: Negative] had [Gender: Male]. 42.3% of the participants in the group [Blood Culture: Negative] had [Gender: Female].
Participants in the group Blood Culture: Positive had the larger proportion of Gender: Male. Participants in the group Blood Culture: Negative had the larger proportion of Gender: Female.

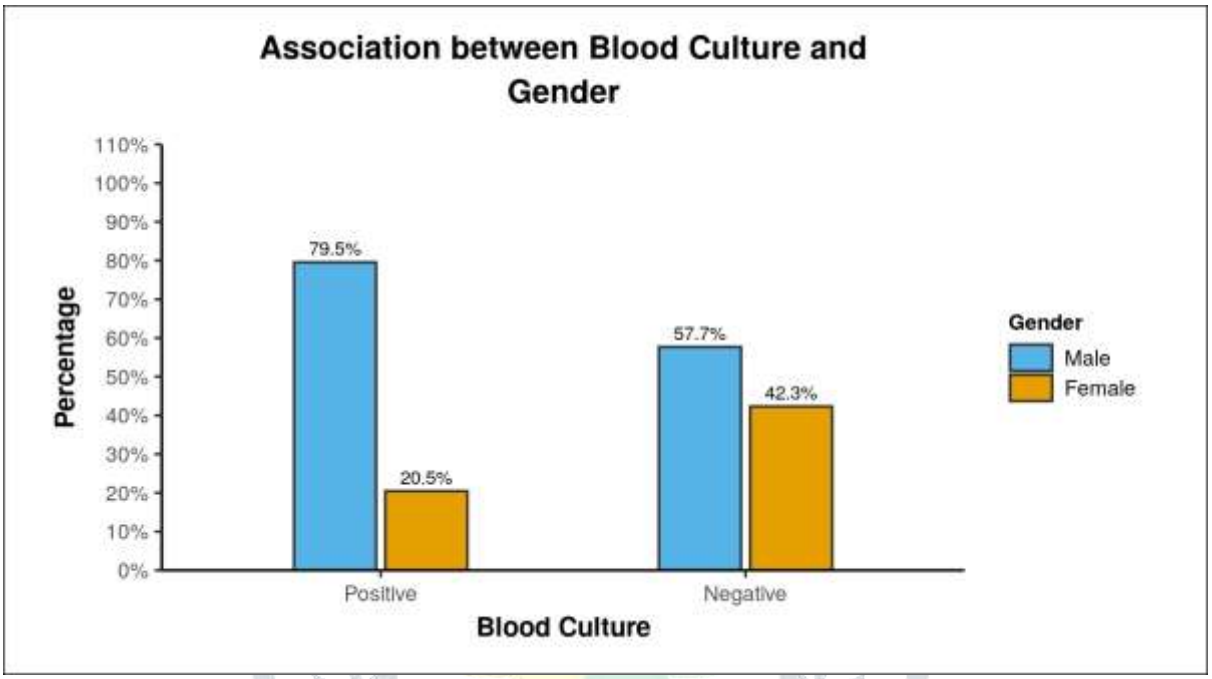

Fig. 5 - Association between Blood Culture and Gender

Table 6: Distribution of the Participants in Terms of TLC *1000 cu/mm) (n = 122)

TLC *1000 /mm^3)	
Mean (SD)	11.84 (6.89)
Median (IQR)	11.55 (5.35-17.17)
Range	1.6 - 28.5

The variable TLC *1000 /mm^3) was not normally distributed (Shapiro-Wilk Test: p = <0.001).
The mean (SD) of TLC *1000 /mm^3) was 11.84 (6.89). The median (IQR) of TLC *1000 /mm^3) was 11.55 (5.35-17.17).
The TLC *1000 /mm^3) ranged from 1.6 - 28.5

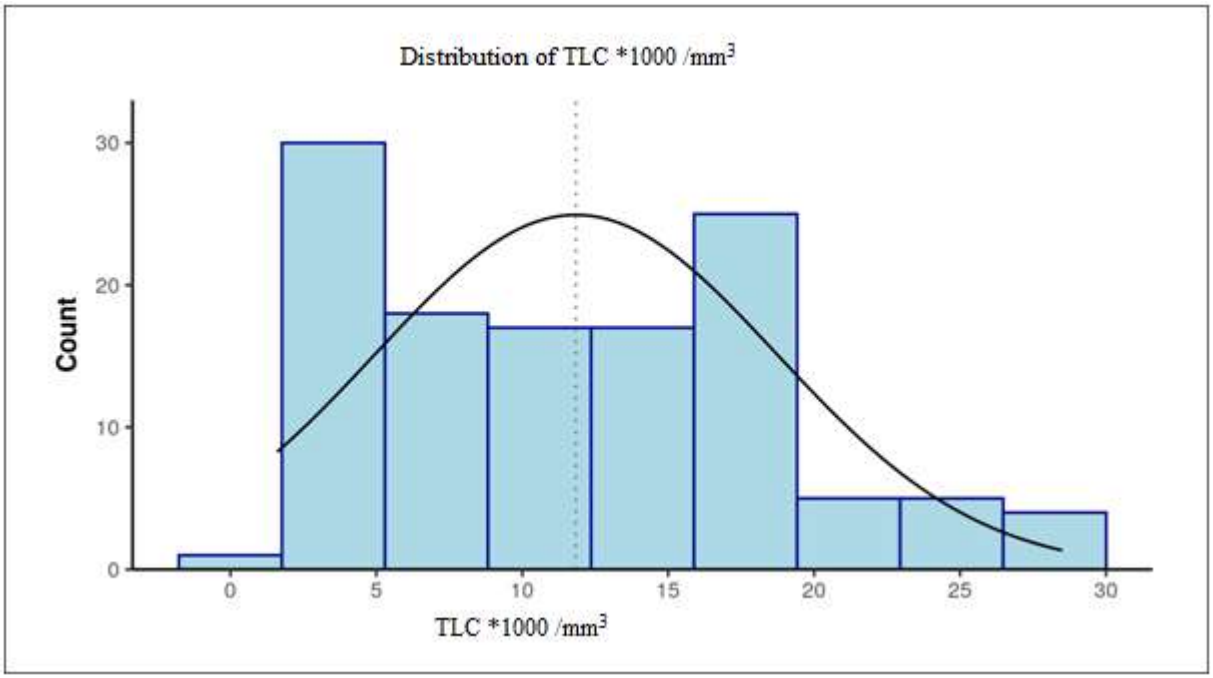

Fig. 6- Distribution of TLC *1000 /mm^3

Table 7: Distribution of the Participants in Terms of CRP (n = 122)

CRP	
Mean (SD)	50.52 (78.79)
Median (IQR)	6.12 (2.26-50.45)
Range	0.6 – 338

The variable CRP was not normally distributed (Shapiro-Wilk Test: p = <0.001).
The mean (SD) of CRP was 50.52 (78.79). The median (IQR) of CRP was 6.12 (2.26-50.45). The CRP ranged from 0.6 - 338.

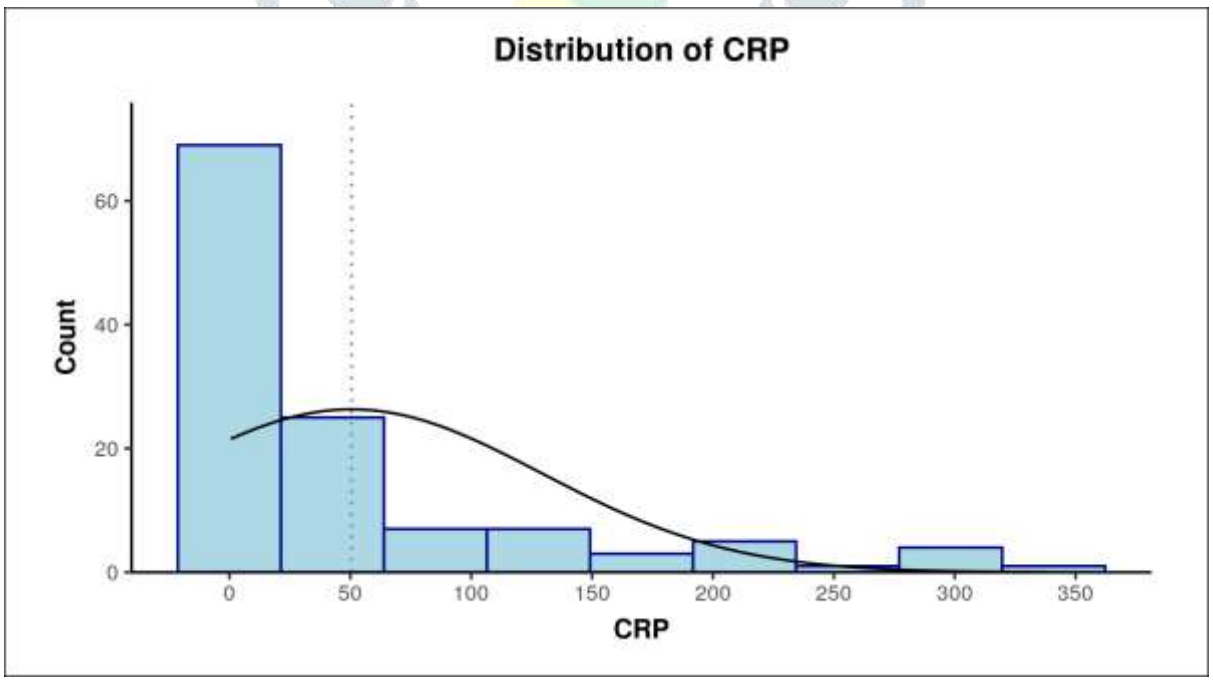

Fig. 7- : Distribution of the Participants in Terms of CRP

Table 8: Distribution of the Participants in Terms of PCT (n = 122)

PCT	
Mean (SD)	5.34 (8.47)
Median (IQR)	1.72 (0.19-7.25)
Range	0 - 47.23

The variable PCT was not normally distributed (Shapiro-Wilk Test: p = <0.001).
The mean (SD) of PCT was 5.34 (8.47). The median (IQR) of PCT was 1.72 (0.19-7.25). The PCT ranged from 0 - 47.23.

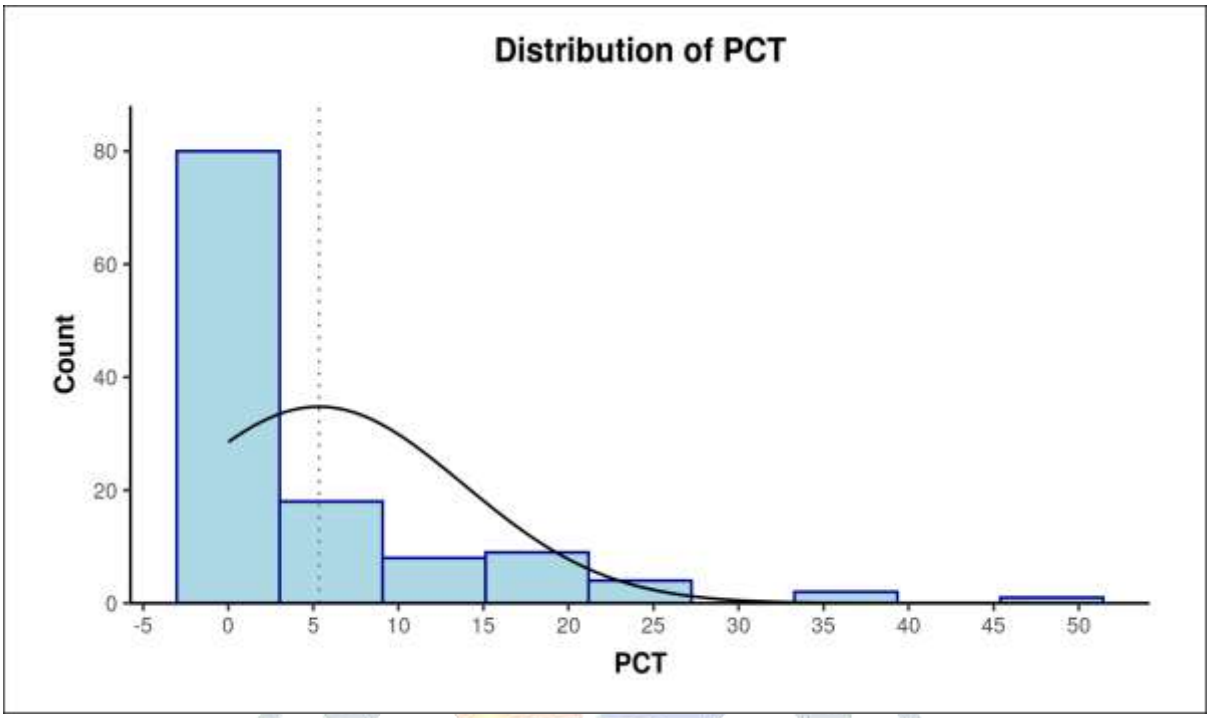

Fig. 8- Distribution of PCT

Table 9: Description of Variables

Variable	Category (s) Suggesting Outcome Present	Category(s) Suggesting Outcome Absent	Total Positives	True Positives	True Negatives	False Positives	False Negatives
Blood Culture	Positive	Negative	44 (36.1%)	-	-	-	-
TLC *1000 cu/mm) (Cutoff: 10.8 by ROC)	>=10.8	<10.8	67 (54.9%)	40 (33%)	51 (42%)	27 (22%)	4 (3%)
CRP (Cutoff: 9.6 by ROC)	>=9.6	<9.6	60 (49.2%)	37 (30%)	55 (45%)	23 (19%)	7 (6%)
PCT (Cutoff: 1.78 by ROC)	>=1.78	<1.78	60 (49.2%)	40 (33%)	58 (48%)	20 (16%)	4 (3%)
Combined Score (Cutoff: -0.498 by ROC)	>=-0.498	<-0.498	46 (37.7%)	38 (31%)	70 (57%)	8 (7%)	6 (5%)

Table 10: Primary Diagnostic Parameters

Variable	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
TLC *1000 cu/mm) (Cut-off: 10.8 by ROC)	90.9% (78-97)	65.4% (54-76)	59.7% (47-72)	92.7% (82-98)	74.6% (66-82)
CRP (Cut-off: 9.6 by ROC)	84.1% (70-93)	70.5% (59-80)	61.7% (48-74)	88.7% (78-95)	75.4% (67-83)
PCT (Cut-off: 1.78 by ROC)	90.9% (78-97)	74.4% (63-84)	66.7% (53-78)	93.5% (84-98)	80.3% (72-87)
Combined Score (Cut-off: -0.498 by ROC)	86.4% (73-95)	89.7% (81-95)	82.6% (69-92)	92.1% (84-97)	88.5% (81-94)

Among 122 cases sensitivity of TLC was 90.9%, specificity was 65.5%, PPV was 59.7% and NPV was 92.7%. PCT had sensitivity 90.9%, specificity 66.7%, PPV 66.7% and NPV 93.5%. CRP had sensitivity 84.1%, specificity 70.5%, PPV 61.7% and NPV 88.7%. The combine score of these three parameters demonstrated sensitivity 86.4%, specificity 89.7%, PPV 82.5% and NPV 92.1% with the highest diagnostic accuracy of 88.5%.

Table 11: Blood Culture: Positive vs Blood Culture: Negative (Full Sample)

Predictor	AUROC	95% CI	P	Sn	Sp	PPV	NPV	DA
TLC *1000 cu/mm)	0.822	0.74-0.903	<0.001	91%	65%	60%	93%	75%
CRP	0.847	0.782-0.913	<0.001	84%	70%	62%	89%	75%
PCT	0.867	0.795-0.938	<0.001	91%	74%	67%	94%	80%
Combined Score	0.916	0.864-0.968	<0.001	89%	90%	83%	93%	89%

AUROC: Area under ROC curve; CI: Confidence interval; P: P value; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; DA: Diagnostic Accuracy

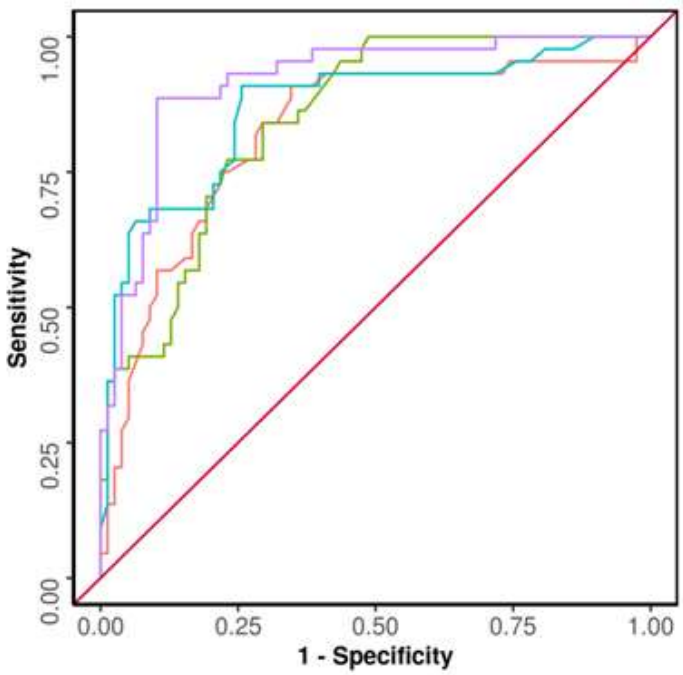

Fig. 9- ROC Curve Analysis Showing Diagnostic Performance of Combined Score in Predicting Blood Culture Positive vs Blood Culture Negative (n = 122)

Trends:

Best parameter in terms of AUROC: Combined Score.
Best parameter in terms of sensitivity: PCT, TLC.
Best parameter in terms of specificity: Combined Score.
Best parameter in terms of positive predictive value: Combined Score.

Best parameter in terms of negative predictive value: PCT.
Best parameter in terms of diagnostic accuracy: Combined Score.

Discussion:

Despite recent advancement in health care, we are unable to control the morbidity and mortality due to paediatric sepsis .Morbidity and mortality graphs are raising up time to time. In developing countries, cases of sepsis are three 220 times higher than these reported from hospitalized infants many times a delay in diagnosis and treatment of sepsis is due to lack of sign or symptoms in neonatal sepsis quick diagnosis of neonatal sepsis is considered a significant role to play to prevent the serious outcome so in this study we were interested in evaluating the CR P&PCT as a sepsis marker or early diagnosis of sepsis in children

This study was done on 122 children with clinically suspected sepsis, out of them 80 were males and 42 were females. Age ranged from 2 days to 10 year. In children's, males were more prone to had the disease than female. This could be due to the X-linked immunoregulatory gene factor which contributes to the susceptibility to infection in them (14). There was variability in the PCT diagnostic values in numerous studies with a 60%-100% range of sensitivity and 79%-100% specificities (15). the positive blood care outcome blood culture of three children's were showing low value of the city and several children's were negative of CRP but showing growth in blood culture this may be due to delay in admission of children in hospital

In this study, 36 children with negative blood culture having elevated PCT level means false positive. The average level of PCT in false positive cases was 3.70 ng/ml. This was due to undetected bacteremia. Since the positive blood cultures were reported in only 36% suspected sepsis patients, this poor diagnostic performance of blood culture could have been caused by inadequate blood volume that were used for the culture. One more reason could be that patient already had taken the antibiotics, the timing of blood samples drawing. (16,17,18,19).

One limitation of this study is that the exact onset of sepsis is unknown and all children were assumed to have presented immediately after the onset of sepsis. It may be possible in this study that some cases of true sepsis cannot be confirmed due to the false negative culture results (20,21). The sample size of this study could also be seen as another limitation of this current study when compared with other higher sample size study (22,23,24).

In the present study when we compared the TLC values with the positive blood culture samples the sensitivity of 90.9% and specificity of 65.4%, positive predicted value (PPV) of 59.7%, negative predicted value (NPV) of 92.7%. For CRP sensitivity was 84.1%, specificity was 70.5% positive predictive value was 61.7% and negative 50 value was 88.7% with diagnostic accuracy of 76.4% which was compatible with Emine et al (25). Procalcitonin evaluation demonstrated sensitivity of 90.9% and specificity of 74.4% with positive predictive value (PPN) of 66.7% and negative predicted value (NPV) of 93.5 did with diagnostic accuracy of 80.3% which was comparable two other studies Pavenik Arnold et al (26).

In the presented study when we compared the combined score of all three parameters (TLC, CRP and PCT) then it showed sensitivity of 56.4% specificity of 59.7% with positive predicted value was 82.6% and negative predictive value was 92.1% with diagnostic accuracy of 88.5%. Which was highest of all studied parameters. The area under ROC curve demonstrated that combined score was best parameter in term of AUROC.

Conclusion:

In this study we found that serum PCT has satisfactory and good marker than CRP but the combine use of all three parameters (TLC, CRP and PCT) has highest sensitivity and specificity with high PPN and NPV value appear to be good indicators for early diagnosis of paediatric sepsis. Blood culture remains the gold standard but it has its limitation of taking more time.

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