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To Compare Serum Procalcitonin and CRP as Markers of Neonatal Sepsis

Rafiq Ahmad[1], Israr Liaquat[2], Nadia Mumtaz[3], Sughra Zulfiqar[4], Sidratul Muntaha[5], Nazia Rafique[6]

Abstract

Objective: This study compares serum Procalcitonin (PCT) levels with CRP as predictive markers for neonatal sepsis.
Method: It was a Quasi-experimental study performed in the neonatal intensive care unit (NICU) of Holy Family Hospital, Rawalpindi, for six months from July 2021 to January 2022 after the approval of the ethical board. The study included neonates admitted to the neonatal intensive care unit of Holy Family Hospital with a diagnosis of neonatal sepsis. Parents are permitted via written informed consent. A predesigned proforma was used to record clinical examinations, histories, and outcomes, which included hospital stay duration, complications, neonatal discharge, or mortality.
Results: Seventy neonates meeting the study's inclusion criteria were enrolled. The average age in the study was 6.44 ± 5.24 days, with 40 (57.1%) males and 30 (42.9%) females. The CRP test demonstrated a sensitivity of 85.42%, specificity of 81.82%, positive predictive value (PPV) of 91.11%, negative predictive value (NPV) of 72.00%, and diagnostic accuracy of 84.29% in predicting neonatal sepsis. The PCT test displayed sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 87.76%, 90.48%, 95.56%, 76.00%, and 88.57%, respectively.
Conclusion: This study underscores Procalcitonin as a superior and early predictor compared to CRP in forecasting neonatal sepsis. Procalcitonin emerges as a particular marker for bacterial infections when contrasted with other inflammation indicators such as CRP, white blood cells, or lactate. Notably, Procalcitonin levels remain unaffected in viral or atypical bacterial infections.
Keywords: Serum, Predictor, Neonatal, Sepsis.

[1] Registrar, Holy Family Hospital, Rawalpindi Medical University; [2] AP Paeds, Holy Family Hospital, Rawalpindi Medical University; [3] SR Paeds, Holy Family Hospital, Rawalpindi Medical University; [4] AP Paeds, Watim Medical College, Rawalpindi; [5] Consultant, Paeds, Cantonment General Hospital; [6] SR Paeds, Holy Family Hospital, Rawalpindi Medical University.
Correspondence: Dr. Israr Liaquat, Assistant Professor, Paediatrics, Holy Family Hospital, Rawalpindi Medical University. **Email:** fmc414@hotmail.com
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1. Introduction

Neonatal sepsis, denoting infections arising within the initial 28 days of life, contributes substantially to neonatal morbidity and mortality with 1.3 million cases reported annually worldwide.[1] It is particularly pronounced in developing nations where limited healthcare resources and constrained income prevail. Rapid and accurate diagnosis coupled with timely intervention involving appropriate antibiotics is pivotal, as it effectively mitigates the associated morbidity, mortality, and hospitalisation duration in neonatal infections. In contexts such as Pakistan, the prevalence of neonatal sepsis-induced fatalities remains notably elevated due to resource limitations and fragile healthcare infrastructure.

Diagnostic challenges are further amplified by the absence of distinctive clinical signs and symptoms for neonatal sepsis, rendering its identification through clinical assessment arduous due to the diverse nature of its presentations. The lack of a singular laboratory parameter capable of conclusively indicating neonatal infection compounds the diagnostic complexity. Despite being the gold standard for diagnosis blood culture is positive only in a quarter of cases.[2] C-reactive protein (CRP) estimation has emerged as a critical player in diagnosing neonatal sepsis. However, the dependence solely on CRP lacks specificity, given its elevation in response to various inflammatory processes beyond infections, with no direct correlation to infection severity.[3] Thus, additional and more specific biomarkers are needed for precise diagnosis and therapeutic decisions.

Serum Procalcitonin (PCT), a protein-based biomarker comprising 116 amino acids with a molecular weight of 13 kDa, holds significant promise. As a precursor to calcitonin, PCT originates from the parafollicular cells of the parathyroid gland, aiding in calcium homeostasis. Assicot et al. initially elucidated PCT's potential in 1993. Upon pathogen intrusion and endotoxin release, serum PCT levels escalate within 4 to 6 hours, culminating in a peak at 24 to 48 hours.[16] This then subsides post-administration of appropriate antibiotics and pathogen

elimination. PCT's value extends to identifying severe bacterial infections, distinguishing between bacterial and non-bacterial infections, and gauging antibiotic efficacy.[4]

PCT's diagnostic potential lies in its elevation during bacterial infections while remaining suppressed in viral infections. Even in atypical bacterial infections like Legionella and Chlamydia, PCT levels remain modest. This characteristic guides clinical decisions, preventing the administration of overly aggressive beta-lactam antibiotics for atypical infections, thereby mitigating potential harm.[5]

While PCT is not a standalone marker for bacterial infection, its integration with other parameters like chest X-rays, complete blood counts, CRP, urine examination and culture, blood culture, clinical assessments, and specific signs and symptoms enhances its diagnostic and treatment utility.

Procalcitonin is a concrete marker for bacterial infection, outshining other inflammation markers such as CRP, white blood cell count, and lactate. Its distinct behaviour of remaining unaffected by viral infections and atypical bacteria renders it invaluable in the diagnostic arsenal. Given the substantial neonatal sepsis mortality rates in regions like Pakistan, the imperative to swiftly diagnose and administer appropriate antibiotics is magnified, as doing so significantly curbs morbidity, mortality, hospitalisation durations, and the development of microbial antibiotic resistance.

2. Materials & Methods

A quasi-experimental study design was employed for this research. The study was conducted in the Neonatal Intensive Care Unit (NICU) of Holy Family Hospital, Rawalpindi. The study was conducted for six months, starting from 31st July 2021, after obtaining approval from BASAR to 31st January 2022. A total of 70 neonates were included in the study.

The sample size was determined using the WHO formula with a confidence interval of 95% based on the expected prevalence of sepsis in the neonatal population. Neonates of both genders, aged 1 to 28 days, who exhibited clinical sepsis based on the operational definition of sepsis were included. Neonates showing signs of suspected neonatal sepsis and admitted to the NICU of Holy Family Hospital were eligible for inclusion.

Neonates with evident congenital anomalies, previous antibiotic treatments, trauma, burns, or congestive heart failure were excluded from the study.

The study was conducted after the Ethical approval was obtained. Neonates meeting the inclusion criteria and admitted to the NICU were enrolled. Informed consent was obtained from the parents/guardians. Clinical examinations and medical histories were documented. Blood samples, including serum CRP levels, were drawn under sterile conditions before commencing treatment and measuring serum Procalcitonin levels.

Empirical antibiotics were administered following the NICU protocol. Ongoing monitoring and relevant investigations (Complete Blood Count, Chest X-ray, PT/APTT, ABGs, RFTs, LFTs, Serum calcium) were conducted. Neonates were followed for a week, and outcomes were evaluated, encompassing hospital stay duration, complications, neonatal discharge, or mortality. Data collection utilized the predesigned Performa.Data entry and analysis were performed using SPSS version 23.0. Quantitative variables, such as age, PCT, and CRP, were presented as mean and standard deviation. Qualitative variables, like gender and birth weight, were calculated as frequency and percentage. One-way ANOVA was used to compare mean serum CRP, PCT, serum LDH, and laboratory parameter levels among culture-positive and culture-negative sepsis cases. In the case of significant ANOVA results, post hoc tests were conducted.

Mortality and morbidity parameters among the two groups were compared using the chi-square test or Fisher's exact test. Sensitivity, specificity, positive predictive value, and negative predictive value of CRP and PCT in diagnosing sepsis were assessed using blood culture as the gold standard. A significance level of $p \leq 0.05$ was considered statistically significant.

3. Results

A total of 70 neonates were enrolled following the predefined inclusion criteria for the study. Descriptive statistics were calculated for the age (days) of the neonates, resulting in a mean period of 6.44 ± 5.24 days. Gender distribution sowed 40 (57.1%) male and 30

(42.9%) female neonates. Regarding hospital stay, the study recorded an average duration of 7.09 ± 1.33 days, ranging from a minimum of 5 to 10 days. Neonatal birth weight yielded a mean value of 2.57 ± 0.30 kg.

The neonatal mortality rate was 21.4% among the 70 cases. Notably, all these instances exhibited positive sepsis diagnoses through blood culture and PCT analysis.

Of the 70 neonates, 49 were identified as having culture-positive sepsis. Among these cases, the predominant pathogens were Klebsiella pneumoniae (20.0%), Pseudomonas (14.3%), and Staphylococcus Aureus (12.9%), followed by Escherichia coli (11.4%), Streptococcus pneumoniae (8.6%), and Acinetobacter (2.9%).

The mean serum CRP, WBC, haemoglobin (HB), and platelet levels were compared through one-way ANOVA analysis between culture-positive and culture-negative sepsis groups, as presented in Table 1.

Table 1: Comparison of Laboratory parameters among Culture Positive Sepsis and Culture Negative Sepsis cases by applying the ANOVA Test

Parameters		n	Mean	Std Deviation	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
CRP	Positive	49	1.12	0.33	1.03	1.22
	Negative	21	1.90	0.30	1.77	2.04
	Total	70	1.36	0.48	1.24	1.47
WBC	Positive	49	49.87	180.50	-1.98	101.72
	Negative	21	15.67	7.82	12.11	19.23
	Total	70	39.61	151.43	3.50	75.72
HB	positive	49	13.06	2.29	12.40	13.72
	negative	21	11.37	2.94	10.03	12.71
	Total	70	12.55	2.60	11.93	13.17
Platelets	positive	49	278.55	153.13	234.56	322.54
	negative	21	304.90	143.18	239.73	370.08
	Total	70	286.46	149.68	250.77	322.15

The accuracy of CRP and PCT as diagnostic markers for sepsis using blood culture as the confirmatory investigation was incurred by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both markers.

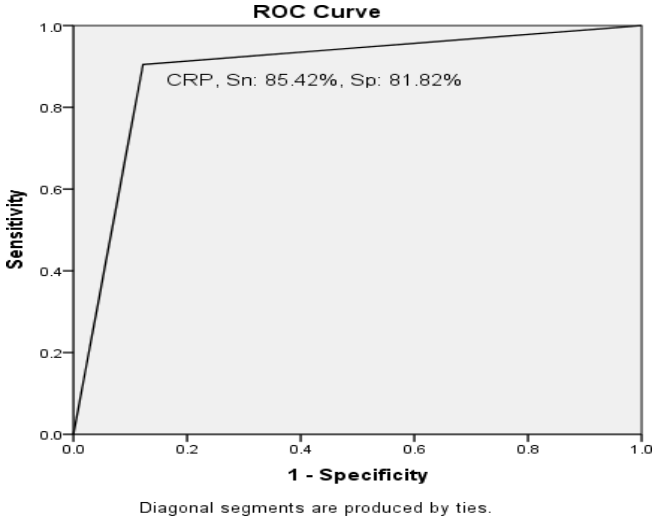
Table 2: ANOVA

		Sum of Squares	f	Mean Square	F	Sig.
CRP	Between Groups	8.99	1	8.997	86.471	000
	Within Groups	7.07	69	.104		
	Total	16.07	70			
WBC	Between Groups	17196.44	1	17196.444	0.747	.390
	Within Groups	1565078.45	69	23015.860		
	Total	1582274.89	70			
HB	Between Groups	41.67	1	41.671	6.645	.012
	Within Groups	426.42	69	6.271		
	Total	468.09	70			
Platelets	Between Groups	10209.43	1	10209.439	0.452	.504
	Within Groups	1535665.93	69	22583.323		
	Total	1545875.37	70			

Regarding CRP, there were 41 cases where both CRP (C-Reactive Protein) and the blood culture test were positive. Additionally, there were 4 cases where CRP was positive, but the blood culture test was negative. Furthermore, 7 cases showed negative CRP results but had a positive blood culture test. Lastly, 18 cases had both negative CRP and negative blood culture test results. The sensitivity and specificity of CRP are reflected in Figure 1 using the ROC curve. The PPV (positive predictive value) stood at 91.1% and the NPV (negative predictive value) was 72% with an overall diagnostic accuracy of 84.2%.

In the context of a blood culture test using Procalcitonin (PCT), there were 43 cases where both PCT and the blood culture test were positive for infection. In 2 cases, PCT was positive, but the blood culture test did not detect an infection.6 cases had negative PCT results, but the blood culture test confirmed the presence of infection. In 19 cases, both PCT and the blood culture

test yielded negative results. The sensitivity and specificity of procalcitonin are displayed in Figure 2.



PPV was 95.56% and NPV 76%. The overall diagnostic accuracy was 88.57%.

Figure 1: ROC curve showing that CRP in predicting neonatal sepsis keeping Blood culture as a gold standard

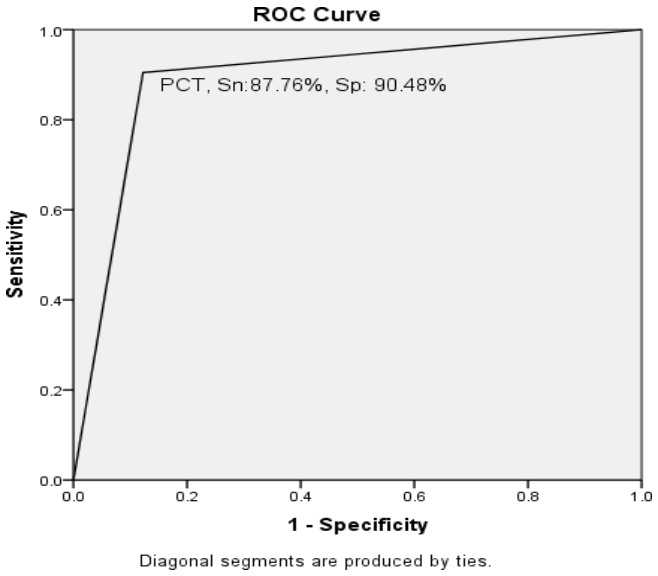


Figure 2: ROC curve showing PCT in predicting neonatal sepsis keeping Blood culture as the gold standard

4. Discussion

The role of Procalcitonin (PCT) has recently emerged prominently as an accurate indicator for early detection of neonatal sepsis, surpassing the efficacy of CRP testing. In Pakistan, characterized by very high neonatal mortality rates primarily attributed to sepsis, PCT's potential as a bedside diagnostic tool is of paramount significance. By expediting diagnosis, PCT saves lives and augments physician efficiency, reduces the financial burdens on healthcare infrastructures, and alleviates families' psychological and financial stresses related to prolonged hospital stays of their newborn babies.[6,7] The sensitivity, specificity, PPV, NPV, and diagnostic accuracy for CRP and PCT were evaluated, revealing promising figures for both markers in our study.

Our study included 70 neonates with an average age of 6.44 ± 5.24 days and a gender distribution of 57.1% male and 42.9% female. The average hospital stay was 7.09 ± 1.33 days. Notably, male infants exhibit higher susceptibility to infections due to the immunoregulatory effects of the X-linked gene.[9,11] Neonatal mortality, accounting for 21.4% of cases, consistently correlated with positive sepsis diagnoses through blood culture and PCT analysis. Apart from these descriptive details of study subjects, we did not evaluate babies regarding the presence or absence of any risk factors for sepsis.

Our observations concerning the sensitivity of both PCT and CRP at 73.6% and 50.9%, respectively, are similar to prior studies. However, our specificity outcomes - 38.6% for PCT and 28.7% for CRP are comparatively lower. Importantly, diverse studies have proven the heightened sensitivity of PCT compared to CRP in detecting neonatal sepsis, though there exist variations in reported specificities. Other investigations done in the past have concluded test sensitivities ranging from 70% to 93%, specificities from 41% to 98%, positive predictive values (PPV) from 6% to 83%, and negative predictive values (NPV) from 97% to 99% [12,13,14]. Morad et al. detected significantly elevated levels of PCT, CRP, and IL-6 in the proven sepsis group compared to suspected neonatal sepsis cases ($p < 0.001$, $p = 0.004$, respectively). Serum PCT levels exhibited exceptional sensitivity (97.6%), specificity (89%), PPV (97%), NPV (88.9%), and accuracy (96%) in contrast to other studied sepsis markers[9.] We did not include IL-6 in our study because of the lack of easy availability and financial constraints.

Utilising PCT to assess neonates with a pre-test probability of sepsis at 12.9% yielded post-test possibilities of 18% and 10% for positive and negative results, respectively, in Chaurasia et al. They conclude that adding PCT to neonatal sepsis assessment yielded no incremental benefit.[10]

Indeed, an extensive body of literature supports the diagnostic power of Procalcitonin (PCT) compared to C-reactive protein (CRP), with a prevailing consensus on the superiority of PCT.[16] Nevertheless, specific reports suggest a semblance of diagnostic reliability between PCT and CRP. For example, Mahale et al. concluded that both markers exhibit comparable diagnostic accuracy for neonatal sepsis.[8] Hasan and colleagues augmented the notion of PCTs being more advantageous over CRP. Notably, PCT's elevation primarily in bacterial infections and its swift restoration to normal levels following antibiotic therapy contribute to its superiority in early diagnosing neonatal sepsis, making it more helpful in gauging the severity of sepsis and evaluating the response to antibiotic treatment.[15]

Considering the distinct cost discrepancy between CRP and PCT and considering CRP is notably cost-effective, PCT's heightened sensitivity further uplifts its suitability for early diagnostics.

The prevalent pathogens in our study were Klebsiella pneumoniae, Pseudomonas, and Staphylococcus Aureus. In another study, the most commonly isolated organisms were Klebsiella (61.3%), followed by E. coli (9.7%) and CONS (9.7%).[10] The bacterial flora displayed in our study was variable, with Klebsiella pneumoniae emerging as the predominant strain, consistent with similar investigations. These variations could be attributed to regional diversity and societal norms.

Acknowledging the limitations of this study, it does not curtail the temporal correlations among sepsis markers, and there was no follow-up to enable prognostic estimations and address clinical challenges. Earlier research has demonstrated a correlation between PCT and CRP levels in confirmed sepsis cases after 12–24 hours of admission. CRP has low sensitivity in the first 12 to 24 as the infection is present 6 to 12 hours before CRP detection. PCT begins to rise as early as 2 to 4 hours in the presence of sepsis, peaks at 6 to 8 hours and remains optimistic for 24 hours. This is in contrast to IL-6, which exhibits a short half-life and becomes undetectable 24 hours after infection onset.[16,17]

Pakistan's socio-economic landscape, marked by a substantial population with a significant segment from low socio-economic backgrounds, necessitates a rapid and efficient screening mechanism for suspected sepsis cases.

The study's implications dovetail with these societal imperatives, suggesting PCT's viability as a bedside test for neonatal sepsis detection. Its superior sensitivity and specificity relative to CRP hold the potential to save lives, enhance physician efficiency, and mitigate the healthcare system's burdens.[8,9,11,16]

5. Conclusion

In conclusion, this study unequivocally establishes Procalcitonin (PCT) as a superior and early predictor of neonatal sepsis compared to CRP. PCT's exceptional specificity for bacterial infections, distinct from markers like CRP, WBC, and Lactate, signifies its diagnostic value. PCT's immunity to viral infections and atypical bacteria enhances its reliability.

CONFLICTS OF INTEREST- None

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Contributions:

R.A, - Conception of study
R.A, - Experimentation/Study Conduction
R.A, I.L, N.M, S.Z - Analysis/Interpretation/Discussion
R.A, I.L, N.M, S.Z - Manuscript Writing
I.L, S.Z, S.M, N.R - Critical Review
I.L, S.M, N.R - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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