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A COMPARISON OF THE DIAGNOSTIC VALUE OF PROCALCITONIN (PCT) AND C-REACTIVE PROTEIN (CRP) IN THE DIAGNOSIS OF NEONATAL SEPSIS – A HOSPITAL-BASED CROSS-SECTIONAL STUDY

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Abstract

Background:
Neonatal sepsis is a leading cause of mortality worldwide, with a high prevalence in low- and middle-income countries. Early diagnosis and timely intervention are crucial for improving outcomes. Procalcitonin (PCT) and C-reactive protein (CRP) are biomarkers used for diagnosing neonatal sepsis, but their diagnostic accuracy is not fully known.

Objective:
To compare the diagnostic performance of PCT and CRP in diagnosing neonatal sepsis, using blood culture as the gold standard.

Study Design:
Cross-sectional

Place and duration of study:
Neonatal Intensive Care Unit, Combined Military Hospital Lahore, from January 2024 to July 2024.

Patients and Methods:
This study enrolled 126 neonates up to 28 days of age with suspected sepsis. Patients with congenital malformations were excluded. PCT and CRP levels were measured, and blood cultures were performed. The diagnostic parameters of PCT and CRP were calculated and compared.

Results:
PCT had a higher sensitivity (84.4%) and specificity (82.7%) compared to CRP (66.6% and 50.6%, respectively) in diagnosing neonatal sepsis. The positive predictive value of PCT was also higher than CRP (73.1% vs 42.8%). The most common pathogens isolated were Klebsiella, Pseudomonas, E. Coli and Candida.

Conclusion:
This study suggests that PCT may be a more sensitive and accurate marker for early diagnosis of neonatal sepsis compared to CRP.

INTRODUCTION

Despite advances in neonatal care, sepsis, the second leading cause of neonatal mortality after prematurity, remains a significant diagnostic and management challenge.[1] The Global Burden of Disease (GBD) Study 2016/2017 estimated that neonatal sepsis affects 1.3 million cases globally each year, resulting in 203000 sepsis-related deaths.[2] It is the primary cause of neonatal mortality in low-income and middle-income countries, which bear the burden of 99% of global neonatal mortality caused by sepsis.[3] Pakistan has one of the highest neonatal mortality rates in the world i.e. 49 per 1000 live births, and among these, 36% deaths are caused by neonatal sepsis. Therefore neonatal sepsis remains a critical concern in Pakistan with a prevalence of 29.25%.[4]

Neonatal sepsis is a systemic inflammatory response to infection in newborns within the first 28 days of life, categorized into early-onset (EONS, within 72 hours) and late-onset (LONS, after 72 hours but within 28 days). In developing countries, the primary causes of neonatal sepsis are *Klebsiella, pneumoniae, Staphylococcus aureus*, and *coagulase-negative Staphylococcus.*[5]

Diagnosing neonatal sepsis is challenging due to several factors that hinder its timely identification and treatment. The nonspecific symptoms in newborns, such as lethargy, poor feeding, and temperature instability, can be attributed to various common neonatal issues, making it difficult to pinpoint sepsis. Furthermore, the immature immune system of newborns leads to atypical or weak host responses to infection, delaying the appearance of clear clinical signs indicative of sepsis. Additionally, the overlap of sepsis with non-infectious conditions like respiratory distress syndrome or metabolic disorders often results in diagnostic confusion. Rapid and precise differentiation between these conditions is crucial but remains inherently difficult.[6] Blood cultures, considered the gold standard for diagnosing sepsis, can also be problematic. Obtaining an adequate blood sample from a neonate is technically challenging and may yield false-negative results due to low bacterial loads or prior antibiotic treatment. Similarly a delay of 72 hours before culture report also loses precious time before antibiotic treatment.[7]

Among the biomarkers utilized for diagnosing neonatal sepsis, C-reactive protein (CRP) and procalcitonin (PCT) have got substantial attention. CRP, an acute-phase reactant produced by the liver in response to inflammation, has been traditionally relied upon due to its widespread availability and cost-effectiveness. Conversely, PCT, a precursor of the hormone calcitonin, has emerged as a promising marker with potentially higher specificity for bacterial infections.[8]

A local study led by Ali *et al.* highlighted that the sensitivity of procalcitonin (PCT) was 73.6% and of C-reactive protein (CRP) was 50.9%, while their specificities were 38.6% and 28.7%, respectively. When the results of CRP and PCT were compared with blood culture findings, it was revealed that 50.9% of the CRP-positive cases were confirmed as true positives by blood cultures, while 73.6% of the PCT-positive cases were true positives.[9] another study led by Habib *et al.* showed the sensitivity of PCT as 97.7%; specificity 70.6%; PPV 77.1; NPV 96.8%. On blood culture, 50.3% patients had bacterial growth.[10]

This study compares PCT and CRP in diagnosing neonatal sepsis to develop more accurate and timely diagnostic tools. Enhanced diagnostic precision can lead to earlier intervention, targeted therapy, and better outcomes, while identifying the more reliable marker can optimize clinical protocols and reduce unnecessary antibiotic use, mitigating antibiotic resistance.

The aim is to evaluate and compare the diagnostic roles of PCT and CRP in a clinical setting keeping blood culture as gold standard, providing evidence that can guide future clinical practice and improve the standard of care for neonates at risk of sepsis.

METHODOLOGY

This hospital-based cross-sectional study was conducted in the Neonatal Intensive Care Unit (NICU) of Combined Military Hospital (CMH), Lahore, from January 2024 to July 2024 in which 126 neonates with the suspicion of sepsis were enrolled. The study was approved by the Institutional Review Board (IRB) of CMH, Lahore, and informed consent was obtained from the parents or guardians of each participant. The study was conducted in

accordance with the Declaration of Helsinki [11] and Good Clinical Practice guidelines[12].

A sample size calculation was performed based on previous diagnostic evidence related to procalcitonin, which demonstrated a sensitivity of 97.7% and specificity of 76.6% in detecting neonatal sepsis with an anticipated prevalence of neonatal sepsis of 50.3% based on positive blood culture results. A sample size of 126 was calculated to achieve a confidence level of 90% and a level of precision of 10%. A non-probability convenient sampling method was employed for participant enrollment in this study.

Neonates aged 0-28 days admitted to the NICU with clinical suspicion of sepsis, i.e. presence of at least two of the following criteria: fever (axillary temperature > 38°C or < 36°C), hypothermia (axillary temperature < 36°C), tachycardia (heart rate > 160 beats per minute), tachypnea (respiratory rate > 60 breaths per minute), apnea or bradycardia (heart rate < 100 beats per minute), lethargy or irritability, poor feeding or vomiting, or abnormalities in skin color, tone, or perfusion, such as pallor, mottling, or cyanosis, were eligible for inclusion in this study.

Neonates were excluded from the study if they had a confirmed diagnosis of sepsis or infection prior to admission to the NICU, or if they had congenital anomalies or chromosomal abnormalities. Additionally, neonates who had received antibiotic therapy within 72 hours prior to NICU admission were also excluded.

A structured data collection form was used to collect demographic and clinical data, including gestational age, birth weight, gender, and clinical signs and symptoms of sepsis. Blood samples were collected by trained phlebotomists using aseptic technique, with 1 mL of blood collected in serum separator tubes (SST) for procalcitonin (PCT) assays and 1 mL in ethylenediaminetetraacetic acid (EDTA) tubes for C-reactive protein (CRP) assays. Samples were labeled with a unique identifier and stored at room temperature (20-25°C) for up to 2 hours. Following centrifugation at 3000 rpm for 10 minutes, the resulting serum and plasma samples were aliquoted into cryovials and stored at -80°C until analysis. Prior to analysis, samples were thawed at room temperature and mixed gently to ensure homogeneity. To maintain sample integrity, quality control measures were implemented, including sample labeling and tracking, temperature control, aseptic handling, standardized centrifugation and aliquoting, limited freeze-thaw cycles, quality control samples, and regular instrument calibration. Therapy was initiated based on the following criteria: PCT levels ≥ 2.0 ng/mL and/or CRP levels ≥ 6.0 mg/L, indicating a high likelihood of sepsis or severe infection.

To ensure data quality, data were collected by trained research assistants and reviewed by the principal investigator for accuracy and completeness, with laboratory results verified by the hospital's laboratory quality control process. Data were entered into a password-protected electronic database (Microsoft Excel, Redmond, WA, USA) and backed up regularly, and analyzed using statistical software (SPSS version 26, IBM Corp, Armonk, NY, USA). The study's quantitative variables, including age, weight, CRP, and procalcitonin levels, were summarized using means and standard deviations. The categorical variables, including gender, clinical features, CRP findings, procalcitonin findings, blood culture findings, and pathogen type, were summarized using frequency distributions and percentages. A 2x2 contingency table was constructed to determine the values of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN). Subsequently, the diagnostic accuracy parameters, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated using standardized formulae, based on the values of TP, FP, FN, and TN.

RESULTS

The primary outcome of this study was to compare the diagnostic performance of C-reactive protein (CRP) and procalcitonin (PCT) in diagnosing neonatal sepsis, with blood culture serving as the gold standard. A total of 126 neonates were included in this study, with a mean gestational age of 34.60 ± 3.06 weeks and a mean age of presentation of 1.04 ± 1.76 days. The majority of the neonates presented in the first 24 hours of life (90.6%).The demographic and clinical characteristics of the study population are presented in Table 1, which shows that the

majority of the neonates were females (52.4%), with a mean age of 1.2 days, and a significant proportion had low birth weight (51.5%), prematurity (42%), and respiratory distress (31.7%). Notably, 11.1% of the mothers had urinary tract infection, 7.1% had chorioamnionitis, and 15.9% had prolonged rupture of membranes (>18 hours).

Table-I: Baseline Characteristics of the Patients (n=126)

Demographic characteristics	**n** (%)
Gestational age (weeks)	
28-32	29 (23%)
32-36	50 (39.7%)
36-40	47 (37.3%)
Mean ± SD	34.60 ± 3.60
Age at presentation	
Within 24 hours	114 (90.6%)
4-6 days	7 (5.4%)
≥7 days	5 (4%)
Mean ± SD	1.04 ± 1.76 days
Gender	
Female	72 (57.1%)
Male	54 (42.9%)
Neonatal factors	
Low birth weight	65 (51.5%)
Prematurity	53(42%)
Respiratory distress	40(31.7%)
Feeding intolerance	31(24.6%)
Lethargy	29(23%)
Maternal factors	
PROM (≥18 Hours)	20 (15.9%)
UTIs	14(11.1%)
Chorioamnionitis	9(7.1)

The findings of C-reactive protein (CRP) and procalcitonin (PCT) were compared according to blood culture findings. The results show that CRP was positive in 66.6% of cases with positive blood culture, while PCT was positive in 84.4% of cases with positive blood culture, suggesting that PCT may be a more sensitive marker for neonatal sepsis compared to CRP.

Table-II: Comparison of CRP and PCT Findings with Blood Culture Results (n=126)

Blood culture	C-reactive protein	Procalcitonin
Positive (n=45)	30 (66.6%) - True Positive	38 (84.4%) - True Positive
Negative (n=81)	40 (49.3%) - True Negative	67 (82.7%) - True Negative

The most common pathogen was *Klebsiella*, seen in 18 (14.3%) study cases, followed by *Pseudomonas* 9 (7.1%), *E. Coli* 8 (6.3%), and *Candida* 7 (5.6%).

Table-III: Bacterial Pathogens Found in Study Patients (n=126)

Pathogen	n (%)
Klebsiella	18 (14.3%)
Pseudomonas	9 (7.1%)
E. Coli	8 (6.3)
Candida	7 (5.6%)
MR-CoNS	3 (2.4)

The diagnostic parameters of CRP and PCT are presented in Table 4, which shows that PCT had a higher sensitivity (84.4%) and specificity (82.7%) compared to CRP (66.6% and 50.6%, respectively) in the diagnosis of neonatal sepsis. The positive predictive value (PPV) of PCT was also higher than CRP (73.1% vs 42.8%).

Table-IV: Diagnostic Parameters of CRP and PCT in the Diagnosis of Neonatal Sepsis

Diagnostic parameter	C-reactive protein	Procalcitonin
Sensitivity	66.6%	84.4%
Specificity	50.6%	82.7%
Positive predictive value	42.8%	73.1%
Negative predictive value	73.2%	90.5%
Diagnostic accuracy	59.5%	85.7%

Discussion

The present hospital-based cross-sectional study aimed to compare the diagnostic role of procalcitonin (PCT) and C-reactive protein (CRP) suggested that PCT may be a more sensitive and accurate marker for diagnosing neonatal sepsis compared to CRP. The demographic and clinical characteristics of the study population revealed a high prevalence of low birth weight, prematurity, and respiratory distress, which are known risk factors for neonatal sepsis. Low birth weight and prematurity are significant risk factors for neonatal sepsis, with studies suggesting that neonates with low birth weight and prematurity are at increased risk of developing sepsis. [13] A study by Raha *et al.* (2021) found that respiratory distress syndrome was a significant predictor of neonatal sepsis in preterm neonates.[14] The presence of maternal factors such as urinary tract infection, chorioamnionitis, and prolonged rupture of membranes (>18 hours) may have contributed to the development of neonatal sepsis in the study population. Maternal factors have been shown to play a significant role in the development of neonatal sepsis, with studies suggesting that chorioamnionitis, urinary tract infection, and prolonged rupture of membranes are associated with an increased risk of neonatal sepsis [15, 16]. The comparison of CRP and PCT findings with

blood culture results showed that PCT was positive in 84.4% of cases with positive blood culture, whereas CRP was positive in 66.6% of cases. This suggests that PCT may be a more sensitive marker for neonatal sepsis compared to CRP. The diagnostic parameters of PCT, including sensitivity (84.4%), specificity (82.7%), positive predictive value (73.1%), and diagnostic accuracy (85.7%), were also higher compared to CRP (66.6%, 50.6%, 42.8% and 59.5% respectively). Our study findings are consistent with previous studies that have shown PCT to be a more sensitive and accurate marker for neonatal sepsis compared to CRP. [9, 17] A study by AHA Mohsen and BA Kamel (2015) found that procalcitonin (PCT) was more sensitive than C-reactive protein (CRP) in diagnosing neonatal sepsis with PCT demonstrating a sensitivity of 80%, specificity of 85.7%, positive predictive value (PPV) of 84.8%, and negative predictive value (NPV) of 81.1%. In comparison, CRP had a sensitivity of 72.9%, specificity of 100%, PPV of 93.2%, and NPV of 69.7%.[18] The high prevalence of Gram-negative bacteria, particularly *Klebsiella*, *Pseudomonas, Methicillin-resistant coagulase negative staphylococci (MR-CoNS),* and *Candida*, suggests that these pathogens may play a significant role in the development of neonatal sepsis. These pathogens have been previously identified as common causes of neonatal sepsis in several studies.[19, 20] The high prevalence of *Candida* in our study is consistent with previous studies that have shown Candida to be a common cause of neonatal sepsis, particularly in preterm neonates.[21]

However, it is worth noting that not all studies have found PCT to be a superior marker for neonatal sepsis. A study by Jimoh *et al.* (2017) found that CRP was a more sensitive marker for neonatal sepsis compared to PCT, especially in monitoring antibiotic therapy.[8, 22].This highlights the need for further studies to establish the optimal diagnostic marker for neonatal sepsis.

In Pakistan, where the healthcare system faces the dual challenges of a large population and poverty, a rapid and accurate diagnostic tool for diagnosing neonatal sepsis is crucial. The current study's findings suggest that procalcitonin (PCT) may be a promising diagnostic tool for neonatal sepsis, potentially enabling healthcare providers to expedite diagnosis and improve patient outcomes. The limitations of our study include its single-center design and small sample size, which may affect the generalizability and precision of the findings. Future studies should aim to recruit larger samples in multiple centers, explore the use of PCT with other biomarkers, and investigate its cost-effectiveness.

Conclusion

In conclusion, the present study's findings suggest that procalcitonin (PCT) may be a more sensitive marker than C-reactive protein (CRP) in the early diagnosis of neonatal sepsis, leading to timely management and improved neonatal outcomes. However, further research is warranted to determine the optimal biomarker for neonatal sepsis and to validate the results of this study.

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