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ORIGINAL ARTICLE

First Clues in Fragile Lives: Can Early Biomarkers Transform Neonatal Sepsis Detection? A Retrospective Analysis

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ABSTRACT

Objectives: This retrospective study aimed to evaluate the diagnostic accuracy of C-reactive protein (CRP), procalcitonin (PCT), and presepsin for the early detection of neonatal sepsis by assessing their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in a tertiary care neonatal unit.

Methodology: Conducted at the Neonatal Unit of the Pediatrics Department at Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad, Pakistan, from May 2024 to May 2025, the study included 80 neonates (44 with confirmed sepsis, 36 without sepsis), determined by a sample size calculation based on a 36.41% sepsis prevalence, 95% confidence level, and 10% margin of error. Data were extracted from medical records, focusing on biomarker levels (CRP, PCT, presepsin) measured within 24 to 48 hours of sepsis suspicion, with analysis performed using SPSS software and Receiver Operating Characteristic (ROC) curves.

Results: The cohort comprised 65% late preterm and 51.2% low birth weight neonates, with 55% diagnosed with sepsis. Mean biomarker levels were higher in septic neonates (CRP: 10.54 ± 1.88 mg/L, PCT: 0.68 ± 0.15 ng/mL, presepsin: 249.3 ± 20.5 pg/mL) compared to non-septic controls (CRP: 8.08 ± 1.11 mg/L, PCT: 0.51 ± 0.13 ng/mL, presepsin: 216.11 ± 21.01 pg/mL). Presepsin showed the highest diagnostic accuracy (AUC 0.865, sensitivity 95.5%, NPV 90.0%), followed by CRP (AUC 0.860, sensitivity 93.2%) and PCT (AUC 0.783, sensitivity 97.7%, but specificity 22.2%).

Conclusion: Presepsin, CRP, and PCT are effective biomarkers for early neonatal sepsis detection, with presepsin offering the best diagnostic profile. A multi-biomarker approach could enhance clinical decision-making and reduce antibiotic overuse in resource-limited settings, necessitating further multicenter validation.

Keywords: *Biomarkers, C-reactive protein, Neonatal sepsis, Procalcitonin, Presepsin, Diagnostic accuracy, Pakistan.*

INTRODUCTION

Neonatal sepsis represents a life-threatening condition affecting newborns within the first 28 days of life, triggered by bacterial, viral, or fungal pathogens entering the bloodstream, resulting in systemic inflammation and potential multi-organ dysfunction.(1) Preterm and low birth weight infants are especially susceptible due to their immature immune systems, limited physiological reserves, and frequent exposure to hospital environments where infections can easily proliferate.(2) Early-onset sepsis (EOS), occurring within the first 72 hours of life, is often linked to maternal infections such as chorioamnionitis or vertical transmission, while late-onset

sepsis (LOS), emerging thereafter, is frequently associated with nosocomial sources, including invasive procedures or prolonged hospital stays. The clinical manifestations, including lethargy, temperature instability, poor feeding, respiratory distress, and sometimes subtle changes in vital signs, are often non-specific, posing significant challenges to early and precise diagnosis, particularly in resource-limited settings where advanced diagnostic tools may be scarce or delayed.[3] This diagnostic difficulty underscores the urgent need for reliable indicators to guide timely intervention and improve survival rates.

Globally, neonatal sepsis continues to impose a substantial health burden, with a reported prevalence of 36.41% in tertiary neonatal units, particularly in low- and middle-income countries where healthcare infrastructure is often inadequate. It is a major contributor to under-5 mortality, with India exhibiting one of the highest incidence rates due to a combination of environmental, socioeconomic, and healthcare-related factors.[4] Key risk factors include maternal conditions such as prolonged rupture of membranes (PROM), chorioamnionitis, Group B Streptococcus colonization, and suboptimal prenatal care, which increase the likelihood of infection transmission during delivery or the postnatal period. The associated mortality rates, coupled with long-term neurodevelopmental sequelae such as cerebral palsy or cognitive impairments, highlight the critical need for timely identification and intervention, especially in resource-constrained settings like Pakistan, where access to neonatal intensive care units (NICUs) and trained personnel may be limited, further complicating effective management.[5]

Despite the reliance on empirical antibiotic therapy as a standard treatment to combat suspected sepsis, diagnostic uncertainty frequently leads to excessive antibiotic use, fostering antimicrobial resistance and potential adverse effects in non-infected neonates, such as gut dysbiosis or allergic sensitization.[6] Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and presepsin have been investigated as tools for early sepsis detection to address this gap. For instance, IL-27 has demonstrated a sensitivity of 78.05% and specificity of 61.54%, indicating moderate diagnostic potential, while a multicenter study identified IL-6, IL-10, and NGAL as highly predictive for LOS, with area under the curve (AUC) values of 0.864, 0.845, and 0.829, respectively, suggesting their utility in distinguishing infected from non-infected cases.[7] Emerging technologies, including biosensors and multi-marker panels, have been proposed to improve diagnostic precision, reduce delays in treatment initiation, and enhance point-of-care applicability, yet no single biomarker has been universally endorsed for definitive sepsis diagnosis due to variability in performance across populations and clinical contexts.[8] This ongoing challenge necessitates further exploration of biomarker combinations to optimize diagnostic accuracy.

A critical research gap exists in the validation of these biomarkers across diverse geographical and clinical contexts, where demographic, genetic, and healthcare delivery differences may influence their performance. The PERSEVERE-II biomarker panel, validated in both high-income and low-middle-income settings including Pakistan, indicates potential applicability by demonstrating comparable profiles in septic children, suggesting that biomarker-based strategies could be adapted to resource-limited environments.[9] However, in Pakistan, there is a paucity of data on the diagnostic performance of common inflammatory biomarkers in neonatal sepsis, particularly in settings with available laboratory infrastructure but inconsistent diagnostic protocols, where reliance on clinical judgment often prevails over evidence-based testing[10]. Local studies have yet to comprehensively stratify biomarker levels by sepsis classification (proven, probable, or no sepsis) or evaluate their practical utility in NICU decision-making, leaving a significant void in understanding their real-world effectiveness in this region.[10] This lack of localized evidence hinders the development of tailored diagnostic and treatment guidelines.

Against this backdrop, the current study seeks to evaluate and compare the levels of early inflammatory biomarkers CRP, PCT, IL-6, and Presepsin between neonates with confirmed sepsis and those without sepsis in a tertiary care neonatal unit in Rawalpindi, Pakistan. By analyzing these biomarkers' early-stage profiles, including their sensitivity, specificity, and association with sepsis outcomes, this research aims to provide evidence for optimized diagnostic strategies that could enhance clinical decision-making, reduce diagnostic delays, and minimize unnecessary antibiotic administration. This study addresses a pressing need by contributing context-specific data to guide healthcare providers in managing neonatal sepsis more effectively within the constraints of local healthcare systems.

The main objective of this study:

1. To evaluate the diagnostic accuracy of selected biomarkers (CRP, PCT, and presepsin) for the early detection of neonatal sepsis by assessing their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

METHODOLOGY

This retrospective study was conducted at the Neonatal Unit of the Pediatrics Department at Pakistan Institute of

Medical Sciences (PIMS) Hospital, Islamabad, Pakistan, spanning a 12-month period from May 2024 to May 2025. The sample size of 80 neonates was calculated based on an expected sepsis prevalence of 36.41%, a confidence level of 95%, and a margin of error of 10%, with 44 diagnosed with confirmed sepsis and 36 classified as having no sepsis based on clinical and laboratory criteria. The research focused on evaluating the diagnostic utility of early inflammatory biomarkers, including C-reactive protein (CRP), procalcitonin (PCT), and presepsin, to enhance early detection and management of neonatal sepsis. Data were extracted from electronic medical records and paper-based charts, ensuring a comprehensive review of patient information while adhering to ethical standards, with approval obtained from the institutional review board prior to data collection.

The study population comprised neonates aged 0 to 28 days admitted to the NICU at PIMS Hospital, reflecting a diverse cohort with varying gestational ages, birth weights, and clinical presentations. Sample selection involved a purposive sampling technique, targeting all neonates with suspected sepsis who underwent biomarker testing and had complete medical records available during the study period. Inclusion criteria encompassed neonates with a confirmed sepsis diagnosis (based on positive blood cultures or clinical signs corroborated by laboratory evidence) and those without sepsis (negative cultures and absence of clinical sepsis signs), ensuring a balanced representation. Data collection involved retrieving demographic details (e.g., gestational age, birth weight, age at admission), clinical parameters (e.g., temperature, respiratory rate), and biomarker levels (CRP, PCT, presepsin) measured within the first 24–48 hours of sepsis suspicion. All data were anonymized, entered into a standardized database, and cross-verified for accuracy to minimize errors, with missing or incomplete records excluded from the final analysis. Data analysis was performed using SPSS software, employing the Mann–Whitney U test to compare biomarker distributions between septic and non-septic groups and the Receiver Operating Characteristic (ROC) curve to evaluate the diagnostic accuracy of the biomarkers.

RESULTS

Table 1 shows a total of 80 neonates were enrolled in this retrospective study. The gestational age distribution showed that a majority of the neonates were late preterm (born between 34 to 36 weeks), accounting for 65% (52 cases), while term neonates (≥37 weeks gestation) comprised 35% (28 cases) of the cohort. In terms of birth weight, 41 neonates (51.2%) were classified as low birth weight (LBW), defined as <2500 grams, whereas 39 neonates (48.8%) had a normal birth weight (≥2500 grams). With regard to gender distribution, 47 neonates (58.8%) were female, and 33 neonates (41.3%) were male, indicating a slight female predominance in the study population. The mode of delivery revealed that 48 neonates (60%) were born via cesarean section**,** while 32 (40%) were delivered through vaginal birth**,** reflecting a high rate of operative delivery consistent with tertiary-level obstetric care trends. Clinically, 44 neonates (55%) were diagnosed with sepsis based on clinical and laboratory findings, while the remaining 36 neonates (45%) were categorized as non-sepsis cases**,** forming the comparative control group for biomarker analysis.

Table 2 provides a foundational overview of the distribution of key inflammatory biomarkers C-reactive protein (CRP), procalcitonin (PCT), and presepsin among neonates with confirmed sepsis and those without. The mean CRP level was notably higher in the sepsis group (10.54 ± 1.88 mg/L) compared to the non-sepsis group (8.08 ± 1.11 mg/L), with a broader interquartile range (3.20 vs. 1.66), suggesting greater variability among infected neonates. A similar pattern was observed for PCT, where septic neonates showed higher values (0.68 ± 0.15 ng/mL) than non-septic ones (0.51 ± 0.13 ng/mL). Presepsin levels were also elevated in sepsis cases (249.3 ± 20.5 pg/mL) compared to controls (216.11 ± 21.01 pg/mL). These descriptive trends establish the baseline biomarker elevations in neonates with sepsis and support their selection for further analysis, and to evaluates their diagnostic accuracy using sensitivity, specificity, and predictive values.

The diagnostic accuracy of CRP, procalcitonin (PCT), and Presepsin in the early detection of neonatal sepsis was evaluated through sensitivity, specificity, predictive values, and area under the ROC curve (AUC). Among the three biomarkers, Presepsin demonstrated the highest overall diagnostic performance, with an AUC of 0.865 (95% CI: 0.788–0.942)**,** sensitivity of 95.5%**,** specificity of 50.0%**,** PPV of 70.0%**,** and NPV of 90.0% at an optimal cut-off value of 205 pg/mL**.** CRP also showed strong discriminative ability, yielding an AUC of 0.860 (95% CI: 0.782–0.939)**,** sensitivity of 93.2%**,** specificity of 38.9%**,** PPV of 65.1%**,** and NPV of 82.4%**,** using a cut-off of 7.67 mg/L**.** PCT demonstrated the highest sensitivity at 97.7%**,** making it highly effective for identifying true positive sepsis cases; however, it had the lowest specificity **(**22.2%**)** and PPV **(**60.6%**),** with an NPV of 88.9%**,** and an AUC of 0.783 (95% CI: 0.685–0.881) at a cut-off of 0.395 ng/mL**.** All three biomarkers showed statistically significant diagnostic capability (p = 0.0000). Overall, Presepsin and CRP offered a more balanced sensitivity-specificity profile,

suggesting they may serve as valuable tools for early identification of neonatal sepsis, while PCT's high sensitivity may support its role as a complementary marker in combination panels.

Table 1: Demographic Characteristics of the Study Population (n=80)

Variable	Categories	Frequency (%)
Gestational Age (weeks)	Late Preterm	52 (65%)
	Term	28(35%)
Birth Weight (g)	Low Birth Weight	41(51.2%)
	Normal Birth Weight	39 (48.8%)
Gender (Male)	Male	33(41.3%)
	Female	47 (58.8%)
Mode of Birth	Vaginal Delivery	32 (40%)
	Cesarean Section	48(60%)
Sepsis Status	Sepsis	44 (55%)
	Non-Sepsis	36(45%)

Table 2: Laboratory Values of Biomarkers by Sepsis Status in Neonates (n = 80)

Biomarker	Sepsis Status	n	Mean (SD)	IQR (Q1–Q3)	Range
C-reactive protein (mg/L)	Positive	44	10.54±1.88	3.20	13.89–6.78
	Negative	36	8.08 ±1.11	1.66	10.34–6.23
Procalcitonin (ng/mL)	Positive	44	0.68±0.15	0.22	0.89–.34
	Negative	36	0.51±0.13	0.19	0.78–0.34
Presepsin (pg/mL)	Positive	44	249.3±20.50	35.00	280.0–190.0
	Negative	36	216.11±21.01	30.00	250.0–180.0

Table 3: Diagnostic Performance of CRP, PCT, and Presepsin for Early Detection of Neonatal Sepsis(n=80)

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)	AUC	Confidence Interval	p-value
CRP	93.2%	38.9%	65.1%	82.4%	0.860	(0.782–0.939)	0.0000
PCT	97.7%	22.2%	60.6%	88.9%	0.783	(0.685–0.881)	0.0000
Presepsin	95.5%	50.0%	70.0%	90.0%	0.865	(0.788–0.942)	0.0000

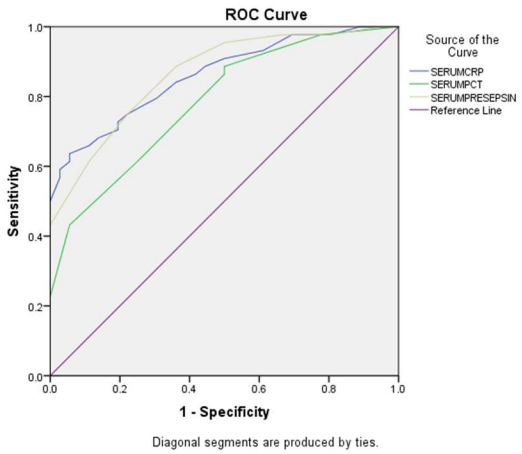

Figure 1: ROC Curve for CRP, PCT, and Presepsin in Neonatal Sepsis Detection

Figure 1 shows that ROC curves for CRP (blue), PCT (green), and Presepsin (gold) illustrate the diagnostic performance of each biomarker in detecting neonatal sepsis. The curves show that Presepsin and CRP demonstrate superior discriminative ability, as indicated by their closer proximity to the top-left corner of the graph. PCT, while having the steepest initial rise (indicating high sensitivity), shows lower overall accuracy due to its closeness to the reference line. The visual representation supports the AUC values reported in Table 3, reinforcing the potential of Presepsin and CRP as effective early diagnostic tools.

DISCUSSION

The current retrospective study we investigated the diagnostic accuracy of C-reactive protein (CRP), procalcitonin (PCT), and presepsin for the early detection of neonatal sepsis among 80 neonates. The results revealed presepsin as the most effective biomarker, with an area under the curve (AUC) of 0.865, closely followed by CRP (0.860) and PCT (0.783), aligning with a growing body of evidence supporting presepsin's role in early neonatal sepsis diagnosis. This finding is consistent with El Sayed et al. (2021), who reported presepsin's superior reliability compared to traditional markers during the initial inflammatory phase.[11] However Hincu et al. (2025)

also highlighted its enhanced diagnostic precision in neonatal cohorts.[12] The observed elevation in presepsin levels (mean 249.3 ± 20.5 pg/mL) among septic neonates further corroborates its sensitivity to bacterial infections, as noted in these prior studies, suggesting its potential as a primary screening tool in resource-limited settings like Pakistan.

Presepsin's diagnostic strength, evidenced by a sensitivity of 95.5% and a negative predictive value (NPV) of 90.0% in this study, underscores its utility as an early warning indicator, a trend supported by Pospisilova et al. (2023), who reported comparable sensitivity and moderate specificity in early-onset sepsis.[13] This is reinforced by Chen et al. (2025), who identified presepsin as having the strongest diagnostic correlation in culture-positive neonatal sepsis when compared to CRP, PCT, serum amyloid A (SAA), and IL-6.[14] The broader interquartile range (IQR) of 35.0 pg/mL in septic neonates suggests variability in inflammatory responses, a pattern consistent with Jin et al. (2025), who advocated for combining presepsin with other markers in diagnostic panels to enhance accuracy and reduce false negatives.[15] These findings suggest that presepsin could serve as a cornerstone biomarker, particularly when integrated into multi-marker strategies, a recommendation echoed across recent literature.

In contrast, PCT exhibited the highest sensitivity (97.7%) but the lowest specificity (22.2%) in this cohort, a profile consistent with its known early elevation in bacterial infections, though its ability to discriminate sepsis from non-infectious inflammation remains limited. This observation aligns with Anugu and Khan (2021), who noted that PCT's diagnostic value improves when paired with other biomarkers due to its early rise.[16] Srinivasan et al. (2023), who, in a Cochrane review also emphasized its effectiveness in ruling out sepsis through serial measurements rather than as a standalone test.[17] The mean PCT level of 0.68 ± 0.15 ng/mL in septic neonates, compared to 0.51 ± 0.13 ng/mL in non-septic cases, supports its role as a complementary marker, though the low specificity (IQR 0.22) indicates a need for cautious interpretation, a point raised in prior studies conducted in diverse neonatal populations.

CRP, a widely utilized biomarker in NICUs, demonstrated a robust AUC of 0.860 and sensitivity of 93.2%, with a mean value of 10.54 ± 1.88 mg/L in septic neonates, affirming its clinical relevance despite a specificity of 38.9% as similar findings are reported by Maddaloni et al. (2021).[18] Similarly, these finding is in line with Ahmad et al. (2024) also, who suggested that CRP is most effective for monitoring infection trends over time rather than as a sole diagnostic indicator.[19] Goyal et al. (2024) further emphasized the practicality of point-of-care CRP testing in resource-constrained settings, a factor pertinent to PIMS Hospital, where cost-effectiveness and accessibility are critical.[20] The IQR of 3.20 mg/L in septic neonates indicates a wider spread, potentially reflecting non-infectious inflammatory contributions, a consideration noted in previous research advocating for its use in combination with other markers.

The collective findings advocate for a multi-biomarker approach to optimize neonatal sepsis diagnosis, a strategy supported by Taneja and Batra (2021), who proposed panels including CRP, PCT, and presepsin to balance sensitivity, specificity, and predictive values.[21] This is further substantiated by Sahu et al. (2025), who demonstrated that bioscore approaches integrating these biomarkers enhance diagnostic accuracy and reduce false positives in neonatal cohorts.[22] Additionally, Pietrasanta C (2024) highlighted the potential of combining hematological indices, such as the CRP/platelet ratio, with these biomarkers for improved diagnostic enrichment.[23] Given the high sepsis prevalence (55%) and demographic profile (65% late preterm, 51.2% low birth weight) in this study, these results underscore the need for tailored diagnostic protocols. Future multicenter studies are recommended to validate these cut-off values (e.g., presepsin at 205 pg/mL) and explore longitudinal biomarker trends to refine clinical guidelines and mitigate antibiotic overuse in settings like Rawalpindi.

CONLUSION

In conclusion, this study, demonstrates that presepsin, CRP, and PCT are valuable biomarkers for early neonatal sepsis detection, with presepsin showing the highest diagnostic accuracy (AUC 0.865). These findings support the adoption of a multi-biomarker approach to enhance clinical decision-making and reduce unnecessary antibiotic use, particularly in resource-limited settings.

Limitations and Recommendations

This study, conducted at PIMS Hospital, Rawalpindi, has several limitations that warrant consideration. The retrospective design relied on existing medical records, which may contain incomplete or inconsistent data, potentially affecting the accuracy of biomarker measurements and sepsis classification. The sample size of 80 neonates, while adequate for initial analysis, limits the generalizability of findings to broader populations, and the single-center setting may not account for regional or institutional variations in neonatal care practices. Additionally, the lack of serial biomarker measurements and the absence of other potential markers, such as IL-6 or hematological indices, may have overlooked

complementary diagnostic insights. To address these limitations, we recommend conducting multicenter prospective studies with larger cohorts to validate the diagnostic cut-offs (e.g., presepsin at 205 pg/mL) and explore longitudinal trends. Incorporating additional biomarkers and advanced statistical modeling, such as machine learning, could further refine diagnostic accuracy and support the development of tailored protocols to optimize sepsis management in resource-constrained settings like Pakistan.

DECLARATION

Funding
This research received no external funding.

Conflict of Interest
The authors declare no conflict of interest.

Ethical Approval
The study was approved by the Institutional Review Board of PIMS Hospital, Islamabad.

Consent
Patient data were anonymized; informed consent was waived due to the retrospective nature of the study.

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