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ROLE OF ELECTROLYTES AND INFLAMMATORY BIOMARKERS (CRP, ESR, PROCALCITONIN AND TLC) IN DEVELOPMENT OF NEONATAL SEPTICEMIA: A CROSS-SECTIONAL STUDY

Original Research

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ABSTRACT

Background: Neonatal septicemia remains a major cause of morbidity and mortality worldwide, particularly in low- and middle-income countries, due to delayed diagnosis and nonspecific clinical presentation. The immature immune system of neonates limits their ability to mount an effective inflammatory response, making laboratory biomarkers essential for early detection. Inflammatory markers and electrolyte disturbances frequently accompany systemic infection, yet their combined diagnostic relevance in late-onset neonatal septicemia remains insufficiently explored in regional clinical settings.

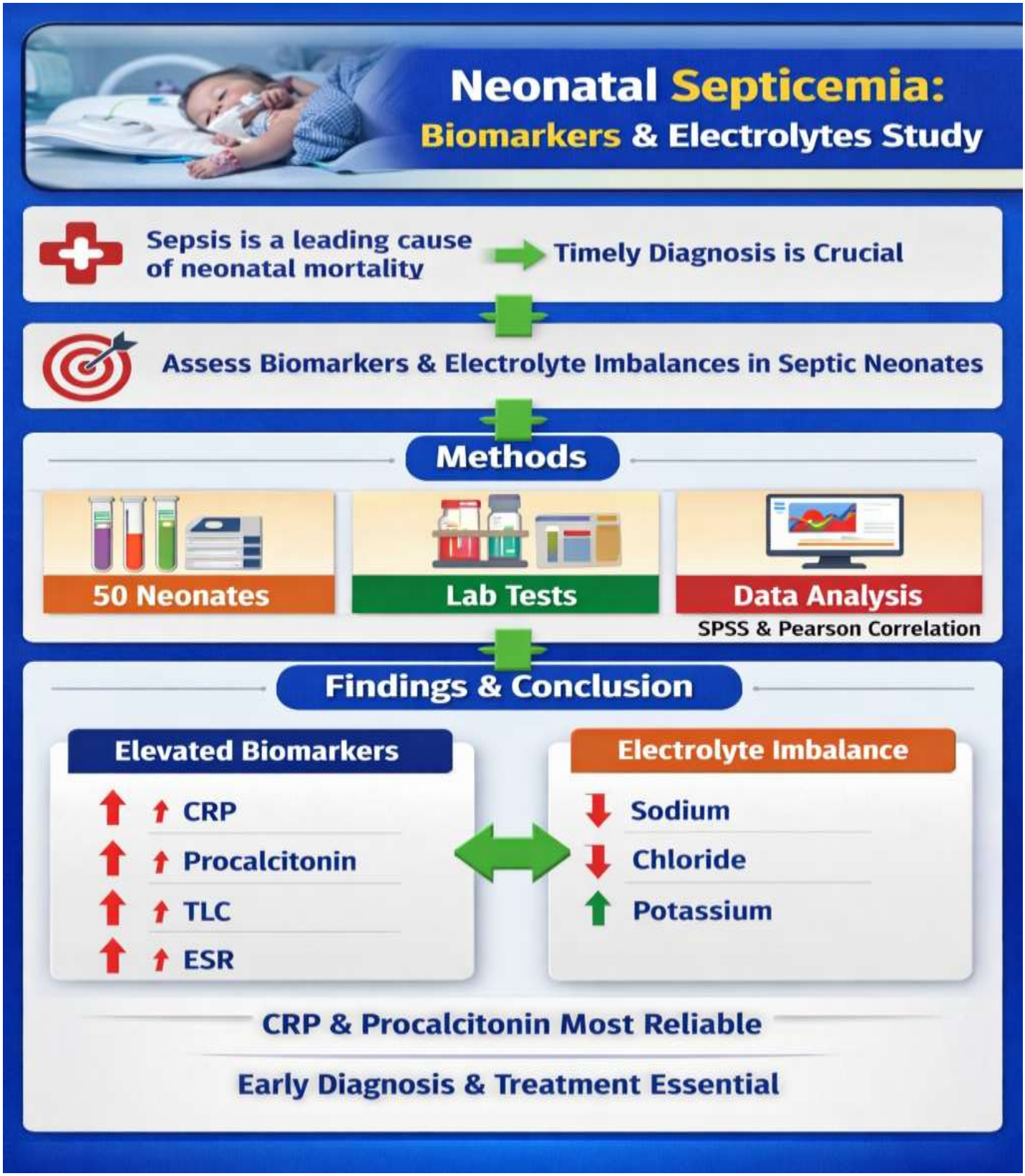
Objective: To evaluate the diagnostic significance of key inflammatory biomarkers—C-reactive protein, procalcitonin, total leukocyte count, and erythrocyte sedimentation rate—and their relationship with electrolyte imbalances in neonates with late-onset septicemia.

Methods: A descriptive cross-sectional study was conducted in neonatal intensive care units of tertiary hospitals in Faisalabad, Pakistan. Fifty neonates were initially screened; thirty-five with early-onset sepsis were excluded. Fifteen neonates aged 3–28 days diagnosed with late-onset septicemia were included. Venous blood samples were analyzed for inflammatory biomarkers and serum electrolytes using standardized chemistry analyzers. Data were analyzed using SPSS, applying descriptive statistics and Pearson correlation analysis.

Results: Elevated C-reactive protein levels were observed in 12 neonates (80%), while procalcitonin was raised in 11 neonates (73.3%). Total leukocyte count was elevated in 7 cases (46.7%), and erythrocyte sedimentation rate in 5 cases (33.3%). Hyponatremia was present in 8 neonates (53.3%), hypochloremia in 6 (40.0%), and potassium imbalance in 7 (46.7%). A strong positive correlation was found between C-reactive protein and procalcitonin ($r = 0.899$), while moderate negative correlations were observed between inflammatory markers and sodium and chloride levels.

Conclusion: C-reactive protein and procalcitonin demonstrated superior diagnostic utility in late-onset neonatal septicemia. Electrolyte imbalances, particularly hyponatremia, were frequent and reflected systemic involvement. A combined assessment of inflammatory biomarkers and electrolytes may enhance early diagnosis and clinical management of neonatal sepsis.

Keywords: C-Reactive Protein, Electrolyte Imbalance, Neonatal Sepsis, Procalcitonin, Sodium Disorders, Systemic Inflammation, Total Leukocyte Count.



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INTRODUCTION

Neonatal sepsis remains a time-critical clinical emergency and a major contributor to preventable neonatal morbidity and mortality, particularly in settings where newborns present late, laboratory capacity is variable, and empiric antibiotics are started before microbiologic confirmation (1,2). Clinically, sepsis in the neonatal period is commonly categorized by timing of symptom onset into early-onset sepsis, typically occurring within the first 72 hours of life, and late-onset sepsis, developing after 72 hours and often linked to prolonged hospitalization and exposure to invasive care (1,3). This distinction matters because early-onset sepsis is more strongly associated with maternal and perinatal factors—such as prematurity and prolonged rupture of membranes—while late-onset sepsis is more frequently driven by nosocomial or community acquisition, including device-related colonization, contact transmission, and the complex care needs of preterm and critically ill infants (4,5). Across both categories, newborns are uniquely vulnerable because immune defenses are developmentally immature; neutrophil function, macrophage activity, and T-cell responses are less coordinated than in older children, which can blunt early inflammatory signals and allow rapid clinical deterioration (6). Despite its clinical importance, neonatal sepsis is notoriously difficult to diagnose at the bedside because early manifestations are often nonspecific and overlap with normal transitional physiology or non-infectious neonatal conditions (2,7). Temperature instability, feeding intolerance, apnea or respiratory distress, lethargy, irritability, tachycardia, abdominal distension, jaundice, and petechiae can all occur in sepsis, yet none are individually diagnostic, especially in preterm infants where baseline instability is common (8,9). Although blood culture is considered the diagnostic reference standard, its practical limitations—including delayed turnaround time and imperfect sensitivity—create a window in which clinical teams must decide whether to treat on suspicion alone (10). This diagnostic uncertainty contributes to widespread empiric antibiotic exposure in neonatal units; while early treatment can be lifesaving in true sepsis, indiscriminate or prolonged antibiotic use increases risks such as antimicrobial resistance, invasive fungal infections, microbiome disruption, and avoidable drug toxicity (3,11). Consequently, improving early diagnostic certainty—without sacrificing safety—remains a central challenge for neonatal care systems worldwide.

Inflammatory biomarkers have therefore been pursued to support earlier, more reliable decision-making, yet no single test has proven sufficiently accurate to stand alone (4,10). C-reactive protein (CRP), a hepatic acute-phase reactant, is widely used because it is inexpensive and operationally feasible; however, CRP has limited sensitivity in the earliest hours of infection and can rise in multiple non-infectious perinatal conditions, making cut-off selection and interpretation difficult (4,12). Procalcitonin (PCT) has attracted attention as a potentially earlier marker in bacterial infection, with levels rising within hours of endotoxin exposure, but physiologic postnatal kinetics and timing of sampling can complicate interpretation, especially at birth (13,14). Similarly, hematological parameters such as total leukocyte count (TLC) and differential indices may reflect systemic inflammation, yet they are influenced by gestational age and perinatal stressors; when used alone, they can misclassify infants, but they may add value as part of a multi-parameter approach (15). The erythrocyte sedimentation rate (ESR) is inexpensive and accessible, and may complement other markers, but it is nonspecific, slower to rise, and affected by neonatal hematologic variables, limiting its utility for early rule-in decisions (16,17). Collectively, the literature increasingly supports combined interpretation of biomarkers—particularly serial measurements and multi-marker strategies—to improve diagnostic performance and antibiotic stewardship, especially where rapid, point-of-care platforms can shorten time to actionable results (18,19). Alongside inflammatory markers, electrolyte disturbances represent an often under-recognized but clinically meaningful component of neonatal sepsis, particularly among critically ill infants in neonatal intensive care settings (15). Sodium and potassium derangements may arise from systemic inflammation, impaired renal perfusion, altered hormonal responses, acid–base shifts, fluid therapy, and evolving organ dysfunction. These abnormalities can worsen outcomes by contributing to arrhythmias, neuromuscular instability, seizures, and acute kidney injury, and they may also signal disease severity and impending deterioration (11,12). Evidence indicates that dysnatremias and hyperkalemia are not uncommon in hospitalized neonates and are associated with increased complications and mortality, emphasizing the need for systematic monitoring and timely correction during septic illness (8,14). However, in many resource-constrained environments, electrolyte patterns are not routinely integrated into sepsis diagnostic frameworks, and local data linking electrolyte profiles with biomarker dynamics and clinical sepsis presentations remain limited (10,13).

A further gap is the shortage of context-specific evidence from many Pakistani urban centers, including Faisalabad, where healthcare delivery is shaped by heterogeneous referral pathways, variable infection-control capacity, and high neonatal unit occupancy. While global studies describe late-onset sepsis as a major driver of morbidity, prolonged hospitalization, and antibiotic exposure in neonatal intensive care units, the organism profile, biomarker performance, and accompanying biochemical disturbances can differ substantially by setting, infrastructure, and antimicrobial practices (3,5). In this context, evaluating the diagnostic value of commonly used inflammatory biomarkers—TLC, ESR, CRP, and PCT—alongside electrolyte abnormalities using contemporary diagnostic platforms

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(such as I Chroma 2, Mini Vidas, and Elite Pro) may provide practical, locally applicable evidence to refine diagnostic pathways, reduce unnecessary antibiotic exposure, and support timely intervention in true sepsis cases (8,12). Accordingly, the central research question guiding this study is whether inflammatory biomarkers (TLC, ESR, CRP, and procalcitonin), interpreted alongside electrolyte profiles, provide clinically meaningful diagnostic value for identifying and characterizing neonatal septicemia—particularly late-onset sepsis—in the local hospital setting. The study is designed to (i) determine the clinical manifestations of neonatal septicemia with emphasis on late-onset presentations, (ii) assess the diagnostic value of key inflammatory biomarkers for suspected sepsis, and (iii) analyze the relationship between biomarker patterns and abnormal electrolyte levels during late-onset sepsis, thereby generating evidence to inform more accurate, timely, and context-appropriate neonatal sepsis evaluation and management.

METHODS

This descriptive cross-sectional study was conducted to evaluate the role of inflammatory biomarkers and electrolyte disturbances in neonates with late-onset septicemia. The study was carried out at Saad Medical Complex and Rabia Trust Hospital, Faisalabad, Pakistan, over a three-month period from April 2024 to June 2024. Faisalabad is a densely populated and industrialized urban center in Punjab, and the selected hospitals serve a large neonatal catchment area, making them appropriate sites for assessing the local burden and laboratory characteristics of neonatal sepsis. Prior to initiation, the study protocol was reviewed and approved by the Ethical Review Board of Riphah International University in coordination with the institutional ethics committees of Saad Medical Complex and Rabia Trust Hospital, Faisalabad. The study was conducted in accordance with internationally accepted ethical standards for biomedical research involving human participants. Written informed consent was obtained from the parents or legal guardians of all enrolled neonates before participation, and strict confidentiality of patient information was maintained throughout the study period. The study population comprised neonates aged 3 to 28 days who were clinically suspected or diagnosed with late-onset sepsis and were receiving care at the study sites during the data collection period. Neonates of either gender were eligible for inclusion. Late-onset sepsis was defined as sepsis occurring after 72 hours of life. Neonates older than 28 days and those diagnosed with early-onset sepsis were excluded to maintain homogeneity of the study population and to minimize confounding related to perinatal and maternal factors. These criteria were applied to ensure that the findings specifically reflected laboratory and biochemical patterns associated with late-onset neonatal septicemia. A total sample of 50 neonates was enrolled using a non-probability, hospital-based sampling approach (4). The sample size was determined based on feasibility, patient availability during the study period, and the exploratory nature of the research, with the intent to generate preliminary local evidence regarding biomarker and electrolyte behavior in late-onset sepsis.

Venous blood samples were collected aseptically from each neonate under strict infection-control precautions. Approximately 5 mL of blood was drawn per participant and divided into appropriate containers for laboratory analysis. Two milliliters were transferred into ethylenediaminetetraacetic acid (EDTA) tubes for hematological assessment, including total leukocyte count. The remaining three milliliters were placed in gel separator tubes for serum separation. All specimens were processed within two hours of collection in the respective hospital laboratories to minimize pre-analytical variability. Laboratory investigations were performed using standardized, calibrated analyzers. Procalcitonin and C-reactive protein levels were measured using Mini Vidas and I-Chroma 2 analyzers, while serum electrolytes—including sodium, potassium, and chloride—were analyzed using the ACCRE 8 specialized chemistry analyzer. These instruments were selected for their clinical reliability, rapid turnaround time, and suitability for routine diagnostic use in hospital laboratories. All tests were conducted according to manufacturer protocols and internal quality-control procedures. Clinical and demographic data were obtained from patient medical records and laboratory request forms. Extracted variables included neonatal age, gender, clinical diagnosis, and laboratory parameters relevant to septicemia. No direct interaction with neonates occurred beyond routine clinical care and blood sampling indicated for diagnostic purposes. Data were entered, cleaned, and analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Descriptive statistics were applied to summarize demographic characteristics and laboratory findings, including frequencies, percentages, means, and standard deviations as appropriate. Inferential statistical analyses were used to explore associations between inflammatory biomarkers and electrolyte abnormalities in neonates with late-onset sepsis. A p-value of less than 0.05 was considered statistically significant for all analytical procedures. Overall, this methodology was designed to provide a clear, ethical, and reproducible framework for examining the diagnostic utility of inflammatory biomarkers and electrolyte disturbances in late-onset neonatal septicemia within a real-world hospital setting.

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RESULTS

A total of 50 neonates were initially screened during the study period; however, 35 neonates were identified as having early-onset sepsis based on maternal infection history and were therefore excluded. The final analysis was conducted on 15 neonates diagnosed with late-onset neonatal septicemia and admitted to the neonatal intensive care units. The results summarize inflammatory biomarker profiles, electrolyte disturbances, correlation patterns, and short-term outcomes in this cohort. Among the inflammatory biomarkers, elevated C-reactive protein levels (>10 mg/L) were observed in 12 of the 15 neonates (80%), while the remaining 3 neonates (20%) had values within the normal range. Procalcitonin levels were raised (>0.5 ng/mL) in 11 neonates (73.3%), with 4 neonates (26.7%) demonstrating normal concentrations. Total leukocyte count was elevated in 7 neonates (46.7%), whereas 8 neonates (53.3%) showed values within the reference range. Erythrocyte sedimentation rate was increased in only 5 neonates (33.3%), while the majority, 10 neonates (66.7%), had normal ESR values. Overall, CRP and procalcitonin demonstrated the highest frequencies of abnormal elevation among the inflammatory markers assessed. Electrolyte analysis revealed frequent biochemical disturbances. Hyponatremia was the most common abnormality, observed in 8 neonates (53.3%), while 6 neonates (40.0%) had normal sodium levels and 1 neonate (6.7%) demonstrated hypernatremia. Potassium imbalance was identified in 7 neonates, with hyperkalemia present in 4 neonates (26.7%) and hypokalemia in 3 neonates (20.0%), whereas 8 neonates (53.3%) maintained normal potassium levels. Chloride levels were reduced in 6 neonates (40.0%), while the remaining 9 neonates (60.0%) had values within the normal range; no cases of hyperchloremia were recorded. These findings indicate that electrolyte derangements, particularly hyponatremia, were common in neonates with late-onset septicemia. Correlation analysis demonstrated a strong positive association between CRP and procalcitonin ($r = 0.899$), indicating parallel rises in these two inflammatory biomarkers. Moderate positive correlations were observed between CRP and ESR ($r = 0.680$) and between CRP and total leukocyte count ($r = 0.662$). In contrast, CRP showed moderate negative correlations with sodium ($r = -0.570$) and chloride levels ($r = -0.670$), suggesting that increasing inflammatory activity was associated with declining electrolyte concentrations. ESR also demonstrated a strong negative correlation with chloride ($r = -0.715$) and a moderate positive correlation with procalcitonin ($r = 0.658$). These relationships reflect concurrent inflammatory activation and biochemical imbalance in septic neonates. Regarding clinical outcomes, 3 of the 15 neonates died during the study period, resulting in a mortality rate of 20%. All recorded deaths occurred among female neonates; however, the limited sample size precluded definitive conclusions regarding gender-based risk. Gender-wise comparison of biomarker and electrolyte levels showed no statistically significant differences between male and female neonates, with all p-values exceeding 0.05, indicating comparable laboratory responses across genders.

Table 1: Distribution of Inflammatory Biomarker and Electrolyte Levels in Neonates with Septicemia

Biomarker	High	Low	Normal
CRP	12	0	03
Procalcitonin	11	0	04
TLC	07	0	08
Sodium	01	08	06
Potassium	04	03	08
Chloride	0	06	09
ESR	**05**	**0**	**10**

Table 2: Correlation Between Inflammatory Biomarkers and Electrolyte Levels in Neonates with Septicemia

Parameter	R-Value	Strength/Direction
CRP & Procalcitonin	0.899	Strong Positive
CRP & ESR	0.680	Moderate Positive

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Parameter	R-Value	Strength/Direction
CRP & TLC	0.662	Moderate Positive
CRP & Chloride	-0.670	Moderate Negative
CRP & Sodium	-0.570	Moderate Negative
ESR & Procalcitonin	0.658	Moderate Positive
ESR & Chloride	**-0.715**	**Strong Negative**

Table 3: Gender-Based Comparison of Inflammatory Biomarkers and Electrolyte Levels in Neonates with Septicemia

Parameter	Mean (M)	Mean (F)	t-statistic	p-value	Interpretation
CRP	48.44	124.15	-1.33	0.222	NS (Not Significant)
Procalcitonin	0.64	12.90	-1.00	0.352	NS
TLC	25.57	24.00	0.97	0.355	NS
ESR	47.71	86.88	-1.71	0.119	NS
Sodium	135.20	137.59	-1.04	0.324	NS
Potassium	4.57	4.75	-0.34	0.738	NS
Chloride	**98.73**	**99.21**	**-0.23**	**0.823**	**NS**

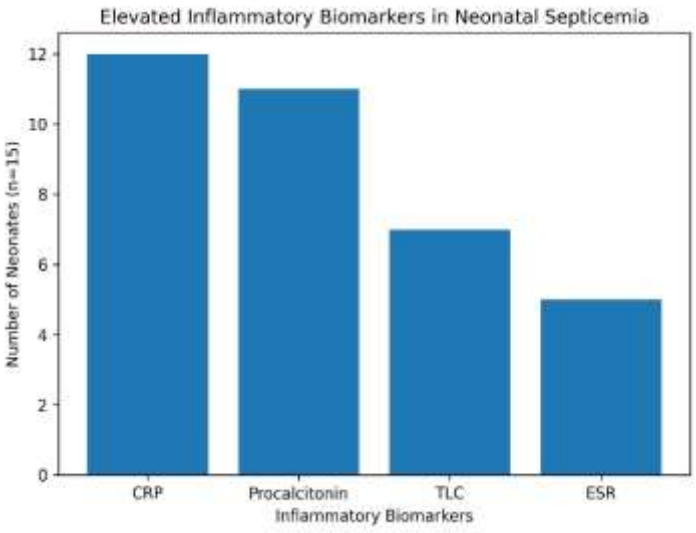


Figure 1 Elevated Inflammatory Biomarkers in Neonatal Septicemia

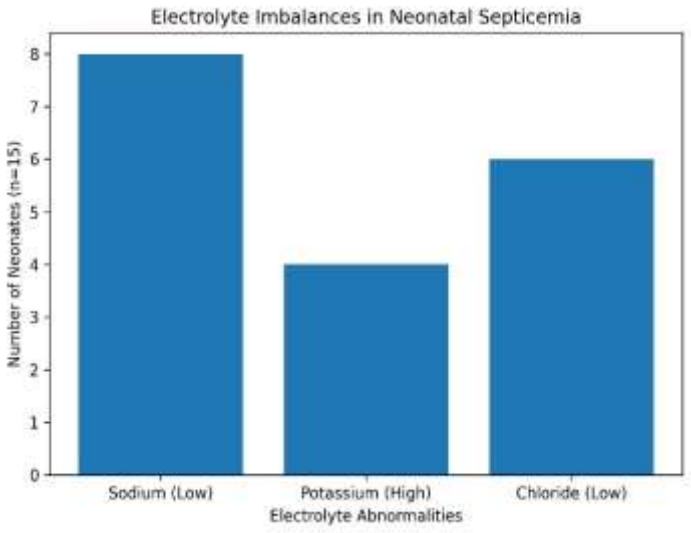
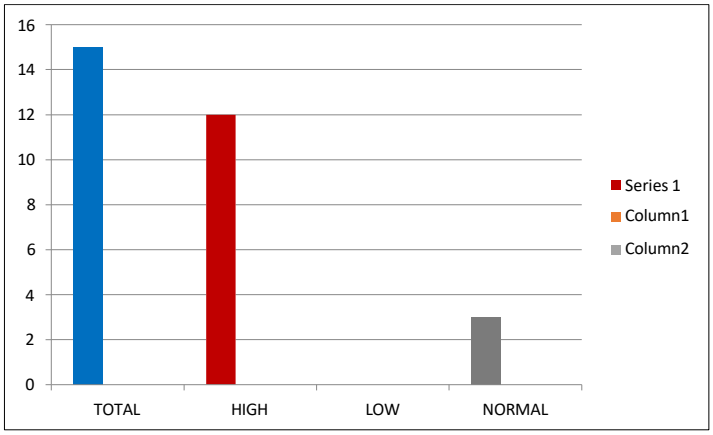
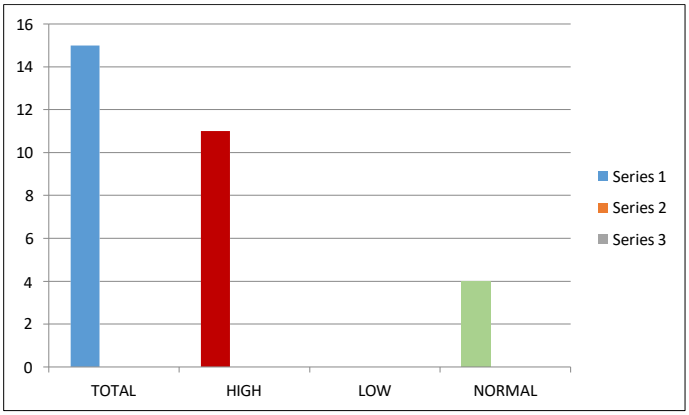


Figure 2 Electrolyte Imbalances in Neonatal Septicemia



Level of CRP

Figure 3 Level of CPR



Level of Procalcitonin

Figure 1 Level of Procalcitonin

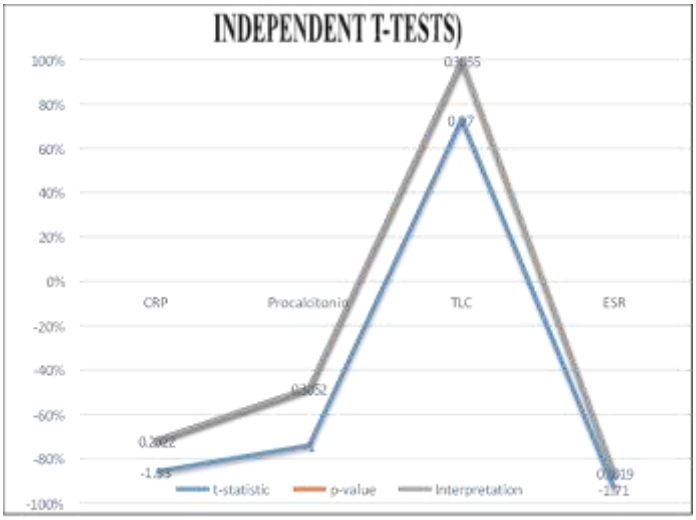


Figure 5 Independent T-Test

DISCUSSION

The present study evaluated the behavior of key inflammatory biomarkers and electrolyte disturbances in neonates with late-onset septicemia admitted to neonatal intensive care units in Faisalabad, with the aim of identifying laboratory parameters that may assist in earlier and more reliable diagnosis. The findings demonstrated that among the inflammatory markers assessed, C-reactive protein and procalcitonin were most frequently elevated, while total leukocyte count and erythrocyte sedimentation rate showed comparatively lower sensitivity. In parallel, electrolyte imbalances—particularly hyponatremia and hypochloremia—were commonly observed, highlighting the systemic nature of neonatal sepsis and its multisystem involvement. A markedly high proportion of neonates exhibited elevated C-reactive protein levels, reflecting an active acute-phase response. This observation aligns with previously published evidence indicating that CRP rises within hours of bacterial infection and remains elevated during ongoing inflammation, making it useful for both detection and monitoring of treatment response (10,17,18). Although CRP lacks absolute specificity, its high frequency of elevation in this cohort supports its role as a sensitive screening marker when interpreted in the appropriate clinical context. Procalcitonin was also elevated in a substantial proportion of cases and demonstrated slightly lower frequency than CRP, consistent with literature describing PCT as a relatively more specific indicator of bacterial infection that rises earlier in the course of sepsis (19). Together, these findings reinforce the complementary diagnostic value of CRP and procalcitonin rather than reliance on a single biomarker. In contrast, total leukocyte

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count showed limited diagnostic yield, with fewer than half of the neonates demonstrating leukocytosis. This supports existing evidence that neonatal immune immaturity and perinatal physiological variability can result in normal leukocyte counts even in the presence of severe infection (18,20). Similarly, erythrocyte sedimentation rate exhibited the lowest sensitivity among the inflammatory markers studied, which is consistent with its delayed response to inflammation and lack of specificity in neonatal populations (21,22). These results suggest that TLC and ESR are better suited as adjunctive parameters rather than primary diagnostic tools in neonatal septicemia.

Electlyte abnormalities emerged as an important biochemical feature in this cohort. Hyponatremia was the most frequently observed disturbance, followed by hypochloremia, findings that mirror earlier reports linking sepsis-related inflammation, capillary leakage, renal dysfunction, and inappropriate fluid management to electrolyte derangements in critically ill neonates (23,24). Such imbalances may not only reflect disease severity but also contribute to adverse outcomes if unrecognized. The observed negative correlations between inflammatory biomarkers and sodium and chloride levels further support the concept that worsening systemic inflammation is accompanied by disruption of electrolyte homeostasis, underscoring the need for integrated biochemical monitoring in septic neonates. The correlation analysis demonstrated a strong positive association between CRP and procalcitonin, along with moderate correlations between CRP, ESR, and total leukocyte count, indicating a coherent inflammatory response across markers. Conversely, the inverse relationships between inflammatory markers and electrolytes highlight the interconnected nature of inflammation and metabolic regulation in sepsis. These findings support a multidimensional diagnostic approach that incorporates both inflammatory and biochemical parameters to better characterize neonatal septicemia. Several strengths of this study merit consideration. The use of standardized laboratory platforms enabled consistent measurement of biomarkers and electrolytes, and the focus on late-onset sepsis provided clinically relevant insight into a subgroup that is often associated with prolonged hospitalization and higher complication rates. Additionally, the generation of local data contributes to addressing regional evidence gaps and may inform context-specific clinical decision-making.

However, important limitations should be acknowledged. The cross-sectional design precluded assessment of temporal trends, causality, or biomarker dynamics over the course of illness and treatment. The small sample size limited statistical power and restricted the ability to perform advanced diagnostic accuracy analyses, such as sensitivity, specificity, and receiver operating characteristic curve evaluation. Furthermore, the study was confined to a single urban district, which may limit generalizability to other regions with differing socioeconomic and healthcare characteristics. Future research would benefit from longitudinal, multicenter designs with larger sample sizes to evaluate biomarker kinetics, establish clinically meaningful cut-off values, and assess prognostic implications. Incorporating control groups and stratifying neonates by disease severity could further strengthen diagnostic inference. Additionally, integrating socioeconomic and healthcare access variables may provide a more comprehensive understanding of neonatal sepsis outcomes and guide targeted public health interventions (25). Overall, the findings suggest that CRP and procalcitonin are the most informative inflammatory biomarkers in late-onset neonatal septicemia, particularly when interpreted alongside electrolyte profiles. A combined, rather than isolated, use of laboratory parameters appears most appropriate for improving diagnostic confidence and supporting timely management in neonatal intensive care settings.

CONCLUSION

This study concludes that C-reactive protein and procalcitonin are the most reliable inflammatory biomarkers for the early identification of neonatal septicemia, offering superior diagnostic value compared with total leukocyte count and erythrocyte sedimentation rate, which showed limited consistency. The frequent occurrence of electrolyte disturbances—particularly reduced sodium and chloride levels—further supports the presence of systemic infection and highlights the importance of routine biochemical monitoring in septic neonates, while potassium levels appeared relatively preserved. The absence of gender-based differences indicates that susceptibility and disease severity are not influenced by sex, emphasizing that all neonates are equally vulnerable to environmental and hospital-acquired infections. Collectively, these findings underscore the practical importance of integrating CRP and procalcitonin into routine diagnostic protocols to support timely diagnosis and prompt treatment, thereby improving clinical decision-making and potentially reducing adverse outcomes in neonatal intensive care settings.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Hafiz Muhammad Siddiq	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Najeeb Ullah	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Dilawaiz Kabir	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Sohail Sajid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Muzammil	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Rashid	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Rafia Anwer*	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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