

ORIGINAL ARTICLE

Comparison of Quantitative C-Reactive Protein with Blood Lactate Levels as Septic Markers in Neonatal Sepsis: A Cross-Sectional Study in a Tertiary Care Setting, Rawalpindi

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ABSTRACT

Objective: To find the relationship between the quantitative C-reactive protein and lactate as septic markers in neonatal sepsis.

Study Design: Cross-sectional study.

Place and Duration of Study: This study was conducted at the Neonatal Intensive Care Unit of Combined Military Hospital (CMH), Peshawar, Pakistan from March 2024 to August 2024.

Methods: Neonates (age 1 day–28 days) diagnosed with sepsis were enrolled. Patients were categorized into two groups: Group I (Survivors) and Group II (Non-survivors). Patient's demographic details, blood cultures, serum C-reactive protein, neutrophil counts, plasma Lactate, and outcome in terms of hospital discharge were assessed and recorded. Data analysis was done using SPSS version 26.

Results: Of the total 136 neonates, there were 76 (55.9%) male and 60 (44.1%) female. The overall mean age was 14.56 ± 7.82 days. Group I had 92 (67.6%) survivors and Group II had 44 (32.4%) non-survivors. The median value of Lactate (millimole/Liter) and C-reactive protein (milligram/deciliter) was 2.3 (IQR 1.4–5.3) and 2.1 (IQR 0.15–8.7), respectively. Survivor group (Group-I) had lower Lactate (1.9 millimole/Liter [1.2–9]) than the non-survivor group (4.5 millimole/Liter [2.15–7.4]), $P < 0.05$. The prevalence of multiple organ dysfunction was significantly higher in Group-II 82 (89.1%) than in Group-I 16 (36.4%). Based on organism causing infections among 136 neonatal sepsis cases, the incidence of Group B Streptococcus, Escherichia coli, Listeria monocytogenes, Coagulase-Negative Staphylococci, Staphylococcus aureus, Enterococcus species, Klebsiella species, and Pseudomonas aeruginosa was 58 (43%), 32 (24%), 9 (7%), 7 (5%), 4 (3%), 14 (10%), 10 (7%), and 2 (1%), respectively.

Conclusion: Lactate is superior to C-reactive protein in predicting prognosis and mortality in neonatal sepsis in the Neonatal intensive care unit. Elevated levels of lactate and C-reactive protein are primarily associated with increased severity of neonatal sepsis, including the progression to multiple organ dysfunction syndrome (MODS), septic shock, and poor clinical outcomes.

Keywords: 2-Hydroxypropanoic Acid, Biomarkers, C-Reactive Protein, Neonatal Sepsis.

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Introduction

Globally, Sepsis remains a prime cause for mortality among neonates admitted for septicemia in the Neonatal Intensive Care Unit (NICU).¹ Clinical diagnosis of septicemia in the neonate is difficult due to the presence of clinical symptoms suggestive of a local or systemic condition caused by adverse reactions in the presence of infectious agents or their toxicity, thus requiring laboratory assistance.²

Neonatal sepsis refers to systemic infection in neonates up to 28 days of age. Early-onset sepsis (EOS) can occur early, within the first 72 hours of life, or late, from the fourth day to the fourth week after birth, referred to as late-onset sepsis (LOS). The standard for the diagnosis of sepsis (bacterial infection) remain the blood cultures. The infection primarily comes from risk factors such as Maternal Fever, Maternal UTI, Premature rupture of the membrane, Prematurity, Indwelling catheters, IV Lines, and Ventilator tubing. The manifestation of clinical signs of neonatal sepsis are usually comes in later stages of infections that are non-specific.³ The delay in diagnosis and management of sepsis leads to mortality of neonates caused by circulatory collapse and multiple organ dysfunction (MODS).⁴ The growing rate of mortality of neonatal sepsis emphasized the requirement of monitoring sepsis in neonates by different biomarkers such as C-reactive protein, Procalcitonin (PCT), and Lactate.⁵

Neonatal sepsis was conservatively diagnosed based on clinical symptoms and signs, including tachycardia, fever, tachypnea, delayed capillary refill time (CRT), and further supported by positive blood culture findings. Lactate and C-reactive protein (CRP) were utilized as key biomarkers to aid in diagnosis and to assess the severity and potential outcomes of sepsis.⁶ Lactate levels have been used as biomarkers to assess muscle oxygen hypoxia and anaerobic metabolism, and stand out as commonly used indicators of organ dysfunction in sepsis.⁷ Findings suggest persistent hyperlactemia acts as a predictor of poor outcome in critically ill neonates with sepsis.⁸ However, sepsis-related factors may contribute to falsely elevated Lactate levels. C-reactive protein (CRP) acts as a marker of the intensity of the inflammatory response, stronger than being pathogen specific, but still an improvement in sepsis severity, and may provide a statistical advantage. CRP has shown a lower predictive power of mortality compared with other biomarkers in the neonatal population.⁹ Biomarkers for sepsis have the potential to facilitate early diagnosis and intervention. Serum biomarkers are essential for assessing prognosis in critically ill neonates during NICU admission or NICU stay. The current study aimed to compare C-reactive protein (CRP) and Lactate levels to evaluate the

intensity and severity of neonatal sepsis, as well as their potential to predict clinical outcomes.

Methods

This cross-sectional study investigated 136 neonatal sepsis cases in the Neonatal Intensive Care Unit (NICU) of Combined Military Hospital (CMH), Peshawar, Pakistan from March 2024 to August 2024 after taking approval from the Ethical Review Committee of the hospital vide letter serial no: 0083/2024 held on 26th February 2024. A non-probability consecutive sampling technique was used. 136 neonates or a sample size calculated by an anticipated effect size of 0.5, a power of 80%, a significance level of 0.05, and a 10% margin for loss or exclusions. Inclusion criteria was all those neonates of either gender aged 1 day to 28 days and diagnosed of sepsis (Fever ($\geq 38^{\circ}\text{C}$), Tachycardia (heart rate >160 beats per minute), Tachypnea (respiratory rate >60 breaths per minute), Delayed CRT (capillary refill >3 seconds), and Positive blood culture) were included. Survivors (Group I) and non-survivors (Group II) were two groups of neonates. Neonates with congenital malformations, perinatal asphyxia, neonates with primary surgical conditions, metabolic errors, and insufficient blood sampling were excluded. Serum C-reactive protein (CRP), Lactate, blood culture, neutrophil count, and white cell count (WBC) with different laboratory parameters were measured and recorded. The photometric lactate oxidase enzymatic method was used for measuring the concentration of plasma Lactate in millimoles per liter (mmol/L). Partial estimation of C-reactive protein (CRP) was performed using a CRP latex kit. The CRP latex reagent was calibrated to detect serum CRP levels equal to or greater than six micrograms per milliliter ($\mu\text{g/ml}$), which reflects the clear-cut agglutination to determine CRP levels in micrograms per milliliter ($\mu\text{g/ml}$), which was considered the minimum clinically significant concentration, multiplied by the highest dilution by 6. Early-onset sepsis (EOS) is defined as sepsis occurring within the first 72 hours of life, typically resulting from vertical transmission of pathogens from the mother before or during delivery. Late-onset sepsis (LOS) is defined as sepsis occurring after 72 hours of life, generally attributed to postnatal environmental exposure, often

involving nosocomial or community-acquired infections. Patient's demographic details, blood cultures, serum CRP, neutrophil counts, plasma Lactate, and outcome in terms of hospital discharge were assessed and recorded.

Data analysis was done using SPSS version 26. Mean \pm standard deviation was used to express the continuous variables such as age, lactate, and C-reactive protein. Categorical variables such as gender and MODs (the dysfunction of two or more organ systems in a neonate, including but not limited to respiratory failure (requiring mechanical ventilation), cardiovascular instability (requiring inotropes or fluid resuscitation), renal impairment (elevated creatinine or reduced urine output), hepatic dysfunction (elevated liver enzymes or bilirubin), or hematological abnormalities (such as thrombocytopenia or coagulopathy) were presented as frequency and percentages. Chi-square test was used for comparing the categorical variables between groups. Mann–Whitney U test and independent tests are used for comparing other parameters. All the descriptive statistics were done taking a 95% confidence interval, and P -value < 0.05 was considered statistically significant.

Results

The overall mean age was 14.56 ± 7.82 days. There were 76 (55.9%) male and 60 (44.1%) female neonates. Group I and II had 92 (67.6%) and 44 (32.4%) patients, respectively. The median value of Lactate (mmol/L) and CRP (mg/dl) was 2.3 (IQR 5.3-1.4) and 2.1 (IQR 8.7-0.15), respectively. Survivor group (Group-I) had lower Lactate (1.9 mmol/L [1.2–.9]) than the non-survivors group (4.5 mmol/L [2.15–7.4]). The prevalence of MODs was significantly higher in Group-II 82 (89.1%) than in Group-I 16 (36.4%). MODs was identified based on the presence of dysfunction in two or more organ systems, assessed using the following parameters: 1. Respiratory dysfunction: need for mechanical ventilation or $SpO_2 < 90\%$ on room air 2. Cardiovascular dysfunction: hypotension requiring fluid boluses or inotropic support 3. Renal dysfunction: serum creatinine > 1.5 mg/dL or urine output < 1 mL/kg/hr 4. Hepatic dysfunction: ALT or AST $> 2 \times$ normal or total bilirubin > 2 mg/dL 5. Hematologic dysfunction: platelet count

$< 100,000/\text{mm}^3$ or prolonged PT/aPTT. The level of Lactate in non-survivors was significantly higher (medium: 2.55 mmol/l, IQR: 7.5-2.1) compared to the survivors (medium: 1.95 mmol/l, IQR: 2.9–1.1), indicating a strong statistical difference between the two groups. Conversely, CRP levels, although slightly higher in non-survivors (medium: 2.6 mg/dL) compared to survivors (medium: 1.9 mg/dL), show no statistical difference ($P = 0.39$), suggesting that CRP may not reliably differentiate between survival outcomes in this cohort. Based on organism causing infections among 136 neonatal sepsis cases, the frequency of Group B Streptococcus, Escherichia coli (E. coli), Listeria monocytogenes, Coagulase-Negative Staphylococci, Staphylococcus aureus, Enterococcus species, Klebsiella species, and Pseudomonas aeruginosa was 58 (43%), 32 (24%), 9 (7%), 7 (5%), 4 (3%), 14 (10%), 10 (7%), and 2 (1%), respectively as demonstrated in Figure 1. Baseline details of neonates shown in Table 1. Table 2 compares the demographic details and laboratory parameters between Group I (survivors) and II (non-survivors). Chi-square test for categorical variables depicted in Table 3. The comparison of Biomarker Levels between Patients with and Without Multiple Organ Dysfunction Syndrome (MODS) has been shown in Table 4.

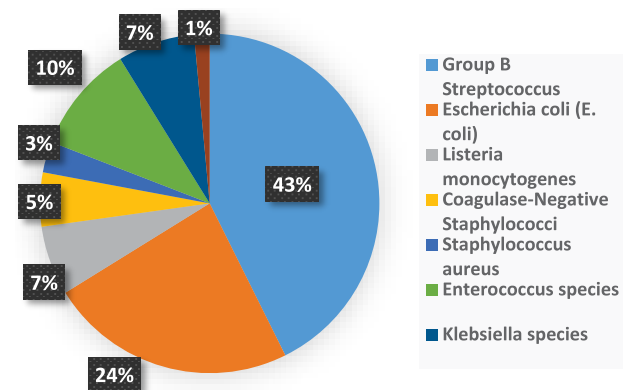


Fig.1: Frequency of different causative organisms in primary diagnoses of neonatal sepsis (N = 136)

Detail baseline characteristics of patients are shown in Table 1. Comparison of different variables between Group I and II are illustrated in Table 2.

Table 3 represents the comparison of lactate and CRP in patients with multiple organ dysfunction (MODs) and no MODs.

Table 1: Baseline characteristics of neonates (N=136)

Variables	N (%)
Mean Age (days)	14.56±7.82
Gender	
Male	76 (55.9%)
Female	60 (44.1%)
Multiple organ dysfunction (MODS)	
Presence	98 (72.1%)
Absence	38 (27.9%)
Type of Infection	
Early-onset sepsis (EOS)	78 (57.4%)
Late-onset sepsis (LOS)	58 (42.6%)
Lactate (median)	2.3 (IQR 5.3-1.4)
C-Reactive Protein (median)	2.1 (IQR 8.7-0.15)
Survivors	92 (67.6%)
Non-survivors	44 (32.4%)

Table 2: Comparison of demographic details and laboratory parameters between Group I (survivors) and II (non-survivors)

Parameters	Group-I (Survivors) N=92	Group-II (Non-survivors) N=44	P-value
Age (days)	16.42±8.67	12.7±6.97	0.1 (Independent Samples <i>t</i> -test)
Intensive Care Unit length of stay (days)	4 (6-2)	4 (6-2)	0.29
Hospital stay	9 (16-5.9)	8 (15.9-4.56)	0.19 (Mann–Whitney <i>U</i> test)
Lactate (median) (mmol/L)	1.95 (2.9-1.1)	2.55 (7.5-2.1)	<0.001 (Mann–Whitney <i>U</i> test)
C-Reactive Protein (median)(mg/dl)	1.9 (6.9-0.2)	2.6 (10.5-0.1)	0.39 (Mann–Whitney <i>U</i> test)
White Blood Cell (median) (×10 ⁹ /L)	10.4 (14.9-6.9)	11.9 (16.8-7.9)	0.09 (Mann–Whitney <i>U</i> test)
Neutrophils (%)	52 (71.9-42)	56 (73.8-36.5)	0.39 (Mann–Whitney <i>U</i> test)

Table 3: Chi-square statistics for categorical variables

Variables	Group-I (N=92)	Group-II (N=44)	χ^2 value	P-value
Gender (Male)	54 (58.7%)	22 (50%)	0.88	0.49
Multiple organ dysfunction (MODs)	57 (62%)	41 (93.2%)	13.42	<0.01

Table 4: Comparison of biomarker levels between patients with and without multiple organ dysfunction syndrome (MODS)

Biomarkers	MODs (N=98)	No MODs (N=38)
Lactate (mmol/L)	3.1 (5.9-1.7)	1.69 (2.6-0.8)
C-Reactive Protein (mg/dl)	2.9 (10.8-0.2)	0.6 (4.7-0.2)

Discussion

The present study mainly focused on the comparison of quantitative C-reactive protein with lactate in neonatal sepsis and found that elevated levels of lactate and CRP were primarily associated with increasing severity of multiple organ dysfunction—indicating more extensive or critical organ failure—in the context of neonatal sepsis. Sepsis refers to systemic and infectious inflammation, which often leads to circulatory failure and severe organ damage. Tissues, including bone, muscle, brain, and blood cells, synthesize Lactate.¹⁰ Neonatal sepsis accounts for a significant proportion of infant morbidity and mortality.¹¹ The use of prognostic biomarkers holds promise for increasing early detection and early intervention in cases of neonatal sepsis, and consequently improving patient outcomes. The findings of the study show that Lactate is superior to CRP in predicting mortality in the Neonatal Intensive Care Unit (NICU). These findings resembled the result of previous studies conducted by Tang et al. and Khadka et al., according to which neonatal sepsis (Early-onset and late-onset) is associated with distinct risk factors and predictive markers of bacteremia, such as serum procalcitonin (PCT), and C-reactive protein (CRP).^{12,13}

Chaudhuri SR et al. performed their studies in India and reported that Lactate clearance showed a significant relationship with the risk of mortality in patients with newborn sepsis.¹⁴ Therefore, lactate clearance can be used as a pathological marker to identify sepsis. Similarly, Sandal et al. performed their study in Turkey and reported that lactate clearance is a simple and rapid risk-stratification tool that is a potential biomarker for managing children's treatment efficacy in the pediatric intensive care unit.¹⁵

Jia et al. carried out their investigation on 90 sepsis cases to associate different biomarkers such as BLA, PCT, CRP, and severity of sepsis and reported that Blood lactate (BLA), procalcitonin (PCT), and C-reactive protein (CRP) levels can serve as an indicator to assess the severity of newborn sepsis and help to diagnose the patient's disease to a certain extent.¹⁶ Advanced PCT levels, especially, are associated with more severe infections and diagnosis of uniform

poor disease.

Siddiqui et al. conducted a study on the association of Serum Procalcitonin, C-reactive protein, and Lactate with Organ Failure and Outcomes in Critically Ill Children and reported that elevated plasma Lactate levels are associated with the development of all-cause multiple organ dysfunction syndrome (MODS) and poor prognosis in critical cases of children.¹⁷ Shabuj et al. carried out their comprehensive analysis on C-Reactive Protein (CRP) as a sole diagnostic marker for Neonatal Sepsis and found that CRP possesses moderate clinical accuracy for newborn sepsis, indicating its usefulness as an auxiliary biomarker in clinical diagnosis.¹⁸

The MOD onset is significantly associated with elevated Lactate and C-reactive protein, which leads to MODs and inadequate intravenous fluid perfusion among neonates.¹⁹ Our study findings suggest that blood lactate (BLA) and C-reactive protein (CRP) levels may serve as indicators for monitoring the severity and extent of neonatal sepsis for the prediction of affected neonates. In general, CRP remains low in healthy neonates. However, in the presence of infection or physical stress, CRP levels increase accordingly. For neonatal sepsis, changes in CRP levels precede changes in inflammation or peripheral white cell counts. In cases of routine infections, CRP levels tend to decrease quickly as the condition improves.²⁰

The present study shows that although C-reactive protein (CRP) levels are frequently elevated in infants with severe neonatal sepsis, a slight difference in CRP levels was observed between survivors and non-survivors. Hisamuddin et al. conducted their study on validation of CRP in the diagnosis of neonatal sepsis in Pakistan, reported that the level of C-reactive protein (CRP) correlated with the severity of newborn sepsis and can serve as a useful marker to predict the results and see the level of medical intervention.²¹

A Chinese study conducted by Sun et al. regarding the Clinical value of blood lactate in predicting the prognosis of neonatal sepsis observed that Elevated initial blood lactate is recognized as a highly sensitive indicator, in assessing the prognosis of neonatal sepsis.²² El-Ashry et al. reported that the mean platelet volume (MPV) and blood Lactate (BLA) are

simple, rapid, and cost-effective practical tests for the diagnosis of newborn bacteria.²³ The current evidence displays significantly elevated MPVs and BLA levels in newborns with bacteria compared to people with non-bacterial causes of sepsis. Therefore, in clinical practice, MPV and BLA can serve as early clinical indicators of sepsis, with BLA also appearing as a predictor of mortality.

Wang et al. conducted their study on 58 newborns with septic shock admitted to the Neonatal Intensive Care Unit to measure the prognostic value of combined Lactate Concentration and Lactate Clearance Rate in Neonatal Septic Shock and found that the combination of lactate concentration and lactate clearance rate provides optimal predictive value for assessing the prognosis of neonatal septic shock.²⁴

Conclusion

Lactate is superior to CRP in predicting prognosis and mortality in neonatal sepsis in the Neonatal Intensive Care Unit (NICU). A higher level of lactate and CRP is mainly associated with the severity of multiple organ dysfunction (MODS) and neonatal sepsis. Simultaneous assessment of blood lactate level (BLA) and C-reactive protein (CRP) levels can predict the severity and prognosis of patients with neonatal sepsis.

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Author Contributions

FR: Writing the original draft, proofreading, and approval for final submission

ARA: Conception and design of the work

NA: Revising, editing, and supervising for intellectual content

SI: Data acquisition, curation, and statistical analysis

MR: Manuscript writing for methodology design and investigation

AU: Validation of data, interpretation, and write-up of results

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