Status of C-Reactive Protein, Cellular and Clinical Parameters in Neonates with Risk of Sepsis in Tertiary Center of Mid-Western Nepal

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ABSTRACT

Introduction: Neonatal sepsis refers to a bloodstream infection which impacts infants under 28 days of age. Symptoms may encompass irregular vital signs and respiratory discomfort. C-reactive protein served as a vital diagnostic marker; nevertheless, its low sensitivity in early identification necessitates periodic assessments for accurate diagnosis and therapy monitoring. **Aims**: This study assessed C-reactive protein levels, cellular parameters, and clinical indicators in neonates predisposed to sepsis at a tertiary care facility. **Methods:** Hospital based prospective study, conducted on 150 neonates in paediatrics and biochemistry department of Nepalgunj Medical College from June 2024 to October 2024. C-reactive protein, whole blood count, platelets count, Immature/total neutrophil ratio were calculated along with the clinical findings suggesting sepsis were recorded. Major neonatal anomalies and prior antibiotic use led to exclusion. **Results:** Among 150 at-risk neonates, 65.3% were male, 46% were preterm and 45.3% had low birth weight. Elevated C-reactive protein (>6 mg/L) was found in 84.7%, with 68% showing tachypnea and 53.3% delayed capillary refill. Temperature variability (90%) and tachycardia (70%) were common. Laboratory findings showed high C-reactive protein (mean 16.8 mg/L), neutrophil predominance (61%), and raised Immature to total neutrophil ratio (0.25). Late-onset cases had more severe clinical and inflammatory profiles than early-onset cases. **Conclusion:** C-reactive protein, as a biochemical marker, was observed in the majority of neonates at risk of sepsis, while temperature variability, tachycardia and reduced urine output were common clinical features indicating systemic compromise.

Keywords: C-reactive protein, immature to total neutrophil ratio, neutrophilia, neonatal risk factors, tachypnoea, tachycardia, temperature variability

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INTRODUCTION

Neonatal sepsis is defined by the World Health Organization as a clinical syndrome marked by signs of infection in infants under 28 days old. Symptoms include temperature instability, respiratory distress, and changes in feeding behaviour. Diagnosis combines clinical assessment with laboratory evidence,like abnormal white blood cell counts.[1,2] Neonatal sepsis is classified into two groups based on when symptoms appear after birth: early-onset sepsis (EOS) and late-onset sepsis (LOS). C-reactive protein (CRP), along with clinical features like temperature variability and tachycardia, and hematological markers such as neutrophilia and elevated I/T ratio, enhances diagnostic accuracy and supports timely intervention in neonates at risk.[1,3,4] Neonatal sepsis commonly presents with respiratory signs such as grunting, nasal flaring, and cyanosis.[5-9] Neurological symptoms may include lethargy, seizures, or hypotonia, while gastrointestinal signs are also frequent. Skin findings such as petechiae or cellulitis may indicate systemic infection.[10-13] Studies done by Hisamuddin et al (2015)[11] and Jeon et al (2014)[12] had shown that CRP has moderate sensitivity and specificity and its diagnostic accuracy improves significantly when used alongside clinical and hematological parameters. The justification for this study lies in its focused evaluation of CRP in conjunction with clinical and cellular indicators to improve early detection of neonatal sepsis in a resource-limited setting. Such an integrated approach is essential for timely intervention and reducing neonatal morbidity and mortality.

METHODS

A Hospital based prospective study, conducted on 150 neonates at paediatrics and biochemistry department of Nepalgunj Medical College from June 2024 to October 2024, aimed at investigating neonates with risk of sepsis. Ethical approval was taken from institutional review committee before starting the study. Considering that the neonatal sepsis has a prevalence of 48%[9], the sample size was formulated. The present study employed an observational design to evaluate clinical, hematological, and biochemical parameters in neonates at risk of sepsis. The data collection was conducted prospectively over a defined period in a tertiary care neonatal unit. Neonates admitted with clinical suspicion of sepsis, either early-onset (≤72 hours of life) or late-onset (>72 hours), were enrolled consecutively after obtaining appropriate written consent from their parents. Baseline informations, including age, sex, gestational age and birth weight, were recorded. Detailed clinical assessments were performed by attending pediatricians, focusing on signs of systemic illness such as temperature instability, tachycardia, respiratory distress, perfusion status, and feeding behavior. Standardized criteria were used to identify symptoms such as tachypnea, cyanosis, grunting, seizures, and abdominal distension.[14] Neonates weighing <1000gm, those with any congenital anomalies and those who received antibiotics prior to the hospital admission were excluded from the study. Blood samples were collected aseptically for laboratory analysis at the time of clinical suspicion. Parameters evaluated included white blood cell count, absolute neutrophil count, platelet count, C-reactive protein (CRP) level and the immature-to-total neutrophil (I/T) ratio. Differential leukocyte counts were also performed. CBC (complete blood count) was estimated using Syxmex (6-part Hematology) analyzer and CRP was estimated using Mispa-I3 (Immunoturbidometric method). The neonates were subsequently stratified into early-onset and late-onset groups based on the timing of symptom onset, and comparative analysis of clinical and laboratory features. The data were tabulated and analyzed to determine the prevalence of key clinical signs, laboratory abnormalities, and their correlation with sepsis onset patterns.

Statistical analysis

The study used SPSS 22 for descriptive analysis and MS Excel for data management. Baseline, clinical, and laboratory data were collected and analyzed across these groups. Descriptive statistics, including means and standard deviations, were used to summarize continuous variables such as age, weight, and blood parameters, while categorical variables like symptoms and clinical signs were reported as percentages to identify trends and associations with sepsis severity and onset.

RESULTS

In the present study, the mean age of the neonates was 16.8 ± 8.5 days, with an average weight of 2.8 ± 0.6 kg. The majority of the participants were male, accounting for 65.3% of the total (Table I).

Characteristic	n	%
Mean Age (days)	16.8 ± 8.5	
Mean Weight (kg)	2.8 ± 0.6	
Male	98	65.30%
Female	52	34.67%

Table I: Baseline characteristics of the patients

Among the clinical and laboratory parameters observed in the 150 neonates at risk of sepsis, elevated C-reactive protein levels (>6 mg/L) were the most frequently recorded finding, presented in 84.7% of cases. This was followed by tachypnoea in 68% and delayed capillary refill, an indicator of poor perfusion was observed in 53.3% of neonates. Additionally, 46% were preterm and 45.3% had low birth weight (Table II).

Parameter	n	Percentage (%)
CRP > 6 mg/L	127	84.70%
Tachypnea	102	68.00%
Late Capillary Refill	80	53.30%
Gestational Age < 37 weeks	69	46.00%
Gestational Age ≥ 37 weeks	81	54.00%
Birth Weight < 2.5 kg	68	45.30%
Birth Weight ≥ 2.5 kg	82	54.70%

Table II: Risk Factors in At-Risk Neonates (n = 150)

The clinical features observed in the study population highlighted several common signs of neonatal distress or sepsis. Temperature variability was the most prevalent symptom, present in 90% of the neonates, representing potential systemic infection or impaired thermoregulation. Tachycardia was observed in 70% of the cases, reflecting a possible compensatory response to infection or hemodynamic instability. Reduced urine output was reported in 62.7% of neonates, suggesting compromised renal perfusion or dehydration. Feeding difficulty was present in 57.3%, which is a common early indicator of systemic illness in neonates. Grunting, a sign of respiratory distress, was noted in 52% of the neonates. Cyanosis, indicating hypoxia, was seen in 36% of cases. Less frequently, seizures were observed in 16% of the neonates, and abdominal distension was present in 28%, both of which may point to more severe systemic contribution or complications (Table III).

Clinical Features	n	Percentage (%)
Reduced Urine Output	94	62.70%
Temperature Variability	135	90.00%
Tachycardia	105	70.00%
Feeding Difficulty	86	57.30%
Grunting	78	52.00%
Cyanosis	54	36.00%
Seizures	24	16.00%
Abdominal Distension	42	28.00%

Table III: Clinical Features in At-Risk Neonates (n = 150)

The hematological parameters observed in the study provide insight into the inflammatory and immune status of the neonates. The mean white blood cell count was 12.3 ± 5.5 ×10³/µL, which falls within the normal range but may reflect a response to infection in some cases. The absolute neutrophil count averaged 7.3 ± 3.4 ×10³/µL, suggesting an active neutrophilic response, commonly seen in bacterial infections. Platelet count was 215 ± 78 ×10³/µL, representing generally adequate platelet levels, though variability suggests some neonates may have had thrombocytopenia. The mean C-reactive protein level was notably elevated at 16.8 ± 14.2 mg/L, reinforcing the presence of an inflammatory or infectious process in many neonates. The immature-to-total neutrophil (I/T) ratio was 0.25 ±0.15, which is higher than the normal threshold (typically <0.2), additional supporting a possible infectious etiology. Differential leukocyte counts showed a predominance of neutrophils (61% ± 16), with lymphocytes at 29% ± 12, monocytes at 5% ± 2, and eosinophils at 3% ± 1. This neutrophil predominance, along with elevated CRP and I/T ratio, strongly suggests an ongoing bacterial infection or systemic inflammatory response in the study population (Table IV).

Parameter	Mean±SD
WBC Count (×10³/µL)	12.3±5.5
ANC (×10³/µL)	7.3±3.4
Platelet Count (×10³/µL)	215±78
CRP (mg/L)	16.8±14.2
I/T Ratio	0.25±0.15
Neutrophils (%)	61±16
Lymphocytes (%)	29±12
Monocytes (%)	5±2
Eosinophils (%)	3±1

Table IV: Laboratory or cellular Parameters (Mean±SD) in At-Risk Neonates

The mean age at risk onset was 1.8 ± 0.7 days in the early-onset group and 17.2 ± 4.3 days in the late-onset group, clearly distinguishing the two categories based on timing. Late-onset cases exhibited more severe inflammatory responses, as reflected by higher CRP levels (36.4 ± 10.5 mg/L vs. 15.2 ± 5.8 mg/L), elevated WBC counts (19.0 ± 5.9 ×10³/µL vs. 12.5 ± 4.2 ×10³/µL), and increased ANC (11.2 ± 3.5 ×10³/µL vs. 6.8 ± 2.1 ×10³/µL). The I/T ratio was also markedly higher in the late-onset group (0.45 ± 0.12 vs. 0.25 ± 0.08), indicating a stronger immature neutrophil response. Late-onset cases had a higher percentage of neutrophils (72% vs. 58%) and a lower percentage of lymphocytes (18% vs. 32%), suggesting a more intense and possibly prolonged neutrophilic response. Platelet counts were lower in the late-onset group (160 ± 55 ×10³/µL) compared to the early-onset group (225 ± 65 ×10³/µL), which may reflect greater severity or progression of illness. Clinically, feeding difficulty (72% vs. 48%), cyanosis (60% vs. 30%), seizures (42% vs. 10%), and abdominal distension (56% vs. 22%) were all more common in the late-onset group, representing more pronounced systemic involvement (Table V).

Parameter	Early-Onset Risk (n = 65)	Late-Onset Risk (n = 45)
Age at Risk Onset (days)	1.8±0.7	17.2±4.3
CRP Level (mg/L)	15.2±5.8	36.4±10.5
WBC Count (x×10³/µL)	12.5±4.2	19.0±5.9
ANC (x×10³/µL)	6.8±2.1	11.2±3.5
Platelet Count (×10³/µL)	225±65	160±55
I/T Ratio	0.25±0.08	0.45±0.12
Neutrophils (%)	58±12	72±15
Lymphocytes (%)	32±10	18±7
Feeding Difficulty	48%	72%
Cyanosis	30%	60%
Seizures	10%	42%
Abdominal Distension	22%	56%

Table V: Risk Profile by Early vs. Late-Onset Sepsis Risk

DISCUSSION

In our study, the analysis of baseline characteristics of neonates at risk of sepsis showed mean age of 16.8 ± 8.5 days and weigh of 2.8 ± 0.6 kg. There was male domination over the female. Male domnation in neonates at risk of sepsis was also the significant finding in other studies done by Worku M et al, Patel U et al, Hisamuddin E et al, Jeon JH et al, the majority of neonates were presented within 10 days of birth and were of low birth weight.[9-12]

Temperature variability was seen in 90% of our neonates, making it the most common symptom. Both hypothermia and hyperthermia were common, reflecting the neonate's impaired thermoregulation during infection. This matches with findings by Ganesan et al (2016)[15], who also reported temperature instability as a frequent sign in septic neonates. Tachycardia occurred in 70% of our cases, compared to 67% reported by Ahmed et al (2005)[5], showing a similar trend. Reduced urine output (62.7%) and feeding difficulty (57.3%) were also common in our study, which was in line with the 60–65% rates observed in previous studies by Yin et al (2024)[16] and Brown et al (2019).[17] In our study, 68.00% of neonates presented with tachypnea, highlighting it as one of the important risk factor of sepsis. The prevalence was slightly higher than reported in other studies, where incidence ranged from 52.3% - 65.0% among septic neonates.[13,15,16] Symptoms like grunting (52%), cyanosis (36%), seizures (16%) and abdominal distension (28%) were also reported, with higher rates of severe symptoms like seizures and abdominal distension in late-onset cases. This was similar to the work of Selimovic et al (2010)[6], who found these signs were more frequent in severe or late-presenting cases. Reduced urine output and feeding difficulties, noted in over half of this current cohort, were indicative of systemic involvement and were consistent with other studies highlighting these as early manifestations of sepsis. Among the laboratory parameters studied, CRP was elevated (>6 mg/L) in 84.7% of our neonates, with a mean value of 16.8 mg/L. This rate was higher than the 69–77% sensitivity and specificity

reported by Jeon et al (2014) and Hisamuddin et al (2015), but could be explained by our higher CRP cut-off, use of prospective protocols, and a larger share of late-onset cases.[15] The mean white blood cell (WBC) count was 12.3 $\times 10^3/\mu L$, which falls within the normal range but slightly higher than the baseline reported by Tappero and Johnson (2010), who found mean counts of around 10 $\times 10^3/\mu L$. Our mean absolute neutrophil count (ANC) was 7.3 $\times 10^3/\mu L$, again higher than in healthy controls from other studies.[16] The immature-to-total neutrophil (I/T) ratio averaged 0.25, exceeding the normal threshold (<0.2). This finding is similar to the 0.22–0.30 range seen in other reports of septic neonates (Benitz et al, 1998).[13] Platelet counts were generally normal (mean 215 $\times 10^3/\mu L$), but late-onset cases showed a drop (160 $\times 10^3/\mu L$), supporting published evidence that thrombocytopenia is linked to advanced infection. Differential leukocyte counts showed a predominance of neutrophils (61% ± 16), with lymphocytes at 29% ± 12, monocytes at 5% ± 2, and eosinophils at 3% ± 1. This neutrophil predominance, along with elevated CRP and I/T ratio, strongly suggests an ongoing bacterial infection or systemic inflammatory response in the study population (Table IV). These values were in line with those reported by other studies, which had demonstrated the utility of these hematological markers in diagnosing neonatal sepsis.[15-17]

Late-onset sepsis (LOS) cases showed higher CRP levels (mean 36.4 mg/L vs. 15.2 mg/L in early-onset), WBC counts (19.0 $\times 10^3/\mu L$ vs. 12.5 $\times 10^3/\mu L$) and ANC (11.2 $\times 10^3/\mu L$ vs. 6.8 $\times 10^3/\mu L$). The I/T ratio and neutrophil percentage were also higher, while platelet counts were lower in LOS, reflecting a stronger inflammatory response. These patterns were nearly identical to those described by Brown et al (2019) and Yin et al (2024), who both found association of LOS with higher CRP, higher neutrophil response, and lower platelets.[13,14] Clinically, feeding difficulty (72% vs. 48%), cyanosis (60% vs. 30%), seizures (42% vs. 10%), and abdominal distension (56% vs. 22%) were all more common in LOS, echoing previous findings (Selimovic et al 2010; Benitz et al 1998) that late-onset sepsis is often more severe.[15] Our study supported the use of CRP as a helpful but imperfect tool for early sepsis detection. In our population, CRP alone was positive in over 80% of suspected cases, while other studies (Jeon et al 2014[12]; Hisamuddin et al 2015[11]) found sensitivity and specificity between 69–77%. The positive predictive value and specificity in those studies ranged from 53% to 80%. The higher rate in our data may be due to case selection or the higher threshold for CRP positivity (>6 mg/L). Other studies suggested combining CRP with other markers- such as I/T ratio, WBC, and clinical features-increases diagnostic accuracy. Our findings supported this combined approach, as most neonates with high CRP also had abnormal hematological and clinical parameters. Studies like Brown et al (2019) suggested that serial (repeated) CRP measurements may help identify trends and track severity, which could be useful in our setting for late-onset cases.[17] Our current results also align with the observation by Jeon et al (2014)[12] that positive maternal CRP predicts risk of early -onset sepsis, although we focused only on neonatal CRP. In our setting, neonatal CRP was highly informative, suggesting that routine neonatal testing may be more practical in resource-limited environments.

LIMITATIONS

One limitation of this study is we did not use Blood culture, which could have been helpful in validation. Additionally, the sample size may not adequately represent all demographic groups, possibly limiting the generalizability of the findings.

CONCLUSION

The study has concluded that risk of sepsis were higher in male babies. Common clinical features included tachycardia, temperature instability, and reduced urine output, while over 80% showed elevated CRP levels. Hematological findings has shown slightly higher WBC counts, increased I/T ratios, and declining platelet levels, indicating systemic inflammation.

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