e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com

International Journal of Pharmaceutical Quality Assurance 2025; 16(10); 297-301

Original Research Article

Association of Cord Blood Neutrophil-to-Lymphocyte Ratio with Placental Inflammation and Neonatal Outcomes

Nikita Agrawal[1], Yogesh Singh[2], Deepak Kumar Pareek[3]

[1]Assistant Professor, Department of Pathology, Government Medical College, Hanumangarh.
[2]Associate Professor, Department of Physiology, Government Medical College, Hanumangarh.
[3]Assistant Professor, Department of Paediatrics, Government Medical College, Hanumangarh.

Received: 25-07-2025 / Revised: 23-08-2025 / Accepted: 26-09-2025
Corresponding Author: Dr. Deepak Kumar Pareek
Conflict of interest: Nil

Abstract:

Background: The neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple and reliable marker of systemic inflammation. In the perinatal setting, cord blood NLR may reflect intrauterine inflammatory status and serve as an early predictor of adverse neonatal outcomes. Placental inflammation, including chorioamnionitis and funisitis, is a well-established contributor to fetal distress and neonatal morbidity. However, data correlating cord blood NLR with placental pathology and neonatal outcomes remain limited.

Objectives: To evaluate the association between cord blood NLR and histopathological evidence of placental inflammation, and to determine its relationship with early neonatal outcomes.

Methods: This cross-sectional, hospital-based study included term and late-preterm deliveries meeting eligibility criteria. Umbilical cord blood samples were collected immediately after birth for complete blood count analysis, and NLR was calculated. Placentas were subjected to standardized histopathological examination for maternal and fetal inflammatory lesions. Neonatal outcomes—including APGAR scores, respiratory distress, NICU admission, birth weight, early-onset sepsis (EOS) evaluation, and need for antibiotic therapy—were recorded. Statistical analysis was performed to assess associations between NLR, placental inflammation grades, and neonatal outcomes.

Results: Mean cord blood NLR was significantly higher in neonates whose placentas demonstrated maternal and/or fetal inflammatory responses compared to those without inflammation. Elevated NLR showed a strong positive correlation with increasing severity of placental inflammation. Neonates with high NLR also had significantly lower APGAR scores, higher NICU admissions, and increased need for sepsis evaluation and antibiotics. Receiver operating characteristic (ROC) analysis identified an optimal NLR cut-off for predicting placental inflammation and adverse neonatal outcomes.

Conclusion: Cord blood NLR is a simple, cost-effective biomarker that correlates strongly with placental inflammation and early neonatal morbidity. Incorporating NLR into routine perinatal evaluation may enhance early identification of at-risk neonates, enabling timely intervention and improved clinical outcomes. Further large-scale prospective studies are recommended to validate these findings.

Keywords: Cord Blood, Neutrophil-to-Lymphocyte Ratio, Placental Inflammation, Chorioamnionitis, Neonatal Outcomes.

Introduction

Inflammation within the intrauterine environment plays a pivotal role in determining perinatal morbidity and mortality. Placental inflammatory lesions—particularly chorioamnionitis and funisitis—are strongly associated with fetal inflammatory response syndrome, preterm birth, neonatal sepsis, and long-term neurodevelopmental impairment [1]. Early recognition of fetuses and newborns exposed to such inflammatory insults is therefore critical for timely clinical intervention. The neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, has emerged as a stable and cost-effective indicator of systemic inflammation across multiple clinical settings [2]. In fetal and neonatal physiology, the placenta acts as an essential immunological interface. Any infectious or sterile inflammatory trigger results in activation of the maternal–fetal inflammatory axis, increased neutrophil recruitment, elevated cytokine release, and altered lymphocyte balance [3]. These shifts are reflected in cord blood leukocyte profiles, making cord blood NLR a potentially useful surrogate biomarker for intrauterine inflammation. Previous studies have reported associations between elevated NLR and neonatal complications such as sepsis, respiratory distress, and perinatal

asphyxia [4,5]. However, evidence directly correlating cord blood NLR with histologically confirmed placental inflammation—particularly in term and late-preterm neonates—remains insufficient.

While placental histopathology is considered the gold standard for diagnosing intrauterine inflammatory lesions [6], it is resource-intensive, time-consuming, and not immediately available to clinicians managing the newborn in the first hours of life. Consequently, there is a need for a rapid, accessible indicator that can bridge the gap between delivery-room assessment and definitive placental diagnosis. Cord blood NLR, being inexpensive, readily available, and physiologically meaningful, fits this requirement well.

Existing literature also suggests that cord blood inflammatory markers show meaningful associations with neonatal outcomes including APGAR score, NICU admission, birth weight, early-onset sepsis (EOS) evaluation, and antibiotic requirement [7,8]. Yet many of these markers—such as CRP, IL-6, and procalcitonin—may be costly or lack availability in low-resource settings. Therefore, exploring the diagnostic and prognostic potential of cord blood NLR could offer significant advantages, particularly in public-sector hospitals.

Given this background, the present study aims to evaluate the association between cord blood NLR and histopathological evidence of placental inflammation, and to determine its relationship with early neonatal outcomes. Establishing cord blood NLR as an early biomarker may strengthen neonatal risk stratification and support cost-effective, evidence-based perinatal care.

Material & Methodology

Study Design and Setting: This study was designed as a hospital-based, observational, cross-sectional study conducted in the Department of Pathology. Ethical clearance was obtained from the Institutional Ethics Committee prior to commencement of the study.

Study Population: All pregnant women delivering in the hospital during the study period were screened for eligibility. Term and late-preterm neonates (≥34 week's gestation) were included.

Mothers with pre-existing systemic infections, autoimmune disorders, hematological diseases, severe pregnancy complications (e.g., eclampsia), prolonged corticosteroid therapy, or incomplete clinical records were excluded. Neonates with congenital anomalies or hemolytic diseases were also excluded.

Sample Size: A total sample size of 120 mother–neonate pairs was included based on the availability of cases during the study period and prevalence of placental inflammatory lesions reported in previous studies. This sample size was considered adequate to detect clinically meaningful differences in cord blood NLR between groups with and without placental inflammation, at a 95% confidence level and 80% statistical power.

Data Collection Procedure: Immediately after delivery, umbilical cord blood (2–3 mL) was collected from the umbilical vein using sterile technique before placental separation. Samples were transferred into EDTA vials and processed within one hour. A complete blood count (CBC) was performed on an automated hematology analyzer, and the neutrophil-to-lymphocyte ratio (NLR) was calculated from the absolute neutrophil and lymphocyte counts. Maternal demographic and obstetric data—including age, parity, gestational age, mode of delivery, presence of maternal fever, premature rupture of membranes (PROM), and meconium-stained liquor—were recorded using a structured proforma.

Placental Examination: Following delivery, placentas were collected and fixed in 10% buffered formalin. Standardized gross and microscopic examination was performed by a certified histopathologist using the Amsterdam Placental Workshop Group criteria for maternal and fetal inflammatory responses. Inflammation was categorized as:

- No inflammation
- Maternal inflammatory response (chorioamnionitis) – graded I–III
- Fetal inflammatory response (funisitis, chorionic vasculitis)

Assessment of Neonatal Outcomes: Neonatal parameters assessed included birth weight, APGAR scores (1 and 5 minutes), respiratory distress, need for resuscitation, NICU admission, early-onset sepsis (EOS) evaluation, duration of hospital stay, and requirement of antibiotics.

Statistical Analysis: Data were analyzed using SPSS version XX. Continuous variables were expressed as mean ± SD and compared using Student's t-test or ANOVA. Categorical variables were compared using chi-square or Fisher's exact test. Correlation between NLR and placental inflammation severity was analyzed using Pearson or Spearman coefficients. Receiver operating characteristic (ROC) curves were used to determine the optimal NLR cut-off for predicting placental inflammation and adverse neonatal outcomes. A p-value <0.05 was considered statistically significant.

Table 1: Distribution of Placental Inflammatory Lesions (n = 120)

Placental Lesion	Histopathological Definition (Amsterdam Criteria)	N (%)
No inflammation	No Neutrophilic infiltrate in membranes /Cord	46 (38.3%)
Acute Maternal Inflammatory Response (MIR)	Chorioamnionitis	---
Stage 1 (Early)	Subchorionic PMN infiltrate	24 (20.00%)
Stage 2(Intermediate)	PMNs in chorion /amnion	18 (15.0%)
Stage 3 (Advanced0	Necrosis of amnion (Amnionitis)	6 (5.0%)
Acute Fetal Inflammatory Response (FIR)	Funisitis/chorionic Vasculitis	---
Stage 1	PMNs in Umbilical Vein	12 (10.0%)
Stage 2	PMNs in Umbilical arteries	8 (6.7%)
Stage 3	Necrotizing funistis	6 (5.0%)

Pathology-specific highlight:

- Total MIR = **48 cases (40%)**
- Total FIR = **26 cases (21.7%)**

Table 2: Cord Blood Hematological Indices in Relation to Placental Inflammation

Inflammation Category	N (%)	Neutrophils ($X10^9$/L) Mean ± SD	Lymphocytes (X 10^9/L) Mean ± SD	NLR Mean ± SD
No Inflammation	46 (38.3%)	6.1 ± 1.0	4.4 ± 0.8	1.38 ± 0.29
MIR- Stage 1	24 (20.0%)	7.2 ± 1.2	3.9 ± 0.7	1.84 v 0.41
MIR- Stage 2& 3	24 (20.0%)	8.0 ± 1.4	3.5 ± 0.6	2.28 ± 0.50
FIR-Stage 1-3 (Funisitis)	26 (21.7%)	9.1 ± 1.6	3.2 ± 0.7	2.94 ± 0.61

Statistical Analysis:

- ANOVA across four groups: **p < 0.001**
- Increasing NLR corresponds directly with **severity of inflammatory stage**.

Pathology emphasis: Higher MIR/FIR stages → progressively higher NLR.

Table 3: Clinicopathological Correlation of Cord Blood NLR with Neonatal Outcomes

Neonatal Outcome	NLR<2.0 (N=64)	NLR>2.0 (N=56)	p- value
Low APGAR (1 min <7)	6 (9.3 %)	18 (32.1%)	0.001
Low APGAR (5 min <7)	2 93.1%)	10 (17.9%)	0.011
Neonatal Respiratory Distress	7 (10.9%)	19 (33.9%)	0.004
NICU Admission	8 (12.5%)	24 (42.9%)	<0.001
Early – Onset sepsis Evaluation	12 (18.7%)	30 (53.6 %)	<0.001
Antibiotic requirement	10 (15.6%)	28 (50.0%)	<0.001
Mean Hospital stay (Days)	2.7 ± 1.1	4.5 ± 1.3	<0.001

High NLR aligns strongly with FIR (Funisitis), which is known to predict neonatal sepsis-like presentations.

Discussion

The present study evaluated the association between cord blood neutrophil-to-lymphocyte ratio (NLR), histopathologically confirmed placental inflammation, and early neonatal outcomes. The findings demonstrate a clear, stepwise rise in NLR corresponding to increasing severity of inflammatory lesions, particularly fetal inflammatory response (FIR). These observations underscore the significant role of cord blood NLR as a surrogate biomarker for intrauterine inflammatory processes. In our study, MIR and FIR together constituted 61.7% of all placental samples, consistent with reported global prevalence rates of 40–70% in symptomatic or high-risk pregnancies [9]. Acute maternal inflammatory response (MIR), especially chorioamnionitis, is classically attributed to ascending bacterial infection and is frequently observed in term and preterm labor [10]. The Amsterdam Placental Workshop Group Criteria utilized in this study remain the standard for grading inflammatory lesions and distinguishing maternal from fetal responses [6]. A significant finding was the progressive increase in mean NLR from 1.38 in non-inflamed placentas to 2.94 in FIR cases, demonstrating a strong correlation between NLR and histological severity. Similar trends have been documented in previous studies where cord

blood NLR rose in neonates exposed to intrauterine infection and funisitis [4, 11]. The pathophysiological basis lies in the cytokine-driven recruitment of neutrophils and suppression or redistribution of lymphocytes following fetal exposure to inflammatory mediators such as IL-6 and TNF-α (12). Funisitis, a hallmark of fetal immune activation, has been strongly associated with elevated fetal neutrophil counts and systemic inflammatory response syndrome at birth [1].

The significant elevation of NLR in FIR cases supports its usefulness as an early biomarker of fetal inflammatory involvement. This is particularly important because FIR, even in the absence of maternal symptoms, predicts early-onset neonatal sepsis, respiratory morbidity, and long-term neurodevelopmental impairment (13). While placental histopathology remains the gold standard for diagnosing inflammatory lesions, the time required for formalin fixation and microscopic evaluation limits its usefulness in immediate neonatal triage. Therefore, cord blood NLR offers a practical, rapid adjunct to pathological evaluation.

The clinical relevance of elevated NLR is further highlighted by the strong associations between high NLR (≥2.0) and adverse neonatal outcomes, including low APGAR scores, respiratory distress, NICU admission, and need for early-onset sepsis evaluation. These findings mirror previous studies in which NLR was significantly higher in neonates who developed sepsis or required NICU care [14,15]. The rate of NICU admission in the high-NLR group (42.9%) was comparable to other studies reporting 30–50% NICU admission in neonates with cord blood markers suggestive of intrauterine inflammatory exposure [16].

Low APGAR scores in neonates with elevated NLR can be explained by impaired fetal oxygenation secondary to placental inflammation, funisitis-associated cord compromise, and fetal hypoxic stress. Respiratory distress, observed more frequently in the high-NLR group, also reflects the lung's heightened sensitivity to inflammatory cytokines, consistent with the fetal inflammatory response syndrome spectrum [17].

The association between high NLR and increased duration of hospital stay further reinforces its prognostic utility. Neonates with high NLR were more likely to undergo sepsis evaluations and receive empirical antibiotics, which aligns with findings from studies where NLR showed moderate predictive value for early-onset neonatal sepsis [8]. While blood cultures remain the diagnostic gold standard, their limitations—delayed results, false negatives, sampling constraints—necessitate adjunctive biomarkers like NLR for early decision-making. From a pathology perspective, the significant correlation between FIR stages and NLR underscores the importance of integrating cord blood findings with placental histology. FIR, especially necrotizing funisitis (stage 3), corresponds to severe fetal systemic inflammation and is strongly linked with adverse clinical outcomes [18]. Our findings further validate FIR as a critical pathological endpoint and suggest that cord blood NLR may help anticipate FIR even before microscopic examination is completed.

The strengths of this study include standardized histopathological grading using internationally accepted criteria and the use of objective hematological parameters. However, certain limitations must be acknowledged. The cross-sectional design precludes causal inference, and cytokine profiling or microbial cultures were not performed, which could have added mechanistic insight. Additionally, gestational age stratification and long-term neurodevelopmental follow-up were beyond the study scope but should be explored in future research.

Conclusion

The study demonstrates that cord blood NLR is significantly associated with both the presence and severity of placental inflammatory lesions, particularly FIR, and that elevated NLR predicts adverse neonatal outcomes. As a rapid, cost-effective biomarker, cord blood NLR can complement histopathological evaluation and may serve as an important tool for early neonatal risk stratification in settings where immediate placental pathology is not available.

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