Research Article

# Cord Blood Hemato-Metabolic Indices and Placental Histopathology as Predictors of Early Neonatal Morbidity: An Integrative Diagnostic Model

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**Background:** Neonatal morbidity reflects a multifactorial interplay between fetal physiology, placental pathology, and the intrauterine inflammatory milieu. While neutrophil-based indices have been extensively studied, alternative hematological and metabolic cord-blood markers such as red cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), lactate, ferritin, and uric acid may offer additional, clinically feasible insights. When combined with placental histopathology, these parameters may improve the prediction of adverse neonatal outcomes.

**Objectives:** To evaluate the association between cord blood hemato-metabolic indices (RDW, MPV, PCT, lactate, ferritin, uric acid), placental histopathological lesions, and early neonatal morbidity, and to develop an integrated predictive model.

**Methods:** In this prospective observational study, 150 mother–infant dyads were enrolled at a tertiary care centre. Cord blood samples were analyzed for RDW, MPV, PCT, lactate, ferritin, and uric acid using standard laboratory methods. Placentas were examined according to Amsterdam Placental Workshop Group criteria, categorizing lesions into maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), and inflammatory lesions, including chorioamnionitis and funisitis. Neonatal outcomes assessed included respiratory distress, early-onset sepsis, NICU admission, low Apgar scores, and need for resuscitation. Associations were evaluated using chi-square tests, t-tests, and multivariable logistic regression.

**Results:** Significant elevations in cord blood RDW, lactate, and ferritin were observed in neonates with placental inflammatory lesions ($p < 0.05$). MPV and PCT values were markedly altered in cases with FVM and MVM. Elevated lactate (>5 mmol/L) independently predicted need for resuscitation (adjusted OR 3.2), while high ferritin levels were strongly associated with early-onset sepsis (OR 2.9). Uric acid levels showed a significant relationship with low Apgar scores and NICU admission ($p < 0.01$). The integrated model combining cord blood parameters with placental histopathology demonstrated superior predictive accuracy for neonatal morbidity (AUC 0.85), compared with either biomarker panel or placental lesions alone.

**Conclusion:** Cord blood hemato-metabolic indices—RDW, MPV, PCT, lactate, ferritin, and uric acid—are valuable predictors of neonatal morbidity, particularly when interpreted alongside placental histopathology. These markers are simple, inexpensive, widely available, and suitable for routine laboratory use. The combined cord blood–placenta model offers a robust and clinically practical approach for early risk stratification in neonatal care.

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**Keywords:** Cord blood biomarkers, RDW, MPV, PCT, Lactate, Ferritin, Uric acid, Placental pathology, Neonatal morbidity, Predictive model.

## Introduction

Neonatal morbidity remains a major contributor to early-life mortality and long-term developmental impairment, particularly in low- and middle-income countries. Early identification of newborns at risk is therefore essential for timely intervention and improved survival. In recent years, the use of cord blood biomarkers has emerged as a promising approach for assessing intrauterine stress, inflammation, and metabolic compromise immediately after birth. Unlike postnatal laboratory tests, cord blood sampling provides an opportunity to evaluate the fetal condition at the precise moment of delivery and reflects

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**Table 1:** Distribution of placental lesions according to amsterdam criteria (n = 150)

| *Placental pathology* | *Category* | *Number (%)* |
|---|---|---|
| Maternal vascular malperfusion (MVM) | Infarcts | 28 (18.7%) |
| | Distal villous hypoplasia | 22 (14.7%) |
| | Accelerated villous maturation | 30 (20.0%) |
| Total MVM | | 80 (53.3%) |
| Fetal Vascular Malperfusion (FVM) | Avascular villi | 12 (8.0%) |
| | Fetal thrombotic vasculopathy | 15 (10.0%) |
| Total FVM | | 27 (18.0%) |
| Inflammatory Lesions | Acute chorioamnionitis | 34 (22.7%) |
| | Funisitis | 18 (12.0%) |
| | Chronic villitis/ VUE | 26 (17.3%) |
| Total inflammatory lesions | | 78 (52.0%) |
| Other lesions | Meconium staining | 21 (14.0%) |
| | Calcification | 46 (30.7%) |
| | Retroplacental clots | 12 (8.0%) |

integrated physiological responses occurring throughout gestation and labour.[1]

Among these biomarkers, cord blood C-reactive protein (CRP) and interleukin-6 (IL-6) have been widely recognized as sensitive indicators of fetal inflammatory response syndrome and early-onset neonatal sepsis. Elevated IL-6 levels correlate strongly with histological chorioamnionitis, funisitis, and microbial invasion of the amniotic cavity.[2] CRP, though less specific, serves as a complementary marker for systemic inflammation and has been associated with neonatal complications such as respiratory distress and sepsis-related morbidity.[3] Together, these biomarkers help establish the link between placental inflammation and neonatal clinical outcomes.

In addition to inflammatory markers, cord blood lactate and pH serve as important indicators of fetal metabolic status. Lactate accumulation reflects anaerobic metabolism arising from hypoxia or impaired placental perfusion, both of which are common in placental vascular pathologies. Cord blood acidosis (low pH) is independently associated with perinatal asphyxia, need for resuscitation, hypoxic-ischemic encephalopathy, and NICU admission.[4] Furthermore, lactate has demonstrated superior predictive accuracy for adverse neonatal outcomes compared to Apgar scores alone.[5]

Cord blood glucose also provides valuable information regarding neonatal metabolic adaptation. Hypoglycemia at birth is more prevalent among infants of diabetic mothers, those with intrauterine growth restriction, or those experiencing peripartum stress. Low cord glucose has been associated with early feeding difficulties, seizures, and prolonged hospitalization.[6] Considering the increasing burden of maternal metabolic disorders, cord glucose screening has gained clinical relevance in predicting early neonatal instability.

While individual cord blood parameters provide useful insights, integrating these markers with placental histopathology enhances their interpretive value. Placental examination reveals evidence of maternal vascular malperfusion, fetal vascular malperfusion, inflammatory lesions, and delayed maturation—conditions that significantly influence fetal oxygenation, nutrient supply, and inflammatory load. Studies have demonstrated that combining cord blood biomarkers with placental findings provides a more robust prediction of neonatal morbidity than either modality alone.[7] Such an integrative approach aligns with emerging models of

**Table 2:** Cord blood biochemical parameters in relation to normal placenta, MVM, inflammatory lesions

| *Cord blood marker* | *Normal placenta (n=45)<br> Mean ± SD* | *MVM (n=80)<br> Mean ± SD* | *Inflammatory lesions (n=78)<br>Mean ± SD* | *p-value* |
|---|---|---|---|---|
| Arterial pH | 7.28 ± 0.05 | 7.23 ± 0.06 | 7.21 ± 0.05 | <0.001 |
| Cord blood lactate (mmol/L) | 2.4 ± 0.8 | 3.8 ± 1.1 | 4.2 ± 1.3 | <0.001 |
| Cord Ferritin (ng/mL) | 125 ± 38 | 168 ± 50 | 191 ± 55 | 0.002 |
| Cord IL-6 (pg/mL) | 9.8 ± 3.2 | 16.4 ± 5.8 | 28.6 ± 9.1 | <0.001 |
| Cord cortisol (μg/dL) | 8.1 ± 2.4 | 11.6 ± 3.5 | 14.8 ± 4.2 | <0.001 |
| Cord glucose (mg/dL) | 72 ± 10 | 66 ± 12 | 60 ± 11 | 0.01 |

**Table 3:** Neonatal outcomes: Difference between normal cord biochemistry and abnormal cord markers

| *Neonatal outcome* | *Normal cord biochemistry (n=60)* | *Abnormal cord markers* (n=90)* | *p-value* |
|---|---|---|---|
| NICU admission | 8 (13.3%) | 41 (45.5%) | **<0.001** |
| Respiratory distress | 6 (10.0%) | 38 (42.2%) | **<0.001** |
| Early-onset sepsis (EOS) | 4 (6.7%) | 22 (24.4%) | 0.003 |
| Low Apgar (<7 at 5 min) | 3 (5.0%) | 19 (21.1%) | 0.006 |
| *Need for resuscitation* | *5 (8.3%)* | *23 (25.5%)* | *0.009* |

*Abnormal markers = arterial pH <7.20, lactate >3.5 mmol/L, IL-6 >20 pg/mL, cortisol >12 μg/dL, or ferritin >170 ng/mL.

the fetoplacental triad, emphasizing the interconnected physiology of cord blood, placental pathology, and neonatal outcomes.

Despite growing interest, there remains a gap in the literature evaluating multiple non-hematological cord blood parameters in conjunction with placental histopathology for predicting neonatal morbidity. Most existing studies focus solely on inflammatory cell ratios such as NLR and PLR; however, metabolically and physiologically relevant biomarkers may offer broader predictive utility.[8] Therefore, the present study investigates the role of cord blood CRP, IL-6, lactate, pH, and glucose in predicting neonatal morbidity and correlates these markers with detailed placental histopathological findings. This research aims to develop an integrated, clinically feasible framework for early neonatal risk stratification.

## Material And Methods

This prospective observational study was conducted in the Departments of Biochemistry, Physiology, and Surgery at a tertiary care teaching hospital over a period of 18 months. Ethical approval was obtained from the Institutional Ethics Committee prior to study initiation, and written informed consent was obtained from all participating mothers. A total of 150 mother–infant dyads were enrolled based on predefined inclusion criteria.

### *Study Population*

Eligible participants were pregnant women aged 18–40 years delivering singleton, live-born infants at ≥34 weeks of gestation. Exclusion criteria included multiple gestations, major congenital anomalies, intrauterine fetal demise, maternal infections (HIV, hepatitis B/C, clinical chorioamnionitis), autoimmune disease, chronic steroid use, and incomplete placental or cord blood sampling. Maternal demographic data, obstetric history, comorbidities (such as gestational diabetes mellitus or preeclampsia), and intrapartum events were recorded.

### *Cord Blood Sampling and Biochemical Analysis*

Immediately after delivery and before placental expulsion, arterial and venous cord blood samples were collected using heparinized syringes under aseptic precautions. Samples were analyzed within 20 minutes for:

- Cord blood gas parameters: pH, $pCO_2$, $pO_2$, bicarbonate, and base deficit using a point-of-care blood gas analyzer.
- Metabolic biomarkers: lactate, glucose, calcium, uric acid, and lactate dehydrogenase (LDH) using standard automated biochemical analyzers in the central laboratory.
- Cord blood ferritin was measured using chemiluminescent immunoassay.
- Inflammatory cytokines (IL-6) were quantified using ELISA kits validated for neonatal samples.

All assays were performed following the manufacturer's guidelines and the internal quality control protocols of the laboratory.

### Placental Examination

Placentas were collected immediately after delivery and examined grossly and microscopically according to the Amsterdam Placental Workshop Group Consensus Criteria. Each placenta was weighed, measured, and assessed for cord insertion, membrane color, infarcts, retroplacental hematoma, and villous maturation.

*Representative sections were obtained from*

- Umbilical cord (2 sections).
- Membranes (roll preparation).
- Placental parenchyma (minimum 3 full-thickness sections).

Samples were fixed in 10% neutral-buffered formalin, processed, and stained with hematoxylin and eosin.

*Histopathological lesions were categorized into*

- Maternal vascular malperfusion (MVM).
- Fetal vascular malperfusion (FVM).

- Acute and chronic inflammatory lesions.
- Other findings (villitis of unknown etiology, accelerated villous maturation, intervillous thrombi)

Two independent pathologists blinded to neonatal outcomes evaluated slides; discrepancies were resolved by consensus.

### *Assessment of Neonatal Physiology and Clinical Outcomes*

Neonatal parameters included gestational age, sex, birthweight, Apgar scores at 1 and 5 minutes, and need for resuscitation. Additional physiological assessments included:

- NICU admission and duration
- Respiratory distress
- Early-onset sepsis (EOS) based on clinical criteria and laboratory markers)
- Metabolic complications such as hypoglycemia or hypocalcemia
- Composite neonatal morbidity score derived from standardized neonatal outcome scales

### *Statistical Analysis*

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD or median (IQR), depending on distribution. Categorical variables were reported as frequencies and percentages. Associations between cord blood biochemical parameters, placental lesions, and neonatal outcomes were assessed using one-way ANOVA and the chi-square test. A p-value <0.05 was considered statistically significant.

## Results

A total of 150 mother–infant dyads were included. Maternal demographic characteristics were comparable across groups with and without adverse neonatal outcomes. The mean gestational age at delivery was 37.8 ± 2.1 weeks, and the mean birth weight was 2780 ± 410 g. Placental examination revealed a high frequency of both vascular and inflammatory lesions (Table 1). Cord blood biochemical parameters (lactate, pH, IL-6, ferritin, glucose, cortisol) demonstrated significant associations with specific placental pathologies and neonatal morbidity.

## Interpretation

Inflammatory placental lesions showed significantly higher IL-6, lactate, ferritin, and cortisol compared with normal placentas. MVM was strongly associated with low arterial pH and high lactate.

Neonatal Outcomes According to Cord Blood Abnormalities using the Chi-square test.

## Discussion

The present study aimed to evaluate whether integrating cord blood biochemical dynamics, specifically inflammatory cytokines (IL-6, TNF-$\alpha$), metabolic stress markers (cord blood lactate, pH, base deficit), and iron-storage marker (ferritin), with detailed placental histopathology can improve the prediction of neonatal morbidity. This triad-based approach acknowledges that neonatal outcomes are not solely a product of fetal physiology or placental structure but of the dynamic interplay between both systems. Our findings demonstrate that elevated cord blood inflammatory and metabolic markers were significantly associated with placental inflammatory lesions and with adverse neonatal endpoints such as NICU admission, respiratory distress, early-onset sepsis, and need for resuscitation.[9]

### *Placental Inflammation and Cord Blood Cytokines*

Placental inflammatory lesions, including acute chorioamnionitis and funisitis, were among the strongest predictors of elevated cord blood IL-6 and TNF-$\alpha$ levels in our study. These findings are consistent with previous reports by Gomez *et al*. (1998),[10] who established IL-6 as the most reliable biochemical marker of fetal inflammatory response syndrome (FIRS).[10] Funisitis, in particular, reflects direct inflammation of the fetal compartment; thus, its association with elevated IL-6 in our cohort reinforces its clinical relevance. Similar patterns have been reported by several researchers who showed that umbilical cord IL-6 strongly correlates with multi-system neonatal morbidity.

TNF-$\alpha$, a proinflammatory cytokine linked to endothelial dysfunction and oxidative stress, also demonstrated significant elevation in neonates born with inflamed placentas. Previous work by Romero *et al*. (2007)[11] suggested that TNF-$\alpha$ plays a role not only in infection-driven inflammation but also in sterile inflammation caused by hypoxia and oxidative stress.[11] Our findings align with this understanding, as TNF-$\alpha$ was elevated even in certain cases of maternal vascular malperfusion (MVM), indicating its responsiveness to ischemic injury.

### *Placental Malperfusion and Metabolic Stress in Cord Blood*

Maternal and fetal vascular malperfusion lesions were closely associated with altered cord blood acid–base

balance in this study. Elevated lactate and higher base deficit were significantly correlated with MVM and fetal vascular malperfusion (FVM), respectively. Hypoxic changes resulting from MVM impair perfusion to the intervillous space, reducing oxygen transfer and predisposing the fetus to anaerobic metabolism. This mechanism is supported by prior work from Redline (2000)[12] and Stanek (2018),[13] who highlighted the prognostic significance of MVM in predicting fetal hypoxic stress.[12,13]

Cord blood lactate has been extensively studied as a marker of fetal hypoxia. In our cohort, lactate levels above 4.5 mmol/L strongly predicted NICU admission, consistent with findings by Malin *et al*. (2010),[14] who reported that cord lactate outperformed pH in predicting neonatal complications.[14] Similarly, a high base deficit was significantly associated with need for resuscitation, paralleling observations by Low *et al*. (1994),[15] who established base deficit as a robust indicator of intrapartum hypoxia.[15]

### *Iron Metabolism Marker (Ferritin) and Placental Dysfunction*

Cord blood ferritin, a marker of fetal iron stores, demonstrated a significant association with both placental inflammation and malperfusion. Elevated ferritin was observed in neonates with chorioamnionitis, likely reflecting inflammatory upregulation, as noted by Goldenberg *et al*.[16] Conversely, neonates with severe MVM exhibited lower ferritin levels, indicating impaired maternofetal nutrient transfer due to placental dysfunction. This dual response has been described by Georgieff (2006),[17] who emphasized that fetal ferritin rises in inflammation but falls when placental perfusion and iron transport are compromised.[17]

In our study, low ferritin was significantly associated with small-for-gestational-age (SGA) births, corroborating previous observations by Puerto *et al*. (2025).[18] These findings highlight ferritin's multifaceted role as both a nutritional and inflammatory biomarker.

### *Integration of Placental Pathology with Cord Blood Biomarkers*

One of the novel contributions of this study is the combined evaluation of structural placental disease and functional fetal biochemical response. The multivariable logistic regression model revealed that integrating cord blood parameters with histopathological findings substantially increased the predictive accuracy for adverse neonatal outcomes, compared to either dataset alone.

This integrative approach is supported by recent literature advocating multidisciplinary assessment to improve risk stratification. For example, Xodo *et al*. (2023)[19] emphasized that placental pathology captures antecedent events, whereas biochemical markers reflect real-time fetal stress. Similarly, combining biomarkers with placental lesions can enhance the prediction of neonatal sepsis and respiratory morbidity.[20] Our study adds empirical evidence to this evolving concept.

### *Neonatal Morbidity and Predictive Value of Cord Blood Dynamics*

NICU admission, respiratory distress, and early-onset sepsis were significantly associated with elevated IL-6, TNF-$\alpha$, lactate, and base deficit. These associations agree with prior neonatal research.

For early-onset sepsis, umbilical IL-6 is one of the earliest reliable markers. Our findings parallel the studies of Cernada *et al*. (2012)[21] and Ng *et al*. (2004),[22] who reported IL-6 levels above 30 pg/mL as strongly predictive of neonatal sepsis.[21,22]

For respiratory distress, high lactate and base deficit indicated hypoxic stress contributing to pulmonary maladaptation, consistent with findings by Campbell *et al*. (2010)[23] and Deepak *et al*. (2025).[9]

For NICU admission, combined abnormalities in metabolic and inflammatory markers significantly predicted admission risk, supporting prior evidence from Kulkarni *et al*. (2021)[24] and Dunne *et al*. (2024).[25]

## Conflicts of Interest

None

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