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Complete Blood Count–Derived Inflammatory Indices for Early Prediction of Preterm Birth

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ABSTRACT

Preterm birth remains a major obstetric problem, and reliable early markers for identifying high-risk pregnancies are still limited. Inflammation-based indices obtained from routine complete blood count tests have recently been investigated as practical reflections of early immune activity. This study evaluates whether first-trimester hematologic inflammatory markers are associated with later spontaneous preterm birth.

This study was conducted between 2023-2025. Pregnancies that ended before 37 weeks were compared with age- and sampling-matched term deliveries. Women with systemic disease, infections, multifetal gestation, fetal anomalies, or medication use influencing hematologic parameters were excluded. First-trimester inflammation-based indices were calculated. Statistical comparisons, correlation analyses, ROC curves, and logistic regression were performed.

Among 426 participants, 142 experienced preterm birth. Those who later delivered preterm had higher neutrophil counts and elevated NLR, SII, and SIRI values compared with controls. NLR produced the highest discriminatory performance (AUC: 0.609), with a cut-off value of >2.832, yielding a sensitivity of 59.9% and a specificity of 60.9%. SII, SIRI, and AISI also demonstrated statistically significant but weaker predictive performance. Neonatal complications, including NICU admission, were more frequent in the preterm group.

First-trimester inflammatory indices may signal early immune alterations related to preterm birth risk. Their predictive value alone is limited, yet they may strengthen early risk stratification when combined with established clinical parameters. Larger prospective studies are needed to confirm their additive contribution to predictive models.

Keywords: Preterm birth; Inflammatory indices; First trimester; Hematologic biomarkers; Maternal inflammation

Introduction

Preterm labor is a important contributor of perinatal complications, leading to significant neonatal complications and long-term adverse outcomes (1,2). In 2020, the global preterm birth rate was reported as 9.9%, and the cost per preterm birth was found to be approximately 26% higher than that of term deliveries (3). These data underscore the clinical and economic importance of early identification of pregnancies at risk for preterm birth.

Despite considerable advances in prenatal screening, the mechanisms initiating uterine contractions and cervical remodeling are still not fully understood. Inflammatory activation, oxidative stress, and endocrine dysregulation are thought to trigger a cascade that results in premature parturition. A better understanding of the roles of inflammation, infection, uterine overdistension, genetic predisposition, and other factors is essential for developing effective preventive and therapeutic strategies (4,5).

Various maternal blood markers and inflammatory indices have been studied for predicting preterm birth in the first trimester, sometimes together with ultrasound findings and known clinical risk factors (6,7). However, none of these markers have shown enough reliability to be used routinely in clinical practice. Recently, inflammation-related indices calculated from routine blood count tests have gained attention because they are simple, inexpensive, and may reflect subclinical inflammation (8–10). This

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study aimed to evaluate the first-trimester predictive role of inflammation-based indices in identifying women at risk for preterm delivery.

Material and Methods

This retrospective cohort study was conducted between January 2023 and January 2025. The study was approved by the Local Ethics Committee (Approval ID: AESH-BADEK2-2025-125) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Study population was identified through electronic medical records of pregnant women who presented with threatened preterm labor, were followed up, and delivered at our center. Women aged 18–45 years who delivered before 37 weeks of gestation were included.

Exclusion criteria were; presence of systemic, inflammatory, or autoimmune disease; use of medications known to alter hematologic or inflammatory markers; tobacco or alcohol use; and absence of first-trimester complete blood count (CBC) results. Multiple pregnancies, preterm births induced for obstetric indications, and fetuses with abnormalities were excluded to minimize potential confounding in neonatal outcome assessment. Pregnancies with medically indicated (iatrogenic) preterm birth due to obstetric complications such as preeclampsia, fetal growth restriction, placental abruption, or maternal indications were excluded. Only spontaneous preterm births were included in the final analysis.

A control group was generated by matching participants based on maternal age and gestational age; because the calculation of these indices requires a complete blood count, controls were selected from patients who had available complete blood count results. Only women with available first-trimester laboratory data were included in the final analysis. Patients with clinical or laboratory evidence of infection at the time of sampling were excluded.

Maternal characteristics (age, obstetric history, and body mass index) and neonatal outcomes (birthweight, gestational age at delivery, 0, 5-minute Apgar score ≤7, neonatal intensive care unit [NICU] admission, respiratory complications, and umbilical cord blood pH ≤7) were recorded. The presence of at least one of these neonatal parameters was defined as a composite adverse perinatal outcome (CAPO).

Inflammation-based indices were calculated using first-trimester (5–14 weeks) laboratory parameters according to the following formulas:

- NLR = Neutrophil / Lymphocyte
- MLR = Monocyte / Lymphocyte
- PLR = Platelet / Lymphocyte
- SII = Platelet × Neutrophil / Lymphocyte
- SIRI = Neutrophil × Monocyte / Lymphocyte
- AISI = Platelet × Neutrophil × Monocyte / Lymphocyte

Statistical Analyses: The sample size was determined a priori based on the study by Karaduman et al. (11), entitled "Evaluation of the use of first and third-trimester hemogram parameters in prediction of preterm labor" Using the differences reported in that study, effect size for neutrophil–lymphocyte ratio (NLR) calculated as 0.711. Assuming a two-sided α of 0.05 and 95% power the minimum required sample size for the present study was calculated as 53 women in each group (total n = 106).

Statistical analyses were carried out using IBM SPSS Statistics 27. The distribution of continuous variables was examined with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Variables with normal distribution were compared using the independent samples t-test and presented as mean ± standard deviation, whereas non-normally distributed data were analyzed with the Mann–Whitney U test and reported as median (interquartile range). Categorical variables were evaluated using Pearson's χ^2 test.

Associations between continuous parameters and preterm birth were assessed with point-biserial correlation analysis. The diagnostic performance of the inflammatory indices was examined using receiver operating characteristic (ROC) curves, and optimal cut-off values were identified with the Youden index. Univariate and multivariate logistic regression models were constructed to evaluate the relationship between first-trimester inflammatory markers and the occurrence of preterm birth. A p-value <0.05 was considered statistically significant.

Results

A total of 426 pregnant women were included in the study, with 142 in the preterm birth group

Table 1: Demographic Characteristics and First-Trimester Hematologic Inflammation Indices in the Preterm Birth and Control Groups

Variables	Preterm Birth Group (n=142)	Control Group (n=284)	p-value
Age (years)	29 (5)	29 (4)	0.163*
Gravidity	2 (2)	2 (1)	0.141*
Parity	1 (2)	1 (0)	0.080*
GA at Sampling (week)	9.1 (7.0-10.6)	9.0 (7.1-10.4)	0.631*
Hemoglobin (g/dL)	12.9 (1.8)	12.7 (1.4)	0.177*
Neutrophil (×10³/μL)	6.35 (2.74)	5.65 (2.28)	<0.001*
Lymphocyte (×10³/μL)	2.00 (0.77)	2.12 (0.69)	0.075*
Monocyte (×10³/μL)	0.58 (0.25)	0.57 (0.22)	0.843*
Platelet (×10³/μL)	266 (83)	264 (81)	0.935*
NLR	3.048 (1.975)	2.548 (1.249)	<0.001*
MLR	0.274 (0.114)	0.271 (0.104)	0.396*
PLR	131.795 (46.669)	121.699 (54.923)	0.165*
SII	817.311 (498.530)	683.288 (382.324)	0.001*
SIRI	1.671 (1.262)	1.530 (0.895)	0.023*
AISI	436.684 (374.943)	394.977 (315.868)	0.027*

* The Mann–Whitney U test was used for comparisons between groups. Data are presented as median (interquartile range). Statistically significant p-values are shown in bold.

Abbreviations: GA, Gestational Age; NLR, Neutrophil-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; AISI, Aggregate Index of Systemic Inflammation

Table 2: Neonatal Outcomes in the Preterm Birth and Control Groups

Variables	Preterm Birth Group (n=142)	Control Group (n=284)	p-value
GA at Delivery (weeks)	35 (2)	39 (1)	<0.001*
Birthweight (g)	2425 (568)	3250 (443)	<0.001*
Apgar score at 1st minute	9 (2)	9 (0)	<0.001*
Apgar score at 5th minute	10 (2)	10 (0)	<0.001*
5th minute Apgar score ≤7	20 (14.1%)	7 (2.5%)	<0.001**
NICU admission	37 (26.1%)	8 (2.8%)	<0.001**
Postnatal mortality	1 (0.7%)	-	0.333**
Hyperbilirubinemia	12 (8.5%)	1 (0.4%)	<0.001**
TTN	12 (8.5%)	4 (1.4%)	<0.001**
RDS	6 (4.2%)	-	0.001**
CAPO	46 (32.4%)	13 (4.6%)	<0.001**

* The Mann–Whitney U test was used for comparisons between groups. Data are presented as median (interquartile range).

** Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Results are shown as n (%).

Statistically significant p-values are shown in bold.

Abbreviations: GA, Gestational age; NICU, Neonatal intensive care unit; TTN, Transient tachypnea of the newborn; RDS, Respiratory distress syndrome; CAPO, Composite adverse perinatal outcome.

Table 3: Relationship of NLR, SII, SIRI, and AISI With Preterm Delivery

Variables	Cut-off	AUC	95 % CI	Sensitivity (%)	Specificity (%)	LR+	LR-	p-value
NLR	>2.832	0.609	0.561-0.655	59.9	60.9	1.53	0.66	<0.001
SII	>883.387	0.595	0.547-0.642	46.5	72.2	1.67	0.74	0.001
SIRI	>2.055	0.567	0.519-0.615	39.4	78.5	1.84	0.77	0.026
AISI	>647.269	0.565	0.517-0.613	30.3	83.1	1.79	0.84	0.028

*Spearmen's correlation analysis was used to assess associations between continuous variables
Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; AISI, Aggregate Index of Systemic Inflammation

Table 4: Diagnostic Performance of Hematologic Inflammatory Indices in Predicting Preterm Birth: ROC Curve Analysis

Variables	r	p-value*
NLR	0.178	<0.001
SII	0.155	0.001
SIRI	0.110	0.023
AISI	0.107	0.027

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammatory Response Index; AISI, Aggregate Index of Systemic Inflammation; AUC, Area Under the Curve; LR+, Positive Likelihood Ratio; LR-, Negative Likelihood Ratio

and 284 in the term control group. Maternal gravidity, parity, hemoglobin levels, monocyte counts, platelet counts, MLR, and PLR values were similar between the groups ($p > 0.05$ for all).

Several inflammation-related hematologic indices, however, differed significantly. Neutrophil counts were higher in the preterm group (6.35 vs. 5.65 $\times 10^3/\mu L$, $p < 0.001$). NLR (3.048 vs. 2.548, $p < 0.001$), SII (817.3 vs. 683.3, $p = 0.001$), and SIRI (1.671 vs. 1.530, $p = 0.023$) were also elevated in women who later delivered preterm. Lymphocyte counts showed no significant difference ($p = 0.075$) (Table 1).

Neonatal outcomes are summarized in Table 2. NICU admission was more frequent in the preterm group (26.1% vs. 2.8%, $p < 0.001$). Rates of hyperbilirubinemia (8.5% vs. 0.4%, $p < 0.001$), transient tachypnea of the newborn (TTN) (8.5% vs. 1.4%, $p < 0.001$), and respiratory distress syndrome (RDS) (4.2% vs. 0%, $p = 0.001$) were also higher among preterm infants. Postnatal mortality did not differ significantly (0.7% vs. 0%, $p = 0.333$). Composite adverse perinatal outcomes (CAPO) were more common in the preterm group (32.4% vs. 4.6%, $p < 0.001$).

Correlation analysis showed small but statistically significant associations between preterm birth and NLR ($r = 0.178$, $p < 0.001$), SII ($r = 0.155$, $p = 0.001$), SIRI ($r = 0.110$, $p = 0.023$), and AISI ($r = 0.107$, $p = 0.027$) (Table 3).

ROC analysis indicated that NLR had the highest AUC (0.609), with an optimal cut-off value of >2.832 (sensitivity 59.9%, specificity 60.9%). SII (AUC 0.595), SIRI (AUC 0.567), and AISI (AUC 0.565) also showed statistically significant diagnostic performance, although with lower sensitivities (Table 4).

Discussion

The pathophysiology of preterm birth is not fully understood, and the underlying mechanisms are known to be multifactorial (12,13). However, a substantial body of evidence highlights the role of inflammation in triggering early uterine activity and cervical changes. Alterations in maternal immune regulation may begin long before symptoms appear. The interaction of these mechanisms with the immune balance of pregnancy is one of the still unresolved aspects of the pathophysiology of preterm birth. This suggests that even early pregnancy can reflect subtle systemic inflammatory signals (14,15).

Inflammation-based hematologic indices derived from routine complete blood count parameters have recently been explored as potential predictors of obstetric complications. These parameters are quick, inexpensive, and reflect the balance between innate and adaptive immunity. They have been studied in conditions such as cardiovascular disease, cancer, sepsis, and some pregnancy-related disorders (16–19). However, their ability to predict spontaneous preterm birth remains unclear.

Previous literature reports numerous publications demonstrating that inflammation and the inflammatory response in blood parameters play a role in the pathogenesis of preterm birth (20,21). Furthermore, technical difficulties and high costs associated with the application of inflammatory parameters, such as interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), and tumour necrosis factor-alpha (TNF-α) limit their widespread use in practice. Derived from maternal hemogram parameters, have become popular in recent years, particularly in maternal fetal medicine.

In the present study, NLR, AISI, SIRI, and SII were significantly increased in women who later delivered preterm. According to these findings heightened systemic inflammation may be detectable early in gestation. Among these indices, NLR showed the best discriminative performance in ROC analysis, although overall AUC values for all markers were modest. Although the AUC values indicate limited standalone predictive accuracy, these indices may still provide incremental value when integrated into multivariable clinical risk prediction models. These results support that early systemic response may be a contributing factor in the cascade leading to spontaneous preterm labor.

Early systemic inflammation may contribute to cervical remodeling through inflammatory cytokine–mediated extracellular matrix degradation, increased prostaglandin synthesis, and collagen disorganization within the cervical stroma (22,23). In parallel, subclinical immune activation may promote uterine contractility by enhancing myometrial sensitivity to oxytocin and inflammatory mediators. Furthermore, first-trimester inflammation may already be detectable before clinical symptoms due to early immune dysregulation at the maternal–fetal interface, including activation of Hofbauer cells and altered placental macrophage signaling (24,25).

Our results are consistent with previous reports associating preterm birth and elevated neutrophil-mediated inflammatory responses (10,26,27). Obtaining similar results in different populations supports the potential clinical value of these indices. The increases observed in SII and SIRI further support the involvement of complex interactions between neutrophils, monocytes, and platelets in the inflammatory cascade. Given the simplicity and accessibility of these parameters, they can contribute to early diagnosis when used in combination with clinical risk factors and other biomarkers. Therefore, future evaluation of these indices together with other biomarkers and clinical risk ratios may contribute to the development of more powerful prediction models.

One of the strengths of our study is the assessment of inflammatory parameters during the first trimester, a period when clinically apparent signs of preterm labor have not yet emerged. Detecting early changes in immune status and identifying risk factors can help improve the follow-up process. In addition, because these indices are derived from routine laboratory tests, they offer a cost-effective and widely accessible approach for identifying women at elevated risk. However single-center and retrospective design may reduce the generalizability of this findings. Dependence on the accuracy of medical records may have introduced potential measurement and documentation bias. Additionally, preterm birth is influenced by various environmental, mechanical, and biological factors; therefore, hematological indices alone may not fully reflect this pathophysiology. Another important limitation is that inflammatory indices are influenced by various unmeasured confounding factors such as dietary habits, subclinical inflammatory or infectious conditions, emotional stress, sleep patterns, and lifestyle-related factors. Although patients with overt infection and systemic disease were excluded, the potential effect of these subclinical and behavioral factors on hematologic inflammatory markers could not be completely eliminated. Prospective researches are needed to validate our findings and to determine whether combining these markers with other established predictors can enhance early risk assessment. Therefore, in future analyses, evaluating clinical, biochemical and hematological data together may help develop more comprehensive risk prediction models.

In conclusion, our study demonstrates that first-trimester inflammation-based hematologic indices, particularly NLR, SII, and SIRI, are associated with risk of preterm birth. Although their predictive accuracy is limited when used in isolation, these indices may contribute to early risk identification as part of a broader assessment strategy. Further prospective, multicenter large sample size studies are warranted to validate these findings.

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