Original Investigation | Özgün Araştırma

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Exploring the Predictive Potential of Systemic Immune Inflammation Index and Hematologic Markers in Preterm Labor Risk Assessment

Preterm Doğum Riskinin Değerlendirilmesinde Sistemik İmmün Enflamasyon İndeksi ve Hematolojik Belirteçlerin Öngörü Potansiyelinin Araştırılması

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ABSTRACT

Objective: This study aimed to evaluate the potential association between the Systemic Immune Inflammation Index (SII) and preterm labor, given the growing interest in inflammatory biomarkers as possible predictors of pregnancy outcomes.

Methods: Conducted as a retrospective observational study at University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital, the study included 200 participants, split equally between those with preterm labor and a control group with term births. The study focused on singleton pregnancies, with the preterm group having gestational ages between 24 and 36+6 weeks; and the control group at 37 weeks or beyond. Hematological data, including SII, along with neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), were collected and compared across groups.

Results: Median SII values showed no significant differences between the preterm and control groups (727 vs. 740, p=0.642). Other inflammatory markers (NLR, PLR, and MLR) also displayed similar values in both groups. Notably, the preterm group exhibited lower gestational ages and birth weights compared to the control group (p<0.001). Cesarean delivery rates were significantly elevated in the preterm group (79%) relative to the control group (43%, p<0.001).

Conclusion: Although SII levels did not significantly differ between preterm and term births, the findings underscore the complex role of inflammation in preterm labor. Further research utilizing combined biomarker models may provide more precise risk assessment for preterm birth.

Keywords: Inflammatory biomarkers, neutrophil-to-lymphocyte ratio, preterm labor, Systemic Immune Inflammation Index

ÖZ

Amaç: Bu çalışma, Sistemik İmmün İnflamasyon İndeksi (SII) ile preterm doğum arasındaki olası ilişkiyi değerlendirmeyi amaçlamaktadır. Enflamatuar belirteçlerin gebelik sonuçlarını öngörmedeki potansiyel rolü giderek daha fazla ilgi görmektedir.

Yöntemler: Çalışma, Sağlık Bilimleri Üniversitesi, Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi'nde yürütülen retrospektif gözlemsel bir çalışmadır. Çalışmaya, 24-36+6 hafta gebelik süresine sahip preterm doğum yapan 100 kadın ve ≥37 hafta gebelik süresine sahip term doğum yapan 100 kadın olmak üzere toplam 200 katılımcı dahil edilmiştir. Hematolojik veriler, SII, nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve monosit-lenfosit oranı (MLR) gibi parametreler gruplar arasında karşılaştırılmıştır.

Bulgular: Medyan SII değerleri preterm ve kontrol grupları arasında anlamlı bir fark göstermemiştir (727 vs. 740, p=0,642). Diğer enflamatuvar belirteçler (NLR, PLR ve MLR) de her iki grupta benzer değerler göstermiştir. Ancak, preterm doğum grubunda gebelik haftası ve doğum ağırlığı belirgin şekilde daha düşük bulunmuş (p<0,001) ve sezaryen oranı anlamlı derecede daha yüksek olmuştur (%79 vs. %43, p<0,001).

Sonuç: SII seviyeleri preterm ve term doğumlar arasında belirgin bir fark göstermemiş olsa da, enflamasyonun preterm doğumdaki karmaşık rolü vurgulanmaktadır. Gelecekte, birden fazla biyomarkerin bir arada değerlendirildiği modellerin preterm doğum riskini öngörmede daha doğru sonuçlar sağlayabileceği düşünülmektedir.

Anahtar Sözcükler: Enflamatuvar belirteçler, nötrofil-lenfosit oranı, preterm doğum, Sistemik İmmün Enflamasyon İndeksi

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INTRODUCTION

Preterm birth is a major perinatal issue, affecting an estimated 13.5 million births globally each year and accounting for approximately 10% of all deliveries. This condition not only poses immediate health risks to the neonate but also contributes to substantial morbidity and mortality rates, particularly in cases where preterm labor occurs spontaneously before 37 weeks of gestation (1,2). Among the complications associated with preterm birth, intrauterine inflammatory processes play a significant role, impacting neonatal health and survival through short-, medium-, and long-term complications (1,3). The wide range of neonatal medical treatments required and the associated costs, as well as the mortality and morbidity caused by preterm birth and the economic consequences, emphasize the importance of early detection and management of this critical perinatal condition.

Preterm labor has a multifactorial etiology. Pathologic, inflammatory and infectious factors, as well as fetal endocrine dysfunction, have been shown to contribute to susceptibility to preterm labor (4). The developing fetus, which is considered a semi-allograft, is not rejected by the immune system (5). Pro-inflammatory processes that occur during the first trimester of pregnancy facilitate migration of the blastocyst and support successful implantation. However, these inflammatory processes must remain in balance for successful implantation. Decreased levels of inflammation can lead to implantation failure, while excessive inflammation can lead to miscarriage (6,7). The increased inflammatory response associated with contractions during the first stage of labor and the inflammatory changes that occur in the cervix and myometrium support the role of inflammatory processes in the development of preterm labor (8,9).

Systemic inflammation can be measured with various biochemical and hematologic markers. Recent evidence suggests that measuring the ratio of cell types in blood, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR), may provide prognostic and diagnostic insights for diseases associated with chronic low-grade inflammation (10,11). The systemic Immune Inflammation Index (SII) and delta-SII, new biomarkers of systemic inflammatory response based on peripheral blood cell counts, have been shown to be effective in predicting the prognosis of esophageal and cervical cancers as well as certain obstetric conditions such as intrahepatic cholestasis and fetal growth restriction in pregnancy (12-14). On the other hand, certain inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are associated with technical challenges and high costs in clinical practice, which limits their widespread use.

Although various biomarkers have been investigated to predict preterm labor and delivery, a cost-effective prediction model with sufficient sensitivity and specificity has not yet been developed. The aim of our study is to retrospectively investigate the association between SII and preterm labor by analyzing the hemogram parameters of patients who were diagnosed with preterm labor and hospitalized.

MATERIALS AND METHODS

Study Design

This retrospective observational cohort study was conducted at University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital. Patients diagnosed with preterm labor between January 1, 2016, and August 30, 2022, were included, allowing a comprehensive review of patient records over a 6-year period.

Study Population

The study included two groups: the preterm labor group, consisting of women with singleton pregnancies diagnosed with preterm labor between 24 and 36+6 weeks' gestation, and the control group, consisting of healthy women with singleton pregnancies who had delivered at term (≥37 weeks). Preterm labor was defined based on clinical signs and symptoms, including regular uterine contractions and cervical changes (dilatation and effacement) and, in some cases. The control group was selected by chronological matching of hospital records to ensure demographic similarity with the preterm labor group. A total of 100 patients were included in each group.

Inclusion and Exclusion Criteria

Women with singleton pregnancies who were diagnosed with preterm labor between 24 and 36+6 weeks were included in the study, and healthy women with singleton pregnancies who had delivered at term were included in the control group. Patients with chronic liver or kidney disease, autoimmune disease or chronic inflammation, infections such as urinary tract and respiratory tract infections, pelvic inflammatory disease, or coronavirus disease-2019, as well as those using corticosteroids or other anti-inflammatory drugs, were excluded. In addition, patients with suspected or confirmed chorioamnionitis, cardiovascular disease, or other conditions that could affect the white blood cell ratio or cause systemic inflammation were also excluded. Patients eligible for the control group were randomly selected based on hospital admissions during the same period as the preterm labor group.

Data Collection

Data were collected retrospectively from hospital records, including demographic information such as age, gravidity, parity, abortion history, Body Mass Index, and obstetric history. Hemogram parameters were also collected from blood samples taken at the time of admission for preterm labor or during routine visits for the control group. Complete blood count (CBC) was analyzed and hematological indices such as NLR, PLR, MLR, and SII were calculated. The SII was calculated using the following formula: (neutrophil count x platelet count)/ lymphocyte count. In addition, pregnancy outcomes were recorded, including gestational age at delivery, birth weight, type of delivery (vaginal or cesarean section), and neonatal outcomes.

Outcomes Definations

Primary Outcome: Predictive value of the SII for preterm labor: The primary outcome is to assess whether the SII can predict the occurrence of preterm labor.

Secondary outcomes: (1) neonatal birth outcomes, (2) gestational

age at birth: classified as preterm if the baby is delivered before 37 weeks' gestation. (3) birth weight: documented in grams at birth, (4) birth length: measured in centimeters at birth, (5) type of delivery: defined as vaginal delivery or cesarean section, with rates analyzed according to preterm delivery status. (6) additional inflammatory marker ratios: including NLR, PLR and MLR, which serve as secondary biomarkers of systemic inflammation and are compared between preterm and control groups.

Ethical Approval

This study was approved by the No 1 Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital (approval number: 14/07, date: 24.10.2022).

Statistical Analysis

The collected data were analyzed using SPSS version 23. Descriptive statistical methods included mean, standard deviation, and median. The distribution calculations was analyzed using the Shapiro-Wilk test. If a normal distribution was present, parametric tests (Student's t-test) were used. However, if no normal distribution was present, non-parametric tests (Mann-Whitney U test) were used to compare the groups.

RESULTS

The study included a total of 200 participants, divided equally between two groups: 100 individuals in the preterm labor group and 100 in the control group. The median age in the preterm labor group was 28.5 years [interquartile range (IQR): 24.0-34.0], which was significantly higher than the median age of 24.5 years (IQR: 21.0-28.0) observed in the control group ($p<0.001$) (Table 1).

The median SII values were computed for both groups, yielding 727 (IQR: 543-1032) in the preterm group and 740 (IQR: 603-965) in the control group, with no statistically meaningful difference between the groups ($p=0.642$). Additionally, analysis of other inflammatory markers, such as the NLR, PLR, and MLR, showed similar levels across both groups (NLR: $p=0.788$, PLR: $p=0.690$, MLR: $p=0.798$), indicating no significant variation in these parameters (Table 1).

The median gestational age at delivery was considerably shorter for the preterm labor group, recorded at 34 weeks (IQR: 33-35), as compared to 39 weeks (IQR: 38-40) in the control group ($p<0.001$). Birth weights also followed this trend, with a median of 2270 g (IQR: 1683-2615) in the preterm group, noticeably lower than the control group's median of 3325 g (IQR: 3000-3588) ($p<0.001$). Furthermore, delivery methods varied significantly, with a lower percentage of vaginal deliveries in the preterm labor group (21%) compared to the control group (57%), while cesarean delivery rates were higher among those in the preterm group (79% versus 43%, $p<0.001$). (Table 1).

DISCUSSION

This study investigated the relationship between the SII and preterm labor. Although the analysis showed no significant difference in SII scores between the preterm and control participants, our results indicate possible areas where hematologic markers such as NLR and PLR can be used as predictive indicators of preterm labor. This is consistent with the existing literature, which has frequently emphasized the role of inflammatory markers in pregnancy outcomes. This warrants more comprehensive biomarker panels in future studies to capture the complexity of the inflammatory processes involved.

Preterm labor is a multifactorial condition in which inflammation plays a pivotal role. As previous studies have shown, inflammatory processes within the uterine environment may contribute to early labor onset by promoting contractions of the myometrium and structural changes in the cervix (15,16). In particular, the presence of infection and inflammation in placental tissue and fetal membranes has been consistently associated with an increased risk of preterm birth (17,18). Biomarkers such as IL-6 and TNF-α have been highlighted as key factors in this inflammatory response, as they are involved in signaling pathways that stimulate myometrial activity and cervical remodeling, essential components for the onset of labor (17,18).

The role of maternal blood biomarkers in predicting preterm birth continues to be an important area of investigation. In particular, studies on hematologic parameters have shown that certain metrics, such as NLR and PLR, have promising potential as low-cost, easily accessible tools for identifying systemic inflammation. Daglar et al. (19) found that MLR was significantly elevated in threatened preterm labor, which has important implications for clinical practice. In addition, a study by Ma et al. (20) showed that a combination of hemoglobin, platelet distribution width and NLR had high sensitivity and specificity for predicting preterm birth in asymptomatic women. These findings suggest that the combination of different inflammatory markers could provide a more comprehensive understanding of inflammatory status than single indices such as SII alone.

The results of this study are consistent with previous research highlighting the importance of inflammatory markers in preterm labor. However, the non-significant results in SII scores between preterm and control groups may be due to the different inflammatory pathways involved in the development of preterm labor, which could limit the diagnostic utility of a single inflammatory marker. Other systemic markers, such as CRP and IL-6, have been found to have different predictive power in different populations due to this heterogeneity in inflammatory responses (16,21).

Given the growing evidence for an association between inflammation and preterm labor, it is clear that isolating a single biomarker does not adequately capture the complexity of the disease. Instead, a composite biomarker approach, possibly incorporating NLR, PLR, and additional systemic inflammatory markers, may provide a more robust framework for identifying patients at risk of preterm labor (16,22). Such an approach could not only improve prediction accuracy but also provide a more individualized understanding of each patient's inflammatory profile, leading to more targeted treatment strategies.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design may introduce selection and information biases, potentially affecting the generalizability of the findings. Additionally, the sample size is relatively modest, which

Table 1. Comparison of demographic, hematological, and pregnancy outcome variables between control and preterm groups

Variables	Control group (n=100)	Preterm labor group (n=100)	p
Age (years)	24.5 (21.0-28.0)	28.5 (24.0-34.0)	**<0.001**
Gravida			
median (Q_1-Q_3)	2 (1-3)	2 (1-3)	**0.039**
Min.-Max.	1-6	1-7	
Parity			
median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.034**
Min.-Max.	0-4	0-6	
Abortion			
median (Q1-Q3)	0 (0-0)	0 (0-0)	**0.764**
Min.-Max.	0-2	0-2	
Living child			
median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.037**
Min.-Max.	0-4	0-6	
Gestational week at admission	8 (7-9)	8 (7-9)	0.838
WBC ($x10^3$/uL)	8.65 (7.28-10.91)	8.81 (7.16-10.10)	0.549
RBC ($x10^6$/uL)	4.61±0.367	4.55±0.390	0.291
Hemoglobin (g/dL)	13.0 (12.4-13.5)	12.8 (11.8-13.6)	0.128
Hematocrit (%)	40.0±2.73	39.3±2.98	0.096
MCV (fL)	87.7 (85.0-90.5)	87.7 (83.3-91.0)	0.909
Platelets ($x10^3$/uL)	271 (236-310)	274 (226-321)	0.940
MPV (fL)	10.5 (9.9-11.4)	10.4 (9.9-11.4)	0.981
PCT (%)	0.29 (0.25-0.31)	0.28 (0.25-0.33)	0.774
Neutrophils ($x10^3$/uL)	5.86 (4.66-7.54)	5.97 (4.44-7.27)	0.517
Lymphocyte ($x10^3$/uL)	2.09 (1.72-2.46)	2.10 (1.66-2.47)	0.841
Monocyte ($x10^3$/uL)	0.61 (0.50-0.73)	0.59 (0.48-0.71)	0.419
Gestational week at delivery	39 (38-40)	34 (33-35)	**<0.001**
Birth length (cm)	51 (50-52)	43 (36-46)	**<0.001**
Birth weight (g)	3325 (3000-3588)	2270 (1683-2615)	**<0.001**
SII	740 (603-965)	727 (543-1032)	0.642
SIRI	1.65 (1.27-2.44)	1.59 (1.14-2.31)	0.508
PIV	477 (319-654)	425 (294-645)	0.603
PLR	132 (112-157)	134 (105-170)	0.690
MLR	0.274 (0.238-0.364)	0.281 (0.234-0.341)	0.798
NLR	2.80 (2.37-3.62)	2.83 (2.08-3.64)	0.788
Type of delivery			
Spontenous delivery	57 (57)	21 (21)	**<0.001**
Ceserean section	43 (43)	79 (79)	
Gender			
Female	52 (52)	53 (53)	N.A.
Male	48 (48)	47 (47)	

Statistical significance is indicated where applicable, with p-values less than 0.05 considered significant. Continuous variables are presented as medians with interquartile ranges (Q1-Q3) or means ± standard deviation, and categorical variables are shown as frequencies and percentages.
WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet count, MPV: Mean platelet volume, PCT: Plateletcrit, NEU: Neutrophil count; LYM: Lymphocyte count, MON: Monocyte count, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Prognostic inflammatory value; PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, Min.-Max.: Minimum-maximum, N.A.: Non-applicable

may limit the power to detect subtle associations between systemic inflammatory markers and preterm labor. Another limitation is the reliance solely on hematologic parameters derived from CBCs; more comprehensive biomarker profiles, including cytokines and other specific inflammatory markers, were not available for analysis. The strength of our study lies in the use of a well-defined patient cohort, which allows for a more targeted analysis. Future research initiatives could expand the range of biomarkers and investigate the interactions between different inflammatory pathways associated with preterm labor in order to refine the predictive models and improve clinical applicability (17).

CONCLUSION

In conclusion, this study found no significant association between SII and the incidence of preterm labor. Nevertheless, our findings contribute to the growing body of evidence highlighting inflammation's crucial role in preterm labor pathogenesis. These results underscore the need for continued research into affordable, clinically applicable biomarkers that could better inform early interventions in preterm labor management. Moving forward, expanding the biomarker profile to include a combination of hematologic and inflammatory markers may offer more nuanced insights into identifying at-risk pregnancies, and support preventive healthcare practices.

Ethics

Ethics Committee Approval: This study was approved by the No 1 Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Etlik Zübeyde Hanım Women`s Health and Research Hospital (Approval number: 14/07, date: 24.10.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.Ö., Design: S.Ö., Supervision: Y.Ü., Data Collection or Processing: S.Ö., Y.Ü., Analysis or Interpretation: S.Ö., Literature Search: S.Ö., Y.Ü., Writing: S.Ö., Critical Review: Y.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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