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Original Research

Diagnostic and predictive role of systemic inflammatory indices in intrauterine growth restriction

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Abstract

Aim: Inflammation is considered to play an important role in the pathogenesis of intrauterine growth restriction (IUGR). Recently, systemic inflammatory indices derived from complete blood count parameters have emerged as practical biomarkers for evaluating inflammatory status. This study aimed to investigate the diagnostic value of systemic inflammatory indices in pregnant women with IUGR.

Methods: This retrospective case–control study included 66 pregnant women diagnosed with IUGR and 68 healthy pregnant controls. Demographic characteristics, laboratory findings, and inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune–inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), and systemic inflammation marker index (SIMI) were compared between the groups. Receiver operating characteristic (ROC) curve analyses were performed to evaluate diagnostic performance.

Results: Maternal age and gestational week were similar between the groups, whereas parity was significantly higher in the IUGR group ($P < .001$). Neutrophil and monocyte counts were significantly lower in patients with IUGR. NLR, SII, SIRI, and AISI values were also significantly decreased in the IUGR group compared with controls (all $P = .001$). ROC analysis demonstrated moderate diagnostic performance for NLR (AUC = 0.667), SII (AUC = 0.663), SIRI (AUC = 0.667), and AISI (AUC = 0.664) (all $P < .001$). PLR and SIMI were not significantly associated with IUGR.

Conclusion: Systemic inflammatory indices, particularly NLR, SII, SIRI, and AISI, may serve as useful and easily accessible biomarkers in the evaluation of IUGR. Further large-scale prospective studies are needed to clarify their clinical utility and underlying pathophysiological significance.

Keywords

intrauterine growth restriction, inflammation, biomarkers, diagnostic value

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Introduction

Intrauterine growth restriction (IUGR) is one of the major causes of perinatal morbidity and mortality and is characterized by the inability of the fetus to achieve its genetically determined growth potential.[1] Beyond the prenatal period, IUGR has also been associated with an increased risk of cardiovascular diseases, metabolic syndrome, and neurodevelopmental disorders later in life.[2,3,4] Therefore, understanding the pathophysiological mechanisms underlying IUGR and identifying reliable biomarkers for its early diagnosis remain important areas of research in obstetric practice.

The etiology of IUGR is multifactorial and results from the complex interaction of maternal, fetal, and placental factors.[5] Among these, uteroplacental insufficiency is considered one of the most common underlying causes.[6] Reduced placental perfusion, chronic fetal hypoxia, and the resulting oxidative stress (OS) are known to play central roles in the pathogenesis of IUGR. In recent years, increasing evidence has suggested that inflammation is at least as important as OS in this pathological process.[7,8]

Although a certain degree of inflammation is physiologically present during normal pregnancy, an excessive or dysregulated inflammatory response may adversely affect placental function. Elevated levels of proinflammatory cytokines have been associated with endothelial dysfunction, impaired trophoblast invasion, and inadequate spiral artery remodeling. These pathological alterations may ultimately compromise the transport of oxygen and nutrients to the fetus, leading to fetal growth restriction.

In addition to conventional inflammatory markers used in clinical practice, systemic inflammatory indices derived from complete blood count parameters have gained considerable attention in recent years because they are inexpensive, easily accessible, and practical. Among these indices, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Inflammatory Response Index (SIRI), and the systemic immune–inflammation index (SII) have emerged as promising indicators of systemic inflammatory status. These markers have been widely investigated in clinical studies due to their ability to reflect the severity of inflammatory responses in a cost-effective manner.[9,10]

The aim of this study was to evaluate systemic inflammatory indices in pregnant women diagnosed with intrauterine growth restriction (IUGR) and to investigate the relationship between these parameters and the clinical characteristics of the disease. The findings obtained from this study may contribute to the early diagnosis and management of IUGR.

Materials and Methods

Study Design and Population

This study was designed as a retrospective case-control study and included patients who presented to the Department of Obstetrics and Gynecology at Aksaray Training and Research Hospital during early pregnancy between January 2020 and December 2025. Patients diagnosed with IUGR and with a surgical indication were assigned to the case group, while patients with similar demographic characteristics and gestational age were selected as the control group. (Figure 1)

Maternal demographic characteristics, including age, parity, gestational age, and routine hematological parameters, were retrospectively obtained from the hospital electronic database. Using these laboratory findings, several systemic inflammatory indices were calculated, including the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI), and Systemic Inflammation Modulation Index (SIMI). Since this was a retrospective study, no additional blood samples were collected from the participants.

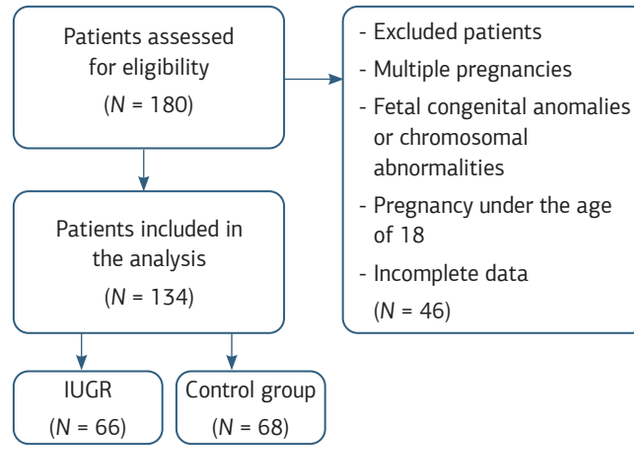


Figure 1. *Flowchart of patient selection and group allocation in the study*

The inflammatory indices were calculated using the following formulas:

- NLR = neutrophil/lymphocyte
- PLR = platelet/lymphocyte
- SII = (neutrophil × platelet)/lymphocyte
- SIRI = (neutrophil × monocyte)/lymphocyte
- AISI = (neutrophil × platelet × monocyte)/lymphocyte
- SIMI = (monocyte × platelet)/lymphocyte

Inclusion and Exclusion Criteria

This retrospective case–control study included pregnant women aged between 18 and 45 years who were diagnosed with intrauterine growth restriction (IUGR) and followed at the Department of Obstetrics and Gynecology between January 2020 and December 2025. Only singleton pregnancies between 24 and 37 weeks of gestation were included in the study. The diagnosis of IUGR was established according to ultrasonographic findings demonstrating an estimated fetal weight below the 10th percentile for gestational age. Patients with available complete blood count parameters necessary for calculating systemic inflammatory indices were enrolled. The control group consisted of age- and gestational age-matched healthy pregnant women without fetal growth restriction.

Patients with multiple pregnancies, fetal congenital anomalies, chromosomal abnormalities, preeclampsia, gestational hypertension, chronic hypertension, diabetes mellitus, gestational diabetes mellitus, autoimmune diseases, active infections, inflammatory disorders, hematological diseases, malignancies, hepatic, renal, or cardiovascular diseases were excluded from the study. In addition, patients using corticosteroids, immunosuppressive agents, or other medications that could affect inflammatory parameters were excluded. Pregnant women with premature rupture of membranes, active labor, smoking, alcohol consumption, or insufficient medical records and missing laboratory data were also excluded from the analysis.

Ethical Approval

The study was approved by the Aksaray University Ethics Committee (Date: 08.01.2026, Decision No: SAGETİK 2025-166).

Statistical Analysis

Sample size calculation was performed using G-Power software (v3.1.2). Based on a medium effect size (Cohen's d = 0.50), an alpha level of 0.05, and the study sample sizes (66 IUGR and 68 controls), the statistical power of the study was calculated as

95%. Statistical analyses were conducted using SPSS version 26.0. Data distribution was assessed with the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± standard deviation and compared using the independent samples t-test, whereas non-normally distributed variables were presented as median (25th–75th percentile) and analyzed with the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of inflammatory indices. Optimal cut-off values were determined using the Youden J index, and sensitivity, specificity, positive predictive value, negative predictive value, area under the curve (AUC), and 95% confidence intervals were calculated. A *P* value < .05 was considered statistically significant.

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

A total of 134 pregnant women were included in the study, comprising 66 patients diagnosed with IUGR and 68 healthy controls. Demographic characteristics of the study population are presented in Table 1.

Maternal age and gestational week were comparable between the groups (*P* = .497 and *P* = .472, respectively). However, parity was significantly higher in the IUGR group compared to the control group (*P* < .001).

The comparison of laboratory findings and systemic inflammatory indices is shown in Table 2.

Hemoglobin, urea, creatinine, ALT, AST, lymphocyte count, platelet count, PLR, and SIMI values did not differ significantly between the groups (*P* > .05). In contrast, neutrophil and monocyte counts were significantly lower in the IUGR group than in controls (*P* < .001 and *P* = .040, respectively). Similarly, NLR, SII, SIRI, and AISI values were significantly decreased in patients with IUGR compared to healthy pregnant women (*P* = .001).

Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic performance of inflammatory indices for predicting IUGR (Table 3, Figure 2).

NLR demonstrated an AUC value of 0.667 (95% CI: 0.575–0.759, *P* < .001) with 94% sensitivity and 40% specificity at a cut-off value of ≤4.90. SII showed an AUC of 0.663 (95% CI: 0.571–0.755, *P* < .001), while SIRI and AISI demonstrated AUC values of 0.667 and 0.664, respectively (*P* < .001). Among the evaluated markers, NLR, SII, SIRI, and AISI exhibited moderate diagnostic performance with high sensitivity but relatively low specificity. PLR and SIMI did not demonstrate significant diagnostic value for predicting IUGR.

Discussion

In this study, we investigated the diagnostic value of systemic inflammatory indices in pregnancies complicated by IUGR. Our findings demonstrated that several hemogram-derived inflammatory markers, particularly NLR, SII, SIRI, and AISI, were significantly lower in the IUGR group compared with healthy pregnant controls. In addition, ROC analysis demonstrated moderate diagnostic performance, suggesting that systemic

Table 1. *Demographic information of the study groups*

	Groups, median (25th-75th) percentile or mean ± SD				*P* value
	IUGR (*N* = 66)		Control (*N* = 68)		
Age,y	28.3	(6.6)	29.0	(4.8)	.497
Parity	3	(2-4)	1	(0-2)	< .0001*
Gestational, we	9	(8-10)	9	(8-10.5)	.472

Mann-Whitney U

Table 2. *Comparison of the blood parameters of the study and control groups*

	Groups, median (25th-75th) percentile or mean ± SD				*P* value
	IUGR (*N* = 66)		Control (*N* = 68)		
Hb, g/dL	12.7	(12-13)	12.5	(11-13)	.589
UREA,mg/dL	17.5	(14-21)	16	(14-20)	.197
CREA, mg/dL	0.55	(0.1)	0,55	(0.1)	.872
ALT, IU/L	16	(13-21)	18	(15-22)	.063
AST, IU/L	13	(10-16)	14	(10-17)	.757
NEU, 10^3/L)	6.2	(4.5-7.7)	8.0	(5.9-12.3)	< .0001*
LYMPH, 10^3/L	2.22	(0.63)	2.03	(0.66)	.090
MONO, 10^3/L	0.50	(0.46-0.57)	0.56	(0.42-72)	.040*
PLT, 10^3/L	243	(218-297)	245	(203-273)	.167
NLR	2.76	(2.22-3.68)	3.68	(2.49-8.31)	.001*
PLR	119	(92-142)	118	(96-142)	.996
SII	686	(536-939)	841	(646-1512)	.001*
SIRI	1.42	(1.05-1.86)	2.16	(1.13-5.46)	.001*
AISI	335	(271-471)	497	(292-967)	.001*
SIMI	60	(44-73)	66	(52-88)	.064

Mann-Whitney U

Table 3. *Diagnostic performance of inflammatory markers*

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)		*P* value
NLR	≤4.90	94	40	60.2	87.1	0.667	(0.575-0.759)	< .001
PLR	≤88.63	24	87	64.0	54.1	0.500	(0.401-0.599)	.997
SII	≤1238	94	34	57.9	85.2	0.663	(0.571-0.755)	< .001
SIRI	≤2.44	91	49	63.2	84.6	0.667	(0.574-0.761)	< .001
AISI	≤656	92	44	61.6	85.7	0.664	(0.571-0.758)	< .001
SIMI	≤65	65	53	57.3	61.0	0.593	(0.497-0.689)	.059

AUC: Area under curve ; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

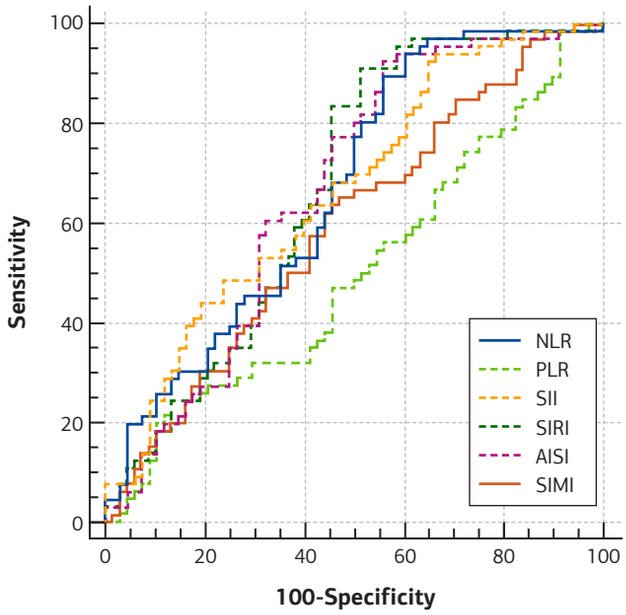


Figure 2. *ROC curve comparison of inflammatory markers*

inflammatory markers may have potential clinical utility in the evaluation of IUGR.

IUGR is a complex obstetric condition characterized by impaired fetal growth, most commonly resulting from placental insufficiency and chronic fetal hypoxia.[11] Increasing evidence suggests that inflammation plays a crucial role in the pathophysiology of placental dysfunction. Alterations in inflammatory pathways may contribute to endothelial dysfunction, impaired trophoblast invasion, and abnormal placental vascular development, ultimately leading to restricted fetal growth. Therefore, identifying easily accessible inflammatory biomarkers may provide valuable insight into disease mechanisms and improve early detection.

In recent years, systemic inflammatory indices derived from complete blood count parameters have attracted considerable attention because they are inexpensive, rapidly available, and easily reproducible. Previous studies evaluating inflammatory markers in obstetric complications such as preeclampsia,[9] gestational diabetes mellitus,[12] and preterm birth[13] have generally reported elevated inflammatory indices. However, findings regarding IUGR remain inconsistent.

In the study conducted by Aydogan and colleagues on patients with preeclampsia, they evaluated the systemic inflammatory index and reported that SII has higher sensitivity than PNI in detecting prematurity in infants of preeclamptic mothers. They also found that low PNI and SII were independent predictors of mortality. They concluded that low SII and NLR values at the time of hospital admission are important in predicting mortality in infants of preeclamptic mothers.[14] In the present study, NLR, SII, SIRI, and AISI values were found to be significantly lower in patients with IUGR. These findings suggest that these inflammatory markers may have an important role in the identification and diagnosis of IUGR.

Another study conducted by Dereli and colleagues with patients with idiopathic late-onset fetal growth restriction concluded that NLR, SII, PIV, and SIRI/ body mass index (BMI) were significantly higher in the late-onset idiopathic FGR (IL-FGR) group. They demonstrated that elevated SII, SIRI, PIV, and SIRI/BMI values were associated with an increased risk of future IL-FGR. Furthermore, they suggested that SIRI/BMI may serve as an important component of regression models for future FGR prediction and screening.[15] Our findings differ from those reported by Dereli et al., who demonstrated significantly increased NLR, SII, PIV, and SIRI/BMI values in patients with idiopathic late-onset fetal growth restriction (IL-FGR), suggesting that elevated inflammatory indices may be associated with an increased future risk of FGR. In contrast, in the present study, NLR, SII, SIRI, and AISI values were significantly lower in the IUGR group compared with healthy controls, despite showing moderate diagnostic performance in ROC analyses.

In this study, ROC curve analyses revealed that NLR, SII, SIRI, and AISI had moderate diagnostic accuracy with relatively high sensitivity but low specificity. Although these indices alone may not be sufficient as definitive diagnostic tools, they may still serve as supportive and cost-effective biomarkers in clinical practice, particularly when combined with ultrasonographic and Doppler findings.

Limitations

The present study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, inflammatory markers were evaluated only at a single time point, and dynamic changes during pregnancy could not be assessed. Nevertheless, the study also has important strengths, including the evaluation of multiple novel inflammatory indices and the inclusion of a well-matched control group.

Conclusion

In conclusion, our findings suggest that systemic inflammatory indices, particularly NLR, SII, SIRI, and AISI, are significantly altered in pregnancies complicated by IUGR and may have potential value in the clinical evaluation of these patients. Additionally, these markers exhibited moderate diagnostic performance with high sensitivity, suggesting their potential utility as supportive biomarkers in the evaluation of IUGR. Further large-scale prospective studies are needed to better clarify the role of systemic inflammation in IUGR and to determine the clinical applicability of these biomarkers.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was waived due to the retrospective design of the study.

Data Availability
The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest
The authors declare that there is no conflict of interest.

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Author Contributions (CRediT Taxonomy)
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Methodology: H.E., R.B
Software: AB.G
Validation: H.E, R.B
Data curation: R.B, AB.G
Formal analysis: AB.G
Investigation: H.E., R.B, AB.G
Writing – original draft: H.E
Writing – review & editing: H.E., R.B, AB.G
Visualization: H.E., R.B, AB.G
Supervision: H.E
Project Administration: H.E

AI Usage Disclosure
Artificial intelligence tools were used only for language editing and improving readability. No AI tool was used for data analysis, interpretation of results, or generation of scientific content. The authors take full responsibility for the content of the manuscript.

Abbreviations
AISI: Aggregate index of systemic inflammation
BMI: Body mass index
CI: Confidence interval
IL-FGR: Late-onset idiopathic fetal growth restriction
IUGR: Intrauterine growth restriction
NLR: Neutrophil-to-lymphocyte ratio
NPV: Negative predictive value
PIV: Pan-immune inflammation value
PLR: Platelet-to-lymphocyte ratio
PPV: Positive predictive value
ROC: Receiver operating characteristic curve
SII: Systemic immune-inflammation index
SIMI: Systemic inflammation marker index
SIRI: Systemic inflammation response index

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