Experimental
&
Clinical Article

Obstetrics; *Maternal Fetal Medicine and Perinatology*

Predictive Value and Prognostic Significance of Pan-Immune-Inflammation Value, Systemic Immune-Inflammation Index, and Systemic Inflammatory Response Index in Placenta Accreta Spectrum and Placenta Previa

Ruken DAYANAN[1], Ahmet Arif FILIZ[1], Gizem AKTEMUR[1], Betul TOKGOZ CAKIR[1], Gulsan KARABAY[1], Zeynep SEYHANLI[1], Merve AYAS OZKAN[1], Dilara DUYGULU BULAN[1], Ali Turhan CAGLAR[1]

Ankara, Türkiye

ABSTRACT

OBJECTIVES: Placenta accreta spectrum (PAS) and placenta previa (PP) are major obstetric complications associated with significant maternal and perinatal morbidity. Inflammatory markers have been increasingly studied for their role in predicting adverse pregnancy outcomes. This study aims to evaluate the predictive and prognostic significance of the Pan-Immune-Inflammation Value (PIV), Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Platelet-to-Lymphocyte Ratio (PLR) in patients diagnosed with PAS and PP.

STUDY DESIGN: A retrospective cohort study was conducted on pregnant women diagnosed with PAS and PP, along with a control group of healthy pregnancies. Preoperative inflammatory markers, including PIV, SII, SIRI, NLR, MLR, and PLR were analyzed. The predictive value of these indices for PAS was assessed using receiver operating characteristic (ROC) curve analysis,

RESULTS: Inflammatory markers were significantly higher in PAS and PP cases ($p<0.001$). PIV demonstrated the highest predictive value (AUC=0.695, cut-off >692, sensitivity 69.3%, specificity 66.7%). SIRI (AUC=0.671, cut-off >2.76, sensitivity 58.7%, specificity 69.2%), SII (AUC=0.630, cut-off >1012, sensitivity 64%, specificity 57.7%), MLR (AUC=0.673, cut-off >0.3584, sensitivity 68%, specificity 60.3%), and PLR (AUC=0.612, cut-off >144.9, sensitivity 60%, specificity 62.8%) also showed predictive potential.

CONCLUSION: PIV, SII, SIRI, MLR, and PLR are valuable inflammatory markers for predicting PAS and PP, with PIV demonstrating the highest diagnostic accuracy. These indices may serve as useful biomarkers for early risk stratification, potentially contributing to enhanced prenatal management and better-informed perinatal care in high-risk pregnancies.

Keywords: Pan-Immune-inflammation value; Placenta accreta spectrum; Placenta previa; Systemic Immune-Inflammation Index; Systemic Inflammation response index

Gynecol Obstet Reprod Med 2025;31(2):110-117

Introduction

Placenta accreta spectrum (PAS) and placenta previa (PP) are serious placental implantation anomalies that increase maternal and perinatal morbidity and mortality (1,2). PAS is characterized by trophoblast invasion across the decidual barrier into the myometrium, and in some cases, into adjacent organs (3). This is associated with defective decidualization, inadequate development of the fibrinoid matrix, and an uncontrolled increase in trophoblast invasion (4). PAS is divided into three subtypes: placenta accreta, increta, and percreta. In placenta accreta, the villi adhere directly to the myometrium

[1] Department of Perinatology Ankara Etlik City Hospital, Ankara, Türkiye

Address of Correspondence: Ruken Dayanan
Department of Obstetrics and Gynecology, Division of Perinatology, Ankara Etlik City Hospital 06170 Ankara, Türkiye
rukendayanan@gmail.com

Submitted for Publication: 03.03.2025 Revised for Publication: 20.03.2025
Accepted for Publication: 08.08.2025 Online Published: 10.08.2025

ORCID IDs of the authors:
AAF: 0000-0002-6137-0270
BTC:0000-0003-0202-4981
ZS:0000-0003-3924-3723
DDB: 0000-0001-9983-2306
RD: 0000-0002-8192-8841
GA: 0000-0001-6824-881X
GK:0000-0003-2567-2850
MAO: 0000-0002-2437-9719
ATC: 0000-0002-7022-3029

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	DOI:10.21613/GORM.2025.1587

How to cite this article: *Dayanan R. Filiz AA. Aktemur G. Tokgoz Cakir B. Karabay G. Seyhanli Z. Ayas Ozkan M. Duygulu Bulan D. Caglar AT. Predictive Value and Prognostic Significance of Pan-Immune-Inflammation Value, Systemic Immune-Inflammation Index, and Systemic Inflammatory Response Index in Placenta Accreta Spectrum and Placenta Previa. Gynecol Obstet Reprod Med. 2025;31(2):109-116*

in the absence of the decidua basalis, whereas in placenta increta, the invasion progresses to the myometrium, and in placenta percreta, the invasion may extend beyond the serosa and invade adjacent organs (1). Clinically, PAS poses serious maternal risks, including massive bleeding during labor, the need for hysterectomy, and surgical complications (5).

PP is a pathology characterized by the placenta lodging lower in the uterine cavity than the normal implantation site, partially or completely covering the internal os (6). It can present clinically in the third trimester with painless vaginal bleeding, preterm labor, and severe obstetric hemorrhage (7). Defective decidualization, trophoblast hyperactivity, and increased vascularization in uterine scar areas play an important role in the development of PP (4). The coexistence of PAS and PP is more common in patients with a history of previous cesarean section or uterine surgery, and the placement of the placenta in the lower uterine segment may lead to inadequate development of the decidual barrier and uncontrolled trophoblast invasion (8). Early recognition of these pathologies in the prenatal period is of great importance in order to optimize obstetric management and minimize maternal-fetal complications.

In recent years, the role of inflammation in obstetric complications has become increasingly important. Pan-Immune-Inflammation Value (PIV), Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Platelet-to-Lymphocyte Ratio (PLR) are important biomarkers derived from peripheral blood cells and used to assess systemic inflammatory response. These indices are increasingly preferred for the assessment of various inflammatory and immunologic processes due to their low cost and easy applicability. The pathophysiology of inflammation may play a critical role in placental implantation disorders and perinatal complications. In placental invasion anomalies, a disturbed balance between trophoblast invasion, decidual reaction, vascular remodeling, and immune response can lead to the activation of inflammatory processes (9). In this context, the predictive and prognostic value of hematological inflammatory indices in cases of PAS and PP is important to optimize clinical management. In this study, we aimed to evaluate the predictive value and prognostic significance of inflammatory indices in the diagnosis of PAS and PP.

Material and Method

This retrospective cohort study was conducted at Ankara Etlik City Hospital, including pregnant women with PAS and PP and a control group with normal placentation. A total of 229 pregnant women were included in the study and divided into three groups: PAS, PP, and control. The PAS group consisted of 76 cases diagnosed by prenatal imaging and confirmed intraoperatively at delivery. The PP group included 78 cases defined ultrasonographically on the basis of partial or complete placental coverage of the internal os. The control group consisted of 75 pregnant women without any placental abnormality who underwent elective cesarean section. Multiple pregnancies, placental anomalies, chronic systemic diseases, history of infection or sepsis during pregnancy, hypertensive pregnancy complications, maternal malignancy or immunodeficiency syndromes, and cases with incomplete medical records were excluded. The study period covered the period from 01/11/2022 to 01/12/2024 and was conducted in accordance with the Declaration of Helsinki with ethics committee approval of the Ankara Etlik City Hospital Ethics Committee (approval number: AESH-BADEK–2024-1227).

Demographic characteristics (maternal age, body mass index, number of pregnancies, number of deliveries, previous cesarean section, history of in vitro fertilization), obstetric characteristics (gestational week, mode of delivery, complications during delivery), laboratory results, and perinatal outcomes were retrospectively reviewed from patient files. In addition, postpartum hemorrhage, need for hysterectomy, application of Bakri balloon, need for blood transfusion, and need for postpartum intensive care were evaluated among delivery complications. Perinatal outcomes included gestational age, birth weight, APGAR scores, and neonatal intensive care unit (NICU) admission rate.

The inflammatory indices of PIV, SII, SIRI, MLR, PLR, and NLR were calculated from hemogram parameters measured in the third trimester of pregnancy. These calculations were made as follows: NLR, total neutrophil count divided by lymphocyte count; MLR, monocyte count divided by lymphocyte count; PLR, platelet count divided by lymphocyte count. SII was calculated by multiplying the number of platelets by the number of neutrophils and dividing by the number of lymphocytes (SII=[Platelet × Neutrophil] / Lymphocyte). SIRI was calculated as the number of neutrophils multiplied by the number of monocytes divided by the number of lymphocytes (SIRI=[Neutrophils × Monocytes] / Lymphocytes). PIV is a comprehensive index covering all inflammatory cells and was calculated as the product of platelet, neutrophil, and monocyte counts divided by the number of lymphocytes (PIV=[Platelet × Neutrophil × Monocyte] / Lymphocyte).

Using these parameters, we evaluated the diagnostic and prognostic value of inflammatory indices in cases of PAS and PP and their relationship with obstetric complications (postpartum hemorrhage, need for hysterectomy, and need for blood transfusion) and perinatal (gestational age, birth weight, neonatal intensive care admission, and respiratory distress syndrome) outcomes.

Statistical analysis

Statistical analyses were performed using IBM SPSS 22.0 software. The normal distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test, and variables with normal distribution were presented as mean ± standard

deviation, and variables without normal distribution were presented as median (interquartile range). Analysis of variance (ANOVA) and the Bonferroni test were used to determine the differences between groups for continuous variables with normal distribution, and the Kruskal-Wallis test and Mann-Whitney U test were used for variables without normal distribution. Pearson's chi-square and Fisher's exact test were used for categorical variables. ROC curve analysis was performed to determine the predictive value of inflammatory indices in the diagnosis of PAS and PP. The best threshold values were calculated based on the Youden index. P<0.05 was considered statistically significant.

Results

A total of 229 pregnant women were included in the study and divided into three groups: PAS (n=76, 33.2%), PP (n=78, 34.1%), and control (n=75, 32.8%). Demographic and delivery characteristics are presented in Table I. Maternal age was significantly higher in the PAS and PP groups compared to the control group (p<0.001). There was no significant difference between the groups in terms of height, weight, BMI, and weight gain during pregnancy (p>0.05). In terms of obstetric history, gravida, parity, and number of previous cesarean sections were significantly higher in the PAS group compared to the other groups (p<0.001). The nulliparity rate was lowest in the PAS group and highest in the control group (p<0.001). The history of in vitro fertilization was significantly higher in the PP group compared to the PAS and control groups (p=0.030).

In Table II, when complications during cesarean section were evaluated, the hysterectomy rate was 48.7% in the PAS group, while no hysterectomy was performed in the PP group (p<0.001). The incidence of postpartum hemorrhage was 25% in the PAS group and 16.7% in the PP group; however, there was no statistically significant difference between the groups (p= 0.203). The rate of Bakri balloon application was significantly higher in the PP group (35.9%) than in the PAS group (18.4%) (p=0.015). The requirement for blood transfusion was significantly greater in the PAS group (51.3%) compared to the PP group (16.7%) (p<0.001). The need for postpartum intensive care was observed in 6.6% only in the PAS group (p=0.027). These findings indicate that surgical complications were more common in PAS cases, and the rates of hysterectomy, need for blood transfusion, and intensive care unit hospitalization were significantly higher in the PAS group.

In terms of neonatal outcomes, the gestational week was 34 weeks in the PAS group, 35 weeks in the PP group, and 39 weeks in the control group, and there was a significant difference between the groups (p<0.001). The prematurity rate was 85.5% in the PAS group, 64.1% in the PP group, and 10.7% in the control group (p<0.001). Birth weight was significantly lower in the PAS and PP groups compared to the control group (p<0.001), but no significant difference was observed between the PAS and PP groups. Apgar scores were significantly lower in the PAS and PP groups compared to the control group (p<0.001). NICU hospitalization rate was 50% in the PAS group, 29.5% in the PP group, and 6.8% in the control group (p<0.001). Respiratory distress syndrome was 40.8% in the PAS group, 19.2% in the PP group, and 6.8% in the control group, with the highest rate in the PAS group (p<0.001). The need for mechanical ventilation was 23.7% in the PAS group and 10.3% in the PP group, which was significantly higher compared to the control group (p=0.001) (Table III).

Table I: *Descriptive and comparative analysis of demographic and delivery characteristics of the groups*

	PAS n=76 (33.2%)	Placenta Previa n=78 (34.1%)	Control n=75 (32.8%)	p
Maternal age (years)	32.2 ± 5.1	33.1 ± 5.9	28.5 ± 5.4	**<0.001**[a]
Height (cm)	160 ± 5.6	161 ± 6	162 ± 6.1	0.183[a]
Weight (kg)	75.6 ± 11.5	72.3 ± 15.6	76.4 ± 15.2	0.156[a]
BMI (kg/m2)	29.5 ± 5.2	28.3 ± 6.9	28.7 ± 5	0.394[a]
Weight gain during pregnancy (kg)	9.8 ± 4.1	10.3 ± 4.7	10.8 ± 4.2	0.400[b]
Gravida (n)	4 (4)	2 (3)	2 (2)	**<0.001**[b]
Parity (n)	2 (2)	1 (2)	1 (2)	**<0.001**[b]
Previous c/s count (n)	2 (2)	0 (1)	0 (0)	**<0.001**[b]
Nulliparous	10 (13.2%)	26 (33.3%)	36 (48%)	**<0.001**[c]
In vitro fertilization	2 (2.6%)	6 (7.7%)	0 (0%)	0.030[d]
Cesarean section	74 (97.4%)	78 (100%)	42 (56%)	**<0.001**[c]
Hysterectomy	37 (48.7%)	0 (0%)	0 (0%)	**<0.001**[d]
Postpartum hemorrhage	19 (25%)	13 (16.7%)	0 (0%)	**<0.001**[c]
Bakri balloon application	14 (18.4%)	28 (35.9%)	0 (0%)	**<0.001**[c]
Need for blood transfusion	39 (51.3%)	13 (16.7%)	0 (0%)	**<0.001**[c]
Need for ICU after delivery	5 (6.6%)	0 (0%)	0 (0%)	**0.007**[d]

Data are expressed as n (%), mean ± SD, or median (interquartile range) where appropriate. A p-value of <0.05 indi-cates a significant difference, and statistically significant p-values are in bold. a: Analysis of variance with Bonferro-ni test, b: Kruskal-Wallis test, c: Pearson chi-square, d: Fisher's exact test, PAS: Placenta accreta spectrum, BMI: Body mass index, c/s: Caesarean section, ICU: Intensive care unit.

Table II: *Complications of cesarean section in placenta accreta spectrum and placenta previa patients*

	PAS n=76 (49.4%)	Placenta Previa n=78 (50.6%)	p
Hysterectomy	37 (48.7%)	0 (0%)	**<0.001**[a]
Postpartum hemor-rhage	19 (25%)	13 (16.7%)	0.203[b]
Bakri balloon appli-cation	14 (18.4%)	28 (35.9%)	**0.015**[b]
Need for blood trans-fusion	39 (51.3%)	13 (16.7%)	**<0.001**[b]

Data are expressed as n (%), mean ± SD, or median (interquartile range) where appropriate. A p-value of <0.05 indi-cates a significant difference, and statistically significant p-values are in bold. a: Fisher's exact test, b: Pearson chi square, PAS: Placenta accreta spectrum, ICU: Intensive care un

Table III: *Birth characteristics and neonatal outcomes of the newborns*

	PAS n=76 (33.2%)	Placenta Previa n=78 (34.1%)	Control n=75 (32.8%)	p
Gestational age at delivery (week)	34 (3)	35 (3)	39 (2)	**<0.001**[a]
Prematurity (<37 weeks)	65 (85.5%)	50 (64.1%)	8 (10.7%)	**<0.001**[b]
Birth weight (gram)	2417 ± 569	2504 ± 672	3121 ± 535	**<0.001**[c]
Cesarean section	74 (97.4%)	78 (100%)	42 (56%)	**<0.001**[d]
Apgar score at 1st minute	8 (2)	8 (2)	9 (1)	**<0.001**[a]
Apgar score at the 5th minute	9 (2)	9 (2)	10 (0)	**<0.001**[a]
CAPO	40 (52.6%)	23 (29.5%)	9 (12.2%)	**<0.001**[b]
NICU admission	38 (50%)	23 (29.5%)	5 (6.8%)	**<0.001**[b]
Umbilical cord pH	7.30 (0.1)	7.34 (0.12)	7.35 (0.06)	**<0.001**[a]
Transient tachypnea of the new-born	9 (11.8%)	7 (9%)	6 (8.1%)	0.718[b]
Neonatal sepsis	2 (2.6%)	0 (0%)	0 (0%)	0.215[d]
Antenatal corticosteroid	65 (85.5%)	38 (48.7%)	6 (8%)	**<0.001**[b]
Neuroprotective magnesium treatment	5 (6.6%)	12 (15.4%)	2 (2.7%)	**0.014**[b]
Respiratory distress syndrome	31 (40.8%)	15 (19.2%)	5 (6.8%)	**<0.001**[b]
Continuous positive airway pres-sure	25 (32.9%)	9 (11.7%)	4 (5.4%)	**<0.001**[b]
Mechanical ventilation	18 (23.7%)	8 (10.3%)	3 (4.1%)	**0.001**[b]
Phototherapy for neonates	5 (6.6%)	11 (14.1%)	6 (8.1%)	0.247[b]
Neonatal hypoglycemia	9 (11.8%)	5 (6.4%)	7 (10.1%)	0.505[b]
Intraventricular hemorrhage	1 (1.3%)	1 (1.3%)	0 (0%)	1[d]

Data are expressed as n (%), mean ± SD, or median (interquartile range) where appropriate. A p-value of <0.05 indi-cates a significant difference, and statistically significant p-values are in bold. a: Kruskal-Wallis test, b: Pearson chi-square, c: Analysis of variance with Bonferroni test, d: Fisher's exact test, PAS: Placenta accreta spectrum, CAPO: Composite adverse perinatal outcome, NICU: neonatal intensive care unit.

Inflammatory markers were significantly higher in PAS compared to PP. MLR was 0.42 (0.25) vs. 0.32 (0.15), p<0.001. Similarly, PLR was significantly elevated in PAS patients, 147.20 (62.61) vs. 132.19 (65.01), p=0.017. SII 1155.99 (903.58) vs. 938.89 (669.3), p=0.005, SIRI 3.04 (3.89) vs. 2.31 (1.49), p<0.001, and PIV 812.08 (912.88) vs. 535.55 (480.85), p<0.001 were also significantly higher in PAS cases. However, NLR did not differ significantly between the groups 4.02 (3.76) vs. 3.94 (2.11), p=0.151. These findings suggest a more pronounced inflammatory response in PAS compared to PP (Table IV).

Table IV: *Comparison of the indices based on laboratory results of the groups*

	Control n=75 (32.8%)	Placenta Previa n=78 (34.1%)	PAS n=76 (33.2%)	p	Control vs. Pla-centa Previa (p)	Control vs. PAS (p)	Placenta Previa vs (p)
PIV	411.38 (346.06)	535.55 (480.85)	812.08 (912.88)	**<0.001**[a]	**0.007**[b]	**<0.001**[b]	**<0.001**[b]
SII	705.53 (479.65)	938.89 (669.3)	1155.99 (903.58)	**<0.001**[a]	**0.028**[b]	**<0.001**[b]	**0.005**[b]
SIRI	1.92(1.52)	2.31 (1.49)	3.04 (3.89)	**<0.001**[a]	**0.119**[b]	**<0.001**[b]	**<0.001**[b]
MLR	0.3 (0.15)	0.32 (0.15)	0.42 (0.25)	**<0.001**[a]	**0.163**[b]	**<0.001**[b]	**<0.001**[b]
PLR	112.9 (64.13)	132.19 (65.01)	147.20 (62.61)	**<0.001**[a]	**0.039**[b]	**<0.001**[b]	**0.017**[b]
NLR	3.72 (2.2)	3.94 (2.11)	4.02 (3.76)	0.050[a]	0.313[b]	0.015[b]	0.151[b]

Data are expressed as n (%), mean ± SD, or median (interquartile range) where appropriate. A p-value of <0.05 indicates a significant difference, and statistically significant p-values are in bold. a: Kruskal Wallis, b: Mann U test, PAS: Placenta accreta spectrum, 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, PIV: Pan-immune inflammation value.

In Table V, the diagnostic power of MLR, PLR, SII, SIRI, and PIV evaluated for the prediction of PAS was analyzed by ROC analysis. The most appropriate cut-off value for MLR was determined as >0.3584, with a sensitivity of 68%, specificity of 60.3%, and AUC of 0.673 (p<0.001). The cut-off value for PLR was >144.9, with a sensitivity of 60%, specificity of 62.8%, and AUC of 0.612 (p=0.017). The cut-off value for SII was >1012, with a sensitivity of 64%, specificity of 57.7%, and AUC of 0.630 (p=0.005). The optimal cut-off value for SIRI was >2.76, with a sensitivity of 58.7%, specificity of 69.2%, and AUC of 0.671 (p<0.001). The cut-off value for PIV was >692, with a sensitivity of 69.3%, specificity of 66.7%, and AUC of 0.695 (p<0.001) (Figure 1).

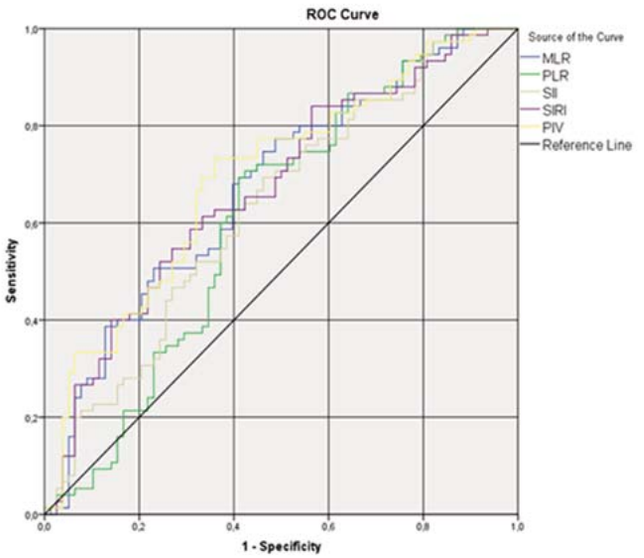

Figure 1: *ROC curve for the prediction of placenta accreta spectrum based on PIV, SII, SIRI, MLR, and PLR*

Discussion

PAS is an important obstetric pathology associated with increased inflammatory response and severe maternal-fetal complications in pregnancy (10). In our study, we found that inflammatory markers such as PIV, SII, SIRI, MLR, and PLR were significantly higher in patients with PAS. Inflammatory markers were also increased in PP patients compared to the control group, but this increase was more pronounced in PAS patients. This suggests that the inflammatory response may be effective at different levels in placental invasion disorders. The fact that these indices were especially high in the PAS group suggests that inflammation may play a central role in the pathophysiology of PAS and that these parameters could have predictive value for the disease.

In recent years, inflammatory mechanisms associated with placental vascular development and trophoblast invasion have been increasingly implicated in the etiopathogenesis of both PP and PAS. In PAS, it has been reported that invasion of trophoblasts through the normal decidual barrier into the myometrium may lead to the activation of both local and systemic inflammatory responses. This process involves the activation of immune cells, upregulation of proinflammatory cytokines, and inflammatory pathways triggered by tissue hypoxia (9). Similarly, it is thought that mechanisms including placental hypoxia, disruption of vascular integrity, and activation of the immune response may trigger inflammation in PP (11).

In a study conducted by Biswas et al. on biopsy samples obtained from the placental bed, it was found that trophoblast infiltration and inflammatory cell density were significantly increased in myometrial spiral arterioles in patients with PP (12). In addition, interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and interferon-gamma levels have been reported to be increased in the serum of pregnant women with PP (13). These findings suggest that PP may be closely related to inflammatory mechanisms, and systemic inflammation may play an important role in the pathophysiology of this disease. The inflammatory markers evaluated in our study, such as PIV, SII, SIRI, MLR, and PLR, stand out as potential biomarkers for objectively assessing these inflammatory processes. By reflecting the severity of systemic inflammation, these markers may be clinically useful in the diagnosis of placental invasion disorders and in determining the severity of the disease.

PIV is a hematologic index that has attracted attention in recent years as a comprehensive indicator of systemic inflammation and immune response. Evaluated as a prognostic biomarker in breast cancer, colorectal cancer, and other malignancies, PIV is important because it reflects the effect of in-

Table V: *Evaluation of PIV, SII, SIRI MLR, and PLR in PAS and placenta previa groups for the prediction of placenta accreta spectrum using ROC analysis*

	LR+	LR-	Cut-off*	Sensitivity	Specificity	AUC	%95 CI	p
PIV	2.08	0.46	>692	69.3%	66.7%	0.695	0.612 - 0.778	**<0.001**
SII	1.51	0.62	>1012	64%	57.7%	0.630	0.542 - 0.718	**0.005**
SIRI	1.91	0.60	>2.76	58.7%	69.2%	0.671	0.586 - 0.757	**<0.001**
MLR	1.71	0.53	>0.3584	68%	60.3%	0.673	0.588 - 0.758	**<0.001**
PLR	1.61	0.64	>144.9	60%	62.8%	0.612	0.522 - 0.702	**0.017**

**Cut-off values were found according to the Youden index. LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, AUC: Area under the curve, CI: Confidence Interval, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, PIV: Pan-immune inflammation value.*

flammation at the systemic level (14,15). It is known that the placenta is an immunologically active organ during pregnancy, and fetomaternal immune interactions play a critical role in a healthy pregnancy (16). During normal pregnancy, the immune system develops a balanced response between tolerance and protection mechanisms to prevent rejection of the fetus by the maternal immune system (17). However, this balance can be disrupted in placental implantation disorders.

Zhou and colleagues conducted a study on mice, reporting that in PAS, there is an increased pro-inflammatory status. The study found elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-4, along with decreased levels of anti-inflammatory cytokines, such as IFN-γ and IL-10. This imbalance may contribute to the abnormal progression of trophoblast invasion across the decidual barrier into the myometrium, leading to pathological villous invasion. (18). This process can lead to an activation of immune cells and disruption of vascular integrity, resulting in exacerbation of inflammation. These inflammatory processes can lead to increased neutrophil activation and, thus, elevated PIV levels. Furthermore, monocyte activation and changes in lymphocyte levels may also contribute to the role of PIV as a biomarker reflecting inflammatory burden. In PP, disruption of vascular integrity and hypoxia-induced triggering of inflammatory processes may lead to increased local inflammation and, thus, elevated PIV levels.

In recent years, PIV has received increasing attention for its potential to predict clinical outcomes and guide treatment strategies. In combination with other inflammatory markers, it has been reported to be evaluated for the prediction and management of pregnancy-related conditions such as unexplained infertility and intrahepatic cholestasis (19). However, to our knowledge, PIV has not been previously analyzed in PAS patients, and our study is the first of its kind. Our findings indicate that PIV levels were significantly elevated in the PAS group compared to both the PP and control groups. The highest PIV levels were found in PAS patients, suggesting that this group has a higher burden of systemic inflammation and that inflammatory processes may play an important role in the development of PAS. These findings suggest that PIV may be a clinically relevant biomarker not only in malignancies but also in obstetric pathologies such as placental invasion disorders.

SII and SIRI are hematologic markers reflecting the balance of immune and inflammatory responses in the body and have been evaluated for their prognostic value in various inflammatory diseases. In recent years, the potential of these parameters to be used as a diagnostic and prognostic tool in pregnancy-related conditions, such as intrahepatic cholestasis, gestational diabetes, and preeclampsia, has been investigated. In this context, studies investigating the role of inflammation in various obstetric pathologies have revealed that hematologic markers such as SII, SIRI, and NLR can be evaluated as potential biomarkers in the prediction and management of pregnancy complications. Gao et al. showed that SII, SIRI, and NLR values were significantly higher in the cesarean scar pregnancy group compared to the control group (20). Similarly, in a study by Yıldırım et al., pregnant women with PP were compared with healthy pregnant women, and patients in the PP group were divided into two subgroups: those who underwent peripartum hysterectomy due to PAS during labor (PAS-positive) and those with no evidence of invasion (PAS-negative). This value was found to be significantly higher in the PAS-positive group (21). In addition, Keles et al. compared PAS and PP patients and found that SII, PLR, and NLR values were statistically significantly higher in the PAS group (22). Similarly, in our study, inflammatory indices such as SII, SIRI, PLR, and MLR were found to be statistically significantly higher in the PAS group. Although it was observed that inflammatory markers increased in the PP group compared to the control group, this increase was more pronounced in PAS patients.

Our study revealed results consistent with previous literature examining the role of inflammatory markers in patients with PP and PAS. Our findings show that hematologic inflammatory indices, especially NLR, PLR, and MLR, were significantly higher in the PAS group. NLR levels showed a significant increase in the PAS group compared to the control group, but no statistically significant difference was found between the PP and PAS groups. On the other hand, PLR levels were highest in the PAS group and were found to be significantly higher compared to both the control and PP groups. Similarly, MLR levels were significantly higher in the PAS group, suggesting that monocyte-mediated inflammation may be effective in the development of PAS. Several studies investigating the relationship between PP and PAS and inflammatory markers also support our findings. Ersoy et al. showed that NLR increased in the presence of invasion anomaly in PP patients, and Abide Yayla et al. showed that NLR and PLR levels increased in PAS patients (23,24). In a study by Ozgen et al. comparing whole blood parameters in PP, PAS, and control groups, it was found that NLR was significantly higher in the PAS group (25). Keles et al. showed that PAS patients had higher NLR and PLR levels compared to PP patients (22). These findings suggest that the inflammatory response is more prominent in PAS patients and that hematologic inflammatory markers such as NLR, PLR, and MLR may play a role in the pathophysiology of PAS.

Studies have shown that inflammatory indices are significantly elevated in placental invasion anomalies, supporting that inflammation may play a central role in the pathophysiology of PAS. Increased levels of inflammatory markers can be considered an indicator of the immune system's response to trophoblast invasion, and it is envisioned that these markers may be clinically useful as biomarkers for the diagnosis and prognosis of PAS. In this context, our study contributes to filling the knowledge gap in this field by demonstrating the rela-

tionship between inflammation and placental invasion abnormalities. PAS is associated with high maternal morbidity and mortality, and early diagnosis and accurate risk stratification are critical in the management process. Our study showed that inflammatory indices such as PIV, SII, SIRI, PLR, and MLR were significantly higher in PAS patients, suggesting that inflammation may be effective in the development and progression of this pathology. Although there are studies addressing the relationship between inflammatory markers and placental invasion anomalies in the existing literature, the fact that this is the first study evaluating PIV in PAS patients increases the originality and scientific contribution of our study. Accordingly, the integration of inflammatory markers into clinical practice as biomarkers in the diagnosis of PAS and in determining the severity of the disease may contribute to the development of more effective strategies to optimize birth planning and reduce maternal complications.

Our study has some limitations. First, it has a retrospective design. Prospective and multicenter studies may better demonstrate the value of inflammatory indices in the diagnosis of PAS. Secondly, the generalizability of the results is limited due to the single-center design of our study. Further studies in different centers and larger patient populations will allow a stronger evaluation of the diagnostic and prognostic value of these indices. Third, inflammatory markers were evaluated only in the third trimester in our study, and dynamic changes could not be monitored during pregnancy. To better understand the early pathophysiology of PAS, longitudinal follow-up studies starting from the first trimester may be valuable to examine the changes in inflammation over time. Future studies should investigate whether inflammatory indices can be combined with ultrasonographic findings and other biochemical markers to create stronger predictive models for the diagnosis of PAS.

Conclusion

This study supports the possible role of inflammation in the pathophysiology of PAS by evaluating the relationship between PAS and inflammatory markers. PIV, SII, SIRI, PLR, and MLR were significantly higher in PAS patients, suggesting that the inflammatory response may be effective in the process of placental invasion. In particular, the fact that our study is the first study in which PIV was evaluated in PAS patients provides an important contribution to the prognostic value of this index in obstetric pathologies. These findings suggest that inflammatory markers can be used as biomarkers in the early diagnosis of PAS, determining the severity of the disease. Integration of these parameters into clinical practice may help to develop more effective approaches to the management of high-risk pregnancies.

Declarations

Ethics approval and consent to participate: Approval was obtained from the Institutional Review Board of Ankara Etlik City Hospital (approval number: AESH-BADEK–2024-1227). In this study, due to its retrospective nature, informed consent was waived with the approval of the Ethics Commit-tee of Ankara Etlik City Hospital. All data were anonymized, and participant confidentiality was strictly maintained.

Consent for publication: With the approval of the Ankara Etlik City Hospital Ethics Committee, in-formed consent was waived due to the retrospective nature of the study.

Availability of data and materials: If requested, data can be shared by the corresponding author with patient names anonymized.

Competing interests: The authors declare no conflicts of interest.

Funding: The study did not receive funding.

Authors' Contributions: Concept: RD, GA, BTC, ATC. Design: RD, GA, BTC, ATC. Data Collection or Processing: RD, GA, BTC, MAO, DDB. Analysis or Interpretation: RD, AAF, GK, ZS. Literature Review: RD, AAF, ZS. Writing: RD, AAF. Critical Review: GK, ZS, ATC.

Acknowledgments: None

References

1. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol. 2018; 218(1):75-87. Doi: 10.1016/j.ajog.2017.05.067. PMID: 28 599899.

2. Vural T, Bayraktar B, Karaca SY, Golbasi C, Odabas O, Taner CE. Indications, risk factors, and outcomes of emergency peripartum hysterectomy: A 7-year retrospective study at a tertiary center in Turkey. Malawi Med J. 2023; 35(1):31-42. Doi: 10.4314/mmj.v35i1.7. PMID: 381246 96, PMCID: PMC10645903.

3. Ma J, Liu Y, Guo Z, Sun R, Yang X, Zheng W, et al. The diversity of trophoblast cells and niches of placenta accreta spectrum disorders revealed by single-cell RNA sequencing. Front Cell Dev Biol. 2022;10:1044198. Doi: 10.3389/fcell.2022.1044198. PMID: 36420138, PMCID: PMC9676682.

4. Sharma S, Godbole G, Modi D. Decidual control of trophoblast invasion. Am J Reprod Immunol. 2016;75(3): 341-50. Doi: 10.1111/aji.12466. PMID: 26755153.

5. Schwickert A, van Beekhuizen HJ, Bertholdt C, Fox KA, Kayem G, Morel O, et al. Association of peripartum management and high maternal blood loss at cesarean delivery for placenta accreta spectrum (PAS): A multinational database study. Acta Obstet Gynecol Scand. 2021;100 Suppl 1:29-40. Doi: 10.1111/aogs.14103. PMID: 33524 163.

6. Jung EJ, Cho HJ, Byun JM, Jeong DH, Lee KB, Sung MS, et al. Placental pathologic changes and perinatal outcomes in placenta previa. Placenta. 2018;63:15-20. Doi:10.1016/ j. placenta.2017.12.016. Erratum in: Placenta. 2019;78:54.

Doi: 10.1016/j.placenta.2018.12.011. PMID: 29486851.

7. Anderson-Bagga FM, Sze A. Placenta Previa. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539818/.
8. Matsubara S, Takahashi H. Prior cesarean section and placenta accreta spectrum disorders: some clarifications. Arch Gynecol Obstet. 2018;298(2):447-8. Doi: 10.1007/s00404-018-4817-2. PMID: 29916109.
9. Lizárraga-Verdugo E, Beltrán-Ontiveros SA, Gutiérrez-Grijalva EP, Montoya-Moreno M, Gutiérrez-Arzapalo PY, Avendaño-Félix M, et al. The underlying molecular mechanisms of the placenta accreta spectrum: A narrative review. Int J Mol Sci. 2024;25(17):9722. Doi: 10.3390/ijms25179722. PMID: 39273667, PMCID: PMC11395310.
10. Bartels HC, Postle JD, Downey P, Brennan DJ. Placenta accreta spectrum: A review of pathology, molecular biology, and biomarkers. Dis Markers. 2018;2018:1507674. Doi: 10.1155/2018/1507674. PMID: 30057649, PMCID: PMC6051104.
11. Özgökçe Ç, Öcal A, Ermiş IS. Expression of NF-κB and VEGF in normal placenta and placenta previa patients. Adv Clin Exp Med. 2023;32(3):297-306. Doi: 10.17219/acem/154858. PMID: 36374543.
12. Biswas R, Sawhney H, Dass R, Saran RK, Vasishta K. Histopathological study of placental bed biopsy in placenta previa. Acta Obstet Gynecol Scand. 1999;78(3):173-9. PMID: 10078576.
13. Li L, Zhang J, Gao H, Ma Y. Nestin is highly expressed in foetal spinal cord isolated from placenta previa patients and promotes inflammation by enhancing NF-κB activity. Biomarkers. 2018;23(6):597-602. Doi: 10.1080/1354750X.2018.1468824. PMID: 29697001.
14. Lin F, Zhang LP, Xie SY, Huang HY, Chen XY, Jiang TC, et al. Pan-Immune-Inflammation Value: A new prognostic index in operative breast cancer. Front Oncol. 2022;12:830138. Doi: 10.3389/fonc.2022.830138. PMID: 35494034, PMCID: PMC9043599.
15. Fucà G, Guarini V, Antoniotti C, Morano F, Moretto R, Corallo S, et al. The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer. 2020;123(3):403-9. Doi: 10.1038/s41416-020-0894-7. PMID: 32424148, PMCID: PMC7403416.
16. Tong M, Abrahams VM. Immunology of the Placenta. Obstet Gynecol Clin North Am. 2020;47(1):49-63. Doi: 10.1016/j.ogc.2019.10.006. PMID: 32008671.
17. Borzychowski AM, Croy BA, Chan WL, Redman CW, Sargent IL. Changes in systemic type 1 and type 2 immunity in normal pregnancy and preeclampsia may be mediated by natural killer cells. Eur J Immunol. 2005;35(10):3054-63. Doi: 10.1002/eji.200425929. PMID: 16134082.
18. Zhou J, Chen H, Xu X, Liu Y, Chen S, Yang S, et al. Uterine damage induces placenta accreta and immune imbalance at the maternal-fetal interface in the mouse. Placenta. 2022;119:8-16. Doi: 10.1016/j.placenta. 2022.01.002. PMID: 35066308.
19. Özkan S, Aksan A, Kurt D, Kurt A, Fıratlıgil FB, Sucu S, et al. Are systemic inflammation markers reliable for diagnosing intrahepatic cholestasis of pregnancy? A retrospective cohort study. Am J Reprod Immunol. 2024;92(4):e13937. Doi: 10.1111/aji.13937. PMID: 39367767.
20. Gao J, Jiang N, Chen Q, Zhao M, Tang Y. Systemic Immune-Inflammation Indices could be additional predictive markers for cesarean scar pregnancy. Am J Reprod Immunol. 2024;92(3):e13924. Doi: 10.1111/aji.13924. PMID: 39221973.
21. Yıldırım M, Sahin D. Evaluation of complete blood count inflammatory indices in pregnant women diagnosed with placenta previa. JGON. 2024;21:88-94. Doi: 10.38136/jgon.1290004.
22. Keles A, Dagdeviren G, Yucel Celik O, Karatas Sahin E, Obut M, Cayonu Kahraman N, et al. Sys-temic immune-inflammation index to predict placenta accreta spectrum and its histological sub-types. J Obstet Gynaecol Res. 2022;48(7):1675-82. Doi: 10.1111/jog.15254. PMID:35365935.
23. Ersoy AO, Ozler S, Oztas E, Ersoy E, Kirbas A, Danisman N. The association between placenta previa and leukocyte and platelet indices - a case control study. Ginekol Pol. 2016;87(5):367-71. Doi: 10.5603/GP.2016.0006. PMID: 27304653.
24. Abide Yayla C, Ozkaya E, Tayyar A, Senol T, Senturk MB, Karateke A. Predictive value of com-plete blood count parameters for placental invasion anomalies. J Matern Fetal Neonatal Med. 2017;30(19):2324-8. Doi: 10.1080/14767058.2016.1247266. PMID: 27734722.
25. Ozgen G, Ozgen L. Complete blood count parameters in the antepartum diagnosis of placental invasion anomalies. Ann Clin Anal Med. 2020;11. Doi:10.4328/ACAM.2031 5.