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Research

Can Systemic Inflammation Response Index (SIRI) and Neutrophil-to-lymphocyte Ratio (NLR) Predict the Presence of Placenta Accreta Spectrum in Pregnant Women with Placenta Previa?

Sistemik Enflamasyon Yanıt İndeksi (SIRI) ve Nötrofil-lenfosit Oranı (NLR), Plasenta Previalı Gebe Kadınlarda Plasenta Akreta Spektrumunun Varlığını Öngörebilir mi?

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ABSTRACT

Objective: Can systemic inflammation response index (SIRI) and neutrophil-to-lymphocyte ratio (NLR) predict the presence of placenta accreta spectrum (PAS) in pregnant women with placenta previa (PP)?

Methods: This retrospective case-control study included 415 singleton pregnancies diagnosed with PP, of which 119 were in the study group with PAS, and 296 were with no evidence of placental invasion. Demographic characteristics, laboratory parameters, and SIRI values of the groups were compared. Cut-off values that could predict PAS were calculated.

Results: The mean gravidity, parity, abortion, and number of previous cesarean sections were higher in the PAS group compared to the control. Gestational age was lower in the PAS group. There was no significant difference between the groups regarding body mass index and maternal age. Mean lymphocyte and platelet counts were lower in the PAS group, while red cell distribution width (RDW) was higher than the control group. The cut-off value for RDW was 3.63 (66% sensitivity, 48% specificity) in the receiver operating characteristic (ROC) curve. The optimal sensitivity/specificity balance for NLR was 4.49, with 46% sensitivity and 69% specificity in the ROC curve.

Conclusion: RDW and NLR are useful auxiliary indicators for predicting PAS. The increases in SIRI values in the PAS group were not statistically significant. The relationship between inflammatory parameters and the histological subtypes of PAS should be investigated in larger case groups.

Keywords: Inflammatory biomarkers, placenta accreta spectrum, placenta previa, systemic inflammatory response index

ÖZ

Amaç: Sistemik enflamasyon yanıt indeksi (SIRI) ve nötrofil-lenfosit oranı (NLR) plasenta previalı (PP) hamile kadınlarda plasenta akreta spektrumunun (PAS) varlığını tahmin edebilir mi?

Gereç ve Yöntem: Bu retrospektif olgu-kontrol çalışmasına PP tanısı konulan 415 tekil gebelik dahil edildi, 119'u PAS çalışma grubundaydı ve 296'sında plasenta istilası kanıtı yoktu. Demografik verileri, laboratuvar sonuçları ve SIRI değerleri gruplar arasında karşılaştırıldı. PAS'yi öngören alıcı çalışma karakteristiği (ROC) eğrisi kesme değerleri hesaplandı.

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ÖZ

Bulgular: Ortalama gravida, parite, düşük ve önceki sezaryen sayısı PAS grubunda kontrol grubuna göre daha yüksekti. PAS grubunda gebelik yaşı daha düşüktü. Gruplar arasında vücut kitle indeksi ve anne yaşı açısından önemli bir fark yoktu. PAS grubunda kontrol grubuna göre ortalama lenfosit ve trombosit sayıları daha düşük, kırmızı hücre dağılım genişliği (RDW) ise daha yüksekti. ROC eğrisinde RDW için kesme değeri 3,63 idi (%66 duyarlılık, %48 özgüllük). NLR için optimal duyarlılık/özgüllük dengesi 4,49 idi (%46 duyarlılık, %69 özgüllük).

Sonuç: RDW ve NLR, PAS'yi tahmin etmede faydalı yardımcı göstergelerdir. SIRI değerlerindeki artışlar PAS grubu için istatistiksel olarak anlamlı değildi. Enflamatuvar parametreler ve PAS'nin histolojik alt tipleri arasındaki ilişki daha büyük olgu gruplarında araştırılmalıdır.

Anahtar Kelimeler: Enflamatuvar biyobelirteçler, plasenta acreta spektrumu, plasenta previa, sistemik immün enflamatuvar indeks, sistemik enflamatuvar yanıt indeksi

INTRODUCTION

Placental invasion anomalies indicate abnormal trophoblast invasion into the myometrium, sometimes extending to the serosa or beyond, without decidua. The level of placenta intrusion might include placenta accreta, placenta increta, or placenta percreta (1,2). These histological subtypes often coexist and are generally called the placenta accreta spectrum (PAS).

Placenta previa (PP) is identified as one of the most important risk factors of PAS, defined by an internal cervical os with a placental edge distance of less than 20 mm. Another significant risk of PAS is prior cesarean section. In a prospective study evaluating the frequency of PAS in women with PP who underwent cesarean delivery, an increase in the number of cesarean deliveries corresponded to a higher frequency of PAS. While the coexistence of PAS was 3% after one cesarean delivery in a patient with PP, it rose to 67% after five or more cesarean deliveries (3). Other risk factors include maternal age, multiple pregnancies, multiparity, a history of prior uterine surgeries, pelvic radiation history, manual removal of the placenta, postpartum endometritis, infertility, and fertility treatments (4,5).

PAS is a significant cause of maternal morbidity because the placenta does not spontaneously separate during childbirth. Attempts to manually remove it can result in life-threatening bleeding, often necessitating a hysterectomy. Perinatal outcomes significantly improve when PAS is diagnosed before delivery. However, a large proportion of PAS cases cannot be diagnosed until childbirth (6). The first step is identifying risk factors in the mother. While PAS is often asymptomatic in the antenatal period, it is diagnosed through findings on obstetric ultrasound (USG) screenings. For women without clear risk factors for placental invasion anomalies, incidental findings can occur during routine USG examinations. Still, in most cases, the diagnosis is not made until after the placenta is delivered. Postpartum haemorrhage is a common indication for peripartum hysterectomy in PAS. Transfusion is the most frequently encountered complication, followed by other surgical complications, most commonly bladder injuries.

USG is the preferred choice for diagnosing PAS when performed by experienced professionals (7). Magnetic resonance imaging could be utilised if USG poses challenges, such as maternal obesity, a posteriorly located placenta, or laterally extending placental invasion. However, the success of imaging methods may vary depending on the experience of the specialist evaluating the method and the clinical characteristics of the patient. Considering the increasing prevalence of PAS and its adverse fetal and maternal outcomes, diagnostic tools that do not require clinical experience and are easy to apply have become the focus of attention. Inflammatory markers are widely utilised to predict overall morbidity and mortality in various cancer types. Numerous studies have suggested that the invasion of trophoblasts also shares many common features with the invasion of cancer cells (8). Based on this, markers such as mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR) and platelet-lymphocyte ratios (PLR) have been extensively investigated in diagnosing the presence of PAS (9-11).

Systemic immune-inflammation index (SII) and systemic immune response index (SIRI), are new indices that offer insights into the prognosis of certain cancer types, response to treatment, and risk assessment for cardiovascular diseases (12-14). Within the scope of this research, we aimed to elucidate the predictive value of SIRI and other inflammatory indices in PAS and diagnose its subtypes in PP.

METHODS

This case-control study included 415 singleton pregnancies diagnosed with PP, of which 119 were in the study group with PAS, and 296 were without evidence of placental invasion. Ethics committee approval has been granted by University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, on 11/10/2023 with protocol number 2023-466.

Since the study was retrospective, informed consent was not obtained from the participants.

The location of placental implantation and the depth of myometrial invasion were determined by perinatology department physicians using transabdominal and transvaginal 2D grayscale and Doppler ultrasonography (Arietta 850, Hitachi, Tokyo, Japan) at the time of admission. The diagnosis of PAS was confirmed by macroscopic evaluation at the time of cesarean section and by histopathological evaluation postoperatively. The PAS group comprised pregnant women who underwent partial uterine resection or cesarean hysterectomy due to the detection of PAS during surgery; the diagnosis was histologically confirmed. The PP group included pregnant women confirmed to have PP during surgery but with no detected placental invasion.

Pregnant women with chronic systemic disorders such as hypertension and diabetes mellitus, those with ongoing infections, and smokers were excluded from the study. Additionally, for individuals with multiple pregnancies, complications such as preeclampsia, preterm premature rupture of the membranes (PPROM), intrauterine growth restriction, gestational diabetes mellitus, intrauterine fetal death, and pregnancy cholestasis were also excluded.

Patient data were sourced from our hospital management information system. Data reliability and validity were ensured by having one author enter the data, which another author then validated. Complete blood count components obtained from patients before medical or surgical intervention were used for analysis. Haematological analyses were performed in the same laboratory. NLR, PLR, monocyte-lymphocyte ratio (MLR), SII, and SIRI were calculated using neutrophil, platelet, monocyte, and lymphocyte values.

SIRI was calculated as the monocyte × neutrophil/lymphocyte; SII was calculated as the platelet × neutrophil/lymphocyte. Variables such as age, gravidity, parity, miscarriage history, previous cesarean count, gestational age at birth and body mass index at the time of delivery, along with the histological subtype of PAS, were evaluated in the patients. The predictive success of all variables in estimating PAS in pregnant women was calculated, and the cut-off values of significant variables were determined. The relationship between inflammatory indices of PAS histological subtypes was also investigated. Tubes containing K3EDTA were used for CBC analysis. CBC parameters were measured using an automated haematology analyser (XT2000i, Sysmex, Osaka, Japan).

Statistical Analysis

All statistical analyses were conducted using R software. Normality was assessed with the Shapiro-Wilk test. Continuous variables are expressed as means and standard deviations. The Mann-Whitney U test was employed to compare two groups for variables not normally distributed. For dependent variables with more than two categories, the Kruskal-Wallis test was used. Categorical data are presented as counts and percentages and analysed using chi-square and Fisher's exact tests as appropriate. The predictive ability of inflammatory parameters for PAS was assessed using receiver operating characteristic (ROC) curve analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the study, 119 (26.7%) patients were in the PAS group, and 296 (73.3%) patients were in the PP group. The mean age of the patients in the PAS group was higher than the PP group, although the difference was not statistically significant (p=0.059). The patients' mean gravidity, parity, abortus, and number of previous c-sections were significantly higher in the PAS group than in the PP group (p-value <0.001 for all the variables). A significant difference was observed between the PAS and PP groups regarding gestational age (p<0.001). Additionally, the mean lymphocyte and platelet counts were significantly lower in the PAS group compared to the PP group (p=0.044 and p=0.018, respectively). Furthermore, the RDW and NLR were significantly higher in the PAS group than in the PP group (p=0.009 and p=0.011, respectively). The groups had no significant differences in MPV, PDW, PLR, MLR, SII, and SIRI. The demographic characteristics of the study population, haematological parameters, SII, SIRI, and other inflammatory indices are presented in Table 1.

The performance of inflammatory parameters in predicting PAS was analysed using the ROC curve. The Youden index was utilised to find the cut-off points for PAS diagnosis. The ROC curve cut-off value for RDW that yielded the best sensitivity/specificity balance was determined to be 3.63 (66% sensitivity, 48% specificity). The optimal sensitivity/specificity balance for NLR was achieved at a cut-off value of 4.49, resulting in 46% sensitivity and 69% specificity. The corresponding area under the curves and 95% confidence ıntervals can be found in Table 2 and Figure 1.

We compared the subtypes of PAS (accreta, increta, and percreta) based on the inflammatory parameters outlined in Table 3. Although there was a lower mean for both SII and SIRI in the increta subtype, no significant differences were observed across the various PAS subtypes.

Table 1. Comparison of demographic features. Laboratory test results and inflammatory parameters between healthy pregnant women and pregnant women with PAS

Parameters	PP (n=296)	PAS (n=119)	p-value
	Mean ± SD	Mean ± SD	
Maternal age (tear)	31.6±5.4	32.7±0.5	0.059[t]
Gravidity (n)	3.1±0.1	4.5±0.2	**<0.001**[*m]
Parity (n)	1.6±0.1	2.6±0.1	**<0.001**[*m]
Abortus (n)	0.5±0.1	0.9±0.1	**<0.001**[*m]
Number of previous cesarean section (n)	0.8±0.1	2.2±0.1	**<0.001**[*m]
Gestational ages at birth (week)	35.7±0.2	34.3±0.2	**<0.001**[*m]
BMI	28.0±5.1	28.5±5.2	0.444[m]
Neutrophil count (µL)	8.3±6.0	8.4±3.4	0.092[m]
Lymphocyte count (µL)	2.2±0.1	1.9±0.1	**0.044**[*m]
Monocyte count (µL)	0.7±0.02	0.7±0.03	0.359[m]
Platelet count (10^3/µL)	237.6±4.1	220.7±6.1	**0.018**[*m]
Mean platelet volume (fL)	10.9±0.1	10.7±0.1	0.087[m]
Platelet distribution width	13.2±0.2	12.9±0.2	0.231[m]
Red cell distribution width	14.9±0.2	15.3±0.2	**0.009**[*m]
Neutrophil-to-lymphocyte ratio	4.3±2.6	5.3±4.0	**0.011**[*m]
Monocyte-to-lymphocyte ratio	0.4±0.2	0.4±0.3	0.247[m]
Platelet-to-lymphocyte ratio	127.7±58.9	131.3±59.3	0.570[m]
Systemic immune-inflammation index (10^9/L)	1033.2±42.6	1149.7±86.5	0.281[m]
System inflammation response index	3.0±2.2	3.7±3.3	0.087[m]

PP: Placenta previa, PAS: Placenta accreta spectrum, BMI: Body mass index, [t]: Independent t-test, [m]: Mann-Whitney U test, SD: Standard deviation, [*]: A significant p-value is <0.05

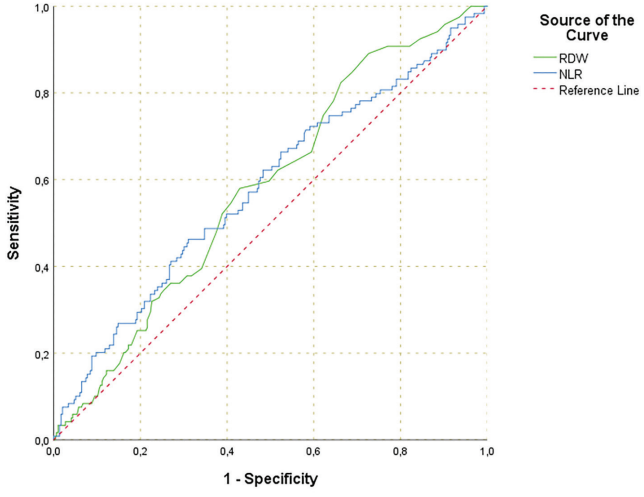

Figure 1. Receiver operating characteristic curve for the placental invasion anomalies in pregnant women with placenta previa

NLR: neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width

DISCUSSION

In the presence of PP, high sensitivity is required for PAS because when PAS is diagnosed prenatally, maternal and perinatal outcomes significantly improve. Imaging techniques can help predict the extent of placental invasion (15). However, the diagnosis is not established in most PAS cases until delivery. The need for an accurate, easily detectable, and cost-effective diagnosis of PAS has led to the investigation of alternative diagnostic biomarkers. For this purpose, the effectiveness of serum biomarkers used in the screening for growth factors, cell-free DNA, fetal aneuploidy, and cardiac function disorders was investigated (16,17).

In this study, pregnant women with PP and PAS, were retrospectively examined regarding routinely measured hemogram parameters, and newly identified inflammatory markers. We found that some serum inflammatory markers

Table 2. ROC curve analysis to assess the performance of inflammatory parameters in predicting placenta accreata spectrum

Parameters	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	p-value	95% confidence interval
RDW	3.6	66	48	0.582	**0.006***	0.523-0.640
NLR	4.5	46	69	0.580	**0.011***	0.518-0.642
SIRI				0.554	0.087	0.492-0.615
MLR				0.536	0.247	0.472-0.601
SII				0.534	0.283	0.472-0.596
PLR				0.518	0.565	0.457-0.579
PDW				0.462	0.234	0.401-0.524
MPV				0.446	0.087	0.384-0.508

RDW: Red cell distribution width, NLR: Neutrophile to lymphocyte ratio, SIRI: Systematic inflammation response index (calculated as monocyte*neutrophile/lymphocyte), MLR: Monocyte to lymphocyte ratio, SII: Systemic immune-inflammation index, PLR: Platelet count to lymphocyte ratio, PDW; Platelet distribution width, MPV: Mean platelet volume, ROC: Receiver operating characteristic, AUC: Area under the curve. *: A significant p-value is <0.05

Table 3. Inflammatory parameters according to histological subtypes of PAS

Parameters	Accreta (n=29)	Increta (n=22)	Percreta (n=35)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
SII	1171.2±881.4	978.2±561.7	1401.3±1355.4	0.203[k]
NLR	5.0±3.7	4.8±2.8	6.3±5.5	0.345[k]
PLR	128.3±50.1	123.6±42.9	145.9±83.1	0.396[k]
MPV	12.6±0.9	10.8±1.6	10.5±1.0	0.391[k]
PDW	17.6±2.2	13.4±2.8	12.2±2.5	0.077[k]
SIRI	4.2±24.9	3.3±2.0	4.1±3.3	0.100[k]
MLR	0.4±0.3	0.4±0.2	0.4±0.3	0.123[k]
RDW	19.9±1.9	15.1±2.4	16.1±3.2	0.141[k]

SII: Systemic immune-inflammation index, NLR: Neutrophile to lymphocyte ratio, PLR: Platelet count to lymphocyte ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, SIRI: System inflammation response index, MLR: Monocyte to lymphocyte rate, RDW: Red cell distribution width, SD: Standard deviation, [k]: Kruskal-Wallis test, *: A significant p-value is <0.05

could predict PAS in women with PP. Our study determined that RDW could predict PAS in PP, while no significant relationship was found between SII and SIRI. Additionally, no significant relationship was found between the histological subtypes of PAS and inflammatory markers.

The previous literature shows conflicting results regarding the relationship between PP and PAS, and inflammatory markers obtained from complete blood count. Ersoy et al. (10) found that the MPV and platelet large cell ratio values were reduced in patients diagnosed with placenta percreta in the third trimester compared to PP patients. In another study, it was reported that the NLR and PLR values in PP cases were significantly higher than in non-PP pregnant women (11). Abide Yayla et al. (9) demonstrated that NLR and MPV increased in PAS patients compared to those without placental invasion, while RDW decreased Karakoç et al. (18) stated that no significant difference was found in NLR and PLR values, but the delta neutrophil index was significantly higher in PP and PAS cases. According to Keles et al. (19), there was no difference in RDW between PAS and PP cases; however, PDW was lower, and MPV, NLR, and PLR were higher in PAS cases compared to PP cases. In our study, RDW and NLR were significantly higher in PAS than in PP cases. This result is consistent with a study suggesting that elevated RDW values indicate increased inflammation and oxidative stress (20).

Peripheral blood cells include pro-inflammatory cells, such as neutrophils, platelets, and monocytes; and anti-tumour immune cells, such as lymphocytes, that can indirectly reflect the tumour microenvironment (21). Keles et al. (19) found that the platelet and neutrophil counts were high, while the lymphocyte count was low in PAS cases compared to PP cases. Ersoy et al. (10) demonstrated a significant increase in the neutrophil count in PP patients compared to healthy controls. In our study, although there was no significant difference in the monocyte count between PAS and PP cases, compared to PP cases, the neutrophil count was higher, and the lymphocyte and platelet counts were lower in PAS cases.

SIRI is a new prognostic marker reflecting the inflammatory response. Elevated SIRI has been associated with poor prognosis in various cancers and inflammatory diseases (22,23). Wang et al. (24) associated high SIRI levels with reduced survival time, accelerated tumour progression, and increased rates of recurrence or metastasis in cancer patients. A higher SIRI level correlates with a stronger systemic immune-inflammatory response (25). In the obstetric field, SIRI has been utilised in several studies. In a recent study, SIRI was reported to have the highest diagnostic power among inflammatory parameters in determining the diagnosis of early pregnancy loss (26). Fang et al. (27), in their study comparing cervical cerclage with non-invasive procedures, found that initial SII and SIRI values were important biochemical markers in predicting maternal and neonatal outcomes. The relationship between SIRI levels and PAS has not been published yet. In our study, although we found higher SIRI values in PAS cases compared to PP cases, we could not establish a significant relationship between them.

SII is an objective marker reflecting systemic inflammation. Recently, SII has been associated with the diagnosis, prognosis, and response to treatment in various malignant tumours (13). Tanacan et al. (28) identified a relationship between elevated SII values in pregnant women with PPROM and negative neonatal outcomes. Keles et al. (19) found a significant increase in SII in pregnant women with PAS. In our study, although we observed higher SII values in PAS patients than in PP patients, we could not establish a significant relationship between the higher SII values and PAS patients.

In the literature, only a few studies have investigated the relationship between inflammatory parameters and the histological subtypes of PAS. Our study could not find a significant relationship between the histological subtypes of PAS and SII, SIRI, and inflammatory markers. Thus, we concluded that in addition to the depth of invasion, the extent of invasion could also influence inflammatory parameters in PAS patients. Our findings are consistent with the study that did not find a relationship between SII and other inflammatory markers and PAS (19).

The basic limitations of this study are that the data were obtained from a single clinical research centre, along with its retrospective design. The study cohort size was reduced due to patients not being included, adversely affecting the study's power. However, its strengths include a greater number of cases compared to previous studies and the evaluation of numerous haematological inflammatory parameters. The relationship between SIRI and the presence of PAS, and the histological subtypes of PAS, has been investigated for the first time.

Conclusion

As a result, PAS leads to changes in inflammatory parameters due to its invasive nature. In cases suspected to have placental invasion anomalies, parameters from complete blood count can also be utilised, in addition to imaging methods. RDW and NLR can be used to predict PAS in pregnancies with PP. However, the strength of this proposition should be supported by more comprehensive studies. Furthermore, the relationship between inflammatory parameters at different trimesters and maternal-fetal morbidity and mortality should be investigated. The association between inflammatory parameters and the histological subtypes of PAS should be explored in larger case groups.

ETHICS

Ethics Committee Approval: Ethics committee approval has been granted by University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, on 11/10/2023 with protocol number 2023-466.

Informed Consent: Since the study was retrospective, informed consent was not obtained from the participants.

FOOTNOTES

Authorship Contributions

Concept: N.Ç., Design: N.Ç., E.K., İ.Ö.A., S.A.Ş., İ.P., I.T.B., T.T.A., Data Collection or Processing: E.K., İ.Ö.A., S.A.Ş., İ.P., I.T.B., T.T.A., Analysis or Interpretation: E.K., İ.Ö.A., S.A.Ş., İ.P., I.T.B., T.T.A., Writing: N.Ç.

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