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CORRELATION BETWEEN NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR), PLATELET-TO-LYMPHOCYTE RATIO (PLR), AND SYSTEMIC IMMUNE INFLAMMATION INDEX (SII) WITH PLACENTA ACCRETA SPECTRUM (PAS)

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ABSTRACT

Background: Placenta accreta spectrum (PAS) is a severe obstetric complication characterized by abnormal placental invasion into the myometrium due to defects in the decidual layer. This condition is associated with massive postpartum hemorrhage and increased maternal morbidity and mortality. Early identification of PAS remains challenging. Systemic inflammatory biomarkers derived from routine blood tests, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been proposed as potential predictors of abnormal placentation.
Objective: This study aimed to analyze the relationship between NLR, PLR, and SII and the occurrence of placenta accreta spectrum and to evaluate their predictive accuracy for PAS.
Methods: This study used an analytic observational design conducted at H. Adam Malik General Hospital and affiliated hospitals. The study included pregnant women with placenta previa who underwent delivery and histopathological evaluation. Demographic characteristics, obstetric history, and laboratory parameters including neutrophil count, lymphocyte count, platelet count, NLR, PLR, and SII were collected. The diagnosis of PAS was confirmed based on histopathological findings. Statistical analysis was performed to determine differences between PAS and non-PAS groups and to evaluate the predictive performance of NLR, PLR, and SII using receiver operating characteristic (ROC) curve analysis.
Results: Significant differences were found in laboratory inflammatory parameters between PAS and non-PAS groups. Higher values of neutrophils, NLR, PLR, and SII were observed in patients with PAS compared to those without PAS. ROC curve analysis demonstrated that NLR, PLR, and SII had diagnostic value in predicting PAS, with SII showing the highest predictive performance among the evaluated indices. These findings indicate that increased systemic inflammatory activity is associated with abnormal placental invasion.
Conclusion: NLR, PLR, and SII are significantly associated with placenta accreta spectrum. These hematological indices derived from routine blood tests may serve as simple and accessible biomarkers for predicting PAS and may assist clinicians in early identification and management planning for high-risk pregnancies.

Keywords : Inflammatory Biomarkers, Neutrophil-to-Lymphocyte Ratio, Placenta Accreta Spectrum, Platelet-to-Lymphocyte Ratio, Systemic Immune-Inflammation Index,.

BACKGROUND

Placenta accreta spectrum (PAS), also known as *Abnormally Invasive Placenta* (AIP), is an obstetric-gynecological pathological condition in which there is a failure of the physiological detachment of the placenta from the uterine wall after delivery. This causes severe bleeding that can threaten the lives of both the mother and the fetus. PAS is caused by defects in the basal decidua that allow chorionic villi and trophoblast cells to invade deeper. Based on the degree of attachment to the myometrium, PAS is classified into three variants: *Placenta accreta* (PA), where chorionic villi attach to the surface of the myometrium without a decidual layer but do not invade muscle fibers;

Placenta increta (PI), where chorionic villi invade the myometrium more deeply without reaching the serosa; and *Placenta percreta* (PP), where villi reach the uterine serosa and often involve surrounding pelvic organs, particularly the bladder.[1,2] Manual removal and curettage are difficult due to deep invasion of chorionic villi. Therefore, diagnosis before and during labor is crucial to determine the optimal therapeutic approach. In 2019, FIGO (International Foundation for Gynecology and Obstetrics) introduced various degrees of PA. *Placenta accreta* Grade I is characterized by failure of placental separation during delivery and severe bleeding during manual removal, which may require hysterectomy for histological evaluation. Grade II PI shows a blue or purple placenta with neovascularization spreading toward the peritoneum, although no invasion into the uterine wall is visible macroscopically invasion into the uterine wall. However, chorionic villi may be found in the myometrium or uterine blood vessels on histological examination. PP Grade III, the most invasive form, is further divided into Grade 3a (invasion limited to the uterine serosa), Grade 3b (macroscopically, the placenta invades the bladder, with chorionic villi found in the uterine serosa and bladder wall), and Grade 3c (more extensive invasion into other pelvic organs).[1,3]

A study conducted by Brennan K found that the incidence of *placenta accreta* worldwide ranges from 1.7 to 900 cases per 100,000 pregnancies, with the average incidence of *placenta accreta* worldwide being 189 cases per 100,000 pregnancies. This shows a significant increase compared to the incidence of *placenta accreta* in the 1960s, which was 1 case per 30,000 pregnancies. It is reported that countries such as the United States have an incidence of *placenta accreta* of 40 cases per 100,000 pregnancies and in the United Kingdom 17 cases per 100,000 pregnancies.(*The International Federation of Gynecology and Obstetrics* estimates that if the trend of *cesarean section* (CS) deliveries continues to increase, it will lead to an increase in the incidence of *placenta accreta* by 4,500 cases per year and 130 deaths due to pregnancy complications.(Kharisma Y *et al*. stated that in 2022, the incidence of *placenta accreta* in Asia was 1 case per 1,000 pregnancies and in Indonesia itself 20 cases per 1,000 pregnancies.[6] A study conducted by Savira DP showed an increase in the incidence of placenta accreta at Adam Malik Hospital. In 2017, there were 9 cases *of placenta accreta*, in 2018 there were 26 cases, and the number continued to increase with a total of 23 cases from January 2019 to July 2019.[7]

The increase in the incidence of *placenta accreta* over the past few decades reflects the global increase in the number of cesarean deliveries. In addition, the more previous cesarean deliveries a woman has had, the higher the risk of *placenta accreta*. Approximately 6.7% of patients with a history of 5 cesarean deliveries experienced *placenta accreta*, compared to 0.3% of patients who had only 1 previous cesarean delivery.[6]

In Indonesia, there were 5,050,637 births out of a total population of 260 million. In East Java, the number of births reached 599,360 out of a population of 39.29 million, while at Dr. Soetomo General Hospital in Surabaya, there were 1,300 births out of a population of 3,457,404 million, with 159 cases *of placenta accreta spectrum* (PAS). In comparison, in Jakarta there were 174 cases of PAS in 7 tertiary hospitals. This was also followed by an increase in cesarean deliveries, where data from 2007 to 2017 showed an increase in the SC rate of around 10% in Indonesia. In comparison, the increase in Bangladesh from 2004 to 2014 reached 20%, while in Egypt it was 50%. Several other studies also show this increasing trend in developing countries;[7]

Based on the 2018 Basic Health Research (RISKESDAS), the proportion of *cesarean* deliveries in Indonesia reached 17.6%. The province with the highest rate was DKI Jakarta at 31.1%, while in North Sumatra itself it was 23.9%. According to data from the North Sumatra Provincial Health Office in 2021, the number of deliveries performed via cesarean section reached 25,602 cases.

Meanwhile, based on a preliminary survey at Mitra Sejati Hospital in Medan, in 2021 there were 282 pregnant women who underwent delivery through *cesarean section*.[8.9]

Based on research conducted by Dwi Putri, *et al*. in Medan, the number of *placenta accreta* cases has increased over the past four years. In January 2016, there was only 1 case, then it increased to 9 cases in 2017, 26 cases in 2018, and decreased slightly to 23 cases in 2019. This occurred alongside an increase in the number of deliveries via *cesarean section* (CS), which also showed an upward trend. In 2016, there were 288 cases of C-sections, then increased to 332 cases in 2017, and rose again to 368 cases in 2018. By July 2019, the number of C-sections had reached 206 cases.[8]

Placenta accreta spectrum (PAS) is a serious obstetric complication characterized by abnormal invasion of the placenta into the myometrium due to defects in the decidual layer. This condition is classified based on the level of invasion into *Placenta accreta* (PA), *Placenta increta* (PI), and *Placenta percreta* (PP). PAS is often associated with high maternal morbidity and mortality due to massive postpartum hemorrhage, which in many cases requires hysterectomy to save the patient's life.[2,6]

The pathophysiological mechanism of PAS involves chronic inflammation and changes in vascularization in the area of placental implantation. Several studies have shown that systemic inflammation plays a role in the development of PAS, with changes in various hematological parameters such as *the neutrophil-to-lymphocyte ratio* (NLR), *platelet-to-lymphocyte ratio*

(PLR), and *mean platelet volume* (MPV). The *Systemic Immune-Inflammation Index* (SII), calculated based on the number of neutrophils, lymphocytes, and platelets, has been proposed as a potential biomarker for predicting various inflammatory conditions, including cancer and cardiovascular disease. However, its role in the diagnosis and prognosis of PAS still needs further research.[10,11]

The Neutrophil-to-Lymphocyte Ratio (NLR) is the ratio between the number of neutrophils and lymphocytes that reflects the balance between systemic inflammatory processes (mediated by neutrophils) and adaptive immune responses (mediated by lymphocytes), so that an increase in NLR indicates the dominance of inflammatory responses over adaptive immunity in pathological conditions.[13] ROC analysis in previous studies showed that a *cut-off* value of NLR = 3.95 provided meaningful diagnostic performance, with a sensitivity of 70.2% and specificity of 73.9% at that *cut-off*, with an area under the curve (AUC) of 0.797 (95% CI;
0.739–0.855, $p < 0.001$).[10]

The Platelet-to-Lymphocyte Ratio (PLR) is the ratio between the number of platelets and lymphocytes that describes the interaction between platelet activation as an inflammatory mediator and decreased adaptive immunity, making it an indicator of systemic inflammatory status and physiological stress.(For PLR, previous studies established *a cut-off* of PLR = 122.5 x^{10^3}, which showed a sensitivity of 76.6% and specificity of 72.6%, with an AUC of 0.820 (95% CI:
0.739–0.855, $p < 0.001$).[10]

The Systemic Immune-Inflammation Index (SII) is calculated from the formula *(platelet × neutrophil)/lymphocyte* and represents a combination of the body's overall inflammatory and immune status, thus considered a more comprehensive marker for assessing the degree of systemic inflammation compared to NLR or PLR alone. SII has the highest diagnostic value with *a cut-off* 9.85 (10^5/µL), sensitivity of 57.4%, and specificity of 72.2%, making it useful as an additional hematological biomarker for identifying placenta previa patients at risk of placental invasion. SII has the advantage of being *a biomarker* that is easily obtained from routine blood tests, making it a potential tool for detecting the inflammatory processes underlying various diseases, including *placenta accreta spectrum* (PAS). Previous studies have shown that higher SII may be associated with deeper placental invasion, which contributes to an increased risk of bleeding and other obstetric complications.[10]

PAS is one of the most serious obstetric complications. Although prenatal diagnosis through ultrasound and MRI has been widely used, definitive diagnosis still depends on postpartum histopathological findings. In recent years, attention to the role of systemic inflammation in the pathogenesis of PAS has increased. Hematological biomarkers such as NLR, PLR, and SII have been proposed as simple yet sensitive indicators for assessing systemic inflammation and immunity status. However, evidence regarding the relationship between NLR, PLR, and SII and the occurrence of PAS is still limited and has not been extensively studied in the Indonesian obstetric population. Therefore, this study aims to analyze the relationship between these three systemic inflammatory indices and the occurrence of PAS, in order to evaluate the potential of simple hematological *biomarkers* as a predictive tool for abnormal placental invasion.

METHODS

Study Design and Setting

This study was an analytic observational study with a cross-sectional design conducted at Haji Adam Malik General Hospital, Medan, Indonesia, and its affiliated hospitals. The study included pregnant women diagnosed with placenta previa who underwent cesarean delivery and histopathological examination of placental tissue.

Study Population and Participants

The study population consisted of pregnant women with placenta previa treated at the study centers during the study period. Eligible participants were selected based on predefined inclusion and exclusion criteria. Inclusion criteria were pregnant women with placenta previa who underwent cesarean delivery and had complete clinical, laboratory, and histopathological data. Patients with incomplete medical records, hematologic disorders, active infections, or other systemic inflammatory conditions that could affect inflammatory parameters were excluded.

Data Collection

Demographic and obstetric characteristics were obtained from medical records, including maternal age, gestational age, body mass index (BMI), parity, history of cesarean section, and history of other intrauterine procedures. Laboratory parameters were obtained from routine preoperative complete blood count examinations, including platelet count, neutrophil count, and lymphocyte count.

Inflammatory indices were calculated using the following formulas:

- Neutrophil-to-Lymphocyte Ratio (NLR) = neutrophil count / lymphocyte count
- Platelet-to-Lymphocyte Ratio (PLR) = platelet count / lymphocyte count
- Systemic Immune-Inflammation Index (SII) = (platelet count × neutrophil count) / lymphocyte count

Diagnosis of Placenta Accreta Spectrum

Placenta accreta spectrum (PAS) was confirmed based on histopathological examination, which served as the gold standard for diagnosis. Histopathological findings classified cases into placenta accreta, placenta increta, or placenta percreta.

Preoperative ultrasound examinations were evaluated using the PAS scoring system to assess placental invasion.

Statistical Analysis

Statistical analysis was performed using SPSS software. Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparative analysis between PAS and non-PAS groups was conducted using appropriate statistical tests. Receiver Operating Characteristic (ROC) curve analysis was used to determine the diagnostic performance of NLR, PLR, and SII and to identify optimal cutoff values. The predictive accuracy of these indices was evaluated using sensitivity, specificity, and area under the curve (AUC). A p-value < 0.05 was considered statistically significant.

Ethical Approval

This study was conducted in accordance with ethical standards and was approved by the institutional ethics committee. All patient data were anonymized to ensure confidentiality.

RESULTS

Demographic characteristics

This study involved 69 pregnant patients diagnosed with placenta previa, either with or without placenta accreta spectrum, who underwent surgery at Adam Malik Hospital and Prof. dr. CPL USU Hospital. A total of 69 pregnant women who met the inclusion and exclusion criteria were recruited as research participants.

The following table presents an overview of the study subjects' characteristics, including age, gestational age, body mass index (BMI), parity, history of cesarean section (CS), and history of other intrauterine surgeries such as curettage.

Table 1. Demographic Characteristics

Subject Characteristics	n = 69
Age, mean ± SD, years	33.59 ± 5.49
Gestational age, median (min-max), years	37 (31–40)
Body Mass Index, n (%)	
Normal weight	15 (21.7)
Overweight	8 (11.6)
Obesity I	28 (40.6)
Obesity II	18 (26.1)
Parity, n (%)	
Primigravida	7 (10.1)
Second gravida	7 (10.1)
Multigravida	44 (63.8)
Grandemultigravida	11 (15.9)
History of cesarean section, n (%)	
Never	13 (18.8)
1 time	10 (14.5)
Twice	30 (43.5)
≥ 3 times	16 (23.2)
History of intrauterine surgery, n (%)	
Curettage	11 (15.9)
None	58 (84.1)

The mean age of the subjects was 33.59 ± 5.49 years, with a median gestational age at the time of termination of 37 weeks (range: 31-40 weeks). The distribution of nutritional status based on body mass index (BMI) showed that most subjects were overweight or obese: 40.6% were classified as Obesity I, 26.1% as Obesity II, while only 21.7% were of *normal* weight and 11.6% were classified as *overweight*.

In terms of parity, the majority of subjects were multigravida (63.8%), followed by grandemultigravida (15.9%), while the proportion of primigravida and secundigravida was 10.1% each. Cesarean section (CS) history was also dominant in this population: 43.5% of subjects had a history of two CS, 23.2% had undergone CS three times or more, 14.5% had undergone CS once, and only 18.8% had never undergone CS before.

Additionally, the majority of subjects (84.1%) had no history of intrauterine surgery, while 15.9% had undergone curettage. Overall, the characteristics of the subjects reflect a high-risk population for *Placenta Accreta Spectrum* (PAS), given the high prevalence of multiparity, history of repeated cesarean

deliveries, and obesity, factors known to be strong predictors of PAS.

Relationship between demographic characteristics and *placenta accreta spectrum*

A comparative analysis was performed between subjects with PAS diagnosis (n = 56) and without PAS (n = 13). Table 2 presents a comparison of maternal characteristics including age, gestational age, body mass index, parity, history of cesarean delivery, and history of intrauterine surgery, as well as the statistical significance level of each variable.

Table 2. Relationship between demographic characteristics and *placenta accreta spectrum*

Demographic Characteristics	PAS n = 56	Non-PAS n = 13	*p*
Age, mean ± SD, years	34.46±5.12	29.85±5.66	0.005[a]
Gestational age, n (%)			
Full term	37 (82.2)	8 (17.8)	0.756[b]
Preterm	19 (79.2)	5 (20.8)	
Body Mass Index, n (%)			
Normal weight	14 (93.3)	1 (6.7)	0.597[c]
Overweight	6 (75)	2 (25)	
Obesity I	22 (78.6)	6 (21.4)	
Obesity II	14 (77.8)	4 (22.2)	
Parity, n (%)			
Primigravida	0	7 (100)	<0.001[c]
Second gravida	7 (100)	0	
Multigravida	38 (67.9)	6 (13.6)	
Grandemultigravida	11 (100)	0	
History of cesarean section, n (%)			
Never	0	13 (100)	<0.001[c]
1 time	10 (100)	0	
2 times	30 (100)	0	
≥ 3 times	16	0	
History of other surgeries, n (%)			
Curettage	11 (100)	0	0.109[b]
None	45 (77.6)	13 (100)	

Data are presented as mean±SD, n (%) and median (min-max),
[a]T-test, [b]Fischer's Exact test, [c]Kruskal-Wallis test

Analysis of the relationship between demographic characteristics and the occurrence of *Placenta Accreta Spectrum* (PAS) showed that maternal age, history of cesarean section (CS), and parity were statistically significantly associated with PAS diagnosis. The mean age of subjects with PAS was 34.46 ± 5.12 years, significantly higher than the non-PAS group, which was 29.85 ± 5.66 years ($p = 0.005$).

The distribution of gestational age (term and preterm) and body mass index (BMI) categories showed no significant differences between the PAS and non-PAS groups ($p = 0.756$ and $p = 0.597$, respectively). However, parity showed a very strong association with PAS ($p < 0.001$). All primigravida cases were included in the non-PAS group, while all secundigravida and grandemultigravida cases were diagnosed with PAS. Among multigravida, 38 of 44 cases or 86.4% were also classified as PAS.

Similarly, a history of cesarean delivery showed a perfect association with PAS ($p < 0.001$): all subjects with PAS had a history of at least one cesarean section, while all cases without a history of cesarean section were included in the non-PAS group. non-PAS group. No PAS cases were found in subjects who had never undergone cesarean section.

A history of intrauterine surgery, which in this study was only found in curettage, did not show a statistically significant relationship with PAS ($p = 0.109$), although all subjects with a history of curettage were diagnosed with PAS, possibly due to the limited number of cases.

Overall, these findings confirm that advanced gestational age, a history of more than one parity, and especially a history of previous cesarean delivery are the main risk factors significantly associated with the occurrence of PAS in this study population. These results support the importance of intensive screening of pregnant women with these demographic characteristics to minimize maternal morbidity due to PAS.

PAS score from preoperative ultrasound findings and histopathology

This study evaluated the severity of *Placenta accreta spectrum* (PAS) conditions based on two assessment methods: the

PAS score (*Placenta Accreta Spectrum Score*) using preoperative ultrasound examination and histopathology findings as the gold standard. Table 3 below shows the frequency distribution of both examinations in 69 respondents.

Table 2. Distribution of preoperative ultrasound results based on PAS scores and histopathological findings in *placenta accreta spectrum*

Examination	n = 69
Preoperative Ultrasound Results, n (%)	
PAS 0	13 (18.8)
PAS 1	19 (27.5)
PAS 2	34 (49.3)
PAS 3	3 (4.3)
Histopathological examination results, n (%)	
Normal	13 (18.8)
Accreta	20
Increta	26 (37.7)
Percrista	10 (14.5)

The distribution of *Placenta Accreta Spectrum* (PAS) scores among 69 respondents showed differences between preoperative ultrasound (USG) findings and definitive diagnoses based on histopathological examination. Based on preoperative USG, 13 respondents (18.8%) were classified as PAS 0 (not PAS), while 19 (27.5%) were categorized as PAS 1, 34 (49.3%) as PAS 2, and only 3 (4.3%) as PAS 3.

In contrast, histopathological examination results as the gold standard for PAS diagnosis showed a different distribution: 13 cases (18.8%) remained confirmed as normal placenta, but there was an increase in percreta cases, namely 10 cases (14.5%), compared to USG estimates. Additionally, histopathological diagnosis recorded 20 cases (29.0%) as accreta and 26 cases (37.7%) as increta.

The level of agreement between preoperative ultrasound examination results based on PAS scores and histopathological examination results

To evaluate the level of agreement between PAS scores identified through preoperative ultrasound examination and histopathological examination, this study conducted a cross-tabulation analysis and calculated the *kappa* statistic. The results of the analysis are presented in Table 4.

Table 4. Level of agreement between preoperative ultrasound examination results based on PAS scores and histopathological examination results

	Histopathology				*p*
Ultrasound	Normal	Accreta	Increta	Percruent	
PAS 0	13 (18.8%)	0	0	0	<0.001
PAS 1	0	19 (27.5)	0	0	
PAS 2	0	1 (1.4)	26 (37.7)	7 (10.1)	
PAS 3	0	0	0	3 (4.3)	

*Kappa test, kappa value=0.833

Of the total 69 cases analyzed, 61 cases (88.4%) showed perfect concordance between ultrasound findings and histopathology results, while 8 cases (11.6%) were *discordant*. In detail, all non-PAS cases (13 cases, 18.8%) and all accreta cases (19 cases, 27.5%) and percreta cases (3 cases, 4.3%) were accurately diagnosed by ultrasound without classification errors. In the increta group, out of a total of 34 histopathologically confirmed cases, ultrasound successfully identified 26 cases (37.7%) as increta accurately. However, there were 8 cases of increta that were misclassified: one case (1.4%) was classified by ultrasound as accreta, and seven cases (10.1%) were classified as percreta, both of which were overdiagnoses of PAS severity, although they still recognized the presence of PAS in general. There were no cases in which ultrasound failed to detect PAS altogether (no false negatives for the overall PAS diagnosis). The agreement rate between the two methods was very high, with a kappa coefficient of 0.833 ($p < 0.001$), indicating almost perfect agreement.

These findings reinforce the role of ultrasound as a highly reliable preoperative diagnostic tool for assessing PAS severity, despite a slight tendency to overestimate the degree of placental invasion in some increta cases.

Differences in laboratory characteristics between the PAS and non-PAS

To evaluate differences in laboratory parameters as potential biomarkers of inflammation and hemostasis in *Placenta Accreta Spectrum* (PAS), a comparison was made between the PAS group (n = 56) and the non-PAS group (n = 13). Table 5 presents platelet, neutrophil, lymphocyte, and systemic inflammation index levels, including *Neutrophil-to-Lymphocyte Ratio* (NLR), *Platelet-to-Lymphocyte Ratio* (PLR), and *Systemic Immune-Inflammation Index* (SII), along with statistical tests to assess the significance of differences between the two groups .

Table 3. Differences in laboratory characteristics between the PAS and non-PAS

Characteristics Laboratory	PAS n = 56	Non-PAS n = 13	*p*
Platelets (10^3/µL)	261.5 (160-529)	210 (23.6–311)	0.001[a]
Neutrophils (10^3/µL)	8.09 (4 – 74)	5.49 (5–9)	<0.001[a]
Lymphocytes (10^3/µL)	1.72 ± 0.62	1.99 ± 0.61	0.160[b]
NLR (/µL)	4.67 (2.14-93.76)	3.26 (1.71–6.6)	<0.001[a]
PLR (/µL)	158.58 (79.72–1328.57)	107.41 (20.52–132.51)	<0.001[a]
SII (10^5 /µL)	12.7 s (7.25–261.59)	5.83±1.75	<0.001[a]

Data are presented as mean±SD and median (min-max) [a]Mann Whitney, [b]T Independent

Analysis of laboratory characteristics showed that most systemic inflammatory parameters differed significantly between the PAS and non-PAS groups. The platelet counts in the PAS group (median = 261.5 ×10³/µL; range: 160–529) was significantly higher than in the non-PAS group (median = 210 ×10³/µL; range: 23.6–311)($p = 0.001$). Similarly, neutrophil levels were significantly higher in the PAS group (median = 8.09 ×10³/µL; range: 4–74) compared to the non-PAS group (; median = 5.49 ×10³/µL; range: 5–9) ($p < 0.001$). Conversely, there was no significant difference in lymphocyte levels between the two groups (PAS 1.72 ± 0.62 and non-PAS 1.99 ± 0.61; *p-value* = 0.160).

The calculated ratio index showed a striking difference, with the NLR value in the PAS group (median = 4.67; range: 2.14–93.76) being significantly higher than in the non-PAS group (median = 3.26; range: 1.71–6.60) ($p < 0.001$). A similar pattern was also seen in the PLR, with a median of 158.58 in PAS compared to 107.41 in non-PAS ($p < 0.001$).

Differences in SII (*Systemic Immune-Inflammation Index*), which reflects the interaction between platelets, neutrophils, and lymphocytes. In the PAS group, the median SII value was 12.7 x 10^5/µL (range: 7.25–261.59), which was significantly higher than in the non-PAS group, which had a mean of 5.83 ± 1.75 x 10^5/µL ($p < 0.001$). These findings indicate that systemic inflammatory responses, particularly those characterized by increased neutrophils and platelet activation, play an important role in the pathophysiology of PAS.

Accuracy values of *the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio,* and *systemic immune-inflammation index* as predictors of *placenta accreta spectrum*

Neutrophil-to-lymphocyte ratio

To assess the performance of *the Neutrophil-to-Lymphocyte Ratio* (NLR) in predicting the occurrence of *Placenta Accreta Spectrum* (PAS), a *Receiver Operating Characteristic* (ROC) curve analysis was performed. The ROC curve allows for the evaluation of the NLR's discriminatory ability between cases with and without PAS, by measuring the area under the curve (AUC) as an indicator of overall predictive accuracy.

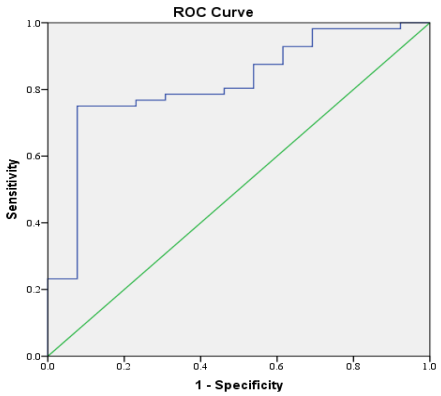

Figure 1. ROC Curve of NLR as a Predictor of PAS

ROC curve analysis showed that *the Neutrophil-to-Lymphocyte Ratio* (NLR) has good discriminatory ability in predicting *Placenta Accreta Spectrum* (PAS). The area under the curve (AUC) of 0.817
(SE = 0.063; $p < 0.001$; 95% CI: 0.694–0.941) indicates that NLR is significantly superior to random prediction (AUC = 0.5). This AUC value falls within the high diagnostic accuracy category, indicating that NLR has the potential to serve as a non-invasive predictive biomarker for identifying high-risk PAS cases before clinical onset. These findings support the consideration of integrating NLR into multivariate prediction models to improve early detection of PAS in at-risk populations. The optimal cutoff value of NLR for predicting PAS based on the line graph in Figure 2 is 3.7
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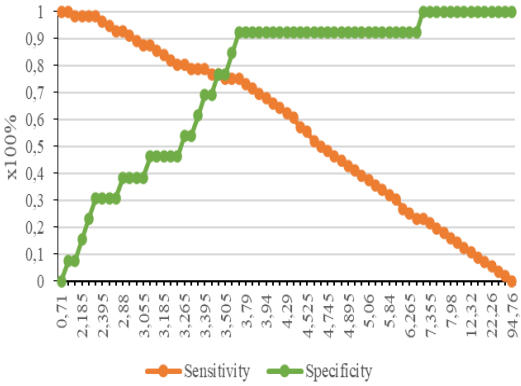

Figure 2 Line Graph Determining the Optimal Cutoff Value for NLR as a Predictor of PAS

Platelet-to-Lymphocyte Ratio

To evaluate the performance of *the Platelet-to-Lymphocyte Ratio* (PLR) in predicting PAS, a ROC curve analysis was performed. This analysis involved 69 valid cases (56 PAS cases and 13 non-PAS cases), assuming that higher PLR values reflect a greater likelihood of PAS.

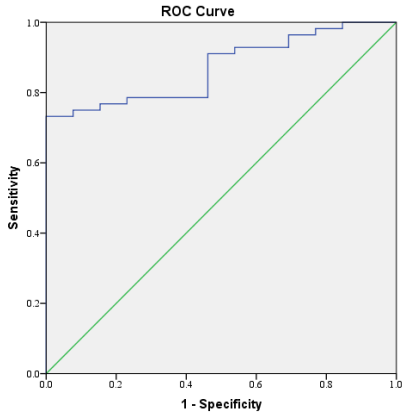

Figure 3 ROC Curve of PLR as a Predictor of PAS

ROC curve analysis showed that PLR has excellent discriminatory ability in predicting *Placenta Accreta Spectrum* (PAS). The area under the curve (AUC) was 0.871 (SE = 0.043; $p < 0.001$; 95% CI: 0.787–0.955) is statistically significantly higher than the reference value of 0.5 (random prediction), indicating that PLR can accurately distinguish between cases with and without PAS. With an AUC approaching 0.9, PLR can be categorized as a predictive biomarker with high diagnostic accuracy, making it a potential non-invasive screening tool for early identification of PAS in high-risk populations.

The optimal cutoff value of PLR for predicting PAS based on the line graph in Figure 4 is 127 .

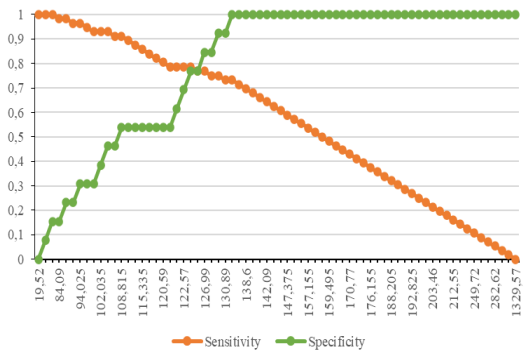

Figure 4 Line Graph for Determining the Optimal Cut-off Value for PLR as a Predictor of PAS

Systemic Immune-Inflammation Index

To evaluate the performance of *the Systemic Immune-Inflammation Index* (SII) as a predictor of PAS, a ROC curve analysis was performed on 69 valid cases (56 PAS cases and 13 non-PAS cases). In this analysis, higher SII values were considered to reflect stronger evidence of PAS.

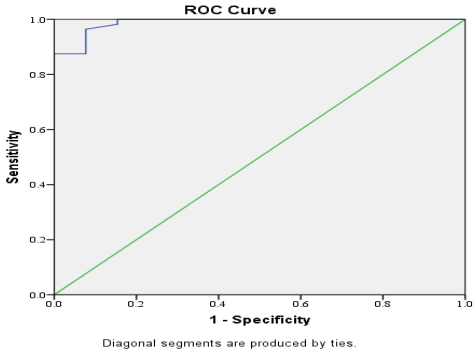

Figure 5 ROC curve of SII as a predictor of PAS

Receiver Operating Characteristic (ROC) curve analysis shows that *the Systemic Immune-Inflammation Index* (SII) has excellent discriminatory ability in predicting *Placenta Accreta Spectrum* (PAS). The area under the curve (AUC) reached 0.988 (SE = 0.011; $p < 0.001$; 95% CI: 0.967–1.000), which was statistically significant compared to the reference value of 0.5 (random prediction). The AUC value, which is close to perfect (1.000), indicates that SII is almost able to perfectly distinguish between cases with and without PAS in this sample.

SII has the potential to be a highly accurate predictive biomarker for early PAS screening. With near-optimal diagnostic performance, the integration of SII into clinical prediction models, especially in high-risk populations, could strengthen early detection strategies and safer obstetric management planning.

The best cutoff value of SII for predicting PAS based on the line graph in Figure 6 is 7.37.

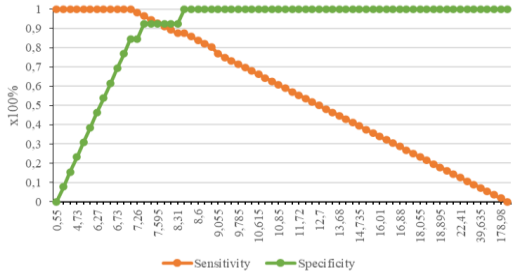

Figure 6 Line Graph Determining the Optimal Cut-off Point for SII as a Predictor of PAS

Table 6 presents the summary results of the AUC values, significance levels, and *cutoff* values of NLR, PLR, and SII in predicting PAS.

Table 4 Area Under the Curve (AUC) values, significance levels, and *cut-off* values of NLR, PLR, and SII in predicting PAS

Variable	AUC	95% CI	*p*	*Cut-off* Value
NLR (/µL)	0.817	0.694–0.94	0.001	3.7
PLR (/µL)	0.871	0.787–0.955	0.096	127
SII (10° /µL)	0.988	0.967–1.000	<0.001	7.37

Table 7 shows the accuracy values of NLR, PLR, and SII as predictors of PAS using the *cut-off* values from the ROC curve analysis results.

Table 5 Accuracy values of NLR, PLR, and SII as predictors of PAS

Variable	PAS		Sensitivity	Specificity	NDP	NDN	I-ration
	PAS	NO PAS					
NLR (/µL)							
≥3.7	42	1	75	92.3%	97.7%	46.2	78.3%
<3.7	14	12					
PLR (/µL)							
≥127	43	2	76.8%	84.6	95.6	45.8	78.3
<127	13	11					
SII (10° /µL)							
≥7.37	54	1	96.4%	92.3	98.2%	85.7	95.7%
<7.37	2	12					

Diagnostic performance evaluation shows that the three inflammatory indices *Neutrophil-to-Lymphocyte Ratio* (NLR), *Platelet-to-Lymphocyte Ratio* (PLR), and *Systemic Immune-Inflammation Index* (SII) have good ability in predicting *Placenta Accreta Spectrum* (PAS), but with different levels of accuracy.

At an NLR cutoff point of ≥ 3.7, the sensitivity and specificity were 75.0% and 92.3%, respectively, with a positive predictive value (PPV) of 97.7%, a negative predictive value (NPV) of 46.2%, and an overall accuracy of 78.3%. Meanwhile, a PLR ≥ 127 yielded a sensitivity of 76.8%, specificity of 84.6%,

NPV of 95.6%, NPN of 45.8%, and accuracy of 78.3%, similar to NLR, but with a slight decrease in specificity.

The performance of SII $\geq 7.37 \times 10^5/\mu L$ showed very high sensitivity (96.4%) and high specificity (92.3%), accompanied by NPV 98.2%, NPN 85.7%, and diagnostic accuracy reaching 95.7%. This indicates that SII can identify almost all PAS cases while minimizing false-positive diagnoses, with only 1 non-PAS case incorrectly classified as PAS.

Comparatively, SII is the best predictive biomarker among the three, with an optimal balance between sensitivity and specificity and much higher diagnostic accuracy. These findings reinforce the potential of SII as a reliable preoperative screening tool for PAS, especially in a clinical context where early detection and high accuracy are crucial for safe delivery management planning.

DISCUSSION

This study involved 69 pregnant women with placenta previa who underwent cesarean section. Most of the confirmed cases were PAS, namely 56 cases or 81.2%, with a predominance of moderate to severe invasive degrees (increta and percreta), reflecting the characteristics of a tertiary referral hospital with a high-risk caseload. This pattern is consistent with reports from various referral centers, where the increasing rates of repeat cesarean sections and invasive intrauterine procedures contribute to the surge in PAS cases and make this condition one of the leading causes of severe obstetric hemorrhage and peripartum hysterectomy. These findings are consistent with the literature stating that PAS is now a global health problem with an increasing incidence and requires early detection, careful delivery planning, and a multidisciplinary approach to reduce maternal morbidity and mortality.[12–14]

The characteristics of the subjects in this study showed that the PAS group tended to be older, with a mean age of 34.46 ± 5.12 years compared to the non-PAS group with a mean age of 29.85 ± 5.66 years ($p = 0.005$). with the majority being multigravida and grandemultigravida, and almost all PAS cases had a history of repeat cesarean section (≥1 CS). Most subjects were also in the *overweight* to obese category, although body mass index did not show a significant relationship with PAS occurrence. This picture reflects a high-risk population, in which older maternal age, multiparity, and a history of repeated cesarean sections are reported as major risk factors for PAS.[12,13,15]

Further analysis showed that parity and history of cesarean section had a highly significant association with PAS occurrence: there were no cases of PAS in primigravida and mothers without a history of CS, while all subjects with a history of ≥1 CS were in the PAS group. This pattern is consistent with several large studies and systematic reviews confirming that the combination of placenta previa or low-lying placenta with a previous cesarean section is the strongest risk determinant for PAS, with the risk increasing progressively with the number of previous CS.[16–19]

Conversely, gestational age at delivery, body mass index, and history of intrauterine surgery (curettage) in this study did not show statistically significant differences between the PAS and non-PAS groups. These findings differ slightly from some case-control studies reporting a history of curettage as a significant risk factor for PAS, possibly due to limited sample size, the dominance of patients with a history of repeated CS (which "masks" the effect of curettage), and variations in curettage practices across centers.

The demographic and obstetric characteristics in this study were very similar to the profile of PAS patients reported in various referral hospitals, both in Indonesia and abroad, namely dominated by mothers of advanced reproductive age, multiparity, and a history of repeat C-sections. Descriptive studies at Hasan Sadikin Hospital in Bandung and several other teaching hospitals in Indonesia also found that most PAS cases occurred in multiparous mothers with a history of two or more cesarean sections, often accompanied by a history of abortion or curettage, although the contribution of intrauterine procedures to the risk of PAS may vary between populations.[14,15,22]

Based on histopathological examination, the distribution of PAS degrees in this study showed that 18.8% were non-PAS, 29.0% were accreta, 37.7% were increta, and 14.5% were percreta. This means that more than half of the confirmed cases were moderate to severe invasive forms (increta and percreta ≈ 52.2%), which correlates with an increased risk of massive bleeding, the need for large transfusions, and the possibility of peripartum hysterectomy. This pattern illustrates that referred patients tend to already be at a more severe degree of invasion, a phenomenon that has also been widely reported in tertiary referral hospitals with maternal-fetal medicine services.[12,23]

The distribution of PAS grades in this study is consistent with a study at Hasan Sadikin Hospital in Bandung, which found a proportion of accreta 37.0%, increta 43.4%, and percreta 19.3%, with a predominance of increta and percreta in the referral population. Globally, PAS epidemiology reports also show variations in proportions between degrees, but a consistent trend is an increase in the proportion of more invasive cases at referral centers, which is related to referral patterns for difficult cases, an increase in the number of repeat CS, and delays in early detection in primary care.[13,15, 17, 22]

This study shows a very high level of agreement between PAS assessment based on preoperative ultrasound and histopathological results. Of the 69 cases, 61 cases (88.4%) had perfect agreement *(concordant)*, while 8 cases (11.6%) *were discordant*. No *false negative* PAS cases were

found: all PAS cases were histopathologically identified as PAS by ultrasound, and discrepancies only occurred in the determination of the degree (increta assessed as accreta or percreta). A kappa coefficient of 0.833 ($p < 0.001$) indicated an "almost perfect" level of agreement between ultrasound and histopathology, confirming the reliability of ultrasound as the primary modality for prenatal PAS detection at this center.

These results are consistent with the meta-analysis by Maged *et al.* in 2023, which reported that ultrasound has high sensitivity and specificity for PAS diagnosis in at-risk populations, especially mothers with placenta previa and a history of previous cesarean section. The study by Baumann *et al.*, conducted in a universal screening population, also showed that ultrasound can detect PAS with high accuracy, particularly increta and percreta forms, although its ability to accurately distinguish the degree of invasion remains limited. The findings of this study, with no *false negatives* and a tendency to overestimate the degree in some increta cases, are consistent with the literature stating that experienced operators tend to be more cautious in anticipating the need for more aggressive operative preparation.[24-28]

The tendency to overestimate the PAS grade by ultrasound in some cases of increta in this study has important clinical implications. On the one hand, overestimation may lead to more aggressive surgical planning (e.g., preparation for hysterectomy and a complete multidisciplinary team). On the other hand, this strategy may actually improve maternal safety by minimizing risks due to inadequate preparation in cases with a potential for massive bleeding. A similar pattern has been reported in various studies evaluating ultrasound scores or indices for PAS, where high sensitivity is often accompanied by a slight decrease in specificity, particularly in distinguishing between accreta, increta, and percreta.[18,24]

Overall, the findings of this study reinforce the consensus that ultrasound remains the primary modality for PAS detection and risk stratification, while other modalities such as MRI play a more supportive role in complex or posterior anatomical cases.(On the other hand, the development of research on hematological biomarkers such as *the neutrophil-to-lymphocyte ratio* (NLR), *platelet-to-lymphocyte ratio* (PLR), *systemic immune-inflammation index* (SII), and other inflammatory indices shows that these parameters have the potential to become non-invasive tools for predicting the presence of PAS. Several studies, such as those conducted by Kelecs *et al.*, Balkacs *et al.*, and Calio *et al.*, have demonstrated that inflammatory indices can correlate with the degree of invasion.[30-32]

Thus, in a clinical context, comprehensive prenatal ultrasound remains the mainstay of diagnosis, while hematological biomarkers, including the SII evaluated in this study, are more appropriately positioned as supportive tools to improve the accuracy of risk stratification and aid in perioperative management planning.[30,33]

In this study, the *Neutrophil-to-Lymphocyte Ratio* (NLR) values showed clear differences between the PAS and non-PAS groups. The median NLR in the PAS group was 4.67 (range 2.14–93.76), while in the non-PAS group it was only 3.26 (range 1.71–6.60), with a statistically significant difference ($p < 0.001$). ROC curve analysis showed that NLR had good discriminatory ability to predict PAS with an AUC value of 0.817 (95% CI 0.694–0.941; $p < 0.001$) and an optimal cutoff point of 3.7. At this *cutoff*, the sensitivity of NLR reached 75.0% and specificity 92.3%, with an overall accuracy of 78.3%, indicating that higher NLR values are strongly associated with the presence of PAS in high-risk populations at this referral hospital.[32]

Clinically, the direction of the relationship observed in this study aligns with the concept that an increased NLR reflects a predominance of neutrophil inflammatory responses and a relative decrease in adaptive immune capacity represented by lymphocytes. Each increase in NLR describes a higher degree of systemic inflammation, so that the higher the NLR value, the higher the probability of finding PAS in pregnant women with placenta previa and a history of cesarean section. These findings are consistent with other studies reporting higher NLR in the PAS group compared to placenta previa without invasion.[30,32,35]

NLR is a simple index that reflects the balance between the two main components of the immune system: neutrophils as innate inflammatory effector cells and lymphocytes as indicators of adaptive immune function. An increase in neutrophils reflects systemic inflammatory activation, production of free radicals, proteolytic enzymes, and formation of neutrophil extracellular traps (NETs), while a decrease in lymphocytes is often associated with immunological stress, immune suppression, or redistribution of lymphocytes to peripheral tissues. The combination of increased neutrophils and decreased lymphocytes raises the NLR value and has been shown to correlate with various chronic inflammatory conditions, cardiovascular disease, and obstetric complications such as preeclampsia, preeclampsia-related kidney injury, and preterm birth.[36-38]

In the context of PAS, the inflammatory process is closely related to decidual defects and abnormal remodeling of the lower uterine segment after cesarean section or curettage. Myometrial scar tissue formed after previous surgery tends to undergo chronic inflammation, impaired decidual maturation, and changes in cytokine and angiogenic factor expression, allowing deeper trophoblast invasion into the myometrium. This chronic inflammatory condition is reflected systemically as an increase in leukocytes, particularly neutrophils, with a relative decrease in lymphocytes, resulting in an increased NLR in patients with PAS compared to those without invasion. Recent

studies show that hematological inflammatory indices such as NLR, PLR, SII, and SIRI are elevated in pregnant women with placenta previa and PAS, and even correlate with the degree of histopathological invasiveness of the placenta [30,31,33].

Additionally, the pattern of trophoblastic invasion in PAS is often compared to the invasive characteristics of tumor cells, where a proinflammatory microenvironment, rich in neutrophils and platelets and relatively poor in lymphocytes, facilitates aggressive tissue invasion and vascular remodeling. In various solid cancers, NLR has been shown to be an independent prognostic marker associated with the degree of invasion, metastasis, and therapeutic response. This analogy is supported by research integrating NLR into a PAS prediction model in patients with placenta previa, where the addition of NLR to clinical factors and ultrasound findings improves prediction accuracy compared to the use of clinical factors alone.[32,39]

The results of this study, showing higher NLR values in the PAS group compared to the non-PAS group with a significant difference and an AUC of 0.817 for predicting PAS, consistent with the findings of several international studies. Keleş *et al.* (2022) reported that in addition to SII, other hematological parameters including NLR were also higher in PAS cases compared to controls, and contributed significantly to distinguishing PAS from pregnancies without placental invasion. Çallıoğlu *et al.* (2025) in a large case-control study of women with placenta previa also found that NLR was significantly higher in the PAS group and acted as an independent predictor in a multivariate model along with other inflammatory indices (SIRI).[30,32]

Other studies evaluating complete blood count parameters in PAS also support the role of NLR as an inflammatory biomarker. Abd El Megeed in 2024 reported that in a cohort of PAS patients, there were significant differences in neutrophil count, platelet count, and NLR between the group with more severe PAS compared to the less invasive group.(Beyond PAS, various obstetric studies also show similar patterns, where NLR increases in conditions involving placental inflammation and endothelial dysfunction, such as preeclampsia, preeclampsia-related kidney injury, preterm birth, and other complications related to placental dysfunction.[36,37,40]

Overall, the consistent direction of the relationship, namely higher NLR in PAS, reinforces the findings of this study that NLR reflects the characteristic inflammatory state in PAS and should be considered as one component in the prediction model.

The NLR *cut-off* of 3.7 obtained from the ROC analysis in this study provides a combination of 75.0% sensitivity and 92.3% specificity, with 78.3% accuracy in distinguishing PAS from non-PAS. In high-risk populations such as placenta previa with a history of repeat cesarean section, this profile is quite advantageous: the high specificity means that most patients with an NLR $\geq$ 3.7 actually have PAS, so this *cutoff* can help identify patients who require more aggressive surgical planning (e.g., large blood preparation, multidisciplinary team, and ICU facilities). These findings align with studies conducted by Balkas G *et al.*, and Calliouglu N *et al.*, which position NLR as part of a panel of hematological biomarkers to improve PAS risk stratification before delivery.[31,32]

Practically speaking, the main advantage of NLR is its ease of use and very low cost, as it only requires routine blood tests without additional tests. NLR can be calculated automatically from neutrophil and lymphocyte parameters available in almost all hospital laboratories, including secondary care facilities, making it suitable as an additional screening tool, especially in developing countries with limited resources. This approach is in line with the global trend that encourages the use of hematological inflammatory indices (NLR, PLR, SII, SIRI) as easily accessible markers of obstetric complication risk that can be integrated into routine antenatal examinations.[33,36,41]

However, the use of NLR in clinical practice also has several limitations that must be considered. NLR values are greatly influenced by other conditions that also cause systemic inflammation, such as acute infection, autoimmune disease, preeclampsia, obesity, smoking, and the use of certain medications (e.g., corticosteroids). Several studies have shown that when these confounding factors are not controlled, NLR values may increase in pregnancies without PAS, thereby reducing the specificity of this marker. Additionally, NLR does not provide anatomical information regarding the location and depth of placental invasion, so it cannot replace ultrasound or MRI as the primary diagnostic modality for PAS. Therefore, the NLR with *a cut-off* of 3.7 in this study is most appropriately positioned as a supporting indicator interpreted alongside clinical risk factors and ultrasound findings, not as the sole basis for diagnosis.[30,38,39]

In this study, it was found that the PLR value in the PAS group was significantly higher than in the non-PAS group. The median PLR in the PAS group was 158.58 (range 62.44–529.94), while in the non-PAS group, the median PLR was only 107.41 (range 49.62–263.16) with *a p-value* < 0.001. These findings indicate that an increased platelet-to-lymphocyte ratio is strongly associated with abnormal placental invasion, consistent with significant differences in platelet and neutrophil counts between the two groups in baseline laboratory analysis. Thus, PLR in this study reflects a higher systemic inflammatory status in PAS patients compared to non-PAS patients.[30]

ROC curve analysis showed that PLR has good discriminatory ability to distinguish PAS and non-PAS, with an AUC of 0.871 and *an* optimal *cut-off of* approximately 127. At this *cut-off* point, a sensitivity of 76.8%, specificity

of 84.6%, and accuracy of 78.3% were obtained; the majority of patients with PLR ≥127 were indeed confirmed to have PAS based on histopathology (43 out of 45 positive cases). This pattern confirms that the higher the PLR, the greater the likelihood that a patient is in the PAS group, so PLR can be considered as one of the relevant inflammatory indices for early screening of PAS.[31,33,42]

PLR reflects the interplay between platelets as hemostatic effector cells that also play a role in inflammation and angiogenesis, and lymphocytes as markers of adaptive immune response. Platelets contain and release various proinflammatory and proangiogenic mediators such as VEGF, PDGF, and TGF-β, which can modify endothelial and extracellular matrix responses, including in uterine and placental tissues. An increase in platelet count accompanied by a relative decrease in lymphocytes will result in a high PLR value, which biologically describes a state of systemic inflammation and ongoing immune stress. Other research findings in high-risk pregnancies, such as preeclampsia, also show that an increased PLR is associated with the degree of inflammation and disease severity, thereby reinforcing the use of PLR as a simple blood count-based inflammatory biomarker.[43–45]

PAS involves decidual defects that cause deeper trophoblast invasion into the myometrium and surrounding blood vessels. Scar tissue in the lower uterine segment triggers chronic inflammation and excessive matrix remodeling, which then attracts immune cells and platelets to the site. Recent molecular studies show that scar matrix in cesarean section scars can activate mechanosensory pathways such as Piezo1 and trigger persistent stromal inflammation that contributes to PAS. In this context, increased platelets and platelet indices such as PLR reflect a chronic inflammatory response associated with abnormal uterine and placental remodeling.[46,47]

On the other hand, lymphocytes play an important role in the regulation of adaptive immunity and maternal-fetal immune tolerance. A relative decrease in lymphocytes in chronic inflammatory conditions will increase PLR values and can be interpreted as a decrease in balanced immune regulatory capacity. Several studies have shown that elevated PLR values are not only found in PAS but also in other placental and pregnancy complications characterized by systemic inflammation, such as preeclampsia and gestational hypertension. Recent meta-analyses and observational studies report that high PLR is associated with an increased risk and severity of preeclampsia, supporting the concept that an imbalance between the platelet and lymphocyte compartments is an important reflection of vascular dysfunction and pregnancy inflammation.[44,45,48]

The results of this study, which show higher PLR values in the PAS group and good discriminatory ability (AUC 0.871), are consistent with several recent studies evaluating hematological inflammatory indices in PAS. Balkaş and Çelen involved 545 pregnant women and found that the placenta percreta group had significantly higher NLR, PLR, SII, and other inflammatory indices compared to placenta previa without invasion, and these parameters contributed to predicting intraoperative bleeding ≥1000 mL. These findings support that PLR is not only associated with the presence of PAS but also with the severity and risk of bleeding.[57]

Al-Nuaimi's study, which assessed first-trimester hematological indices in women with high suspicion of PAS, showed that several parameters, including PLR, were independently associated with the occurrence of accreta after adjusting for other clinical factors. However, the discriminatory ability of PLR alone in the first trimester was still limited (AUC < 0.7), and red cell distribution width (RDW) was the best predictor in the study. This illustrates that the strength of PLR as a predictor may vary depending on the timing of sample collection, the population studied, and the combination with other variables.[33]

A PLR *cut-off* of 127 in this study provided a sensitivity of 76.8% and specificity of 84.6% with an accuracy of 78.3%, making it practically useful as a screening tool to identify patients with placenta previa who are at high risk of PAS. The large proportion of patients with PLR ≥127 who were confirmed to have PAS on histopathology indicates a high positive predictive value, meaning that a significantly elevated PLR value should raise clinical suspicion of possible placental invasion. However, there is still a proportion of PAS patients with PLR <127, so this *cutoff* cannot be used as a single exclusion tool.[33]

Clinically, the main advantage of PLR is its ease and very low cost, as it is derived from routine blood counts (complete blood count) that are almost always performed on obstetric patients, including in hospitals with limited resources. PLR can be calculated automatically from platelet and lymphocyte data without requiring special equipment or additional reagents, and results can be obtained quickly prior to cesarean section in cases of placenta previa with suspected PAS. In this context, PLR has the potential to be used as an additional risk indicator combined with ultrasound findings and classic clinical risk factors to plan delivery management, including blood preparation, multidisciplinary teams, and intensive care facilities.[30,31,42]

However, PLR is not without limitations. PLR values are greatly influenced by other comorbid conditions that affect platelet or lymphocyte counts, such as acute infection, autoimmune disease, hematological disorders (primary thrombocytopenia or thrombocytosis), malignancy, and the use of certain medications. In high-risk pregnancies, PLR may also increase in antiphospholipid syndrome or other systemic inflammatory conditions, so PLR interpretation must always be performed in a clinical

context and compared with specific PAS ultrasound findings. In this study, SII was found to have the highest diagnostic value compared to PLR and NLR, so conceptually, PLR should be viewed as a supporting biomarker that complements SII and imaging modalities, not as a single diagnostic tool for PAS.[30,44]

In this study, the systemic inflammation index with the most notable difference between the PAS and non-PAS groups was *the Systemic Immune-Inflammation Index* (SII). The median SII in the PAS group was 12.7 (range 7.25–261.59), which was significantly higher than that in the non-PAS group with a mean of 5.83 ± 1.75; this difference was statistically significant ($p < 0.001$). The SII itself is calculated from the formula (platelets × neutrophils)/lymphocytes, thereby simultaneously reflecting neutrophil activation, relative thrombocytosis, and lymphopenia as signs of adaptive immunity suppression. The increased SII values in the PAS group in this study indicate that systemic inflammation and immune dysregulation are more prominent in cases with placental invasion than in pregnancies with placenta previa without invasion. This finding is consistent with the study by Keleş *et al.*, which reported a significantly higher SII in PAS patients compared to placenta previa controls, with significant differences in both median values and overall distribution.[30,31]

Clinically, this pattern reinforces the interpretation that the higher the SII, the greater the likelihood of PAS. In this study, the significant median difference between the two groups, coupled with a very small *p-value*, indicates a strong and consistent effect. This difference is also consistent with the concept of SII as a more "comprehensive" inflammatory marker than NLR or PLR alone, as it integrates the three main components of the hematological inflammatory response. A number of studies in high-risk obstetric populations, including patients with placenta previa and major obstetric hemorrhage, have also found that SII tends to increase in conditions with heavier inflammatory and hemostatic burdens, including severe PAS and cases with significant intraoperative bleeding. [30,31]

SII combines three key parameters—neutrophils, platelets, and lymphocytes—thus more comprehensively reflecting the interaction between inflammation, coagulation, and immune status. Neutrophils are the primary effector cells of acute inflammation, capable of producing reactive oxygen species, proteolytic enzymes, and *neutrophil extracellular traps* (NETs) that can damage the extracellular matrix and vascular walls. In contrast, lymphocytes, particularly T and B subsets, represent adaptive immunity and immune regulation; a decrease in lymphocytes is often interpreted as a sign of chronic immune stress or relative immunosuppression. Platelets play a role not only in hemostasis but also in the release of proinflammatory cytokines, growth factors, and proangiogenic mediators. The combination of high neutrophils, high platelets, and low lymphocytes—which mathematically results in a high SII—reflects severe systemic inflammation accompanied by immune dysregulation.[49-51]

In the context of PAS, these mechanisms are consistent with the pathogenesis theory emphasizing the role of decidual defects at the cesarean section scar, chronic inflammation of scar tissue, and uncontrolled trophoblast invasion into the myometrium. Scar tissue in the lower uterine segment after previous surgery is thought to be a focus of chronic inflammation that triggers the release of proinflammatory cytokines, proangiogenic factors, and matrix remodeling mediators, creating an environment similar to a "tumor microenvironment" in which trophoblasts can invade more deeply. Studies on PAS show that inflammatory biomarkers such as NLR, PLR, and SII increase progressively with increasing degrees of invasion, from accreta to percreta, although the relationship with histological subtypes has not always been consistent[30,31]

In addition to local inflammation, increased SII also reflects systemic inflammation that can worsen the body's response to obstetric bleeding and major surgical procedures. Activated platelets can interact with neutrophils and endothelium, forming neutrophil-platelet aggregates that enhance thrombus formation and alter uteroplacental microcirculation. This has the potential to worsen local hypoxia, stimulate further release of angiogenic factors, and ultimately reinforce the pathological cycle of inflammation–angiogenesis–trophoblast invasion. In several other disease models, elevated SII has been associated with higher mortality and cardiovascular complications as well as chronic inflammation, suggesting that a similar pattern is likely relevant in PAS as a form of "neoplasm-like placental invasion."

Specifically in PAS, the findings of this study are in line with the study by Keleş *et al.*, who first reported the role of SII in distinguishing PAS patients from placenta previa without invasion. In that study, the mean SII in the PAS group was significantly higher than in the control group, and the optimal SII *cutoff* was approximately 9.85 x^{105} /µL with a sensitivity of 57.4% and specificity of 72.2%.(The study by Balkaş & Çelen (2025), involving 545 pregnant women with placenta previa and PAS, also found that SII, along with other inflammatory indices such as SIRI and DNI, increased significantly, especially in the perkreta group, and correlated with bleeding ≥1000 mL during surgery. The results of this study, which showed that SII was much higher in the PAS group than in the non-PAS group reinforces the consistency of findings that SII is one of the sensitive inflammatory indices for detecting placental invasion. [30,31]

Beyond PAS, various other obstetric studies show a similar trend, where higher SII is associated with high-risk pregnancy complications. Several recent cohort and case-control studies show that SII increases in preeclampsia, pregnancies with thrombophilia, early pregnancy loss, and pregnancies with a risk of poor perinatal outcomes, and correlates with the severity and maternal-perinatal outcomes.(A common pattern among these studies is that SII provides additional predictive value over single inflammatory parameters, such as total leukocytes or CRP, thereby reinforcing the concept that the combination of neutrophils, platelets, and lymphocytes has a better ability to capture the dynamics of inflammation and immunity during pregnancy.[14]

More broadly, these findings are also consistent with the literature in oncology and cardiovascular medicine, which positions SII as a strong prognostic marker. Meta-analyses and large cohort studies show that high SII is associated with poorer prognosis in various malignancies (e.g., breast cancer, lung cancer, and lymphoma), as well as an increased incidence of Major Adverse Cardiovascular Events (MACE) and cardiovascular mortality.[752]

Several of these studies also show that SII has better prognostic value than NLR or PLR alone, supporting the findings of this study that SII is the most superior inflammatory index in predicting PAS compared to NLR and PLR.

ROC curve analysis in this study showed that SII has superior predictive performance compared to NLR and PLR. The AUC value of SII reached 0.988 (SE 0.011; $p < 0.001$; 95% CI: 0.967–1.000), which is statistically close to perfect accuracy. The best SII *cut-off* value for predicting PAS was 7.37 x 10^5/µL with a sensitivity of 96.4%, specificity of 92.3%, positive predictive value of 98.2%, negative predictive value of 85.7%, and overall accuracy of 95.7%. Practically, this means that most pregnant women with SII above the cut-off value will indeed have PAS, while SII below *the cutoff* is sufficient to rule out PAS in most high-risk cases. Compared to NLR (AUC 0.817) and PLR (AUC 0.871), SII shows a larger area under the curve and consistently better accuracy parameters, statistically positioning it as the most superior index in this study.

These findings are consistent with the report by Keleş *et al.*, and several other studies showing that SII has comparable diagnostic performance, often surpassing NLR and PLR in predicting PAS and other obstetric complications. [30,31]

From a clinical perspective, *the* SII *cut-off* of approximately 7.37 x 10^5/µL in this study has the potential to be used as a hematological screening tool in pregnant women with PAS risk factors, such as placenta previa above a cesarean section scar, a history of repeated curettage, or other uterine surgery. SII has major advantages: it is obtained from routine complete blood counts, is relatively inexpensive, rapid, and widely available even in hospitals with limited facilities. Thus, SII can be included in the preoperative risk assessment algorithm along with clinical factors and ultrasound findings to help identify patients who require multidisciplinary team preparation, adequate blood availability, and definitive action planning such as hysterectomy. Experience from the cardiovascular and oncology literature also shows that integrating SII into clinical prediction models can improve discrimination and risk stratification capabilities, making a similar approach highly rational for PAS.[52]

However, it is important to emphasize that SII is not a specific marker for PAS and its value can be influenced by various other conditions, such as acute infection, autoimmune disease, neoplasms, cardiovascular disease, and hematological disorders. Several obstetric and non-obstetric studies confirm that SII can increase in other systemic inflammatory conditions, so the interpretation of SII values must always consider the clinical context, other supporting examination results, and the exclusion of concomitant conditions that can affect blood counts.[29]

Therefore, although this study demonstrates the high diagnostic performance of SII, its use should be positioned as a screening tool and to reinforce clinical suspicion, not as the sole basis for establishing a PAS diagnosis without imaging confirmation and ultimately histopathological verification. Larger prospective studies are needed to validate *the* SII *cutoff*, evaluate the stability of values across different populations and sampling times, and assess the benefits of integrating SII into multimodal PAS prediction models.

Based on the ROC curve analysis in this study, the three inflammatory indices NLR, PLR, and SII all showed good ability to distinguish PAS and non-PAS cases, but with different levels of performance. The AUC value for NLR was 0.817 (95% CI; 0.694–0.94; $p = 0.001$) with *a cut-off* of 3.7, while PLR had a slightly higher AUC of 0.871 (95% CI; 0.787–0.955; $p < 0.001$) with *a cut-off* of 127. SII showed the best performance with an AUC of 0.988 (95% CI; 0.967–1.000; $p < 0.001$) and *a cut-off* of 7.37 x 10^5/µL, which was statistically close to perfect accuracy. Thus, the order of discriminatory ability in this study was SII > PLR > NLR, where SII was clearly superior, while PLR had a slight AUC advantage over NLR but was still far below SII. [30,31]

When evaluated using the optimal *cutoff point*, NLR ≥ 3.7 provides a sensitivity of 75.0%, specificity of 92.3%, positive predictive value of 97.7%, negative predictive value of 46.2%, and accuracy of 78.3%. PLR ≥ 127 provides sensitivity of 76.8%, specificity of 84.6%, positive predictive value of 95.6%, negative predictive value of 45.8%, and the same accuracy of 78.3%. SII ≥ 7.37 x 10^5/µL showed a much better profile: sensitivity of 96.4%,

specificity of 92.3%, positive predictive value of 98.2%, negative predictive value of 85.7%, and accuracy of 95.7%. Comparatively, SII not only has the highest AUC but also the most balanced combination of sensitivity–specificity and accuracy, confirming that SII is the strongest inflammatory index in predicting PAS in the high-risk population in this study. [30,31]

From a practical standpoint, all three indices (NLR, PLR, and SII) have the main advantage of being derived from the same parameter, namely routine blood count (*complete blood count*) tests that include neutrophils, lymphocytes, and platelets. The calculation of NLR, PLR, and SII does not require additional tests or special reagents, so it does not significantly increase the cost of testing and can be performed in almost all health facilities with basic laboratories. This makes these three indices very attractive for use in developing countries and referral hospitals with a high burden of PAS cases but limited resources, especially as an additional screening tool alongside imaging modalities. [30,31]

In clinical practice, the application of these indices can be adapted to the availability of time, information systems, and clinical needs. If clinicians only have time to calculate simple indices such as NLR or PLR (e.g., in emergency departments or facilities with computational limitations), these two indices still provide added value as they show a significant difference between PAS and non-PAS groups.

Conversely, if further calculations are possible—for example, through a computerized laboratory system—calculating the SII will provide better predictive value, given its significantly higher AUC and accuracy. This tiered approach is consistent with reports from several studies showing that SII and other composite inflammatory indices (e.g., SIRI, PIV) often outperform NLR or PLR in predicting PAS and other obstetric outcomes, without significantly increasing costs.[31,32]

Although NLR, PLR, and especially SII demonstrate strong predictive capabilities, antenatal ultrasound remains the primary modality in PAS diagnosis because it provides anatomical information regarding placental location, invasion depth, and involvement of surrounding organs. The inflammatory hematological indices in this study are more appropriately positioned as supportive tools that complement clinical and imaging data, rather than as a substitute for ultrasound. This integrative approach aligns with various modern prediction models that combine clinical factors, ultrasound findings, MRI, and biomarkers (e.g., NLR, PLR, or SII) to improve the accuracy of PAS identification compared to the use of a single modality alone.[39]

In practice, the integration of ultrasound with NLR or PLR or SII can be used for risk stratification and management planning. For example, in patients with placenta previa with a history of cesarean section and ultrasound findings highly suggestive of PAS, a high SII value ($\geq 7.37 \times 10^5/\mu L$) or a combination of elevated NLR and PLR may reinforce suspicion and prompt delivery planning at a tertiary referral center with a multidisciplinary team, blood product readiness, and ICU facilities. Conversely, in patients with questionable ultrasound findings, low inflammatory index values may reduce the probability of PAS and assist clinicians in risk–benefit discussions and tiered referral planning. This multimodal approach combining ultrasound and hematological inflammatory indices has been recommended in recent studies as a rational method to improve early detection of PAS and reduce maternal morbidity through more thorough delivery planning.[1,31]

The limitations of this study include the use of a retrospective cohort design based on medical records of patients with placenta previa and PAS at Adam Malik Hospital and affiliated hospitals. This design is efficient for evaluating the relationship between NLR, PLR, and SII and the incidence of PAS, but it has inherent limitations, such as dependence on the completeness and accuracy of records.

As a study in a tertiary referral hospital, there is potential for selection bias because the population tends to be dominated by severe and complex cases referred from other facilities. This may result in a higher proportion of PAS (especially increta–perkreta degrees) compared to the general population, so that the reported NLR, PLR, and SII values may reflect the spectrum of severe cases in referral centers rather than the entire clinical spectrum of PAS in primary and secondary services. The phenomenon of overrepresentation of severe cases due to referral bias has also been reported in retrospective studies and PAS case series in various referral centers in Bahrain, India, and other countries.

In addition, the timing and method of blood sampling were not entirely uniform. Complete blood counts were performed in a real clinical context, often prior to surgery, and may have been influenced by acute conditions such as bleeding, impending surgical stress, or other temporary comorbidities that were not fully documented, even though exclusion criteria had been applied for certain chronic diseases.

In clinical practice, elevated inflammatory index values may reinforce clinicians' suspicion of PAS in patients who already have risk factors and suspicious ultrasound findings, thereby aiding decision-making regarding referral to tertiary referral centers and planning safer delivery timing and techniques.

Since NLR, PLR, and SII are all derived from routine blood count parameters (differential leukocyte count and platelets), the use of these indices does not significantly increase examination costs and can be applied at various levels of care, including in hospitals with limited resources.

In facilities that only have the capacity to calculate NLR or PLR, both indices still provide meaningful risk information; while in referral centers with computerized laboratory systems, automatic SII calculation can provide better predictive value. This approach is in line with the latest trend of using hematological inflammatory indices as additional risk markers in various obstetric complications and is supported by research showing the role of these indices in distinguishing PAS from non-invasive placenta previa.

In the context of perioperative management, the results of this study can help clinicians determine the level of suspicion for PAS before surgery and prepare for more thorough management. Patients with high clinical risk, ultrasound findings consistent with PAS, and very high SII values should be planned for delivery at a referral center with an experienced multidisciplinary team, a blood bank ready for massive transfusion, and obstetric ICU facilities. Current guidelines and reviews on PAS emphasize the importance of structured delivery planning, involving obstetricians, gynecologic surgeons, anesthesiologists, radiologists, and urologists, to reduce blood loss, organ injury, and maternal mortality, and inflammatory indices such as SII can contribute to the early stages of such risk stratification.

At the hospital policy level, particularly in referral hospitals that frequently receive cases of placenta previa and PAS, these findings support the need to include hematological inflammatory index calculations (NLR, PLR, and SII) in standard antepartum evaluations for patients at risk of PAS. Guidelines could include preoperative complete blood count examinations that are not only evaluated for anemia and thrombocytopenia but also systematically calculate NLR, PLR, and SII as part of an integrated risk assessment. Thus, laboratory results can be combined with clinical risk factors and ultrasound findings to produce a low–moderate–high risk stratification that aids in determining the location of delivery and referral needs.

The implementation of this policy needs to be supported by a hospital information system that allows for the automatic calculation of inflammatory indices from laboratory data, as well as training for health workers on the interpretation of NLR, PLR, and SII in the context of PAS. At referral centers, PAS teams or high-risk obstetrics committees can use these indices as one parameter in integrated case conferences to plan surgical strategies (e.g., whether elective hysterectomy is necessary, the need for radiological intervention, or the possibility of uterine conservation). Current consensus and guidelines on PAS also emphasize the need for structured management standards, multidisciplinary teams, and adaptation of international recommendations to the local context, making the integration of hematological inflammatory indices into hospital clinical pathways a rational step to improve the quality of care.

CONCLUSION

In conclusion, pregnant women with placenta accreta spectrum were predominantly in their early thirties, mostly obese, multiparous, and had a history of previous cesarean sections. Maternal age, parity, and previous cesarean delivery were found to be associated with the occurrence of placenta accreta spectrum. Preoperative ultrasound assessment using the PAS score demonstrated an almost perfect agreement with histopathological findings as the gold standard for diagnosing placenta accreta spectrum. Patients with PAS showed higher mean values of platelet count, neutrophil count, NLR, PLR, and SII compared with those with non-PAS placenta previa. Furthermore, platelet count, neutrophil count, NLR, PLR, and SII were significantly associated with the occurrence of placenta accreta spectrum. Among these inflammatory markers, NLR, PLR, and SII demonstrated good predictive performance for PAS. Using cut-off values of NLR $\geq$ 3.7, PLR $\geq$ 127, and SII $\geq$ 7.37, the accuracy for predicting placenta accreta spectrum reached 78.3%, 78.3%, and 95.7%, respectively, with SII showing the highest predictive value. These findings suggest that inflammatory hematological indices derived from routine blood tests may serve as simple and useful biomarkers for predicting placenta accreta spectrum and may support early detection and clinical decision-making in high-risk pregnancies.

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