Original Article

Can We Predict Spontaneous Abortion Cases Using the Systemic Immune Inflammation Index?

Kübra Baki Erin[1] , Abdulkerim Omar Ali[2] , Ömür Erden[1] , Deniz Kulaksız[1] , Recep Erin[1]

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Trabzon, Türkiye
[2]Department of Obstetrics and Gynecology, University of Health Sciences, Somalia Recep Tayyip Erdoğan Health Practice and Research Hospital, Mogadishu, Somalia

ORCID iDs of the authors: K.B.E. 0000-0002-6626-1735, A.O.A. 0000-0002-7094-0191, Ö.E. 0000-0003-3025-7790, D.K. 0000-0003-2351-1367, R.E. 0000-0002-9488-5414.

ABSTRACT

Objective: The aim of this study was to find out if the systemic immune-inflammation index is linked to cases of spontaneous abortion.

Methods: The retrospective analysis included 828 pregnant women who had a spontaneous abortion (study) and 825 women who had a viable intrauterine pregnancy (control) up to 20 weeks. The neutrophil-to-lymphocyte ratio was calculated by dividing neutrophils by lymphocytes. Splitting platelets into lymphocytes calculates the platelet-to-lymphocyte ratio. Systemic immune-inflammation index was determined using the neutrophil x platelet/lymphocyte formula. The study and control groups were compared using an independent *t*-test. The systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio values were evaluated for their ability to predict spontaneous abortion using receiver operating characteristic curves.

Results: The systemic immune-inflammation index values, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio demonstrated a significant difference between the groups. In the logistic regression analyses, we found a positive predictive effect of systemic immune-inflammation index in the prediction of spontaneous abortion. For systemic immune-inflammation index at a cut-off level of 435.26, the sensitivity was 71.2% and the specificity was 67.6. The sensitivity and specificity of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were found to be lower than systemic immune-inflammation index in spontaneous abortion cases.

Conclusion: Systemic immune-inflammation index may be used as a marker of inflammation in spontaneous abortion cases. It appears to be a more specific marker for indicating inflammation than neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio.

Keywords: Complete blood count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, spontaneous abortion, systemic immune-inflammation index

INTRODUCTION

Abortion is the spontaneous or induced expulsion of the fetus from the uterus in the case of a fetus weighing less than 500 g, as a result of the fetus's loss of vitality.[1] Loss of a pregnancy before 20 weeks of gestation without any intervention from a medical professional is considered a spontaneous abortion.[1] Because "abortion" is often connected with intentional termination, the term "miscarriage" is typically used with patients as an alternative.[2] Patients preferred the phrases "miscarriage" and "early pregnancy loss" over "early pregnancy failure" and "spontaneous abortion," which were considered less obvious in a survey of 145 English-speaking patients being treated for first-trimester pregnancy loss in the United States.[2] Up to 20% of confirmed pregnancies result in miscarriage. When women were monitored with serial serum human chorionic gonadotropin measures, the actual miscarriage rate was determined to be 31%.[3] Genetic problems, chromosomal abnormalities, endocrinological imbalances, and immunologic dysfunctions are only a few of the many causes linked to spontaneous miscarriages.

Inflammation is a pathogenetic component that contributes to the etiology of the disease.[4,5] Numerous well-known hematological indicators of systemic inflammation, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), correlate with signs of a pro-inflammatory state (PLR). There is research documenting the association between spontaneous abortions and inflammatory indicators in the complete blood count (NLR, PLR). In cases of spontaneous abortion, there have been reports of significant alterations in NLR and PLR.[4-9]

A new indicator of inflammation called the systemic immune-inflammation index (SII) has been identified.[10] This novel inflammatory indicator combines NLR and platelets. It has been studied in ovarian cancers in gynecology and preterm labor in obstetrics.[11-14] There have been reports of its use in monitoring cranial hemorrhages, diagnosing cancer, and detecting premature membrane rupture (SII).[11,12,15-17] There is only 1 study in the literature examining the relationship between SII and spontaneous abortion cases.[18]

The aim of this study was to find out if SII is linked to spontaneous abortions and if it can be used as a marker in these cases.

METHODS

A total of 1653 women who were followed up at a tertiary training and research hospital's gynecological polyclinic between January 2018 and December 2020 were included in this retrospective analysis. The University of Health Science, Somalia Recep Tayyip Erdoğan Health Practise and Research Hospital ethics committee approved the study protocol. Patient files were scanned for data. All the information gathered from the patient files were then digitally scanned into a secure database and analyzed to determine the variables. All research on human subjects followed the ethical requirements of the institutional and national research committees and the 1964 Helsinki statement and its later amendments.

MAIN POINTS

- Inflammation can cause spontaneous abortions.
- Systemic immune-inflammation index is a new marker for inflammation.
- Systemic immune-inflammation index can be used as an inflammation marker in cases of spontaneous abortion.
- Systemic immune-inflammation index appears to be a more specific marker for indicating inflammation than neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in spontaneous abortion cases.

Patients with all inflammatory, systemic, autoimmune, and chronic diseases that may affect a complete blood count for inflammation markers were excluded from the study (hematological, cardiovascular, renal-liver, asthma, recurrent abortions, arthritis, neoplastic illnesses such as androgen-secreting tumors and ovarian tumors, glucocorticoid use, infectious, and parasitic diseases). In addition, assisted reproductive technologies and recurrent pregnancy losses were excluded from the study.

The G*Power 3.1 program was used for the power analysis of the study. Assuming an effect size of 0.9 and a type 1 error value of 0.05, it was calculated that the sample size of 1325 individuals corresponds to a power of 1.0. The research included 828 spontaneous abortions and 825 healthy pregnant women with similar demographics. This study was conducted on black African women in Somalia who had spontaneous abortions. Spontaneous abortion was defined as the elimination of the fetus before the 20th gestational week or less than 500 grams. Transvaginal ultrasound or transabdominal ultrasonography measured the crown-rump length to determine the fetal heart rate and gestational age (Samsung® HS70, Seoul, Republic of Korea).

In the tubes containing ethylene diamine tetraacetic acid, venous blood samples were collected. Blood tests were taken when the patients were hospitalized with the diagnosis of abortion. The complete blood count was measured by an automated hematology analyzer (Beckman UniCel DXL 600 Coulter Cellular, Calif, USA). Platelets (10^3/μL), neutrophils (10^3/μL), lymphocytes (10^3/μL), and hemoglobin (g/dl) were measured. The NLR was calculated by dividing neutrophils by lymphocytes. Splitting platelets into lymphocytes calculates PLR. The SII was determined using the neutrophil × platelet/lymphocyte formula. Age, BMI, and gravida were recorded for all instances. The NLR, PLR levels were measured in patients and controls.

Statistical Analysis
The data were analyzed with Statistical Package for Social Sciences 23.0 (IBM SPSS Corp., Armonk, NY, USA). Kolmogorov–Smirnov proved that the data set had a normal distribution. The study group and the control group were compared using an independent t-test. Receiver operating characteristic (ROC) curves were used to see if the SII, NLR, and PLR values could predict spontaneous abortion. Using the Youden index, the ROC curve was analyzed to determine the best threshold [19]. The P-value of <.05 was statistically significant.

Ethical Approval
Written consent was obtained from all the cases participating in our study, in accordance with the Declaration

of Helsinki. University of Health Science Somalia Recep Tayyip Erdoğan Health Practise and Research Hospital Ethics Committee permission was obtained from the Tertiary Health Practice and Research Hospital Ethics Committee, with the decision dated November 13, 2018, and numbered MSTH/5236.

RESULTS

While the mean age of the study group was 26.61 and the mean BMI was 25.71, the mean age of the control group was 25.44 and the mean BMI was 26.10. The neutrophil, lymphocyte, and platelet values in the study group were 3.87, 2.37, and 261.71, respectively, while in the control group, they were 3.61, 2.47, and 248.15, respectively. In terms of age, body mass index, neutrophils, lymphocytes, and platelets, there was no significant difference ($P > .05$) between the spontaneous abortion and control groups (Table 1). The NLR was calculated by dividing the mean of neutrophils by the mean of lymphocytes, and the findings revealed a statistically significant difference ($P = .049$) between the groups. The PLR calculated by dividing the platelet mean by the lymphocyte mean differed significantly across groups ($P = .039$) (Table 1). The SII was determined using the neutrophil × platelet/lymphocyte formula, and statistically significant differences were identified across the groups.

In the logistic regression analysis, we found a positive predictive effect of SII in the prediction of spontaneous abortion. For SII at a cut-off level of 435.26, the sensitivity was 71.2% and the specificity was 67.6 (Figure 1). The SII, NLR, and PLR ROC curve data are shown in Table 2.

DISCUSSION

This study provides valuable information about the relationship between spontaneous abortion cases and SII levels. According to our findings, SII increases spontaneous abortion cases. This is a rare study in the literature examining the relationship between SII and spontaneous abortion cases.

Spontaneous abortion is considered to occur due to improper implantation, placentation, or the development of blood vessels. Different parts of the immune system work together to get the intervillous area ready for the semi-allogeneic fetus, which is essential for a healthy pregnancy. Adverse perinatal outcomes may result from placental inflammation, which destroys cellular components of the intervillous region.[10] As a result, there has been a rise in the number of studies looking into inflammatory obstetric problems. The NLR and PLR have been shown to be elevated in a number of illnesses, making them a popular tool for gauging the severity of inflammation.[20-23] The NLR and PLR are two blood cell count indices that have been studied for their potential as biomarkers in cases of spontaneous abortion.[4-6,9]

Table 1. Comparison of the Inflammation Markers and Demographic Characteristics of the Groups

	Study (n = 828)	Control (n = 825)	P*
Age (year)	26.61 ± 3.11	25.44 ± 3.87	.228
BMI (kg/m²)	25.71 ± 4.12	26.10 ± 4.14	.199
Gestational week	13.2 ± 4.3	13.9 ± 3.9	.212
Hemoglobin (g/dL)	11.89 ± 1.78	12.21 ± 1.69	.213
Neutrophil count (10³/μL)	3.87 ± 1.23	3.61 ± 1.21	.143
Lymphocyte count (10³/μL)	2.37 ± 0.51	2.47 ± 0.48	.164
Platelet count (10³/μL)	261.71 ± 51.15	248.15 ± 49.27	.112
NLR	1.61 ± 0.59	1.42 ± 0.52	**.049**
PLR	111.61 ± 31.56	99.55 ± 19.15	**.039**
SII	428.35 ± 52.31	361.63 ± 48.12	**.009**

BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.
Data are presented as mean ± SD.
*Independent *t*-test.
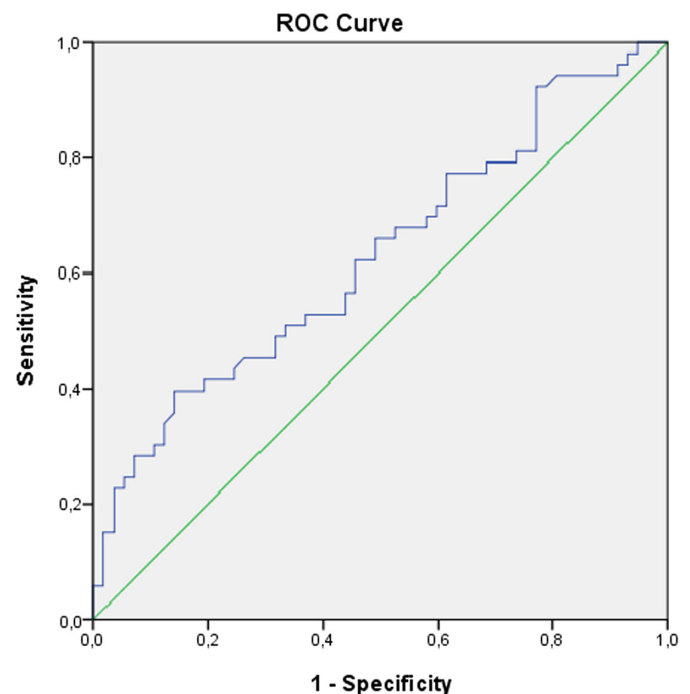*P* < .05 was considered significant.

Figure 1. Specificity and sensitivity are seen in the ROC curve. AUC: 0.630 (95% CI: 0.525-0.734). ROC, receiver operating characteristic.

Table 2. ROC curve analysis of the SII, NLR, and PLR

		Sensitivity	Specificity	P *
Composite spontaneous abortion in group: AUC: 0.630 (95% CI: 0.525-0.734)	Cut-off value for SII (10^9/L): 435.26	71.2	67.6	**.019**
Composite spontaneous abortion in group: AUC: 0.616 (95% CI: 0.514-0.667)	Cut-off value for NLR: 1.98	62.1	60.3	**.021**
Composite spontaneous abortion in group: AUC: 0.616 (95% CI: 0.514-0.657)	Cut-off value for PLR: 121.32	59.8	57.9	**.015**

AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; SII, systemic immune inflammation index.
P < .05 was considered significant.

Tanacan et al[11] conducted an analysis of the SII to determine its accuracy in predicting unfavorable newborn outcomes in preterm pre-labor rupture of membranes (PPROM). They reached the conclusion that the SII is a cost-effective and useful tool for predicting PPROM. The factors that cause PPROM are similar to those that cause spontaneous abortion in terms of infection and inflammation.

Bas et al[4] examined the relationship between spontaneous abortion and complete blood count inflammation markers and found a significant difference between the groups. While NLR was reported as a positive predictive marker in spontaneous abortion cases, PLR was reported as a negative predictive marker. In their study, they studied complete blood count inflammation markers, but SII, a new inflammation marker, was not studied. In their study, they used healthy puerperal women who had just given birth as a control group. In our study, we included healthy pregnant women as a control group with a similar pregnancy. According to the results of our study, SII can be used as a positive predictive marker in cases of spontaneous abortion.

Biyik et al[5] studied NLR and PLR in missed abortion cases and reported a significant increase in the missed abortion group. They did not study the SII marker in their studies. In addition, all abortion cases were not included in the study group; only missed abortions were studied. In the present study, all spontaneous abortion cases below 20 weeks comprised the study group.

In the literature, NLR, PLR, missed abortion, early pregnancy loss, and spontaneous abortion cases have been studied. However, SII has been studied rarely in the literature.[4-9] Turgut et al[18] studied SII in miscarriage cases. In their study, they found SII and NLR values to be significantly higher in miscarriage cases. In the ROC curve analysis, they reported a cut-off of 883.95, a sensitivity of 62.6%, and a specificity of 62% for SII. They reported that high SII values can be used to predict miscarriage cases. However, they only included first-trimester pregnancies (8.3 ± 2.5 weeks) in their study. In our study, the number of cases was higher, and we included all pregnancies below 20 weeks (13.2 ± 4.3 weeks). In addition, the most important difference between our studies was that their study was conducted among the white race, while ours was conducted among the black race. Although our SII sensitivity and specificity rates were similar, the cut-off values were different. The reasons for this may be the gestational week and racial differences.

According to our study results, the SII cut-off value was 435.26 in spontaneous abortion cases, the sensitivity was 71.2%, and the specificity was 67.6. The sensitivity and specificity of NLR and PLR were found to be lower in spontaneous abortion cases. It appears to be a more specific marker for indicating inflammation than NLR and PLR in spontaneous abortion cases.

The study was limited by its retrospective. Diseases and disorders that could have influenced the Complete blood count (CBC) inflammatory markers have been ruled out; however, these indicators could still be influenced by a variety of unpredictable factors. Another limitation of our study is that chromosome analysis was not performed on abortion materials. Our study was conducted with blacks. It may not cover the entire community. A significant number of future investigations should support the findings of our research.

Our findings suggest that higher SII values are strongly associated with an increased risk of spontaneous abortion. A complete blood count can be used as an inflammation marker in cases of spontaneous abortion because it is simple, inexpensive, easy to work with, and can be studied in almost every laboratory. The SII complete blood count can be used as a marker of inflammation in spontaneous abortion cases.

Ethics Committee Approval: Ethics Committee permission was obtained from University of Health Sciences, Somalia Recep Tayyip Erdoğan Health Practice and Research Hospital (Date: November 13, 2018, No: MSTH/5236).

REFERENCES

1. Griebel CP, Halvorsen J, Golemon TB, Day AA. Management of spontaneous abortion. *Am Fam Physician*. 2005;72(7):1243-1250.
2. Clement EG, Horvath S, McAllister A, Koelper NC, Sammel MD, Schreiber CA. The language of first-trimester non-viable pregnancy: patient-reported preferences and clarity. *Obstet Gynecol*. 2019;133(1):149-154. [CrossRef]
3. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. *N Engl J Med*. 1988;319(4):189-194. [CrossRef]
4. Bas FY, Tola EN, Sak S, Cankaya BA. The role of complete blood inflammation markers in the prediction of spontaneous abortion. *Pak J Med Sci*. 2018;34(6):1381-1385. [CrossRef]
5. Biyik I, Albayrak M, Keskin F. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in missed abortion. *Rev Bras Ginecol Obstet*. 2020;42(5):235-239. [CrossRef]
6. Wang Q, Liu F, Zhao Y, Cui B, Ban Y. Can neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios be useful markers for predicting missed abortion in the first trimester of pregnancy? *J Obstet Gynaecol Res*. 2020;46(9):1702-1710. [CrossRef]
7. Feng QT, Chen C, Yu QY, et al. The benefits of higher LMR for early threatened abortion: a retrospective cohort study. *PLOS ONE*. 2020;15(4):e0231642. [CrossRef]
8. Christoforaki V, Zafeiriou Z, Daskalakis G, Katasos T, Siristatidis C. First trimester neutrophil to lymphocyte ratio (NLR) and pregnancy outcome. *J Obstet Gynaecol*. 2020;40(1):59-64. [CrossRef]
9. Ata N, Kulhan M, Kulhan NG, Turkler C. Can neutrophil-lymphocyte and platelet-lymphocyte ratios predict threatened abortion and early pregnancy loss? *Ginekol Pol*. 2020;91(4):210-215. [CrossRef]
10. Orgul G, Agbal T, Celen S, Caglar AT. Neuroprotective magnesium sulfate administration increases maternal neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index. *Arch Gynecol Obstet*. 2021;303(6):1433-1437. [CrossRef]
11. Tanacan A, Uyanik E, Unal C, Beksac MS. A cut-off value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. *J Obstet Gynaecol Res*. 2020;46(8):1333-1341. [CrossRef]
12. Hrubaru I, Motoc A, Moise ML, et al. The predictive role of maternal biological markers and inflammatory scores NLR, PLR, MLR, SII, and SIRI for the risk of preterm delivery. *J Clin Med*. 2022;11(23):6982. [CrossRef]
13. Nie D, Gong H, Mao X, Li Z. Systemic immune-inflammation index predicts prognosis in patients with epithelial ovarian cancer: a retrospective study. *Gynecol Oncol*. 2019;152(2):259-264. [CrossRef]
14. Ji Y, Wang H. Prognostic prediction of systemic immune-inflammation index for patients with gynecological and breast cancers: a meta-analysis. *World J Surg Oncol*. 2020;18(1):197. [CrossRef]
15. Geraghty JR, Lung TJ, Hirsch Y, et al. Systemic immune-inflammation index predicts delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2021;89(6):1071-1079. [CrossRef]
16. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol*. 2017;23(34):6261-6272. [CrossRef]
17. Fest J, Ruiter R, Mulder M, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer—a population-based cohort study. *Int J Cancer*. 2020;146(3):692-698. [CrossRef]
18. Turgut E, Yildirim M, Sakcak B, Ayhan SG, Tekin OM, Sahin D. Predicting miscarriage using systemic immune-inflammation index. *J Obstet Gynaecol Res*. 2022;48(3):587-592. [CrossRef]
19. Fluss R, Faraggi D, Reiser B. Estimation of the Youden index and its associated cutoff point. *Biom J*. 2005;47(4):458-472. [CrossRef]
20. Tanoglu A, Karagoz E. Predictive role of the neutrophil-to-lymphocyte ratio in patients with advanced hepatocellular carcinoma receiving sorafenib. *Asian Pac J Cancer Prev*. 2014;15(2):1063-1063. [CrossRef]
21. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer*. 2013;109(2):416-421. [CrossRef]
22. Azab B, Jaglall N, Atallah JP, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology*. 2011;11(4):445-452. [CrossRef]
23. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. *Oncology*. 2007;73(3-4):215-220. [CrossRef]