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RESEARCH ARTICLE

Can the Systemic Immune-inflammation Index Be Used As a Marker to Predict Postpartum Depression?

Sevcan Sarıkaya[1], İlenay Aydın[1], Hasan Bedri Aydın[1], Oğuzhan Günenc[1], Emre Uysal[2], Alpay Tuncar[3]

[1]Department of Obstetrics and Gynecology, Konya City Hospital, Konya, Türkiye
[2]Department of Obstetrics and Gynecology, Yusufeli State Hospital, Artvin, Türkiye
[3]Department of Emergency Medicine, Ankara Etlik City Hospital, Ankara, Türkiye

ABSTRACT

Objective: In this study, we looked at the impact of the systemic immune-inflammation index (SII), the neutrophil/lymphocyte ratio (NLR), and the platelet/lymphocyte ratio (PLR) in predicting postpartum depression (PPD).

Materials and Methods: Age, body mass index, educational attainment, marital status, smoking, and other demographic details of patients who attended the regular outpatient clinic control in the third trimester were noted. The Beck Depression Inventory in the third trimester and Edinburgh PPD Scale (EPDS) in the 1st month postpartum were applied to the patients. PLR, NLR, and SII were calculated from the whole blood test performed at the time of delivery. Patients with EPDS score ≤11 (Group I=210) were considered to have no risk of PPD. Patients with an EPDS score >11 (Group II=190) were considered to have PPD risk. Demographic data and parameters obtained from complete blood count of these two groups were compared statistically.

Results: When both groups were compared, their demographic characteristics were similar ($p>0.05$). The mean NLR, PLR, and SII values of Group II were significantly higher than Group I ($p<0.05$). Beck Depression Scale mean score did not differ significantly between the two groups ($p>0.05$).

Conclusion: Significant efficacy of NLR, PLR, and especially SII was observed during pregnancy in predicting PPD. Patients with high these values should be followed closely in terms of PPD.

Keywords: Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, postpartum depression, systemic immune-inflammation index

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INTRODUCTION

Postpartum depression (PPD) usually occurs in the first 2–3 weeks after birth, such as pessimism, anhedonia, feeling inadequate, losing energy, thinking that you do not pay enough attention to your baby, thinking that you may harm your baby, thoughts of harming yourself, isolating yourself from the environment, increase or decrease in appetite, concentration. It presents with depressive symptoms such as difficulty in remembering, lack of self-confidence, marked anger and restlessness, excessive sleeping or insomnia, thinking about death, and, rarely, suicide.[1]

The frequency of PPD is extremely high. Worldwide, PPD affects 20% of women in the postpartum period. The prevalence of PPD was found to be 11.5% in the United States.[2] It is thought to affect approximately 750,000 mothers each year in the United States.[3]

It has been reported that PPD is 7–70% in mothers of infants hospitalized in the neonatal intensive care unit.[4] This rate is 13% in mothers of premature babies and 23.5% in mothers of infants with infantile colic.[5]

Changes in biochemical markers such as cytokines, brain-derived neurotrophic factor, and stress hormones in depression

Address for Correspondence: Sevcan Sarıkaya, Department of Obstetrics and Gynecology, Konya City Hospital, Konya, Türkiye
E-mail: simsek_svcn_@hotmail.com **ORCID ID:** 0000-0002-0922-4671

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have shown that there is a relationship between inflammation pathways and depression.[6] High levels of proinflammatory cytokines and C-reactive protein in the plasma and cerebrospinal fluid of major depressive patients suggest a strong relationship between depression and inflammation.[7] A novel, straightforward, and reasonably priced indicator of systemic inflammatory response is the neutrophil/lymphocyte ratio (NLR).[8] There are not many studies on the connection between NLR and psychiatric diseases. Chronic stress and NLR have been linked in research on animals.[9,10] NLR levels were shown to be greater in patients with significant depression compared to the control group in two different studies conducted on these patients in 2015.[11,12] Platelet/lymphocyte ratio (PLR) is a cost-effective and readily available clinical marker of peripheral inflammation.[13] Platelet and hemostatic changes play an important role in psychiatric disorders as well as in the inflammatory process.[14] NLR and PLR rates were found to be significantly higher in both manic and euthymic patients compared to the control group in the study, which included 61 manic and 55 euthymic bipolar patients. These results imply that inflammatory cells may be involved in the pathophysiology of both manic and euthymic phases of bipolar disorder.[15]

A novel and prognostic assessment called the systemic immune-inflammation index (SII) is based on the combination of platelet, neutrophil, and lymphocyte counts (SII = Platelet Neutrophil/Lymphocyte). Psychiatric diseases have just been added to this index's list of uses. Male diabetics with high SII index scores have been found to develop unipolar depression.[16] A different study, patients with bipolar disorder during a manic phase had a higher SII index than patients with bipolar disorder during the depressive phase or patients with major depressive disorder.[17]

We aimed to evaluate the effectiveness of inflammatory markers such as NLR, PLR, and SII in predicting PPD.

MATERIALS and METHODS

Study Groups

Patients who admitted to the Gynecology and Obstetrics Clinic between April 2022 and June 2022 and accepted to participate in the survey, who were in the third trimester, were included in our study. Ethics committee approval of our study was obtained from local ethics committee (Date: September 09, 2022, Decision no: 2022/3926). The study was carried out in accordance with the Declaration of Helsinki after obtaining permission from the Local Committee.

In our study, which initially included 452 patients, 52 patients were excluded for various reasons. 21 patients had a diagnosed psychiatric illness (patients diagnosed with major depression, bipolar disorder, psychotic disorder, sleep disorder, patients with severe anxiety). Ten patients had a chronic systemic disease (chronic obstructive pulmonary disease, heart diseases, hematological disorders, or autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus). 15 patients had a score of 17 and above on the BDI in the 3rd trimester, 5 patients were under the age of 18, and 1 patient had a history of substance use. The Edinburgh PPD Scale (EPDS) is the most commonly used screening method to screen postpartum women for major depression.[18] Because it is short and understandable, it is easy to apply and people can fill it in on their own. The cut-off score of the scale was calculated as 12. A total of 400 patients, 210 patients with EPDS score ≤11 (Group I) and 190 patients with EPDS score >11 (Group II), were included in the study. Informed consent forms were obtained from all patients included in the study. Data including demographic characteristics, number of pregnancies, and chronic diseases were recorded when the pregnant women came to their last routine control examination in the 3rd trimester. Third trimester height and weight were measured and recorded in the study form. Pregnant women were evaluated with the BDI. EPDS was applied to the patients when they came for control examinations after 1-month postpartum. PLR, NLR, and SII were calculated using the platelet count, lymphocyte count, and neutrophil count, which are included in the routine hemogram results of the patients at the time of delivery.

Blood was automatically aspirated from the vials used for hematological blood tests into sterile 3 mL plastic or polypropylene tubes. As an anticoagulant agent, EDTA potassium sodium (potassium ethylene diamine tetraacetic acid) was used at a concentration of 4.55±0.85 mmol/L since it prevents coagulation by binding calcium. To minimize *in vitro* morphological and numerical changes, the maximum amount of time between sample collection and analysis was established at 2 h. Diatron Abacus 5 was used to evaluate the samples, which can analyze 25 parameters, including five populations of leukocytes, using 110 L of whole blood. Hematology analyst "Abacus 5" combines techniques to produce measurement findings. Leukocyte, red blood cell, and platelet concentrations and volume distributions are calculated using the volumetric impedance principle. The percentage of each of the five main types of leukocytes is measured optically using light scattering and diffraction (NEU, LYM, MONO, EOS, and BASO).

NLR, PLR, and SII were calculated using neutrophil, lymphocyte, and platelet counts;

Table 1. Analysis of sociodemographic characteristics of depressed and non-depressed patients

	Group II					
	n	%	n	%	p	
Age (mean±SD)	27.5±5.9		28.4±5.6		0.085	m
Body mass index (mean±SD)	28.5±4.3		28.9±4.9		0.731	m
Marital status						
Married	195	92.9	177	93.2	0.547	X^2
Not married-with a partner	10	4.8	11	5.8		
Single - without a partner	5	2.4	2	1.1		
Education status						
Not literate	3	1.4	2	1.1	0.556	X^2
Literate	5	2.4	5	2.6		
Primary school	30	14.3	39	20.5		
Secondary school	82	39.0	61	32.1		
High school	54	25.7	47	24.7		
University	36	17.1	36	18.9		
Living space						
Village	25	11.9	29	15.3	0.110	X^2
Town	36	17.1	45	23.7		
Town center	149	71.0	116	61.1		
Marriage duration						
<1 year	26	12.4	27	14.2	0.886	X^2
1–5 years	80	38.1	69	36.3		
5–10 years	55	26.2	46	24.2		
Over 10 years	49	23.3	48	25.3		
Working Status						
(+)	21	10.0	23	12.1	0.502	X^2
(-)	189	90.0	167	87.9		
Co-working status						
(+)	179	85.2	158	83.2	0.568	X^2
(-)	31	14.8	32	16.8		
Monthly Revenue						
<2500 TL	42	20.0	44	23.2	0.604	X^2
2500–5000 TL	114	54.3	104	54.7		
>5000 TL	54	25.7	42	22.1		
Alcohol use						
(+)	2	1.0	2	1.1	1.000	X^2
(-)	208	99.0	188	98.9		
Smoking						
(+)	18	8.6	26	13.7	0.103	X^2
(-)	192	91.4	164	86.3		
Family size						
Nuclear family	166	79.0	143	75.3	0.367	X^2
Large Family	44	21.0	47	24.7		

m: Mann–Whitney U-test; X^2: Ki-kare test (Fisher's test). SD: Standard deviation

Table 2. Reasons for admission to hospital and hemogram parameters

	Min-Max	Mean±SD	n	%
Application reason				
Water discharge			72	18.0
Pain			152	38.0
Vaginal bleeding			39	9.8
High blood pressure			18	4.5
Decrease in baby movements			14	3.5
Control			26	6.5
Planned hospitalization			67	16.8
Other reasons			12	3.0
Prenatal hemogram	6.0–15.1	11.9±1.4		
Postnatal hemogram	5.4–14.5	10.6±1.5		
NLR	1.4–22.3	4.3±2.8		
PLR	23.0–585.3	125.5±58.1		
SII	228.9–8984	1017.9±777.1		

SD: Standard deviation; Min: Minimum; Max: Maximum; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio; SII: Systemic inflammatory index

NLR=neutrophil count/lymphocyte count

PLR=platelet count/lymphocyte count

SII index=(platelet count×neutrophil count)/lymphocyte count.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency, and ratio values were employed in the descriptive statistics of the data. The Kolmogorov–Smirnov test is used to determine the distribution of variables. Mann–Whitney U-test and independent sample t-test were employed in the examination of quantitative independent data. While analyzing qualitative independent data, the Chi-square test was utilized, and the Fisher's test was used when the Chi-square test requirements were not met. The ROC curve was used to analyze the effect level and cut-off value. Using univariate and multivariate logistic regression, the effect level was examined. Program version 28.0 of the Statistical Package for the Social Sciences (SPSS; Chicago, Illinois, USA) was used for the analysis.

RESULTS

The mean age of the patients was 27.9±5.8 (min. 18, max. 45). The mean body mass index of all patients was 28.7±4.6 (min. 17.5, max. 44.9). 372 (93%) patients were married and 28 (7%) were unmarried. Of all patients, 72 (18%) were undergraduate graduates, 101 (25.3%) were high school graduates, 143 (35.8%) were secondary school graduates, 69 (17.3%) were primary school graduates, and 15 (3.6%) did not receive any training. While 356 (89%) of the patients were working in a job, 44 (11%) were not working in any job. 265 (or 66.3%) of the patients resided in the city center, 81 (or 20.3%) in the district, and 54 (or 13.6%) in the village. Of the patients, 86 (21.5%) had a monthly household income of <2500 TL, 218 (54.5%) had a monthly household income of 2500–5000 TL, and 96 had a monthly household income of >5000 TL (24%). While 396 (99%) of the patients were not using alcohol, 4 (1%) were using alcohol. Of the patients, 356 (89%) were smokers, while 44 (11%) were non-smokers. Of the patients, 309 lived in a nuclear family and 91 in an extended family. Table 1 provides the sociodemographic details of the study participants' patients. No significant difference was found between the sociodemographic characteristics of the groups ($p>0.05$) (Table 1).

The most common reason for patients to apply to the hospital was pain (n=152, 38%). This was followed by water discharge (n=72, 18%) and vaginal bleeding (n=39, 9.8%). The mean hemoglobin value of the prenatal patients was calculated as 11.9±1.4 (min. 6, max. 15.1). The mean hemoglobin value after delivery was calculated as 10.6±1.5 (min. 5.4, max. 14.5). The patients' hemogram parameters were NLR 4.3±2.8 (min. 1.4, max. 22.3), PLR 125.5±58.1 (min. 23.0, max. 585.3), and SII 1017.9±777.1 at the time of admission (min. 228.9, max. 8984). The reasons for the patients' admission to the hospital and the hemogram parameters taken during delivery are given in Table 2.

Table 3. Analysis of the reasons for admission to hospital and hemogram parameters of depressed and non-depressed patients

	Group I			Group II			p	
	n	%	Mean±SD	n	%	Mean±SD		
Application reason								
Water discharge	44	21.0		28	14.7		0.513	X^2
Pain	76	36.2		76	40.0			
Vaginal bleeding	20	9.5		19	10.0			
High blood pressure	12	5.7		6	3.2			
Decrease in baby movements	8	3.8		6	3.2			
Control	13	6.2		13	6.8			
Planned hospitalization	33	15.7		34	17.9			
Other reasons	4	1.9		8	4.2			
Prenatal hemogram			11.9±1.5			11.9±1.3	0.874	t
Postnatal hemogram			10.6±1.6			10.6±1.3	0.662	t
NLR			3.1±1.0			5.7±3.5	0.000	m
PLR			97.4±29.6			156.6±65.6	0.000	m
SII			622±193			1456±931	0.000	m

t: Independent sample t-test; m: Mann–Whitney U-test; X^2: Ki-kare test (Fisher's test). SD: Standard deviation; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio; SII: Systemic inflammatory index

The reason for admission to the hospital, prenatal and postnatal hemogram values did not differ significantly between the groups (p>0.05). NLR, PLR, and SII values in Group II were significantly higher than Group I (p<0.05) (Table 3).

Figure 1 displays the means and ranges of the three inflammatory markers (NLR, PLR, and SII) compared between the two groups.

In the univariate model, significant efficacy of NLR, PLR, and SII during pregnancy was observed in predicting post-pregnancy depression (p<0.05) (Table 4). SII showed a significant-independent efficacy in predicting postpartum depression in the multivariate reduced model (p=0.05). SII alone was as significant in the regression analysis as the total of the other components (Table 4).

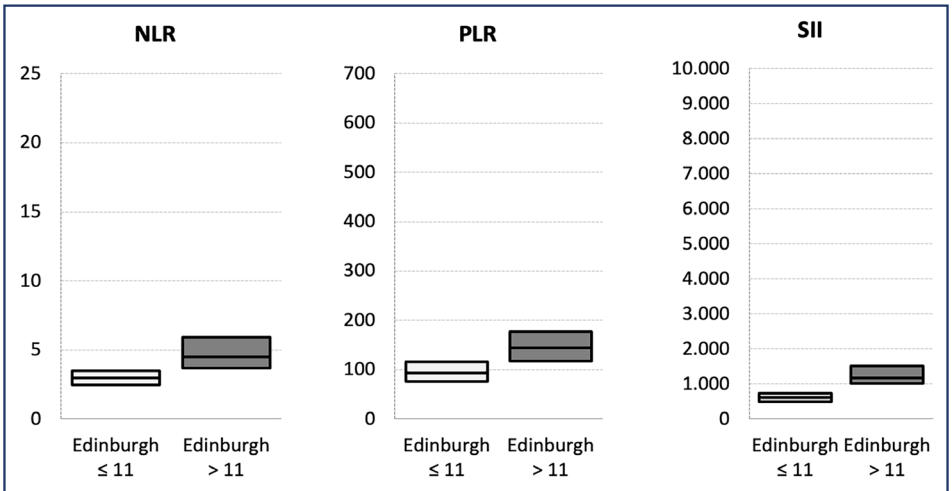

Figure 1. Means and standard deviation (SD) of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic inflammatory index (SII) in depressed and non-depressed patients

Table 4. Parameters for predicting post-pregnancy depression in univariate and multivariate models

	Univariate model			Multivariate model		
	OR	%95 CI	p	OR	%95 CI	p
NLR	3.14	2.42–4.07	0.000			
PLR	1.05	1.04–1.06	0.000			
SII	1.01	1.01–1.01	0.000	1.01	1.01–1.01	0.000

Logistic Regression (Forward LR); OR: Odds ratio; CI: Confidence Interval; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio; SII: Systemic inflammatory index

In the differentiation of Group I and Group II patients, significant effectiveness of NLR value (area under the curve 0.849 [0.811–0.787]), PLR value (area under the curve 0.861 [0.826–0.896]), and SII value (area under the curve 0.964 [0.945–0.982]) were observed (Fig. 2).

DISCUSSION

The findings of the investigations provide evidence that immunological and inflammatory pathways contribute to the development of mood disorders. We investigated whether NLR, PLR, and SII calculated using maternal hematological parameters can be used as predictors of PPD. Our study shows that especially SII is an important marker in PPD.

Stress affects neutrophil function, namely phagocytic capacity and superoxide generation, according to a number of studies.[19–21] These changes may be associated with depressive symptoms.[22] In our investigation, it was found that patients with risk of PPD had higher neutrophil counts than healthy patients without risk of PPD.

The most prevalent form of white blood cell in the body, neutrophils are important components of the innate immune system and serve as the first line of cellular defense against infection.[23] Lymphocytes, which are part of the adaptive immune system, are crucial for the body's immune response, including the creation of antibodies and cell-mediated immunity.[24] Activated platelets have inflammatory roles in a number of physiological and pathological circumstances, controlling the permeability of endothelial cells, the recruitment of neutrophils, macrophages, and their effectors.[25,26] Using the test parameters for a complete blood count, all of them are conveniently accessible. In a study of Chinese pregnant women, it was found that NLR was positively correlated with antepartum depression but not with PPD.[27] A meta-analysis study reported that an inflammatory activation occurs in mood disorders and that NLR and PLR may be useful in detecting this activation.[28] In our study, NLR and PLR values using these parameters were found to be significantly higher in patients with risk of PPD than in patients without risk of PPD.

SII, which combines three counts of inflammatory peripheral cells, such as neutrophils, lymphocytes, and platelets, is becoming more widely accepted as a practical biomarker for systemic inflammation.[29–31] Compared to the aforementioned markers, it can more accurately reflect the body's immunological and inflammatory conditions. Previous

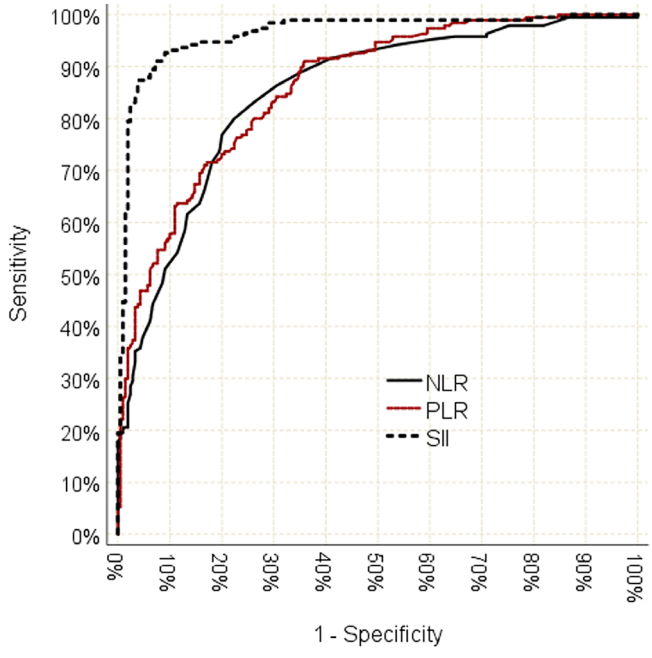

Figure 2. ROC curve showing the sensitivity of NLR, PLR, and SII in predicting postpartum depression

NLR: Neutrophil/lymphocyte; PLR: Platelet/lymphocyte; SII: Systemic inflammatory index

research has revealed that SII is crucial for determining the prognosis of some physical conditions, including malignancies, cerebral infarction, cardiovascular illness, and acute pancreatitis.[29,31–33] There have not been many studies on SII in psychiatric diseases, as far as we know. In our research, it was discovered that PPD patients' SII values were considerably different from those of the control group, and the ROC curve supported this finding.

Our study has certain limitations in specific situations, despite the fact that it underscores the significance of examining new factors to predict PPD. It was not possible to evaluate all of the physiological, hormonal, and biochemical markers brought by pregnancy, as the patients were in the postpartum period. Therefore, we cannot ignore the fact that other parameters may also contribute to depression. Moreover, some confounding variables including smoking, nutrition, and body mass index can have an impact on the rates of inflammation. We were unable to completely show the impact on inflammatory markers, despite the fact that there was no statistically significant difference between the two groups in terms of these values in our study. However, despite all these, our study reveals that NLR, PLR, and especially SII value calculated from routinely checked complete blood count parameters, which do not require an invasive procedure, may be potential predictors of PPD. In this respect, this prospective study shows that our study is valuable.

CONCLUSION

In this study, we aimed to highlight the significance of the link between PPD and the inflammatory markers NLR, PLR, and SII index. NLR, PLR, and SII are noticeably increased in patients with risk of PPD, according to the studies reported here. It is also the first study to indicate the importance of SII in PPD. However, to emphasize the significance of this work and use these parameters as markers, additional research with bigger patient populations is required.

Disclosures

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Non-pharmaceutical and Medical Device Research Ethics Committee (No: 2022/3926, Date: 09/09/2022).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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